The present study investigated the usefulness of the number and distribution of LNM, and LNR as prognostic markers for colon cancer. The location of LNM was an independent risk factor for both recurrence and survival. We used stepwise regression analysis due to the limited sample size. The number of LNM was excluded from further analysis of recurrence and survival partly because of colinearity. However, the number of LNM was an independent risk factor for recurrence and survival, unless LNR or LNM location was used (data not shown).

Some investigators have recently reported the usefulness of LNR for predicting the prognosis of patients after curative resection for colorectal cancer [11–16]. The present study demonstrated that LNR is a good predictor of recurrence after curative resection for right colon cancer. Adding the concept of LNR and location of LNM to conventional TNM staging could improve the accuracy of evaluating nodal status. Patients at high risk for recurrence with n3 LNM or LNR ≥0.15 might be suitable candidates for cytotoxic adjuvant chemotherapy such as folinic acid, fluorouracil and oxaliplatin.

In the present study, high LNR led to both a high number of positive nodes and low number of lymph nodes retrieved. Kim et al. [13] reported the same tendency as in our study. In their study, the numbers of lymph nodes examined were as follows: 21 (LNR <0.1), 18 (LNR 0.1–0.2), 16 (LNR 0.2–0.4) and 16 (LNR >0.4). The reason why the patients with many positive nodes had fewer lymph nodes retrieved is unclear. A recent study showed that increasing the number of examined lymph nodes to more than 6 did not detect more positive nodes in patients with T3 colon cancer [27]. Our hypothesis is that the number of lymph nodes differs from one person to another and that individuals who naturally have fewer lymph nodes have a tendency to easily metastasize to lymph nodes. This issue should be clarified in further studies.

This retrospective study has potential limitations. The usefulness of CME with high ligation for advanced right colon cancer should be validated by a randomized controlled study. None of our patients received powerful adjuvant chemotherapy such as folinic acid, fluorouracil and oxaliplatin, or folinic acid, fluorouracil and irinotecan. The effectiveness of such adjuvant chemotherapy after CME with high ligation should also be clarified in further studies.

In conclusion, CME with high ligation of major vessels should be a standard therapy for patients with T3–T4 right colon cancer. Not only the number of LNM but also the distribution of LNM and the LNR should be considered with regard to prognosis after curative resection for right colon cancer.

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Original Paper

Oncological Outcomes of Laparoscopic Surgery in Elderly Patients with Colon Cancer: A Comparison of Patients 64 Years or Younger with those 75 Years or Older

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KEY WORDS:
Laparoscopic colectomy; Matched case–control study; Elderly

ABBREVIATIONS:
Computed Tomography (CT)

ABSTRACT

Background/Aims: We compared the results of laparoscopic resection of colon cancer between patients 75 years or older and those 64 years or younger, to confirm whether this procedure is warranted in elderly patients.
Methodology: The study group was comprised of patients with stage I to III colon cancer treated by laparoscopic surgery from 1995 through 2006. Oncologic outcomes were compared between 74 patients 75 years or older (elderly group) and 74 patients 64 years or younger (younger group) who were matched for gender, tumor location and pathological tumor-node-metastasis (TNM) stage.
Results: In patients with stage I or II disease, the disease-free survival rate and overall survival rate were similar in the elderly group (100% and 100%, respectively) and the younger group (95.6% and 95.8%, respectively). In patients with stage III disease, the disease-free survival rate and overall survival rate were also similar in the elderly group (76.7% and 88.5%, respectively) and the younger group (88.5% and 88.5%, respectively).
Conclusions: Postoperative complications and long-term oncologic outcomes were similar in elderly patients and younger patients with colon cancer who underwent laparoscopic colectomy in our hospital. These results demonstrate that laparoscopic resection of colon cancer is warranted in patients 75 years or older.

INTRODUCTION

Laparoscopic colectomy was first performed in 1990, and its indication range has been extended from early to advanced cancer. The increased use of laparoscopic surgery is attributed to several distinct advantages over open surgery, such as less postoperative pain, a lower risk of postoperative ileus, a shorter postoperative hospital stay, and earlier recovery and return to social activities, i.e. a better postoperative quality of life (1-3). Aging is generally a risk factor for surgery. In elderly patients, surgery carries increased risks of serious postoperative complications and operative mortality because of age-related declines in physical function and reserve capacity and the presence of various underlying diseases. Once complications occur, elderly patients are at risk for the development of multiple organ failure. They therefore require a careful assessment of the indications for surgery, selection of surgical procedures and close perioperative management (4). Conventional open surgery in elderly patients may prolong the hospital stay, as well as increase mortality and morbidity (5-8). We believe that elderly patients should undergo minimally invasive, laparoscopic colorectal surgery.

Since 1995, we have performed laparoscopic colorectal surgery in more than 800 patients with colorectal cancer in our hospital. To date, few studies have evaluated the safety and invasiveness of laparoscopic surgery specifically in elderly patients (9-13). Short- and long-term outcomes of laparoscopic surgery in elderly patients with colon cancer remain unclear owing to the lack of large, randomized control studies. To gain insight into these problems, we performed a matched case-control study to compare short- and long-term outcomes between patients 75 years or older (elderly group) and patients 64 years or younger (younger group) who underwent laparoscopic surgery for colon cancer. Our ultimate goal was to determine whether laparoscopic surgery is warranted in elderly patients.

METHODOLOGY

Among 344 patients who underwent laparoscopic surgery for colon cancer from April 1995 through December 2006, we studied 74 elderly patients (age, ≥75 years) and 74 younger patients (age, ≤64 years) who

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were matched for gender, tumor location, and pathological tumor-node-metastasis (TNM) stage. Patients with ileus (no response to decompression) and those who did not give informed consent for laparoscopic surgery were excluded from the study. The indications for laparoscopic surgery were assessed in all patients on the basis of the results of barium enema examination, colonoscopy, abdominal ultrasonography and computed tomography (CT) of the chest and abdomen. From 1995 through 2000, the indications for laparoscopic surgery were generally restricted to early cancer. Subsequently, the indications for laparoscopic surgery were extended to include advanced cancer without multiple-organ invasion. The technique for laparoscopic surgery is described in detail elsewhere (14). Briefly, a 12mm trocar was first placed in a small sub-abdominal incision (3-4cm), and a Lap Disc (70x70mm; Johnson and Johnson) was placed on the upper abdomen. The abdomen was insufflated with carbon dioxide at a mean pressure of 8mmHg/h. Three or four 5mm trocars were then placed using a 5mm scope. Postoperative follow-up examinations included the measurement of serum carcinoembryonic antigen levels (at 3-month to 1-year intervals), chest and abdominal CT (at 6-month intervals), and colonoscopy (at 1-year intervals), in addition to routine outpatient visits. Recurrent disease was assessed on the basis of the results of diagnostic imaging and clinical, laboratory, and histopathological examinations. Statistical analysis was performed with the use of chi-square test and Mann-Whitney U test. A p-value of less than 0.05 was considered to indicate statistical significance. Disease-free survival rates and overall survival rates were estimated according to the Kaplan-Meier method. The log-rank test was used to compare these values between the groups.

RESULTS

As for the demographic characteristics of the patients, age ($p<0.001$) and the American Society of Anesthesiologists (ASA) score ($p=0.001$) were significantly higher in the elderly group than in the younger group. The median follow-up period did not significantly differ between the elderly group (76 months) and the younger group (66 months) (**Table 1**). Conversion from laparoscopic surgery to open surgery was not necessary in either group.

Operation time and intraoperative blood loss did not significantly differ between the groups. The median hospital stay after surgery also did not significantly differ between the elderly group (10 days) and the younger group (9 days). The incidence of postoperative complications was similar in the elderly group (11% [8/74]) and the younger group (9% [7/74]) (**Table 2**).

Postoperative recurrence developed in 18% (13/74) of the patients in the elderly group, as compared 9% (7/74) of those in the younger Group (**Table 3**). This difference was not significant. In patients with stage I or II tumors, the disease-free survival rate and the overall survival rate were 100% and 100%, respectively in the elderly group and 95.6% and 95.8%, respectively in the younger group, indicating no significant difference in long-term outcomes between the groups (**Figure 1**). In patients with stage III tumors, the disease-free survival rate and the overall survival rate in the elderly group were 76.7% and 88.5%, respectively, and 88.5% and 88.5%, respectively in the younger group, indicating no significant difference in long-term outcomes between the groups (**Figure 2**).

DISCUSSION

In this single-center, matched case-control, study of patients with colon cancer who underwent

TABLE 1 Demographic Characteristics of the Patients

	Younger (n = 74)	Elderly (n = 74)	p-value
Male:Female	38:36	38:36	NS
Age (years)*	58 (35–64)	79 (75–91)	<0.001
Location			NS
Cecum	10	10	
Ascending colon	31	31	
Transverse colon	5	5	
Descending colon	3	3	
Sigmoid colon	13	13	
Rectosigmoid colon	12	12	
BMI (kg/m²)*	22 (17–28)	22 (14–38)	NS
ASA status			<0.001
I	43	31	
II	28	51	
III	3	18	
Tumor size (cm)*	3.6 (1–9)	3.4 (1–8)	NS
Lymph nodes*	16 (2–58)	14 (4–38)	NS
pT category			NS
pT1	18	18	
pT2	13	13	
pT3	43	43	
pN category			NS
pN0	48	48	
pN1	24	24	
pN2	2	2	
p TNM			NS
I	28	28	
IIA	20	20	
IIIA	3	3	
IIIB	21	21	
IIIC	2	2	
Follow-up period (months)*	80 (10–145)[a]	66 (14–178)[b]	NS

BMI denotes body mass index; ASA status, physical status according to the American Society of Anesthesiologists classification; * Values are expressed as medians (range); a, n (alive at last visit) = 80; b, n (alive at last visit) = 66; NS, not significant.

TABLE 2 Operation Time, Blood Loss During Operation, Hospital Stay and Postoperative Complications

	Younger (n=74)	Elderly (n=74)	*p*-value
Operation time (min)	195 (120–345)	190 (85–380)	NS
Blood loss during operation (mL)	20 (0–720)	20 (0–325)	NS
Hospital stay (days)	9 (4–26)	10 (5–44)	NS
Postoperative complications			
Wound infection	2	2	NS
Ileus	2	4	NS
Postoperative bleeding	1	1	NS
Others	2	1	
Total	7 (9%)	8 (11%)	NS

Values for operation time, blood loss volume, and hospital stay are expressed as medians (range). Values for wound infection, Ileus and postoperative bleeding represent the number of events; NS, not significant.

TABLE 3 Tumor Recurrence in Patients with Colon Cancer

Recurrence site	Younger (n=74)	Elderly (n=74)	*p*-value
Liver	2	5	NS
Lung	1	3	NS
Peritoneum	3	1	NS
Lymph node	1	3	NS
Anastomosis	0	1	NS
Total	7	13	NS

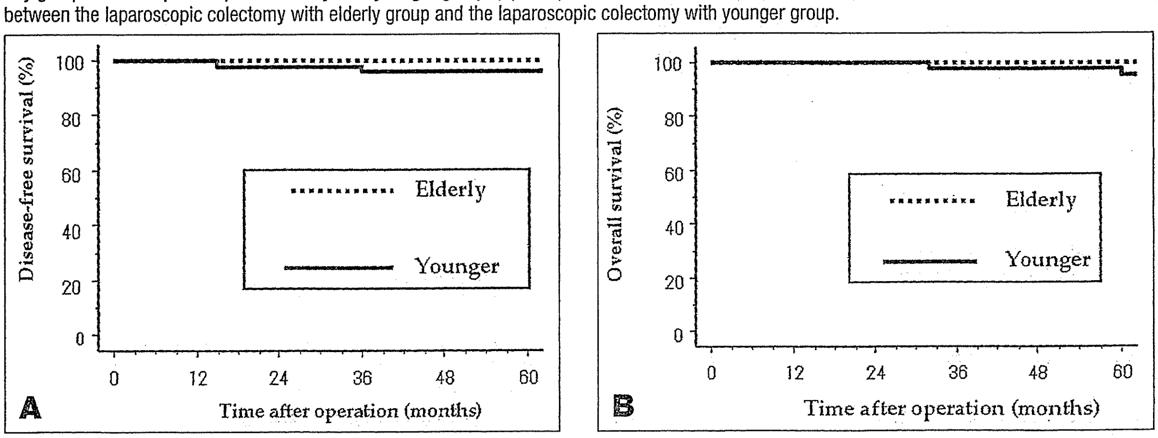
NS denotes not significant

laparoscopic surgery, the ASA score differed significantly between the elderly group and the younger group. Nonetheless, there were no significant differences between the groups in the median hospital stay, postoperative complications, the rate of postoperative recurrence, and long-term outcomes.

In elderly patients, open colorectal surgery has been linked to increased mortality due to postoperative complications, whereas overall survival rate according to disease stage was found to be similar in elderly and younger patients (15-18). Reduced surgical invasion may lead to fewer and less severe postoperative complications, as well as prompter recovery. Minimally invasive laparoscopic surgery is thus considered to offer important advantages over open surgery for elderly patients. All studies evaluating laparoscopic colectomy in elderly patients have demonstrated several advantages of this technique over open surgery (5-13). Hester *et al.* (19) studied short- and long-term outcomes after laparoscopic resection for colorectal cancer in 101 patients 80 years or older. The median age was 83 years (range, 80-95 years). There were no intraoperative complications, and the overall postoperative morbidity rate was 17%. The incidences of wound infection and cardiopulmonary complications were low. The overall postoperative mortality rate was 3%. There was no association between operative mortality the ASA score. The 5-year overall survival rate was 51%. These results are similar to our findings. Because laparoscopic surgery is associated with low postoperative morbidity and good outcomes, we believe it should be recommended for elderly patients.

Elderly patients have a high rate of mortality from cardiovascular causes and a high rate of respiratory complications after open surgery for colorectal cancer (6,7). In one study, 55% of deaths were caused by surgery-related cardiopulmonary

FIGURE 1 (A) Comparison of the disease-free survival rates in patients with stage I or II colon cancer between the laparoscopic colectomy with elderly group and the laparoscopic colectomy with younger group. **(B)** Comparison of the overall survival rates in patients with stage I or II colon cancer between the laparoscopic colectomy with elderly group and the laparoscopic colectomy with younger group.



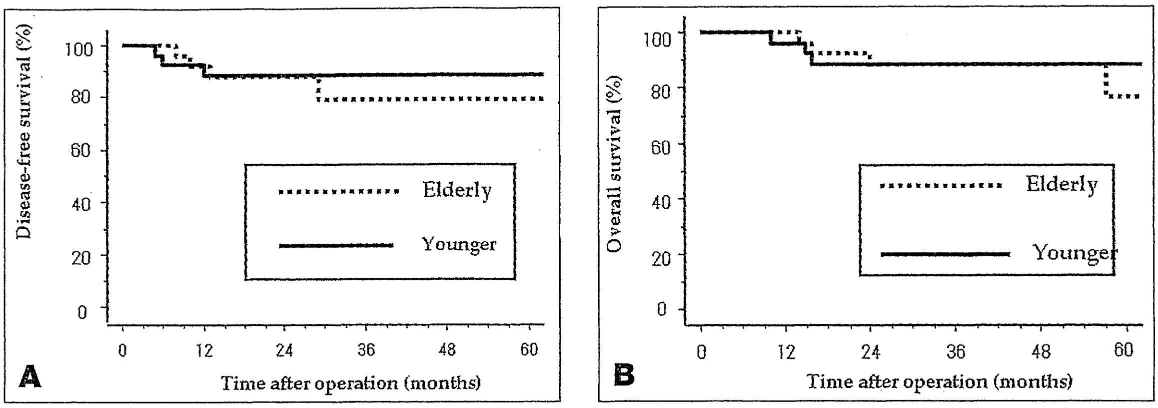


FIGURE 2 (**A**) Comparison of the disease–free survival rates in patients with stage III colon cancer between the laparoscopic colectomy with elderly group and the laparoscopic colectomy with younger group. (**B**) Comparison of the overall survival rates in patients with stage III colon cancer between the laparoscopic colectomy with elderly group and the laparoscopic colectomy with younger group.

complications (6). In our study, however, there were no cardiac complications or deaths after laparoscopic surgery in the elderly group, similar to the results of a study by Law *et al.*, which reported one death among patients who underwent laparoscopic colectomy (11).

The elderly group in our study included patients 75 years or older because the World Health Organization uses this cutoff point to define "late elderly" persons. The ASA score was class II or higher in a significantly higher proportion of patients in the elderly group (88%) than in the younger group (42%). In our study, no elderly patient died during surgery, and the ASA score was not associated with operative mortality or the length of the hospital stay. Most notably, the 5-year survival rate in the elderly group was 100% in patients with stage I or II disease and 76.7% in those with stage III disease. Their results compare favorably with those of other studies in general patients with colorectal cancer (1-3).

In elderly patients with colon cancer, accurate risk assessment before surgery requires close cooperation with internists as well as members of the surgical team, including anesthesiologists (20,21). Further technological advances in laparoscopic surgery and increased experience among surgeons will most likely promote the use of laparoscopic procedures for the treatment of colon cancer in elderly patients. The results of future, multicenter, prospective clinical trials are expected to establish laparoscopic surgery as a safe and effective procedure for elderly patients with colon cancer.

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Original Paper

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

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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.

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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 intestine 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.

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/m²)	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.

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 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%).

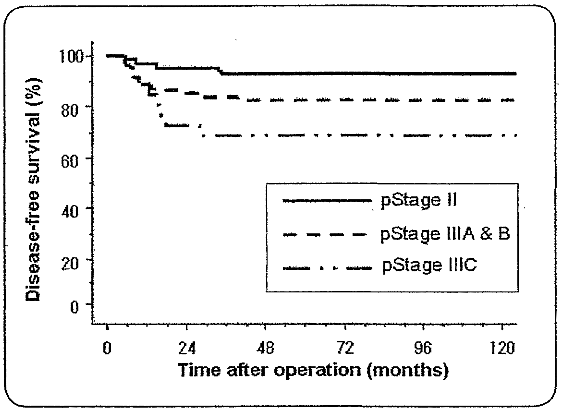

FIGURE 1. Disease-free survival according to tumor-node-metastasis stage in patients with colon cancer.

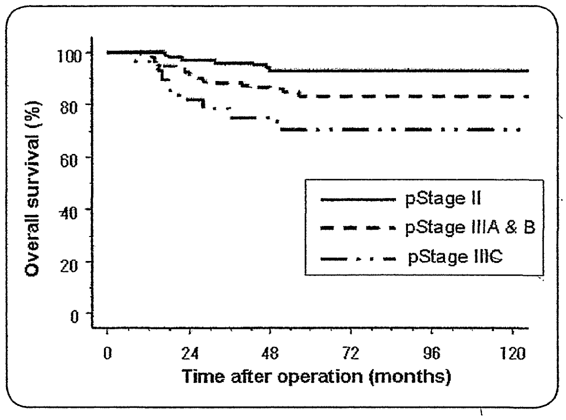

FIGURE 2. Overall survival according to tumor-node-metastasis stage in patients with colon cancer.

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 recurrence 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.

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SURGERY TODAY

Original Article

Association Between Incisional Surgical Site Infection and the Type of Skin Closure After Stoma Closure

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Abstract

Purpose. This study was performed to investigate the effect of subcuticular sutures on the incidence of incisional surgical site infection (SSI) after closure of a diverting stoma.

Methods. The study was carried out as a retrospective analysis of prospectively collected data from 51 patients who underwent closure of diverting stoma following resections of lower rectal cancer between January 2008 and December 2008. This study attempted to determine whether there was an association between the type of skin closure and the incidence of incisional SSI. Moreover, risk factors for incisional SSI after closure of diverting stoma were identified using a multivariate analysis.

Results. An incisional SSI occurred in 12 of the 51 patients (23.5%). The rate of incisional SSI with subcuticular sutures was 11.1% (3/27) in comparison to 37.5% (9/24) with transdermal suture and skin stapler. A subcuticular skin closure was the only favorable factor that was significantly associated with a lower incidence of incisional SSI (odds ratio: 0.19; 95% confidence interval: 0.04–0.92).

Conclusions. A subcuticular skin closure has a protective effect against incisional SSI after closure of diverting stoma. A larger study is necessary to further define the role of subcuticular suture on the prevention of incisional SSI in cases of gastrointestinal surgery.

Key words Subcuticular skin closure · Stoma · Surgical site infection

Introduction

Incisional surgical site infection (SSI) is one of the most frequent complications observed after stoma closure,[1] and previous studies have reported that the rate of occurrence of such complications is as high as 40%.[2] Delayed primary closure or healing by secondary intention is recommended to reduce the occurrence rate of this type of infection.[2,3] However, the wounds take several days to be closed with delayed primary closures. Furthermore, they are accompanied by painful dressing changes. Moreover, healing by secondary intention requires a minimum of several weeks for epithelialization.[4] Several recent reports have suggested that subcuticular suturing is associated with a lower incidence of incisional SSI in cardiovascular, orthopedic, and gynecological surgeries.[5–8] Although previous studies have previously reported that subcuticular sutures are preferred from an aesthetic viewpoint,[9] the protective effect of these sutures against incisional SSI has never been reported in gastrointestinal surgery. In particular, the procedures used for stoma closure are potentially at high risk for the occurrence of incisional SSI.

The aims of this study were to describe the association between incisional SSI and the type of skin closure after diverting stoma closure and to examine the protective effect of subcuticular suture against incisional SSI. Moreover, clinicopathological factors were analyzed to identify the risk factors for incisional SSI after closure of diverting stoma using a multivariate analysis.

Patients and Methods

Fifty-one patients underwent closure of diverting stoma at the National Cancer Centre Hospital East (NCCHE), Kashiwa, Japan, between January 2008 and December 2008. Forty-eight of the 51 patients underwent reconstruction during resections for primary rectal cancer, and 3 were emergently constructed after the occurrence of anastomotic leakage. The stomas were usually closed several months following the previous surgery. The surgeon determined whether ileostomy or colostomy had been constructed.

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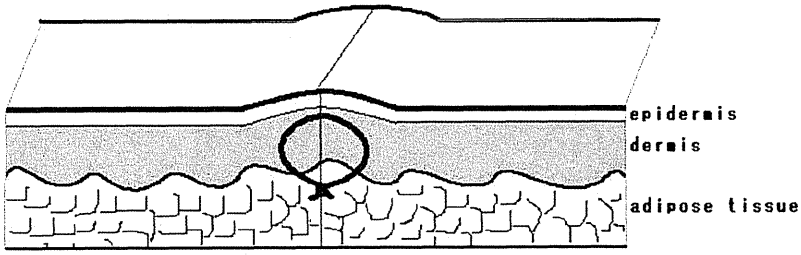

Fig. 1. Schematic illustration of subcuticular sutures. The dermal layer on each edge is properly attached by subcuticular sutures

Stoma Closure Procedures

The skin around the rim of the stoma was excised with 2–3-mm margins, the intestine was mobilized from the abdominal wall, and the stoma was tightly closed with the intestinal mucosa inverted by suturing the skin rim. Intra-abdominal dissections were performed in order to enable complete mobilization of the stomas. The bowels were transected on either side of the stomas, and either stapled functional end-to-end anastomosis or hand-sewn anastomosis was performed.[3] Abdominal fascia was closed with interrupted suturing with a gradually absorbable monofilament material (polydioxanone; Johnson & Johnson, Tokyo, Japan; or Glycomer 631; Covidien, Tokyo, Japan). The wounds were thoroughly irrigated with 300–500 ml of warm saline. Thereafter, the skin was closed by subcuticular suturing with slowly absorbable monofilament material (polydioxanone, or polytrimethylene carbonate; Covidien) as illustrated in Fig. 1, interrupted transdermal suturing using 4-0 nylon, or a skin stapler (Visistat; Teleflex Medical, Durham, NC, USA). No drains were placed in the abdominal cavity.

Perioperative Care

Patients received mechanical bowel lavage treatment with 180 ml of magnesium citrate (Magcorol P; Horii-Yakuhin, Osaka, Japan) for 2 days before the surgery. No chemical bowel preparation was applied. Patients were administered two doses of cefmetazole sodium (CMZ) — a second-generation cephalosporin — as a prophylactic antibiotic. One gram of CMZ was administered to patients within 30 min prior to the skin incision; thereafter, the same dose of the drug was administered 3 h later. Clear liquid intake was allowed in patients on postoperative day (POD) 2, soft food intake was allowed on POD 4, and the patients were discharged from the hospital after removal of nonabsorbable sutures or staples on POD 7 or 8.

SSI Surveillance

Incisional SSI was defined, according to the guidelines issued by the Centers for Disease Control and Prevention, as any infection that involved the skin and subcutaneous soft tissue around incisions within 30 days after the operation,[10] and it included at least one of the following: (1) an infection accompanied by apparently purulent discharge with or without laboratory evidence; (2) culture-positive drainage fluid or soft tissue from the incision; (3) the incision had signs of inflammation, was deliberately opened by a surgeon, and the culture was positive. The wounds were inspected for any problem twice a day during admission and at the outpatient clinic at least once, 30 days after surgery. Incisional SSI was identified retrospectively by an infection-control team that thoroughly reviewed clinical records of patients who underwent stoma closure. All data regarding SSI were prospectively recorded in a database and were analyzed as a retrospective cohort study.

Statistical Analysis

The data were collected in a database for analysis (SPSS 11.0 J for Windows; SPSS, Chicago, IL, USA). Differences between numerical variables were tested using the Mann–Whitney *U*-test and those between categorical variables were tested using chi-square statistics. The multivariate analysis was performed using a logistic regression model. A P value of less than 0.05 was considered to be significant.

Results

Fifty-one patients underwent stoma closure at NCCHE, Kashiwa, Japan during the period of study. The procedures followed for the primary operation included abdominoanal resection ($n = 29$), low anterior resection ($n = 20$), total colectomy ($n = 1$), and pelvic exenteration ($n = 1$). Twelve of the 51 patients (23.5%) developed incisional SSI. Bacteria identified from the incisions with positive SSIs included methicillin-resistant *Staphylococcus aureus* ($n = 2$), *Escherichia coli* ($n = 1$), *Enterococcus faecium* ($n = 1$), *Enterococcus faecalis* ($n = 1$), *Enterococcus raffinosus* ($n = 1$), and *Enterococcus avium* ($n = 1$). The median postoperative day on which patients

Table 1. Clinical background of patients according to the type of skin closure

Factor		Subcuticular (n = 27)	Staple and transdermal (n = 24)	P value
Age (years)	Mean ± SEM	60.2 ± 2.5	63.5 ± 2.1	0.30
Sex (n)	Male/Female	23/4	15/9	0.06
ASA score (n)	1/2	14/12	12/12	0.50
Total protein (g/dl)	Mean ± SEM	6.9 ± 0.1	6.9 ± 0.1	0.62
Albumin (g/dl)	Mean ± SEM	4.1 ± 0.0	4.0 ± 0.1	0.97
DM	+/–	3/24	4/20	0.43
BMI (kg/m^2)	Mean ± SEM	22.4 ± 0.5	22.0 ± 0.7	0.52
Type of stoma (n)	Colostomy/Ileostomy	3/24	12/12	<0.01
Type of anastomosis (n)	FEEA/hand-sewn	26/1	24/0	0.53
Blood loss (g)	Mean ± SEM	56.8 ± 10.5	60.0 ± 7.8	0.29
Operation time (min)	Mean ± SEM	81.2 ± 6.8	72.7 ± 9.7	0.68
Body temperature[a] (°C)	Mean ± SEM	36.4 ± 0.1	36.3 ± 0.1	0.63

There were no statistical differences in the background except for the type of stoma
SEM, standard error of the mean, ASA, American Society of Anesthesiology, DM, diabetes mellitus; BMI, body mass index; FEEA, functional end-to-end anastomosis
[a]Body temperature is demonstrated as the lowest value recorded during operation

Table 2. Analysis of variables associated with incisional surgical site infection (SSI)

Factor		SSI(+) (n = 12)	SSI(–) (n = 39)	P value
Age (years)	Mean ± SEM	65.7 ± 2.9	60.5 ± 1.9	0.20
Age ≥70 (n)	+/–	6/6	10/29	0.11
Sex (n)	Male/Female	10/2	28/11	0.35
ASA score (n)	1/2	6/6	21/18	0.57
Total protein (g/dl)	Mean ± SEM	6.9 ± 0.1	6.9 ± 0.1	0.51
Albumin (g/dl)	Mean ± SEM	4.1 ± 0.1	4.1 ± 0.0	0.51
DM	+/–	2/10	5/34	0.53
BMI (kg/m^2)	Mean ± SEM	21.7 ± 0.8	22.3 ± 0.5	0.63
Type of stoma (n)	Colostomy/Ileostomy	5/7	10/29	0.24
Type of anastomosis (n)	FEEA/hand-sewn	11/1	39/0	0.24
Type of skin closure	Subcuticular/Staple or transdermal	3/9	24/15	0.03
Blood loss (g)	Mean ± SEM	69.8 ± 16.3	54.7 ± 7.0	0.56
Operation time (min)	Mean ± SEM	85.2 ± 14.6	74.7 ± 6.1	0.59
Body temperature[a] (°C)	Mean ± SEM	36.2 ± 0.2	36.4 ± 0.1	0.51

A lower rate of incisional SSI was observed with subcuticular skin closure than with stapler or transdermal closure. All other factors were insignificant
[a]Body temperature is demonstrated as the lowest value recorded during operation.

were diagnosed with incisional SSI was day 5. Eleven patients were diagnosed with incisional SSI during admission and the remaining patient was diagnosed after discharge. All incisional SSIs were treated by wound opening, drainage, and irrigation with normal saline.

Table 1 presents the clinical background of patients on the basis of the type of skin closure. The subcuticular suture group underwent a greater number of ileostomy procedures than the stapler/transdermal suture group. No statistical differences of background between the two groups were found in other clinical factors. Table 2 presents the associations between clinical factors and incidence of incisional SSI. A lower rate of incisional SSI was observed with subcuticular skin closure than with stapler or transdermal closure (P = 0.03). There was a trend toward a higher rate of incisional SSI in patients older than 70 years (P = 0.11).

The multivariate analysis showed that the type of skin closure was the only independent factor associated with incidence of incisional SSI (Table 3). The rate of the incisional SSI decreased from 37.5% in cases closed by transdermal sutures or staples to 11.1% in those closed with subcuticular sutures (odds ratio: 0.19; 95% confidence interval: 0.04–0.92). No statistically significant difference was observed in the postoperative length of the hospital stay between patients with or without subcuticular sutures (the median postoperative hospital stay in both groups was 8 days; P = 0.96). A postoperative reoperation was required in 3 (5.9%) of 51 patients due

Table 3. Multivariate analysis of the risk factors of incisional SSI after closure of diverting stoma

Factor		Odds ratio	(95% CI)	*P* value
Type of stoma	Ileostomy	1		
	Colostomy	1.26	(0.26–6.1)	0.78
Age	<70	1		
	≥70	3.25	(0.73–14.4)	0.12
Type of skin closure	Staple or transdermal suture	1		
	Subcuticular suture	0.19	(0.04–0.92)	0.04

The multivariate analysis demonstrated that the type of skin closure was the only independent factor associated with incidence of incisional SSI
CI, confidence interval

to associated complications, i.e., anastomotic leakage in one case, and intestinal obstruction in the other two patients. No mortalities were observed in this series.

Discussion

Several randomized controlled trials have indicated the protective effects of subcuticular skin closure against incisional SSI in cases of clean surgery.[5,6] Furthermore, some retrospective studies showed that subcuticular suturing is associated with a significantly lower rate of incisional SSI in clean-contaminated wounds following gynecological surgery.[7,8] However, there is no available evidence to support the protective effects of subcuticular suturing against incisional SSI in gastrointestinal surgery, in which the incidence of incisional SSI is rather high. This study is the first to clearly demonstrate that subcuticular suturing reduces the rate of incisional SSI in gastrointestinal surgery.

Although several reports noted the protective impact of subcuticular suturing against incisional SSI,[5–8] none of them clearly explained the mechanism underlying the effect. Subcuticular skin closure approximates the skin by tightly connecting both edges at the level of the dermis; thereafter, suture strings are buried beneath the surface of the skin. This prevents subcutaneous dead space and excessive tissue inflammation, both of which are risk factors of incisional SSI.[11] On the contrary, improper placement of skin staples disturbs the normal contact between the dermis and adipose tissues, which causes subcutaneous dead space and prevents proper wound healing.[12,13] Transdermal suturing with nonabsorbable material might also prevent the formation of subcutaneous dead space, but it is likely to cause excessive inflammation because it penetrates the dermal barrier with foreign material. Transdermal suturing is also likely to damage fragile adipose tissue, because it holds the dermis and subcutaneous tissue together with the same tensile strength.[14] Therefore, subcuticular suturing is superior to skin staples and transdermal suturing because it helps the wound-healing process. Subcuticular skin closure also supports the reconstruction of the dermis. Capillary vessel loops in the dermis provide the main blood supply to cutaneous wound healing while collagen formation in the dermis offers tensile strength to the wound.[15–17] Therefore, proper reconstruction of the dermis is the critical process in the restoration of cutaneous function. The appropriate contact of dermis achieved by subcuticular suturing may promote proper wound healing and restoration of cutaneous function, which, in turn, enhances host defense against infection.[11]

A univariate analysis showed that subcuticular suturing was the only factor that was associated with the incidence of incisional SSI. Although the elderly had an increased likelihood of developing incisional SSI, as seen in previous studies,[18,19] the results did not show statistical significance. In addition, contrary to previous reports,[20] colostomy closure was not associated with a higher incidence of incisional SSI. A multivariate analysis was performed to exclude the possible confounding effect among these three factors. The results clearly demonstrated that subcuticular suturing had the greatest effect in preventing incisional SSI among clinical factors previously reported to be associated with incisional SSI.

The current study has several limitations. First, SSI was identified retrospectively by daily chart review of the infection control doctor. Detection by chart review is suggested to be a less accurate method than direct observation of surgical sites.[10] However, chart review is the most widely employed method of SSI surveillance in the medical literature.[2,7,18,19,21] The reported sensitivity of this method is as high as 83.8%–92.3% in comparison to prospective direct SSI surveillance.[22] Therefore, the surveillance method did not preclude the importance of the findings in the current series. Second, this study was a single-center study, and it involved a relatively small number of cases. Although a multivariate analysis revealed an association between subcuticular suturing and the incidence of incisional SSI, a larger, more scientific study is warranted. A multicenter, randomized controlled trial is currently under way to confirm the effect of subcuticular suturing on the incidence of incisional SSI in gastrointestinal surgery.

In conclusion, subcuticular suturing was found to have a protective effect against incisional SSI after diverting stoma closure. This study was the first to report the effect of subcuticular suturing on the prevention of incisional SSI in gastrointestinal surgery. A large multicenter randomized controlled trial is ongoing to confirm the role of subcuticular suturing in preventing incisional SSI in gastrointestinal surgery.

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ORIGINAL CONTRIBUTION

The Association Between Anal Function and Neural Degeneration After Preoperative Chemoradiotherapy Followed by Intersphincteric Resection

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BACKGROUND: Preoperative chemoradiotherapy for rectal cancer is administered to improve local control, but it can also induce severe anal dysfunction after surgery.

OBJECTIVE: The goals of the study were to assess the influence of preoperative chemoradiotherapy on pathological findings and to examine the correlation of these findings with the cause of severe anal dysfunction after intersphincteric resection.

DESIGN: Peripheral nerve degeneration was evaluated histopathologically with the use of hematoxylin and eosin-stained sections of surgical specimens after intersphincteric resection, based on karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, denucleation, and adventitial neuronal changes. Each item was scored to quantify the level of neural degeneration, and the relationship between degeneration and anal function was examined at 12 months after closure of the stoma. Anal function was assessed by questionnaire, and incontinence was evaluated based on the Wexner score.

SETTING: This study was conducted at the National Cancer Center Hospital East from 2001 to 2006.

PATIENTS: The subjects were 68 patients with lower rectal cancer who underwent intersphincteric resection with (n = 47) or without (n = 21) preoperative chemoradiotherapy.

MAIN OUTCOME MEASURES: The findings in the 2 groups were compared to clarify the association between the degree of histological degeneration and postoperative anal function.

RESULTS: Neural degeneration was significantly higher in the chemoradiotherapy group, and the neural degeneration and Wexner scores had a significant correlation ($P = .003$, $r = 0.477$).

CONCLUSION: Preoperative chemoradiotherapy induced marked neural degeneration around the rectal tumor. The significant correlation between the degeneration score and postoperative anal function suggests that this score may be a useful marker to predict the influence of preoperative chemoradiotherapy on anal function after surgery.

KEY WORDS: Chemoradiotherapy; Internal sphincteric resection; Neural degeneration; Rectal cancer; Anal function.

Innovative treatment for lower rectal cancer has recently tended toward preservation of the anus. Low anterior resection with coloanal anastomosis[1] and intersphincteric resection (ISR)[2] are advanced anus-preserving operations for the treatment of low rectal cancer with avoidance of a colostomy. Anastomoses are made near to or under the dentate line in the anal canal, and the procedures have a tolerable and clinically acceptable local recurrence rate.[3,4] Preoperative chemoradiotherapy (CRT) or

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radiotherapy is also thought to be necessary to decrease local recurrence following ISR.[5–7]

Investigations of functional outcome after ISR[6,8–11] have shown that satisfactory anal function is preserved in most patients, but some have severe dysfunction[11,12] and conversion to colostomy may be necessary as an additional treatment.[8,12] Preoperative CRT has been found to be most strongly associated with poor anal function after ISR, suggesting that patients with rectal cancer who undergo ISR after preoperative CRT are likely to experience incontinence.[13,14] Lim et al[15] reported that a conventionally fractionated 45-Gy dose of preoperative CRT caused poor anorectal function because of damage to the pudendal nerve. Rectal function may also be worsened by radiation-induced proctitis and induction of rectal compliance due to fibrosis of the rectal wall,[16,17] and direct radiation injury to the internal anal sphincter muscles can also cause anal sphincter dysfunction.[18]

Given this background, it is likely that pathological analysis of the anal sphincter muscle area may show an association with anal sphincter dysfunction. However, the relationship between histopathological findings and CRT in the anal sphincter muscle area has not been studied. Therefore, we examined the degree of tissue degeneration, with a particular focus on neural degeneration and tissue fibrosis, in surgical specimens resected from patients who underwent surgery with or without preoperative CRT. In previous reports[19,20] on esophageal carcinoma, toxicities such as neuropathy have been observed during CRT, suggesting that neuropathy may be based on neural degeneration. The aim of this study was to investigate neural degeneration pathologically, because this may cause anal dysfunction. Findings in patients with or without preoperative CRT were compared to clarify the association between the degree of histological degeneration and postoperative anal function.

PATIENTS AND METHODS

Patients

Between 2001 and 2006, 68 patients underwent ISR for very low rectal cancer at the National Cancer Center Hospital East, Chiba, Japan. Of these patients, 47 received CRT before surgery and 21 underwent surgery alone (control group). For ISR cases from 2002 to 2004, CRT was performed for all patients who gave consent. The subjects examined before and after this period and ISR cases in which patients did not consent to CRT were examined as the surgery-only group. Cases in which infiltration in the external sphincter muscle was shown by MRI in the preoperative diagnosis of tumor depth were excluded from our indication for ISR. A diverting stoma was constructed in each patient, and the stoma was finally closed in all the patients. Questionnaires on postoperative anal function[8] were collected from 59 of the 68 patients at 12 months after closure of the stoma. Our operative indications for ISR were a tumor edge 5 cm above the anal verge or 3 cm above the dentate line; adenocarcinoma confirmed histologically by preoperative biopsy; and age less than 76 years.[8] Preoperative stage was determined according to the International Union Against Cancer classification.[21]

Surgical Procedure

ISR was performed as described previously.[8] First, dissection was performed by the abdominal approach until total mesorectal excision was complete. The outside layer of the internal sphincter muscle was then exposed and circumferentially divided from the puborectal muscle and the external sphincter. After the abdominal approach was completed, perianal resection was performed. The mucosa and the internal sphincter muscle were incised 1 to 2 cm distal to the tumor. If the tumor had invaded the external sphincter, ISR plus partial resection of the external sphincter was performed with preservation of at least the subcutaneous part of the external sphincter. The decision of whether to create a pouch (either a J-pouch or a transverse coloplasty pouch) was left to the discretion of the surgeon.

Preoperative Therapy

Forty-seven patients with clinical T3 tumors agreed to undergo CRT. Over a 5-week period, a dose of 45 Gy was administered along with intravenous infusion of 5-fluorouracil (250 $mg \cdot m^{-2} \cdot d^{-1}$) to increase the efficacy of radiotherapy. Nerve-sparing resection surgery was performed 2 weeks after completion of preoperative CRT.[22]

Pathological Evaluation

Hematoxylin and eosin-stained sections of the surgical specimens were used for pathological evaluation. The sections were evaluated by 2 authors (S.F. and Y.N.) who were blinded to the clinical information for the patients.

Pathological Examination of Nerves Near the Internal Sphincter Muscle

Before pathological evaluation, the numbers of nerves in the hematoxylin and eosin-stained sections were counted in low-power magnification fields (10 × 10). Ten nerves around the primary lesion were selected and photographed, and the consistency of features of the nerves in each photograph was evaluated. In this manner, pathological neural degeneration was evaluated for 10 nerves near to the tumor in each patient, based on the following features: karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, denucleation, and adventitial neuronal changes. To obtain a total degeneration score, the presence of the first 4 features was scored as 1 point each. Adventitial neuronal changes were evaluated based on a 3-point scale, with 1, 2, and 3 defined as perineurial hypertrophy, perineurial fibrosis, and intraneural fibrosis.

Therefore, the degeneration score ranged from 0 to 7. The association between this score and anal function was examined at 12 months after surgery.

Fibrosis

The degree of fibrosis of the primary tumor was evaluated on a 4-point scale, with grades 0, 1, 2, and 3 reflecting <10%, 10% to 30%, 30% to 50% and ≥50% replacement of tumor tissue by fibrosis in the section with the maximum tumor diameter.[18]

Abscess Formation

The presence of an abscess in the tumor was examined based on aggregates of neutrophil infiltration (0, absence of abscess; 1, presence of abscess). An abscess was defined as an area of neutrophilic aggregation with a diameter larger than 500 μm observed microscopically.

Assessment of Anal Function

The functional outcome was assessed by the use of the continence score of Jorge and Wexner (Wexner score).[23] Questionnaires were collected from patients during consultation in the physician's office after the patient had filled out the questionnaire by themselves at home. Questionnaires to evaluate the Wexner score were given at 12 months after stoma closure. Thus, the relationship between the degree of degeneration and postoperative anal function was examined based on the Wexner score at 12 months after stoma closure. This score reflects the postoperative anal function, because gradual improvements in Wexner scores are seen from 3 to 6 months and further slight improvements occur between 6 and 24 months.[13]

Statistical Analysis

A Student *t* test and Fisher exact test were used to examine histological differences between the CRT and control groups. A Mann-Whitney *U* test was used to examine the relationship between CRT and Wexner scores. The Mann-Whitney *U* test was also used to examine the relationship between histological findings (karyopyknosis, vacuolar degeneration, acidophilic change, and denucleation) and Wexner scores. A Kruskal-Wallis test was used to examine the relationship between histological findings (adventitial neuronal changes, fibrosis, and abscess) and Wexner scores. Spearman analysis was used to examine the correlation between degeneration scores and Wexner scores. All statistical analyses were performed using SPSS for Windows, v.13.0 J (SPSS-Japan Inc., Tokyo, Japan). A *P* value of <.05 was considered to be significant.

RESULTS

The clinical characteristics of the 68 patients are shown in Table 1, including preoperative CRT, mean tumor distance from the anal verge, extent of excision of the internal sphincter muscle, resection of the external sphincter, and pathological stage. There were no significant differences between the CRT and control groups in age, sex ratio, and anal verge distance. Total ISR was used less frequently in the control group. Regarding the pathological stage, 66% of cases in the CRT group were stages I and II, whereas 58% of cases in the control group were stage III. There were no significant differences in clinical stage (P = .70) and pathology stage (P = .12) between the CRT and control groups. Many cases in the CRT group were stage I or II and total ISR was performed in some of these cases (Table 1).

TABLE 1. Clinical characteristics of the patients

	CRT group	Control group	P
Patients	47	21	
Median age (range)	56 (27–77)	60 (39–72)	.22
Sex, M:F	35:12:00	15:06	.79
Median AV (cm)	3.5 (0–5.0)	4.0 (2.5–5.5)	.66
Operative procedure (%)			
Total ISR	20 (43)	1 (5)	.03
Subtotal ISR	22 (47)	13 (62)	
Partial ISR	5 (11)	7 (33)	
PESR	13 (28)	7 (33)	.63
Clinical/pathology stage (%)			
I	9 (19)/25 (53)	4 (19)/4 (19)	.70/.12
II	16 (34)/6 (13)	8 (38)/5 (24)	
IIIa	9 (19)/5 (11)	5 (24)/6 (29)	
IIIb	11 (23)/8 (17)	3 (14)/6 (29)	
IV	2 (4)/2 (4)	1 (5)/0 (0)	
Postoperative complications (%)	14 (29)	9 (43)	.29
Anastomotic leakage	5 (11)	3 (14)	.67
Pelvic abscess	6 (12)	5 (24)	.25

AV = anal verge; ISR = intersphincteric resection; CRT = chemoradiotherapy; PESR = partial external sphincter resection.

Postoperative complications occurred in 14 subjects (29%) in the CRT group (anastomotic leakage in 5 (11%) and pelvic abscess in 6 (12)), and in 9 subjects (43%) in the control group (anastomotic leakage in 3 (14%) and pelvic abscess in 5 (24%)). There was no significant difference in the rate of postoperative complications between the 2 groups. The average time between the primary operation and closure of the stoma was 227 days (range, 80–665 days) in the CRT group and 247 days (range, 85–558 days) in the control group.

Tissue fibrosis of grade 2 or 3 was observed in 73% of cases in the CRT group, whereas fibrosis of grade 0 or 1 accounted for 86% of cases in the control group. The incidence of more severe fibrosis was significantly higher in the CRT group (P < .001). No intratumor abscess was present in 79% of cases in the CRT group, but abscesses were observed in 52% of cases in the control group, giving a significantly higher incidence of abscess formation in the control group (P = .010).

TABLE 2. Pathologic findings

	CRT group (n = 47)	*Control group (n = 21)*	*P*
Fibrosis grade: 0/1/2/3, n (%)	2/11/13/21 (4/23/28/45)	16/2/2/1 (76/10/10/5)	<.001
Abscess grade: 0/1, n (%)	37/10 (79/21)	10/11 (48/52)	.010
Karyopyknosis, n (%)	19 (40)	0 (0)	.001
Vacuolar degeneration, n (%)	32 (68)	4 (19)	<.001
Acidophilic degeneration of cytoplasm, n (%)	15 (32)	0 (0)	.002
Adventitial neuron change: 0/1/2/3, n (%)	2/25/7/13 (4/53/15/28)	17/4/0/0 (81/19/0/0)	<.001
Denucleation, n (%)	26 (55)	0 (0)	<.001

Karyopyknosis, vacuolar degeneration, acidophilic degeneration of cytoplasm, adventitial neuron change, and denucleation were evaluation items of neurodegeneration.
CRT = chemoradiotherapy.

The incidence of neural degeneration was significantly higher in the CRT group and the incidence of vacuolar degeneration (68%) was particularly high in the CRT group compared with the control group. In the adventitia and perineurium of neurons, only perineurial hypertrophy (grade 1) occurred in the control group, whereas perineurial and intraneural fibrosis (grades 2 and 3) was found in 43% of cases in the CRT group, indicating a significantly higher frequency of severe effects in the CRT group ($P \leq .001$ to $P = .01$) (Table 2). Representative histopathological findings for neurons are shown in Figure 1.

Association with Anal Function 12 Months After Surgery

No patient had a Wexner score of ≥2 preoperatively, and none had problems with preoperative anal function. The median values of the Wexner scores at 12 months after stoma closure in the CRT and control groups were 8.0 and 5.0, indicating that function was significantly poorer in the CRT group ($P = .018$ by Mann-Whitney *U* test) (Fig. 2).

In a comparison of Wexner scores based on background factors in the CRT group, sex, age, type of resection (partial, subtotal, total ISR), and partial resection of the external sphincter were not associated with poor anal function after ISR. Postoperative anal dysfunction did not show a significant association with each feature of neural degeneration or with Wexner score in the CRT group (karyopyknosis, $P = .05$; vacuolar degeneration, $P = .298$; acidophilic change, $P = .090$; denucleation, $P = .067$; and adventitial neuronal changes, $P = .081$). However, there was a significant correlation between the total degeneration score and the Wexner score ($P = .003$, $r = 0.477$ by Spearman analysis) (Fig. 3).

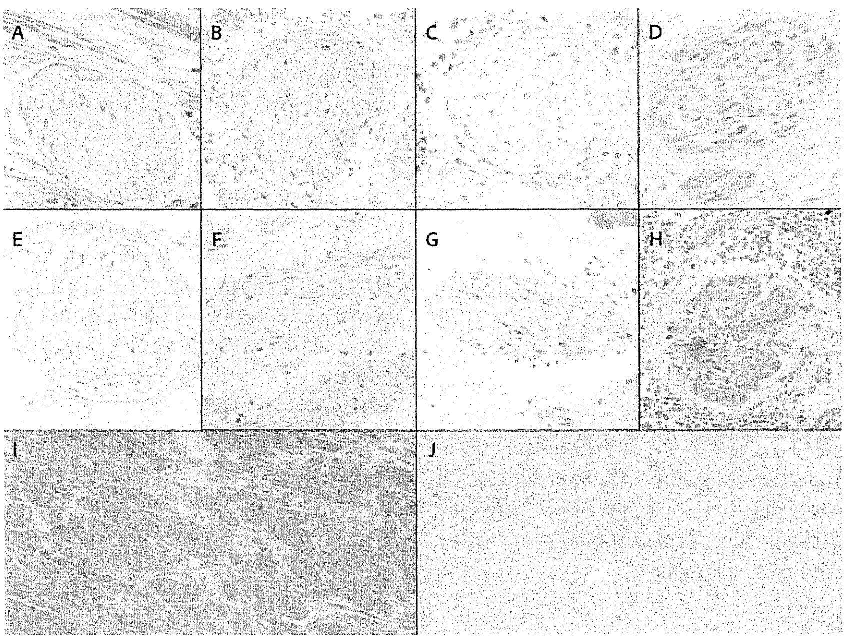

FIGURE 1. Pathological evaluation. The hematoxylin and eosin sections were assessed under a standard light microscope at low-power magnification (×100). The nerve evaluation items are (A–H): A, Normal. B, Karyopyknosis. C, Vacuolar degeneration. D, Acidophilic degeneration of cytoplasm. E, Denucleation. F, Adventitial neuron change grade 1. G, Adventitial neuron change grade 2. H, Adventitial neuron change grade 3. The degree of fibrosis was evaluated by grades: I, grade 1; J, grade 3.