Surg Endosc (2006) 20: 1467–1472
DOI: 10.1007/s00464-005-0651-2

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and Other Interventional Techniques

# Reduction of prolonged postoperative hospital stay after laparoscopic surgery for colorectal carcinoma

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Received: 20 September 2005/Accepted: 23 February 2006/Online publication: 3 July 2006

**Abstract**
*Background:* In evaluating the quality of laparoscopic surgery (LS) for colorectal carcinoma, many previous reports have used median or range values to assess the length of postoperative hospital stay and to show the complication and conversion rates separately. However, with this method, it is impossible to assess the proportion of patients who required prolonged postoperative hospital stay because of perioperative morbidities. This study investigated the proportion of patients who benefited from LS as minimally invasive surgery by assessing the percentage of patients who required prolonged postoperative hospital stay because of major perioperative morbidities.
*Methods:* A review of 202 patients who underwent LS for colorectal carcinoma at the authors' hospital between January 2002 and December 2004 was performed. Short-term outcomes were compared among the patients who underwent LS in 2002, 2003, and 2004.
*Results:* No significant differences were observed in baseline characteristics among the groups, and all the procedures in this study were completed laparoscopically. There were no significant differences in the operative times and intraoperative blood losses among the groups. Most of the patients resumed liquid intake on postoperative day 1 and solid food on day 3. However, there was a significant difference in the rate of postoperative prolonged hospital stays by year of surgery. In 2004, 97.3% of the patients (72/74) undergoing LS could be discharged to home within 8 days postoperatively. Major complications occurred at a low rate of 1.4% (1/74) in 2004. Regarding the reasons for prolonged postoperative hospital stay, inappropriate judgment of the physician in charge, based primarily on requests from patients without medical necessity, disappeared in 2004.
*Conclusions:* When LS is performed properly by specialists who have accumulated sufficient experience in both LS and conventional open surgery for colorectal carcinoma, up to 97% of patients undergoing LS can benefit from minimally invasive surgery.

**Key words:** Colorectal carcinoma — Complication — Laparoscopic surgery — Postoperative hospital stay — Short-term outcome

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In many randomized and nonrandomized studies comparing laparoscopic surgery (LS) and conventional open surgery for colorectal carcinoma, several advantages of LS have been reported, including reduction of postoperative pain, shortened duration of postoperative ileus, shortened hospital stay, and favorable effects on cytokine and hormonal responses. Consequently, LS is now termed "minimally invasive surgery" [1, 10, 15–17].

At our institution, much consideration has been given to the technical and oncologic safety of LS. Since our first LS for colorectal carcinoma in 1993, approximately 400 LS for colorectal malignancies have been performed at our institution. Most of our early experience was confined to early (Tis or T1) colorectal cancer located at the cecum, ascending colon, sigmoid colon, or rectosigmoid because of technical problems and concerns regarding port-site and peritoneal recurrences. In June 2001, we unified our surgical and postoperative management procedures and expanded our indications for LS to include advanced colorectal cancers (i.e., T2 lesions and beyond) located anywhere in the colon or rectum. As a consequence, the complication rate and mean length of hospitalization have been reduced at our institution [23, 24].

If LS is truly minimally invasive surgery, it should reflect a shortened postoperative hospital stay. With regard to assessment of the quality of LS for colorectal carcinoma, many previous reports have used median or range values to assess the length of postoperative hospital stay and to show the complication and conversion rates separately. However, with this approach, it is

impossible to assess the proportion of patients who required prolonged postoperative hospital stay because of perioperative morbidities. Moreover, the effect of major complications on the length of postoperative hospitalization is unknown.

In the current study, short-term outcomes were compared among selected patients who underwent LS for colorectal carcinoma at our hospital in 2002, 2003, and 2004. We investigated the proportion of patients who benefited from LS as minimally invasive surgery by assessing the percentage of patients who required prolonged postoperative hospital stay because of perioperative major morbidities. Moreover, the results of our efforts to reduce postoperative hospitalization also were examined.

## Patients and methods

### *Patients*

Between January 2002 and December 2004, we performed 202 continuous LS for selected patients with colorectal carcinoma. Because the safety of LS for cancer patients remains to be established, our candidates for radical LS were patients with a preoperative diagnosis of T1 or T2. Additionally, our LS cases also included patients with a preoperative diagnosis of T3 who wished to undergo LS, as well as those with colon or upper rectal carcinoma for which palliative resection was considered necessary. Contraindications for LS included tumors larger than 6 cm, a history of extensive adhesions, severe obesity (body mass index > 32 $kg/m^2$), intestinal obstruction, and refusal of a patient to undergo LS.

All patients were evaluated before surgery by clinical investigation including barium enema, total colonoscopy, chest x-ray, abdominal ultrasonography, and computed tomography. For patients with rectal malignancy, a primary rectal carcinoma was defined according to its distance from the anal verge, as determined by colonoscopy. The tumors were grouped according to their location in the lower rectum (0–7 cm), the middle rectum (7.1–12 cm), and the upper rectum (12.1–17 cm). We defined conversion to open surgery as any incision larger than 7cm, except for cases in which the incision was enlarged because of a large specimen that could not be removed through a 7-cm incision.

### *Laparoscopic technique*

The techniques for LS have been thoroughly described previously [23–25]. For right-sided lesions, the right colon was mobilized initially, and the vascular pedicles were divided at their origin, together with the draining lymph nodes intracorporeally. For patients with a preoperative diagnosis of T2–T3 lesions, a laparoscopic no-touch isolation technique was performed. With this technique, mobilization of the right colon was performed after early proximal ligation of the tumor-feeding vessels and resection of the mesentery intracorporeally. The bowel loop was delivered under a wound protector through a small incision, and division of the marginal vessels and anastomosis was performed extracorporeally.

For transverse colon lesions, mobilization of hepatic, splenic, or both flexures was performed according to the tumor location. Proximal ligation of the right, left, or both branches of the middle colic vessels at their origins was performed intracorporeally or extracorporeally. The bowel loop was delivered, and anastomosis was performed in the same way.

Descending colon and proximal sigmoid colon lesions for which extracorporeal anastomosis was considered possible were managed by initial mobilization of the left colon. After mobilization of the splenic flexure, intracorporeal ligation of the tumor-feeding vessels (left colic artery, sigmoid arteries, inferior mesenteric vessels) at their origins was performed. The bowel loop was delivered through a small incision under a wound protector, and division of the mesenterium was performed extracorporeally, followed by extracorporeal anastomosis.

For distal sigmoid colon and rectal lesions, mobilization of left colon and splenic flexure, if necessary, was followed by intracorporeal high ligation of the inferior mesenteric vessels, then by mobilization of the rectum. For higher lesions, mesorectal tissue down to 5 cm below the tumor was excised routinely. Middle and lower rectal tumors were treated by total mesorectal excision. Before rectal transection, laparoscopic rectal clamping immediately above the anticipated point of rectal transection was performed using a bowel-clamping device introduced through the 12-mm mid lower port. Rectal washout was routinely performed using 1,000 ml of 5% povidone–iodine solution. Rectal transection then was performed by the multiple firing technique using Endo GIA Universal staples (Auto Suture; U.S. Surgical Corp., Norwalk, CT, USA) introduced through the 12-mm right midabdominal port. A 4- to 5-cm incision then was made over the mid lower port site, and the bowel was exteriorized under wound protection.

After the anvil head of the circular stapler had been inserted into the end of the proximal colon, the proximal colon was internalized and the incision closed. Intracorporeal anastomosis under laparoscopic view was performed by the double-stapling technique using a circular stapler (ECS 29 or 33mm; Ethicon Endo-Surgery Inc, Cincinnati, OH, USA). For patients with lesions located within 2 cm of the dentate line, laparoscopic intersphincteric rectal resection and hand-sewn coloanal anastomosis (ISR-CAA) were performed [21]. For patients undergoing abdominoperineal resection (APR), laparoscopic procedures were followed by perineal dissection in the standard fashion and end colostomy creation using the left lower abdominal port site.

### *Study parameters*

The parameters analyzed included gender, age, body mass index, prior abdominal surgery, operative time, intraoperative blood loss, conversion rate, days to resumption of diet, duration of postoperative hospital stay, and both intraoperative and postoperative complications within 30 days of surgery. Pathologic staging was performed according to Dukes' stage. In the current study, major complication was defined as morbidity that required the patient to stay in the hospital 9 or more postoperative days. Prolonged postoperative hospital stay was defined as 9 or more days of postoperative hospitalization, regardless of the underlying reasons, because patients are supposed to be discharged by the postoperative day 8 when there is no major complication after LS at our institution. With regard to the operative and postoperative results, patients with colon and rectal carcinoma were evaluated separately, considering the technical difficulties of the laparoscopic procedure.

### *Statistical analysis*

Statistical analysis was performed using one-way analysis of variance (ANOVA) and chi-square testing as appropriate. A $p$ value less than 0.05 was considered significant.

## Results

The demographics for the patients in this study are summarized in Table 1. There were no significant differences in baseline characteristics among the groups. However, the proportion of the patients with Dukes' B, C, and D stages scheduled for LS is increasing, although the difference is not yet significant ($p$ = 0.093). With regard to simultaneously performed surgical techniques, one patient underwent resection of a benign submandibular gland tumor in 2002, and three patients underwent laparoscopic cholecystectomy in 2003. In 2004, three patients underwent combined surgery as follows: laparoscopic enucleation of an 8-cm hysteromyoma, partial resection of the lingua for carcinoma, and hemilateral neck lymph node dissection for

**Table 1.** Patient characteristics[a]

| | 2002 ($n$ = 59) | 2003 ($n$ = 69) | 2004 ($n$ = 74) | $p$ Value |
|---|---|---|---|---|
| No. of patients | 59 | 69 | 74 | |
| Sex ratio (male:female) | 35:24 | 39:30 | 37:37 | 0.533 |
| Age (years) | 58.5 (30–83) | 60.2 (38–88) | 61.1 (34–79) | 0.360 |
| Body mass index (kg/m$^2$) | 22.9 (14.9–32.4) | 23.1 (17.3–30.5) | 23.1 (16.3–31.5) | 0.872 |
| Prior abdominal surgery: $n$ (%) | 15 (25.4) | 16 (23.2) | 16 (21.6) | 0.875 |
| Dukes' stage ($n$) | | | | |
| A | 45 | 52 | 46 | |
| B | 2 | 2 | 9 | |
| C | 8 | 11 | 18 | |
| D | 4 | 4 | 2 | |
| A:B + C + D | 45:14 | 52:17 | 46:29 | 0.093 |
| Location ($n$) | | | | |
| Cecum | 3 | 10 | 5 | |
| Ascending colon | 4 | 13 | 15 | |
| Transverse colon | 6 | 9 | 7 | |
| Descending colon | 6 | 5 | 7 | |
| Sigmoid colon | 23 | 20 | 27 | |
| Rectosigmoid/upper rectum | 10 | 7 | 4 | |
| Middle rectum | 3 | 3 | 4 | |
| Lower rectum | 4 | 2 | 6 | |
| Colon:rectum | 42:12 | 57:12 | 60:14 | 0.238 |
| Laparoscopic colorectal procedures ($n$) | | | | |
| Ileocecal resection | 5 | 7 | 7 | |
| Right hemicolectomy | 5 | 18 | 14 | |
| Transverse colectomy | 4 | 4 | 4 | |
| Left hemicolectomy | 0 | 1 | 1 | |
| Descending colectomy | 5 | 4 | 6 | |
| Sigmoid colectomy | 20 | 17 | 24 | |
| Partial resection | 3 | 6 | 5 | |
| Anterior resection with DST | 16 | 10 | 12 | |
| Anterior resection with ISR-CAA | 1 | 2 | 1 | |
| Abdominoperineal resection | 0 | 0 | 1 | |
| Transverse-coloplasty pouch | 0 | 2 | 2 | |
| Covering ileostomy | 4 | 2 | 5 | |

DST, double-stapling technique; ISR-CAA, intersphincteric rectal resection and handsewn coloanal Anastomosis
[a] Values are mean (range)

metachronous lymph node recurrence from lingual carcinoma. Data on these combined surgical techniques all were included in the analyses of colorectal carcinoma surgeries.

Our operative results are shown in Table 2. All the procedures in this study were completed laparoscopically. There were no significant differences in operative time or intraoperative blood loss among the groups. The postoperative courses are shown in Table 3. Most of the patients started liquid intake on postoperative day 1 and solid food on day 3. However, there was a significant difference in the rates of prolonged postoperative hospital stay by year of surgery. All the patients were discharged to home.

The postoperative complications are listed in Table 4. There were no perioperative mortalities. No significant differences in complication rates over the years were observed, although a major complication, anastomotic leakage, occurred for one patient in 2004 and was successfully treated conservatively. None of the patients in the current series required reoperation.

The reasons for prolonged postoperative hospital stays are listed in Table 5. Inappropriate judgment of the physician in charge, based primarily on requests from patients without medical necessity, disappeared in 2004. By the end of the study period, two patients had experienced recurrence (hepatic metastases). At this writing, in 2005, 49 patients have undergone LS, and all have been discharged to home without major complication.

**Table 2.** Operative results[a]

| | 2002 ($n$ = 59) | 2003 ($n$ = 69) | 2004 ($n$ = 74) | $p$ Value |
|---|---|---|---|---|
| Lap colectomy | | | | |
| Operative time (min) | 201 (115–345) | 200 (117–348) | 214 (140–495) | 0.219 |
| Intraoperative blood loss (ml) | 30 (6–219) | 30 (10–248) | 38 (7–256) | 0.157 |
| Conversion ($n$) | 0 | 0 | 0 | |
| Lap-AR + APR | | | | |
| Operative time (min) | 244 (190–392) | 263 (200–472) | 283 (215–430) | 0.570 |
| Intraoperative blood loss (ml) | 54 (10–265) | 63 (11–250) | 84 (14–477) | 0.661 |
| Conversion (n) | 0 | 0 | 0 | |

Lap, laparoscopic; AR, anterior resection; APR, abdominoperineal resection
[a] Values are medians (range)

**Table 3.** Postoperative results

| | 2002 ($n$ = 59) $n$ (%) | 2003 ($n$ = 69) $n$ (%) | 2004 ($n$ = 74) $n$ (%) | $p$ Value |
|---|---|---|---|---|
| Lap colectomy | | | | |
| Liquid intake range (days) | | | | |
| 1 POD | 38 (90.4) | 54 (94.7) | 59 (98.3) | |
| 2 POD | 2 (4.8) | 3 (5.3) | 0 (0) | |
| 3 ≤ POD | 2 (4.8) | 0 (0) | 1 (1.7) | |
| Solid food (days) | | | | |
| 2 POD | 0 (0) | 0 (0) | 0 (0) | |
| 3 POD | 31 (73.8) | 51 (89.5) | 56 (93.3) | |
| 4 ≤ POD | 11 (26.2) | 6 (10.5) | 4 (6.7) | |
| Hospital stay (days) | | | | |
| 7 POD | 5 (11.9) | 19 (33.3) | 28 (46.7) | |
| 8 POD | 17 (40.5) | 28 (49.1) | 31 (51.7) | |
| 9 ≤ POD | 20 (47.6) | 10 (17.5) | 1 (1.7) | |
| Range | 7–20 | 7–15 | 7–21 | |
| Lap-AR + APR | | | | |
| Liquid intake range (days) | | | | |
| 1 POD | 16 (94.1) | 10 (83.3) | 13 (92.9) | |
| 2 POD | 1 (5.9) | 1 (8.3) | 0 (0) | |
| 3 ≤ POD | 0 (0) | 1 (8.3) | 1 (7.1) | |
| Solid food (days) | | | | |
| 2 POD | 3 (17.6) | 1 (8.3) | 3 (21.4) | |
| 3 POD | 6 (35.3) | 9 (75.0) | 9 (64.3) | |
| 4 ≤ POD | 8 (47.1) | 2 (16.7) | 2 (14.3) | |
| Hospital stay (days) | | | | |
| 7 POD | 2 (11.8) | 4 (33.3) | 5 (35.7) | |
| 8 POD | 3 (17.6) | 6 (50.0) | 8 (57.1) | |
| 9 ≤ POD | 12 (70.6) | 2 (16.7) | 1 (7.1) | |
| Range | 7–12 | 7–17 | 7–23 | |
| Total (Lap-colectomy + AR + APR) | | | | |
| Hospital stay (days) | | | | |
| 7–8 POD | 27 (45.8) | 57 (82.6) | 72 (97.3) | <0.0001 |
| 9 ≤ POD | 32 (54.2) | 12 (17.4) | 2 (2.7) | |

Lap, laparoscopic; POD, postoperative days; AR, anterior resection; APR, abdominoperineal resection

## Discussion

To date, the quality of LS for colorectal carcinoma has been assessed by the median or range of the postoperative hospital stay, the complication rate, and the conversion rate. However, with only these values, it is impossible to assess accurately the degree of the effect that each complication has on the length of postoperative hospitalization for patients overall. This means that the rate of patients undergoing LS who have benefited from minimally invasive surgery has not been properly evaluated. If the greatest advantage of LS is minimal invasiveness, LS must ultimately be linked to shortened postoperative hospitalization. However, no reports have focused on the rate of reduction in the length of postoperative hospital stay after LS. In our hospital, patients are supposed to be discharged after LS until postoperative day 8. As experience with LS cases accumulated, surgical and postoperative management procedures became unified. The timing for the start of solid food intake became earlier in 2004 than in 2002, and this may have contributed to the significantly shortened period of postoperative hospitalization in 2004. Furthermore, major complications that required prolonged postoperative hospital stay were reduced. As a result, in 2004, 97.3% (72/74) of our patients undergoing LS could be discharged to home within 8 days postoperatively. Major complications occurred at a low rate of 1.4% (1/74) in 2004. Needless to say, this low rate contributed greatly to the current results.

The current report deals with the length of postoperative hospital stay. Recent reports from randomized controlled trials (RCTs) and single institutions investigating a number of cases in western countries indicate that the median or mean length of hospital stay after LS for colorectal carcinoma ranges from 5 to 9 days [1, 2, 6, 7, 9, 14, 16]. The appearance of this range may be attributable to social factors such as differences in medical fees, medical insurances, and medical systems among countries rather than differences in the quality of surgery. According to former studies from Japan, Japanese patients tend to stay in the hospital longer than patients in western countries [20]. The reasons for this tendency include the following facts. From the perspective of patients in Japan, public health insurance covers 70% of the total medical cost for every patient, with the patients paying only 30% of the cost. Socially disadvantaged people do not have to bear their medical expense no matter how many days they are hospitalized. Furthermore, for a patient undergoing surgery, the cost of surgery accounts for the greater part of the total medical cost. Hence, if the duration of hospital stay is lengthened by 1 day, the patient pays only several tens of dollars in additional cost. Furthermore, many Japanese patients have private health insurance, which pays the patient a specified amount of money per day of hospitalization. Under some types of insurance contract, the longer the patient stays in hospital, the more the insurance dividend will be, thereby yielding greater "earn-

**Table 4.** Morbidities and mortality[a]

| | 2002 ($n$ = 59) | 2003 ($n$ = 69) | 2004 ($n$ = 74) | $p$ Value |
|---|---|---|---|---|
| Lap colectomy | | | | |
| Mortality | 0 | 0 | 0 | |
| Morbidity | | | | |
| Wound sepsis | 3 (1) | 2 | 6 | |
| Bowel obstruction | 2 (1) | 3 (1) | 1 | |
| Urinary tract infection | 2 (2) | 1 | 0 | |
| Pneumonia | 0 | 1 (1) | 0 | |
| Pneumothorax | 0 | 1 (1) | 0 | |
| Pulmonay embolism | 0 | 1 (1) | 0 | |
| Enterocolitis | 0 | 1 | 0 | |
| Total | 7 (4) | 10 (4) | 7 (0) | |
| Reoperation | 0 | 0 | 0 | |
| Readmissions | 1 | 3 | 0 | |
| Lap-AR + APR | | | | |
| Mortality | 0 | 0 | 0 | |
| Morbidity | | | | |
| Wound sepsis | 0 | 2 | 1 | |
| Bowel obstruction | 0 | 1 (1) | 0 | |
| Anastomotic leakage | 0 | 0 | 1 (1) | |
| Abscess | 0 | 1 (1) | 0 | |
| Pneumonia | 0 | 0 | 1 | |
| Neurogenic bladder | 1 (1) | 0 | 0 | |
| Total | 1 (1) | 4 (2) | 3 (1) | |
| Reoperation | 0 | 0 | 0 | |
| Readmissions | 0 | 0 | 0 | |
| Total complication: $n$ (%) | 8 (13.5) | 14 (20.3) | 10 (13.5) | 0.4595 |
| Major complication: $n$ (%) | 5 (8.5) | 6 (8.7) | 1 (1.4) | 0.111 |

Lap, laparoscopic; AR, anterior resection; APR, abdominoperineal resection
[a] No. of major complications in parentheses

**Table 5.** Reasons for prolonged postoperative hospital stay

| | 2002 ($n$ = 32) | 2003 ($n$ = 12) | 2004 ($n$ = 2) |
|---|---|---|---|
| Major complication | 5 | 6 | 1 |
| Others | | | |
| Treatment for comorbid disease | 3 | 1 | 1 |
| Ileostomy management | 4 | 0 | 0 |
| Inappropriate judgment of the physician in charge | 20 | 5 | 0 |

ings." Under these circumstances, patients do not need to be discharged from the hospital quickly.

In contrast, at our institution, if there is no major complication after LS, the patient is supposed to be discharged by postoperative day 8, but no patients wished to leave hospital earlier than postoperative day 6. Furthermore, the results of the current study in terms of postoperative stay after LS for colorectal carcinoma are some of the shortest reported in Japan. Obviously, this situation in Japan is wasting medical funds. It goes without saying that the situation must be improved. From the results of the current study, we consider that the appropriate duration of postoperative hospital stay after LS is 5 to 7 days. Early discharge within 5 days might be possible for some patients. However, it is necessary to confirm the safety of early discharge, especially for patients with rectal carcinoma who have undergone anterior resection, because for some patients, fatal complications accompanied by anastomotic leakage might occur approximately 7 days after surgery.

With regard to the oncologic outcome of LS for colorectal carcinoma, recently reported RCTs have demonstrated that LS is comparable with open surgery or superior to it [6, 12, 14]. The results of some other RCTs to be published in the near future also are attracting attention. However, in Japan, RCTs for gastrointestinal malignancies have not been widely accepted in the past because of concerns about consequences if one form of treatment is shown to be inferior to the other. For this reason, a prospective multicenter trial with patients undergoing laparoscopic colectomy for advanced carcinoma has not been performed. However, fertile ground for RCTs comparing surgical techniques has finally begun to develop among both patients and surgeons in Japan. Consequently, a multicenter RCT comparing LS and open surgery outcomes for advanced colorectal cancer was begun in 2004 [11]. The distinctive features of this trial are that all the participating institutions have sufficient experience not only in open surgery, but also in LS, and that D3 lymphadenectomy is being required as a rule for all patients because this has been regarded as the standard surgical procedure for advanced colorectal carcinoma in both LS and open surgery. The results of this Japanese study will be published later than those of similar studies in western countries, but this study is receiving attention as an RCT performed by surgeons with sufficient accumulated experience in LS and specializing in colorectal carcinoma surgery using LS.

The issue in the expansion of the indications for LS for colorectal carcinoma is whether it can be performed for patients with middle or lower rectal carcinoma. The technical difficulty of surgery is high in such cases. If the rate of conversion to open surgery increases, the short-term outcomes of LS will be shifted to the outcomes of open surgery, thus making it difficult to detect differences between the two surgeries [9, 22]. In addition, if the complication rate increases, it could lead to prolonged postoperative hospitalization, thereby canceling the advantages of LS. The most important issue is whether LS can yield a treatment outcome comparable with that of open surgery in cases of advanced rectal cancer. The most difficult complication to manage is anastomotic leakage. In cases of middle and lower rectal carcinoma, the occurrence of anastomotic leakage requires not only prolonged hospitalization, but also a temporary or permanent stoma in some patients, thereby resulting in an unavoidable deterioration in quality of life. Moreover, anastomotic leakage may cause fatal peritonitis, or may promote intrapelvic recurrence in some cases [4]. However, with regard to the technical issue, as shown by the results of this study and recently published papers, when surgeons with sufficient experience in LS for rectal carcinoma are in charge of the procedure, it can be performed successfully as minimally invasive surgery in cases of middle and lower rectal carcinoma [2, 3, 5, 8, 13, 18, 19, 24].

In the previous report from our institution, short-term outcomes were compared between patients with

colon carcinoma and those with rectal carcinoma, all of whom underwent LS. The complication rates and postoperative courses between the two approaches were similar [23]. Needless to say, in cases of middle and lower rectal carcinoma as well, further investigations in multicenter RCTs are needed regarding short- and long-term outcomes.

One distinctive feature of LS for rectal carcinoma at our institution is that only one patient underwent APR. The background factor behind this is that whether we select open surgery or LS, we usually perform ISR-CAA in T1–T2 cases of lower rectal carcinoma, and also in many T3 cases if the patient expresses a request. Recently, favorable oncologic and functional outcomes of ISR-CAA have been reported, and the number of patients undergoing ISR-CAA using LS is expected to increase in the coming years [18, 21]. Only one patient who underwent laparoscopic APR in 2004 was preoperatively judged to be a candidate for ISR-CAA by LS. However, that patient's choice was APR.

The mean operative time in the current study was slightly longer than that reported in previous studies. This may be partially because of gradual increases in the proportion of patients with relatively advanced stages of disease who underwent LS. Other reasons might be that trainee doctors perform part or all of the surgical procedure under the guidance of staff doctors in many cases, and that we have been unable to establish a laparoscopic team. However, it is evident that the quality of our operations has not been lowered, as demonstrated by the results of this study.

In conclusion, the surgical outcome for LS at our institution demonstrated that when LS is performed properly by specialists who have accumulated sufficient experience in both LS and open surgery for colorectal carcinoma, up to 97% of patients undergoing LS can benefit from minimally invasive surgery. To expand the use of minimally invasive surgery for advanced colorectal carcinoma, it goes without saying that while making efforts to acquire high-level technical skills, it is also necessary to confirm the oncologic safety of LS.

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ANTICANCER RESEARCH 26: 2833-2840 (2006)

# Allelic Status of Chromosomes 17p, 18q, 22p, 3p and their Clinical Usefulness in Colorectal Cancer

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**Abstract.** *Background: To determine whether the allelic status of chromosomes is clinically useful in colorectal cancer, the allelic losses at chromosomes 17p, 18q, 22q and 3p and their relationships with the clinicopathological features in colorectal cancer (CRC) patients, who had undergone curative surgery without adjuvant chemotherapy, were examined. Materials and Methods: The allelic status at 17p, 18q, 22q and 3p was analyzed by PCR-SSCP (polymerase chain reaction single-strand conformation polymorphism) in 139 CRC from patients who had undergone curative surgery between October 1994 and June 1996. The relationships between these allelic losses and the clinicopathological features were investigated. Results: The lymph node status was significantly associated with the allelic status of 17p, 18q and 22q. The tumor site and tumor differentiation were significantly associated with the allelic status of 18q. When patients with more than two allelic losses were defined as the high allelic loss group and those with no, or only one allelic loss were defined as the low allelic loss group, it was found that the lymph node involvement was significantly higher in the high than in the low allelic loss group. Only three out of 25 patients in the low allelic loss group had lymph node metastasis, and 15 patients in this group without lymphatic invasion had no lymph node metastasis. There was no relationship between the allelic status and survival at any stage. Conclusion: The allelic status was significantly associated with lymph node metastasis. A combination of allelic status and lymphatic invasion assessment can predict the lymph node status before radical surgery.*

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*Key Words:* Colorectal cancer, allelic status, lymphatic invasion, lymph node status.

There have been many reports on the relationships between the clinicopathological features of colorectal cancer (CRC) patients and the allelic status of chromosomes 1p (1, 2), 2p (3), 3p (4), 4p (5), 5q (6), 8p (7, 8), 17p (1, 8, 9) and 18q (8-15), or a combination of different allelic statuses (8, 16). Several reports have shown that the prognosis for patients with allelic losses is worse than for those without allelic losses. However, there have been conflicting results for chromosomes 5q (6), 17p (15, 17-19) and 18q (1, 17, 19, 20) and for combinations of chromosomal alterations (21). Therefore, these genetic alterations of allelic status are not clinically used for CRC.

To determine whether the allelic status is, in fact, clinically useful in CRC, four chromosomes were studied: 17p, 18q, 22q and 3p. Chromosomes 17p and 18q have tumor suppressor genes, p53 and DCC, respectively, and their allelic status has been suggested, in many reports, to be associated with clinicopathological features (1, 8, 10-15). The allelic loss of 22q is relatively frequent in CRC (22-24), but there have been no reports of a relationship between the clinical background and the allelic status of 22q. The allelic status of 3p was reported to be associated with survival prognosis (4), and preferential allelic loss of 3p was observed in metastatic tumors in comparison with primary CRC (25). The status of these four chromosomes in 139 cancers, obtained from CRC patients who had undergone curative surgery without adjuvant chemotherapy, was analyzed. Then, the relationship between the allelic status and clinicopathological features was examined.

## Materials and Methods

*Patients and tissues.* A total of 139 CRC, from patients who had undergone curative surgery without adjuvant chemotherapy at the National Cancer Hospital, Tokyo, Japan, between October 1994 and June 1996, were examined. The primary tumors had been obtained immediately after surgery and stored frozen in liquid nitrogen until DNA extraction. All surviving patients had been followed for more than 5 years, initially at 3-month intervals for

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2 years and at 6-month intervals thereafter. Adjuvant chemotherapy had not been given.

*Blunt-end SSCP analysis of allelic status.* The allelic status was determined by blunt-end SSCP (single-strand conformation polymorphism) analysis (26, 27). Briefly, three intragenic polymorphic markers (intron 1, exon 4 and intron 7) of the *p53* gene, and two 17p13 markers (D17S695, D17S919), a 17p11 marker (D17S969), two 18q21 markers (D18S51, D18S499), a 22q12 marker (D22S685) and a 3p23 marker (D3S2396) were analyzed by blunt-end SSCP. For the amplification of these polymorphic markers, the primers shown in Table I were used. The forward and reverse primers were synthesized and labelled with indodicarbocyanine (Cy5) amidite reagent, a fluorescent dye (Pharmacia, Uppsala, Sweden), using an Oligo 1000 DNA synthesizer (Beckman, Fullerton, CA, USA). In PCR, the first denaturation step was done at 95°C for 5 min. PCR amplification was performed for 30 to 40 cycles under the following conditions: denaturation at 95°C for 30 to 60 sec, annealing at 50 to 67°C for 30 to 60 sec and extension at 72°C for 30 to 60 sec. For the blunting reaction, 0.5 units of Klenow fragment (TAKARA BIO, Shiga, Japan) was added to 5 μL of the PCR product and incubated at 37°C for 30 min. One microliter of the reaction mixture was mixed with 10 μL of the loading buffer and denatured at 80°C for 5 min. One microliter of the aliquot was electrophoresed on 15% polyacrylamide gel at 20°C to 24°C for 10 h at 20 W using an ALFred DNA sequencer (Pharmacia). The data were analyzed using the Fragment Manager (Pharmacia) software package. In the analysis of a normal heterozygote, the ratio of the peak heights of the signal from each allele was constant, with a variation of within 5% (27). Therefore, an allelic loss was defined as when one of the peak heights for a tumor sample was decreased by more than 10% of that of the corresponding normal tissue. Supposing the A1 allele is lost in a heterozygote carrying the A1 and A2 alleles, T is the peak height of the signal from the tumor samples, and N is the peak height of the signal from the normal control. Then, the percent peak height (%) is given as:

$$(N_{A1}/N_{A2} - T_{A1}/T_{A2}) \times 100 / (N_{A1}/N_{A2}) \quad (26).$$

If at least one of the markers of the same chromosome showed an allelic loss, the chromosome was defined as having an allelic loss.

*Statistical analysis.* Statistical analysis was carried out by the Chi-squared test. The survival rates were calculated by the Kaplan-Meier method and survival curves were compared by the log-rank test. Cox's proportional hazard model was used for multivariate analysis. The level of statistical significance was set at <0.05.

Table I. *Primers used for PCR-SSCP analysis.*

| Forward | Reverse |
|---|---|
| 17p11-13 | |
| D17S695 | |
| 5'CTGGGCAACAAG AGCAAAATTC3' | 5'TTTGTTGTTGTTCAT TGACTTCAGTCT3' |
| D17S919 | |
| 5'AGGCACAGAGT GAGACTTG3' | 5'GCTTAATTTTCACGA GGTTCAG3' |
| p53 intron 1 | |
| 5'TCTTAGCTCGCG GTTGTTTC3' | 5'ACTGGCGCTGTGT GTAAATG3' |
| p53 exon 4 | |
| 5'AGCTCCCAGAAT GCGAGAG3' | 5'CTGGGAAGGGACA GAAGATG3' |
| p53 intron7 | |
| 5'AGGTCAGGAGCC ACTTGCC3' | 5' GTGATGAGAGGTG GATGGGT3' |
| D17S969 | |
| 5'ATCTAATCTGTCA TTCATCTATCCA3' | 5'AACTGCAGTGCTG CATCATA3' |
| 18q21 | |
| D18S51 | |
| 5'GAGCCATGTTCA TGCCACTG3' | 5'CAAACCCGACTAC CAGCAAC3' |
| D18S499 | |
| 5'CTGCACAACATA GTGAGACCTG3' | 5'AGATTACCCAGAA ATGAGATCAGC3' |
| 22q12 | |
| D22S685 | |
| 5'TTCTTAGTGGGGA AGGGATC3' | 5'TGAGTTTGATGTTT TTGATAGACA3' |
| 3p23 | |
| D3S2396 | |
| 5'ACCTCTTACTTGT GTTCTTGGG3' | 5'TGACCAAGCC AGTATTGGAT3' |

## Results

*Allelic status and clinicopathological backgrounds.* The allelic status of 17p was informative in all the patients, the allelic status of 18q was informative in 136 patients (98%), that of 22q was informative in 122 patients (88%) and that of 3p was informative in 106 patients (76%). Representative electropherogram profiles from the SSCP analyses are shown in Figure 1. The clinicopathological backgrounds of the informative cases are shown in Table II. The lymph node status was significantly associated with the allelic status of 17p, 18q and 22q ($p<0.01$, $<0.01$ and 0.01, respectively). The tumor site and tumor differentiation were significantly associated with the allelic status of 18q ($p<0.01$ and 0.03, respectively). To examine the relationships between the number of allelic losses and the clinicopathological backgrounds, the examined patients were classified into high and low allelic loss groups. The high allelic loss group contained patients with more than two allelic losses. The low allelic loss group contained patients with no, or only one allelic loss. Patients with more than two non-informative alleles or with one allelic loss and one non-informative allele were excluded, because these patients' allelic status could not be classified into either group. In this way

Table II. *Clinicopathological backgrounds for informative cases.*

| Chromosomes | 17p | | 18q | | 22q | | 3p | |
|---|---|---|---|---|---|---|---|---|
| | Loss | Retained | Loss | Retained | Loss | Retained | Loss | Retained |
| Gender | | | | | | | | |
| Male | 68 | 16 | 68 | 15 | 41 | 31 | 28 | 37 |
| Female | 38 | 17 | 41 | 12 | 27 | 23 | 15 | 26 |
| *p* | 0.11 | | 0.51 | | 0.75 | | 0.51 | |
| Age | | | | | | | | |
| <60 | 40 | 11 | 43 | 8 | 23 | 20 | 16 | 23 |
| 60≤ | 66 | 22 | 66 | 19 | 45 | 34 | 27 | 40 |
| *p* | 0.65 | | 0.35 | | 0.71 | | 0.94 | |
| Tumor site | | | | | | | | |
| Colon | 63 | 25 | 63 | 23 | 42 | 38 | 30 | 39 |
| Rectum | 43 | 8 | 46 | 4 | 26 | 16 | 13 | 24 |
| *p* | 0.09 | | < 0.01 | | 0.32 | | 0.40 | |
| Tumor differentiation | | | | | | | | |
| Well | 46 | 20 | 47 | 18 | 38 | 24 | 19 | 26 |
| Moderate | 60 | 13 | 62 | 9 | 30 | 30 | 24 | 37 |
| *p* | 0.08 | | 0.03 | | 0.21 | | 0.77 | |
| Lymphatic invasion | | | | | | | | |
| Negative | 47 | 19 | 50 | 14 | 30 | 31 | 17 | 31 |
| Positive | 59 | 14 | 59 | 13 | 38 | 23 | 26 | 32 |
| *p* | 0.18 | | 0.58 | | 0.14 | | 0.33 | |
| Venous invasion | | | | | | | | |
| Negative | 56 | 22 | 57 | 19 | 39 | 32 | 24 | 33 |
| Positive | 50 | 11 | 52 | 8 | 29 | 22 | 19 | 30 |
| *p* | 0.16 | | 0.09 | | 0.83 | | 0.73 | |
| Depth of invasion (pT) | | | | | | | | |
| pT1, pT2 | 18 | 10 | 23 | 5 | 11 | 13 | 9 | 14 |
| pT3, pT4 | 88 | 23 | 86 | 22 | 57 | 41 | 34 | 49 |
| *p* | 0.10 | | 0.77 | | 0.28 | | 0.87 | |
| Lymph node status (pN) | | | | | | | | |
| Negative | 49 | 25 | 49 | 22 | 31 | 37 | 22 | 34 |
| Positive | 57 | 8 | 60 | 5 | 37 | 17 | 21 | 29 |
| *p* | <0.01 | | <0.01 | | 0.01 | | 0.77 | |

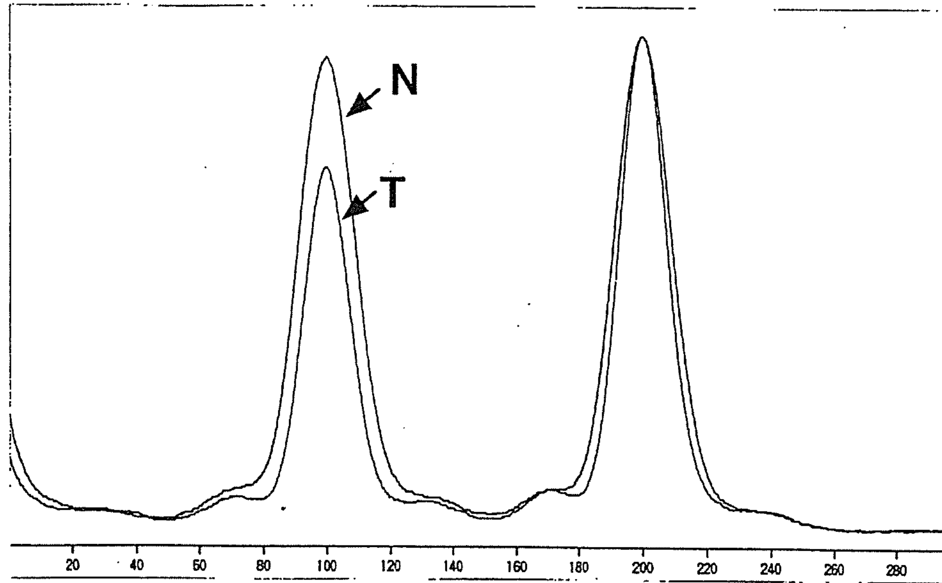
seven patients were excluded. The clinicopathological backgrounds of patients in the high and low allelic loss groups are shown in Table III. The lymph node status was significantly associated with high and low allelic status ($p<0.01$). In the low allelic loss group, only three CRC patients out of 25 (12%) patients had lymph node metastases, while 15 patients without lymphatic invasion had no lymph node metastasis.

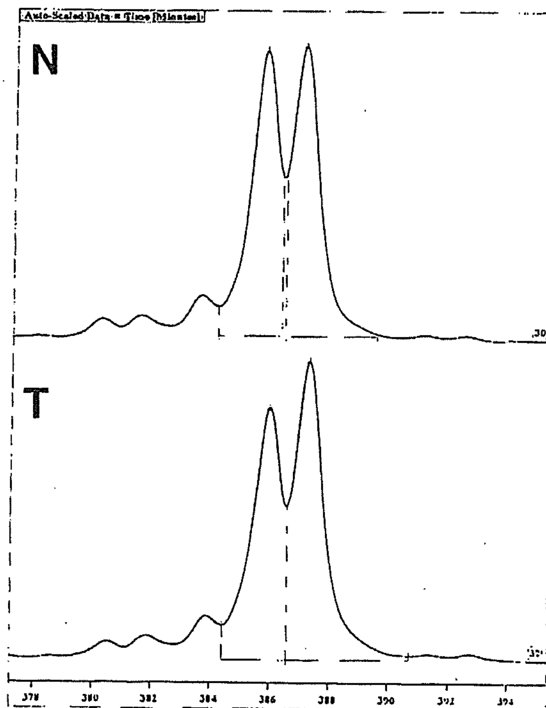
*Allelic status and disease-free survival.* The disease-free survival rates are shown in Table IV. In stages I and II, the high allelic loss group showed slightly worse survival than the low allelic loss group. In stage III, patients with allelic loss at 18q showed worse survival than those without allelic loss at 18q, and the high allelic loss group also showed worse survival than the low allelic loss group (Figure 2). Patients with allelic loss at 3p and those with allelic loss at 22q showed better survival than those without these allelic losses. However, these differences were not significant. In multivariate analysis, only the lymph node status was selected as a significant prognostic factor.

## Discussion

Many reports have shown relationships between the clinicopathological background or prognosis of CRC patients and their allelic status (1-16). However, these allelic status relationships are not used clinically because the results have not been fully validated. Of the four chromosomes examined here, allelic loss at chromosome 18q has been suggested to have a strong association with poor prognosis for CRC patients in many reports (8-15). However, some reports, including our study, did not show a significant association between the allelic status of 18q and prognosis (1, 17, 19, 20). Barratt *et al.* suggested that there was an interaction between the allelic status and response to adjuvant therapy (19). Their results showed that only patients without allelic loss gained survival benefits from adjuvant therapy, while those with allelic loss did not. This explains the conflicting results of the association between allelic status and prognosis, because many studies into allelic status included patients who either did or did not receive

A



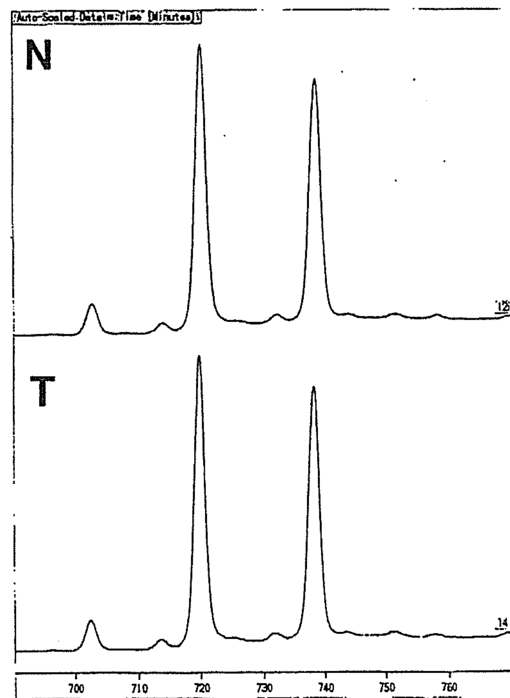
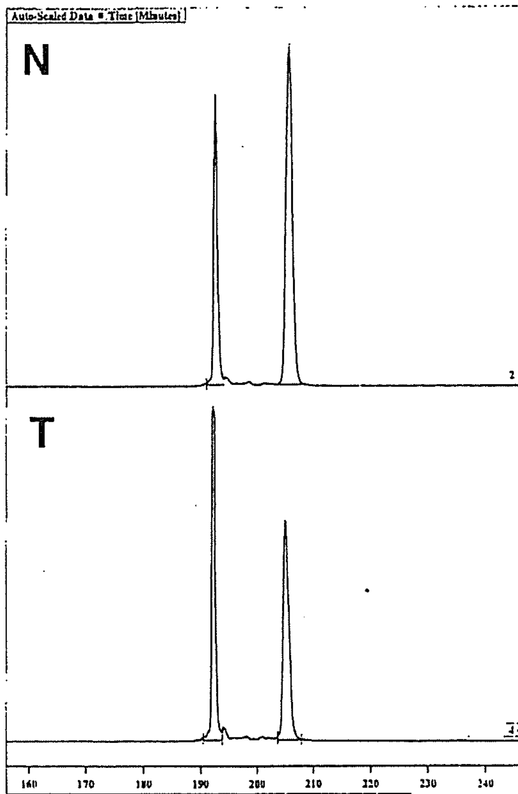
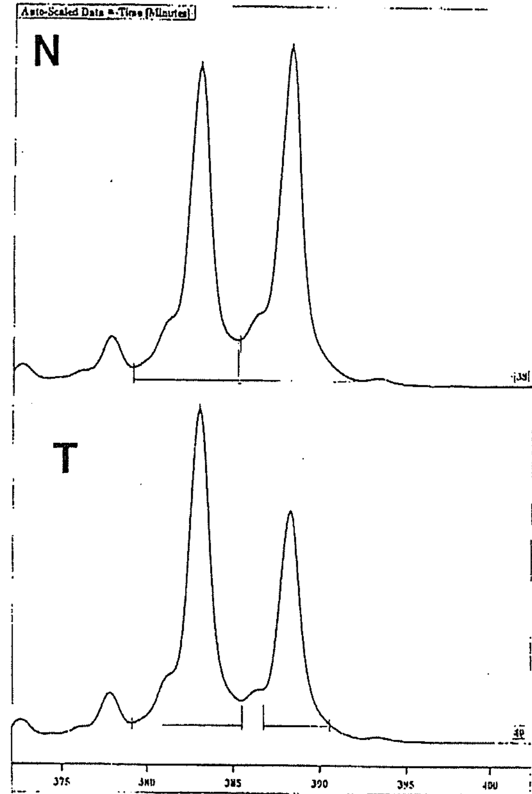
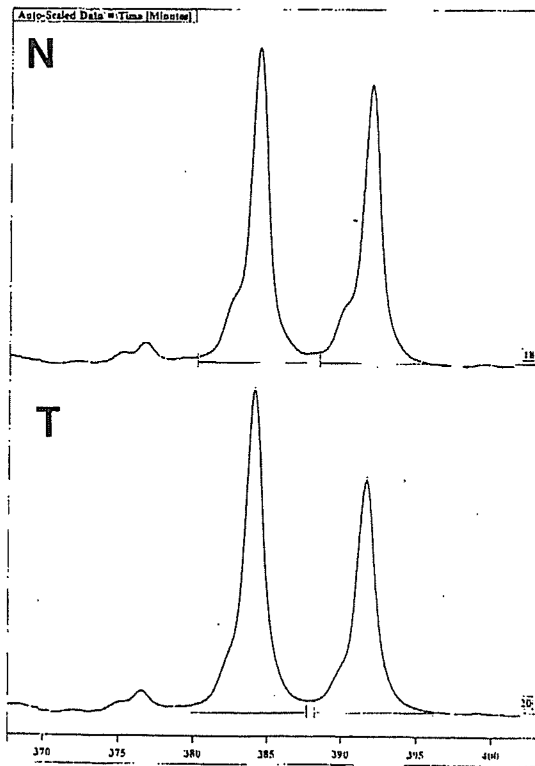




Figure 1. *Electropherogram profiles in SSCP analysis. A: Percent peak height of tumor tissue profile was 23%, 14% and 1% at p53 intron 7, D18S499 and D3S2396, respectively. As defined in Materials and Methods, this patient had allelic loss of 17p and 18q, while the allele of 3p was retained. The allele of 22q was not informative (data not shown). B: Percent peak height of the tumor tissue profile was 43%, 36%, 18% and 22% at D17S969, D18S499 D22S685 and D3S2396, respectively. All the alleles examined were lost in this patient.*

B



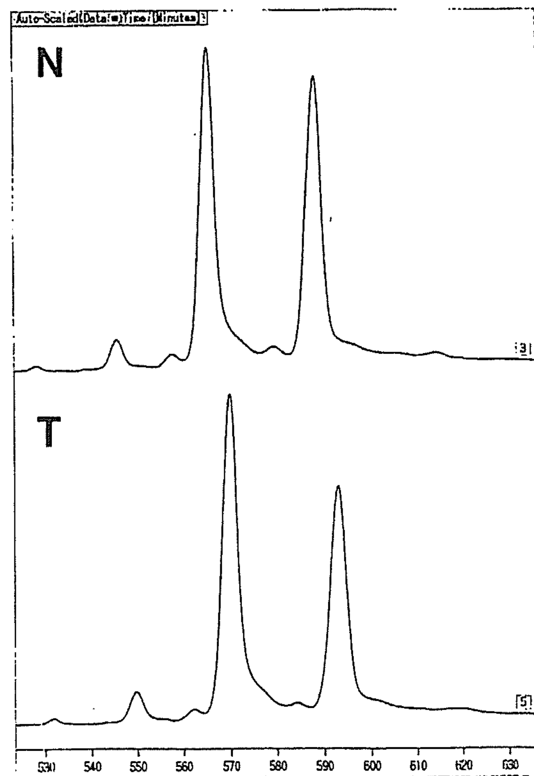



Table III. *Clinicopathological backgrounds of low and high allelic loss groups.*

| Allelic loss | Low (n=25) | High (n=107) | *p* |
|---|---|---|---|
| Gender | | | |
| Male | 12 | 68 | |
| Female | 13 | 39 | 0.29 |
| Age | | | |
| <60 | 8 | 40 | |
| 60≤ | 17 | 67 | 0.61 |
| Tumor site | | | |
| Colon | 19 | 63 | |
| Rectum | 6 | 44 | 0.11 |
| Tumor differentiation | | | |
| Well | 15 | 47 | |
| Moderate | 10 | 60 | 0.15 |
| Lymphatic invasion | | | |
| Negative | 15 | 49 | |
| Positive | 10 | 58 | 0.20 |
| Venous invasion | | | |
| Negative | 17 | 57 | |
| Positive | 8 | 50 | 0.18 |
| Depth of invasion (pT) | | | |
| pT1, pT2 | 7 | 19 | |
| pT3, pT4 | 18 | 88 | 0.25 |
| Lymph node status (pN) | | | |
| Negative | 22 | 47 | |
| Positive | 3 | 60 | <0.01 |

Table IV. *Disease-free survival according to allelic status.*

| | | 5-year disease-free survival rate | | | |
|---|---|---|---|---|---|
| | | Stage I, II | *p* | Stage III | *p* |
| 17p | Loss | 80% (n=49) | | 56% (n=57) | |
| | Retained | 80% (n=25) | 0.96 | 63% (n=8) | 0.80 |
| 18q | Loss | 81% (n=49) | | 54% (n=60) | |
| | Retained | 85% (n=22) | 0.62 | 71% (n=5) | 0.34 |
| 22q | Loss | 83% (n=31) | | 68% (n=37) | |
| | Retained | 83% (n=37) | 0.79 | 47% (n=17) | 0.19 |
| 3p | Loss | 82% (n=22) | | 67% (n=21) | |
| | Retained | 81% (n=34) | 0.79 | 45% (n=29) | 0.36 |
| High and low allelic loss status | | | | | |
| | High | 77% (n=47) | | 59% (n=60) | |
| | Low | 86% (n=22) | 0.30 | 67% (n=3) | 0.83 |

adjuvant therapy. Another explanation for the conflicting data is non-specific allelic loss. Because chromosomal losses and gains are driven by chromosomal instability that persists throughout the lifetime of the tumor cells (28), some of the allelic losses may not affect the malignant potential of cancer cells, and these non-specific alterations may decrease the prognostic importance of the allelic losses, *i.e.*, these non-specific alterations may obscure the effects of allelic loss.

We showed that the allelic status was significantly related to the lymph node status. If the lymph node status could be predicted before radical surgery, it would be useful for clinical decision making. Taking the high-risk factor for lymph node metastasis, lymphatic invasion (29, 30), into account, patients without allelic loss and without lymphatic invasion had a very low incidence of lymph node metastasis. Among 14 patients without allelic loss at 18q or lymphatic invasion, only one patient (7%) had lymph node metastasis. Among 19 patients without allelic loss at 17p or lymphatic invasion, only one patient (5%) had lymph node metastasis. Fifteen patients in the low allelic loss group without lymphatic invasion had no lymph node metastasis. However, the presence of lymphatic invasion cannot be determined before resection, only after. These results suggested that the combination of allelic loss status and lymphatic invasion status can predict lymph node metastasis before radical surgery. This is particularly useful information, especially for T2 or more so for rectal cancer because, *e.g.*, in the absence of these risk factors, such tumors can be treated by local excision, by endoscopic resection or transanal resection. Therefore, further examination of the relationship between allelic status and lymph node status is warranted in future studies.

The DNA of tumor tissues is inevitably not homogeneous because of stromal cell contamination or the genetic heterogeneity of tumor cell populations, which have also been proposed to cause a wide range of allelic losses. In conventional RFLP (restriction fragment length polymorphism) or PCR-based RFLP analysis, to detect allelic loss the proportion of tumor cells in the sample must exceed at least 50% of the total cells, and a large amount of DNA is required. Clinical samples are often contaminated with normal cells, and the tumor cellularity is sometimes less than 50%. In such cases, conventional techniques cannot detect allelic loss and the allelic status is considered to be retained. This suggests that conventional techniques cannot be used to detect clear associations between allelic loss and prognosis. Here, blunt-end SSCP analysis, which can detect allelic losses when the tumor cellularity of the sample is around 10% and requires only a small amount of DNA, was used. These advantages enabled the detection of allelic losses using small amounts of DNA obtained from biopsy specimens, surgical materials and formalin-fixed, paraffin-embedded sections. The method is clinically very useful, because surgical materials and biopsy samples of cancer are usually contaminated with many normal cells.

It was found that the number of allelic losses was not associated with the prognosis of CRC. However, Choi *et al.* showed that the number of allelic losses was associated with prognosis, this factor still being significant in multivariate analysis (8). Because they had examined eight chromosomes (3p, 4p, 5q, 8p, 9p, 13q, 17p and 18q), this conflicting result might be explained by the difference in the chromosomes examined. If the level of chromosomal loss is an important

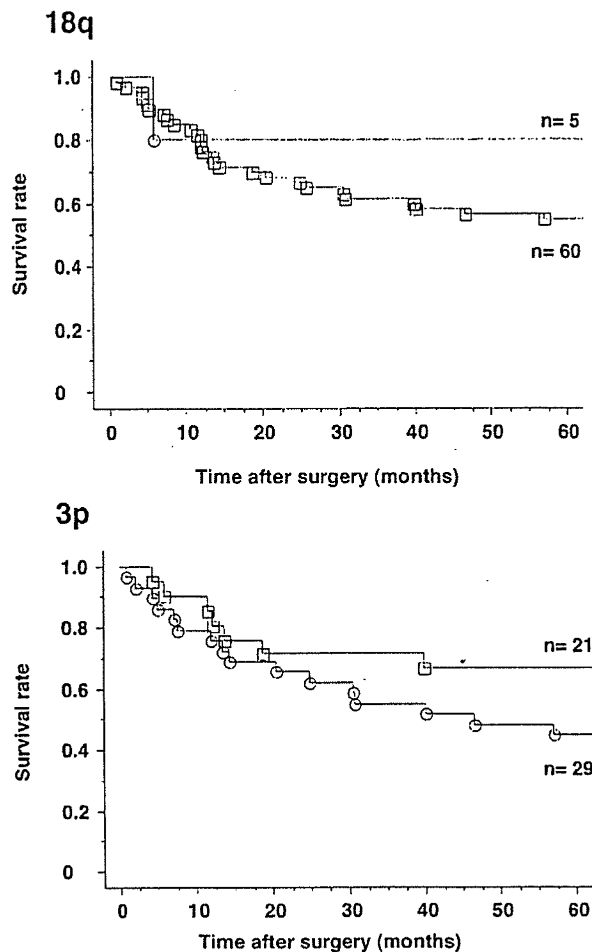



Figure 2. *Disease-free survival curves in stage III CRC. Patients with allelic loss at 18q showed worse survival than those without allelic loss at 18q, and patients with allelic loss at 3p showed better survival than those without this allelic loss. These differences were not significant.* □: *Lost,* O: *Retained.*

prognostic factor, then it is of importance to determine which chromosomes are important for prognosis and how many chromosomes are to be examined. On the other hand, Rooney *et al.* obtained contrary results using comparative genomic hybridization (21). In their study, Dukes' C patients with more than two genomic aberrations had a better survival rate than did patients with fewer regions. Rooney *et al.* also showed that single genomic instabilities were not correlated with survival.

The allelic loss of chromosome 17p is a very common event in CRC. Although the allelic status of chromosome 17p is correlated with some clinicopathological backgrounds, only a small number of reports have suggested the prognostic importance of this allelic loss (1, 8), while other reports, including this study, showed no correlation between prognosis and allelic loss (15, 17-19). For p53, intragenic polymorphic markers were used. Even where the intragenic markers were informative, there was no correlation between prognosis and allelic loss of p53 (data not shown).

The allelic loss of chromosome 22q is relatively frequent in CRC (22, 23, 25, 31). However, there is no report of a tumor suppressor gene on 22q. Although Iino *et al.* have shown that allelic loss of chromosome 22q was correlated with lymph node metastasis (31), there have been no reports of a relationship between the allelic loss of chromosome 22q and prognosis. No relationship was found between the allelic loss of 22q and the clinicopathological background or prognosis, meaning that it probably is not a prognostic factor in CRC patients.

The allelic loss of chromosome 3p is also relatively frequent in CRC, and detailed deletion mapping studies have suggested the existence of tumor suppressor genes on this chromosome, although non have been reported. Iniesta *et al.* showed that allelic loss of 3p was significantly associated with worse prognosis in CRC patients (4). Although theirs was the first report to demonstrate the prognostic significance of the allelic loss of 3p, our study revealed no relationship between the clinicopathological background and allelic status. Choi *et al.* suggested that allelic loss of 3p was correlated with cancer-related death (8). Blaker *et al.* (25) showed preferential loss of chromosome 3p in CRC. However, no additional studies have supported this result, and we were unable to show a relationship between the clinicopathological background or prognosis and allelic loss of 3p.

In summary, although allelic status was not associated with prognosis in CRC patients without adjuvant chemotherapy, it was significantly associated with lymph node metastasis, and a combination of the allelic status and lymphatic invasion status can be used to predict the lymph node status before radical surgery. When allelic loss and lymphatic invasion are not detected after local excision, additional lymph node resection is not required.

## Acknowledgements

We thank Naoko Kudo, Noriko Fukayama, Keiko Wakabayashi and Takahiro Taniguchi (Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan) for their technical assistance.

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*Received January 9, 2006*
*Revised April 10, 2006*
*Accepted April 13, 2006*

Original Paper

# Surgical Outcomes of Laparoscopic *vs.* Open Surgery for Rectal Carcinoma - A Matched Case-control Study

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ABSTRACT
**Background/Aims:** The present study evaluated the short- and middle-term surgical outcomes of laparoscopic surgery (LS) for rectal carcinoma in comparison with a case-control series of open surgery (OS).
**Methodology:** Between February 1998 and December 2004, 47 patients with rectal carcinoma underwent LS. These patients were compared with a conventional OS group matched for age, gender, location of tumor, surgical procedure, extent of resection and pathological stage.
**Results:** The median follow-up period for the LS group and the OS group was 25 and 49 months, respectively. In the LS group, median operative time was significantly longer but median blood loss was lower than those in the OS group. There was one requiring conversion to OS. Postoperative intervals until liquid and solid intakes, and hospital stay were significantly shorter in the LS group. Postoperative complications rates are similar and anastomotic leakage occurred in one patient in each group. In the LS group, the levels of white blood cell count on postoperative day 1 and C-reactive protein on postoperative days 1 and 2 were significantly lower than those in the OS group.
**Conclusions:** LS for rectal carcinoma provides benefits during the early postoperative period without increase in morbidity or mortality.

**KEY WORDS:** Laparoscopic surgery; Laparoscopic anterior resection; Rectal carcinoma; Case-control study; Surgical outcome

**ABBREVIATIONS:** Laparoscopic Surgery (LS); Open Surgery (OS); Intersphinctic Rectal Resection and Handsewn Coloanal Anastomosis (ISR-CAA); Abdominoperineal Resection (APR); Randomized Clinical Trial (RCT); White Blood Cell (WBC); C-Reactive Protein (CRP)

## INTRODUCTION

Since the first report of laparoscopic colectomy in 1991 by Jacobs *et al.* (1), laparoscopic surgery has been tried and applied to a wide range of colorectal disease, including colorectal carcinoma. Recently many studies have demonstrated several advantages of laparoscopic surgery (LS) over conventional open surgery (OS), including reduced surgical blood loss, decreased postoperative pain and ileus, shorter hospital stay and favorable effects on immunologic status (2-5). With regard to long-term oncological safety, which is the most important concern for LS for malignancies, there have been no reports indicating that LS is inferior to conventional OS by randomized clinical trial (RCT) (6-8).

However, laparoscopic approach to rectal carcinoma is very difficult from a technical standpoint compared for that of colon carcinoma. Following laparoscopic anterior resection for rectal carcinoma, anastomotic leakage has been reported to occur in 7.2-20% (9-15), and as a result, some reports recommended routine covering ileostomy with this procedure even for patients who would not require ileostomy if they selected open anterior resection (9). In fact, many RCTs regarding laparoscopic resection for colorectal carcinoma have excluded patients with middle and lower rectal carcinoma (6-8). Due to the lack of comparative studies, it remains controversial as to whether LS for rectal carcinoma can be regarded minimally invasive surgery.

Since our first laparoscopic surgery for colonic carcinoma in 1993, about 400 patients have undergone laparoscopic resection for colorectal disease at our institution. Because the safety of LS in cancer patients remains to be established, candidates for radical surgery were patients preoperatively diagnosed with T1 or T2 disease. Additionally, LS cases also included patients who were preoperatively diagnosed with T3 but who preferred to undergo LS, as well as those with colon or upper rectal carcinoma for which palliative resection was considered necessary. In June 2001, we unified our surgical and postoperative management procedures, as a consequence, the complication rate and mean length of hospitalization have been reduced at our institution (16,17).

The aim of this study was to analyze the short-term and the middle-term surgical outcomes of LS for patients with rectal carcinoma and compare them with a matched group of patients who underwent similar conventional OS.

## METHODOLOGY

### Patients

Between February 1998 and December 2004, we

Hepato-Gastroenterology 2006; 53:531-535
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**TABLE 1 Patient Characteristics**

| | | LS group | OS group | *P* value |
|---|---|---|---|---|
| No. of patients | | 47 | 47 | |
| Sex ratio (male: female) | | 28: 19 | 28: 19 | >0.999 |
| Age (yr; mean and range) | | 60 (35-76) | 60 (39-84) | 0.551 |
| Body mass index ($kg/m^2$, mean and range) | | 23.0 (17.3-32.4) | 23.2 (18.1-33.8) | 0.934 |
| Prior abdominal surgery (%) | | 13 (27.7) | 15 (31.9) | 0.823 |
| Location | Upper rectum | 25 | 25 | |
| | Middle rectum | 10 | 10 | |
| | Lower rectum | 12 | 12 | |
| Surgical procedure | Anterior resection | 43 | 43 | |
| | Abdominoperineal resection | 1 | 1 | |
| | Anterior resection with ISR-CAA | 3 | 3 | |
| | Covering ileostomy | 11 | 9 | |
| | Transverse-coloplasty pouch | 4 | 4 | |
| Year of surgery | 1997-1999 | 1 | 16 | |
| | 2000-2002 | 20 | 21 | |
| | 2003- | 26 | 10 | |
| Pathological stage | UICC Stage 0 | 2 | 2 | |
| | UICC Stage I | 34 | 34 | |
| | UICC Stage II | 1 | 1 | |
| | UICC Stage III | 10 | 10 | |
| Follow-up period (month) | | 24.6 (3.0-65.8) | 49.2 (3.7-99.3) | <0.001 |

ISR-CAA: intersphincteric rectal resection and handsewn coloanal anastomosis.

**TABLE 2 Intraoperative and Postoperative Results**

| | LS group | OS group | *P* valve |
|---|---|---|---|
| Operative time (min.) | 255 (117-472) | 150 (94-475) | <0.001 |
| Blood loss (mL) | 60 (5-477) | 72 (10-945) | 0.021 |
| Conversion | 1 | - | - |
| Liquid intake (days) | 1 (1-4) | 4 (1-7) | <0.001 |
| Solid intake (days) | 3 (2-8) | 5 (3-80) | <0.001 |
| Hospital stay (days) | 8 (7-23) | 15 (10-101) | <0.001 |

Values are medians (range).

**TABLE 3 Morbidities and Mortality**

| | | LS group | OS group | *P* valve |
|---|---|---|---|---|
| Mortality | | 0 | 0 | >0.999 |
| Morbidity | Wound sepsis | 3 | 3 | >0.999 |
| | Bowel obstruction | 1 | 7 | 0.059 |
| | Anastomotic leakage | 1 | 1 | >0.999 |
| | Anastomotic bleeding | 1 | 0 | 0.500 |
| | Neurogenic bladder | 0 | 1 | 0.500 |
| | Pneumonia | 1 | 0 | 0.500 |
| | Pulmonary embolism | 0 | 1 | 0.500 |
| Total (No. of patients) | | 7 (14.9%) | 12 (25.5%) | 0.304 |

performed 47 curative laparoscopic resections for patients with rectal carcinoma. All patients were evaluated before surgery by clinical investigation including total colonoscopy, barium enema and computed tomography. To evaluate co-morbid conditions, cardiopulmonary function and renal function test were performed. We excluded the following groups of patients from LS: patients with tumors larger than 7cm, patients with a history of extensive adhesions, patients with intestinal obstruction, and patients with severe obesity (body mass index >32kg/m$^2$) and patients who did not consent to LS.

The analyzed parameters included age, gender, body mass index, prior abdominal surgery, operative time, blood loss, days until resumption of diet and length of postoperative hospital stay. Pathological staging was performed according to TNM classification. White blood cell (WBC) count and C-reactive protein (CRP) in serum were measured preoperatively and on postoperative day 1 routinely, and on postoperative day 2, if necessary.

Each laparoscopic case was compared with the control OS group of patients matched for age, gender, location of tumor, surgical procedure, extent of resection and pathological stage.

### Laparoscopic Technique

Techniques for laparoscopic resection have previously been described (16,17). Initial port placement was performed using the open technique and pneumoperitoneum was induced using carbon dioxide. Two 5-mm ports were then inserted into the left lower mid-abdominal and the left lower quadrant regions, and two other 12-mm ports were inserted into the mid-lower and right mid-abdominal regions under laparoscopic guidance.

The left colon was initially mobilized laterally to medially until the left ureter and superior hypogastric nerve plexus were identified. The mobilization of splenic flexure was performed if necessary. Then, a window was made between the mesocolon containing the arch of the inferior mesenteric vessels and the superior hypogastric nerve plexus, starting at the bifurcation, with support from an assistant holding the sigmoid mesocolon ventrally under traction and to the left using a 5-mm bowel grasper through the left lower quadrant port. After the dissection proceeding to the origin of the inferior mesenteric artery, taking care not to injure the superior hypogastric nerve plexus and the roots of the sympathetic nerves, intracorporeal high ligation of the inferior mesenteric artery was performed. After cutting the inferior mesenteric vein and left colic artery, mobilization of the rectum and mesorectum was performed. The avascular plane between the intact mesorectum anteriorly, and the superior hypogastric nerve plexus, right and left hypogastric nerves, and Waldeyer's fascia posteriorly was entered by sharp dissection, and extended down to the level of the levator muscle for middle and lower rectal carcinomas, taking care to protect the pelvic nerves. For upper rectal lesions, mesorectal tissue extending down to 5cm below the tumor was excised routinely using ultrasonic shears (Laparoscopic Coagulating Shears, Ethicon Endo-Surgery Inc, Cincinnati, OH). Middle and lower rectal tumors were treated by total mesorectal excision. Immediately before rectal transection, laparoscopic rectal clamping was performed just above the anticipated point of rectal transection, using a bowel clamping device intro-

duced through the 12-mm mid-lower port. Rectal washout was performed routinely using 1,000mL of a 5 percent povidone-iodine solution. Rectal transection was then performed by multiple firing technique, using Endo GIA Universal staples, introduced through the 12-mm right mid-abdominal port. A 4- to 5-cm incision was then made over the mid-lower 12-mm port site, and the bowel was exteriorized under wound protection and divided with appropriate proximal clearance. After inserting the anvil head of the circular stapler into the end of the proximal colon, the proximal colon was internalized and the incision was closed. Intracorporeal anastomosis under laparoscopic view was performed by the double-stapling technique (DST) using a circular stapler (ECS 29mm or 33mm, Ethicon Endo-Surgery Inc, Cincinnati, OH). Patients with low anastomosis within 1cm from the dentate line and incomplete "doughnuts" underwent covering ileostomy.

For patients with lesions located within 5cm of the dentate line with more than 2cm of the distal free margin to the dentate line (with no evidence of carcinoma invasion into the sphincters or pelvic floor), laparoscopic intersphincteric rectal resection and handsewn coloanal anastomosis (ISR-CAA) was performed. This surgical technique was described previously (18). For patients undergoing abdominoperineal resection (APR), laparoscopic procedures were followed by perineal dissection in the standard fashion, and end colostomy creation using the left lower abdominal port site.

**Statistical Analysis**

Statistical analysis was performed using Student's $t$ test, the Mann-Whitney $U$ test, and the Fisher's exact test as appropriate. A $P$ valve of less than 0.05 was considered significant.

## RESULTS

Patient demographic characteristics are summarized in **Table 1**. Cases and controls were well matched for gender, age, tumor site, surgical procedure, extent of resection and TNM stage; however, the follow-up period in the OS group was significantly longer than that in the LS group. There were no significant differences in the patient's characteristics, including BMI and rate of prior abdominal surgery, between the two groups. In both groups, three patients underwent ISR-CAA and a transverse-coloplasty pouch was created in 4 patients. Overall, covering ileostomy was required for 11 patients in the LS group, and 9 patients in the OS group. All the patients with covering ileostomy underwent subsequent ileostomy closure.

Surgical and postoperative results are demonstrated in **Table 2**. In the LS group, operative time was significantly longer but blood loss was significantly lower. There was one case requiring conversion to OS because of severe adhesion after repeated cesarean section. Liquid and solid intakes were started on median postoperative days 1 and 3 in the LS group, which was significantly shorter than that in the OS group. Similarly, the median postoperative hospital stay was 8 days in the LS group, which was significantly shorter than 15 days in the OS group. All patients were discharged to home.

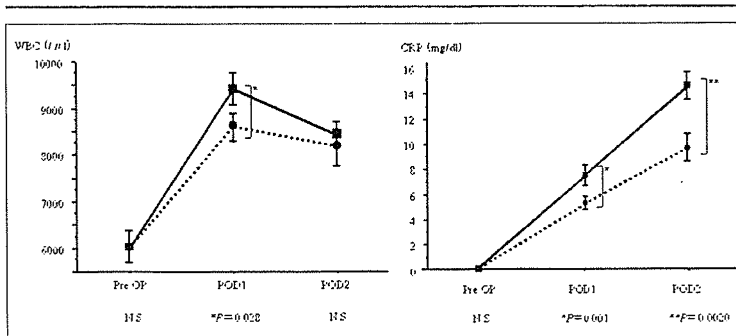


**FIGURE 1** The level of white blood cell (WBC) count **(a)** on postoperative day (POD) 1 and the level of serum C-reactive protein (CRP) **(b)** on POD 1and 2 were significantly lower in LS group (●) than OS group (■). Each bar represents the mean standard error.

The postoperative complications are listed in **Table 3**. There were no perioperative mortalities in either group. The rate of postoperative bowel obstruction was 2.1% (1/47) in the LS group and 14.9 % (7/47) in the OS group ($P$=0.059). An anastomotic leakage occurred in one patient in each group. In the LS group, one patient, who had covering ileostomy during the initial operation, experienced anastomotic leakage that was conservatively managed. In the OS group, a patient with an anastomotic leakage required emergency operation for abdominal drainage and diverting ileostomy. Another patient in the LS group experienced anastomotic bleeding, that was conservatively managed. There was no significant difference in total complication rates between the two groups.

Preoperative and postoperative levels of WBC and CRP in serum are presented in **Figure 1**. In the LS group, the level of WBC on postoperative day 1 and the level of CRP on postoperative day 1 and 2 were significantly lower than those in the OS group.

At the end of the study period, there were no patients who had developed a recurrence or died in this series.

## DISCUSSION

To date, there are few studies comparing surgical outcomes between LS *versus* OS for rectal carcinoma (11,19). In this study, we were able to demonstrate that the minimal invasiveness of LS, which has been demonstrated for colon carcinoma, can be preserved in LS for rectal carcinoma as well. Needless to say, the quality of surgery during LS for rectal carcinoma is important. If the rate of conversion to OS increases, outcomes of LS will be shifted to outcomes of OS, thus making it difficult to detect differences between the two groups. In addition, if the complication rate increases, hospitalization after surgery can be prolonged, resulting in a loss of the advantages of LS. In this study, there was only one case requiring conversion to OS, and the anastomotic leakage rate was

lower (2.1%, 1/47) than the rates previously reported. We consider that these facts contributed greatly to demonstrating the minimal invasiveness of LS for rectal carcinoma. And the fact that WBC on postoperative day 1 and CRP values on postoperative day 1 and 2 were significantly lower in the LS group can be regarded as objective data suggesting the minimal invasiveness of LS.

At our institution, there has been much consideration given to the technical safety of LS, and surgeons with a thorough expertise in OS had accumulated enough experience in LS for colon carcinoma, which is technically relatively easy to perform. Thereafter, the indications were expanded to include rectal carcinoma. As a result, LS for rectal carcinoma has been successfully performed with significantly reduced blood loss, earlier start of oral intake and shortened postoperative hospital stay, as compared to OS. At present, the long-term oncological outcome of LS for rectal carcinoma remains unclear and hence the indications for LS for rectal carcinoma remain limited, but it may be technically possible to gradually reduce those limits and expand our indications.

One of the advantages of LS for rectal carcinoma is that by inserting a flexible scope into the narrow pelvis to magnify the operative field, the surgeon can safely mobilize the rectum because of easy identification of the loose connective tissue between the mesorectum and the surrounding tissues such as the hypogastric nerves and the pelvic nerve plexuses, which is not always easy to recognize under direct vision during OS. Another advantage of LS is that everyone participating in the operation can have the same field of view. However, there are several technical limitations in LS. It is often very difficult to occlude and transect the bowel in LS, especially when the tumor is located in the lower rectum. Furthermore, lateral lymph node dissection combined with total mesorectal excision remains the standard surgical procedure for patients with T3 and T4 lower rectal carcinoma in Japan, and lateral lymph node dissection by laparoscopy remain an unexplored frontier (16,20). In particular, previous studies have reported an anastomotic leakage rate of 7.2 to 20% in patients who underwent laparoscopic low anterior resection (9-15), and some authors have recommended covering ileostomy as a routine in this procedure (9). However, this can deteriorate the short-term quality of life of the patient and can also promote local recurrence in the long term (21). Therefore, the utmost effort should be made to avoid this complication.

At our institution, patients with low anastomosis within 1cm from the dentate line, incomplete doughnuts with DST, and laparoscopic intersphincteric rectal resection and handsewn coloanal anastomosis underwent covering ileostomy. However, the decision to perform protective ileostomy in this series was based on much looser criteria than those used in OS in order to avoid major anastomosis complications that could lead to permanent stoma or fatal outcome, especially in the early LS cases involving lower rectal carcinoma. In the future, it may be appropriate to set the same indications for ileostomy as in OS.

In sphincter-preserving surgery for rectal carcinoma, whether performed by LS or by OS, the procedure for dissection and anastomosis is the phase with the highest technical difficulty. For patients with lesions located more than 2cm of the distal free margin to the dentate line with no evidence of carcinoma invasion into the sphincters or pelvic floor, we usually perform laparoscopic DST anastomosis. However, as we previously indicated, during LS for lower rectal carcinoma, the closer the site of dissection of the rectum is to the anus, the more difficult the rectal dissection technique is, thus increasing the use of endolinear staplers needed to perform the dissection. In such cases, it is important to securely penetrate the first and second crossing points using a circular stapler to prevent anastomotic leakage (17).

One of the distinctive points of the present study is that only one patient underwent laparoscopic APR. Recently, laparoscopic ISR-CAA has been reported for patients with lesions located in the lower rectum with greater than 2cm of distal free margin to the dentate line (18). This technique allows a sufficient distal margin to be obtained under direct vision in order to preserve the sphincter and avoid APR. As a consequence, only one patient underwent laparoscopic APR. Although we considered that laparoscopic ISR-CAA was possible in that case, the patient's choice was laparoscopic APR.

With regard to the oncological outcome which is the most important factor in terms of a carcinoma surgery, recently reported results of three RCTs in patients with colon carcinoma or upper rectal carcinoma indicating that the treatment outcome of LS is equal to or better than that of OS (6-8). However, many RCTs have excluded patients with middle and lower rectal carcinoma because of great technical difficulties, and there has been only case series reporting experiences of a single or multiple institutions (2,9-14). Further investigations based on multicenter RCT are necessary for middle and lower rectal carcinoma cases as well.

In conclusion, the findings of the present study demonstrated that LS for rectal carcinoma could be performed safely compared to OS without increased morbidity or mortality. The radical resection of middle and lower rectal carcinoma is a procedure that requires advanced technical skills in OS, to say nothing of LS. With improvements in technology and surgical experience, the indications for this procedure are expected to expand. However, at present, as the oncological outcome remains unclear, expansion of the indications to include advanced lower rectal carcinoma should proceed cautiously.

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Int J Clin Oncol (2006) 11:339–343
DOI 10.1007/s10147-006-0608-z

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REVIEW ARTICLE

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# Function-preserving surgery for rectal cancer

Received: July 20, 2006

**Abstract** When total mesorectal excision (TME) is accurately performed, dysfunction, theoretically, does not occur. However, there are differences among individuals in the running patterns and the volumes of nerve fibers, and if obesity or a narrow pelvis is present, nerve identification is difficult. Currently, the rate of urinary dysfunction after rectal surgery ranges from 33% to 70%. Many factors other than nerve preservation play a role in minor incontinence. Male sexual function shows impotence rates ranging from 20% to 46%, while 20%–60% of potent patients are unable to ejaculate. In women, information on sexual function is not easily obtained, and there are more unknown aspects than in men. As urinary, sexual, and defecation dysfunction due to adjuvant radiotherapy have been reported to occur at a high frequency, the creation of a protocol that enables analysis of long-term functional outcome will be essential for future clinical trials. In the treatment of rectal cancer, surgeon-related factors are extremely important, not only in achieving local control but also in preserving function. This article reviews findings from recent studies investigating urinary, sexual, and defecation dysfunction after rectal cancer surgery and discusses questions to be studied in the future.

**Key words** rectal cancer · urinary, sexual, defecation dysfunction · adjuvant radiotherapy · quality of life in rectal cancer patients

## Introduction

The goals of surgical treatment of rectal cancer are: firstly, to achieve local control by complete removal of the lesion; secondly, to preserve urinary and sexual functions; and thirdly, to preserve anal sphincteric function if possible; while the ultimate goal is, of course, to cure the rectal cancer. This article reviews findings from recent studies investigating urinary, sexual, and defecation dysfunction after rectal cancer surgery, and discusses questions to be studied in the future.

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## Differences in treatment strategies:

In Western countries, nonanatomical dissections represented by blind hand dissection were the standard operative procedures for rectal cancer. In consequence of this technique, rates of local recurrence as high as 30% were reported.[1,2] In the latter half of the 1980s, total mesorectal excision (TME), proposed by Heald et al.,[3] began to be employed. This procedure, which involves dissecting the rectum with TME under direct vision based on anatomical indexes, came into widespread use in Western countries during the 1990s. The first reason for the spread of its use was the oncological superiority, as indicated by reports of local recurrence rates as low as 4%.[4] The second reason was the benefit from preserving urinary and sexual functions. During the same period, clinical trials examining the use of adjuvant chemoradiation were conducted, with the aim of overcoming the high local recurrence rate.[5] A notable product that resulted from these studies is the Dutch CKVO 95-04 TME Trial.[6]

In Japan, on the other hand, having been influenced by the extended surgery for gastric cancer, leading hospitals began to employ extended surgery for rectal cancer around the beginning of the 1970s, thereby producing good results: firstly, 5-year survival rates were favorable compared with historical controls,[7] and secondly, the topography of lymph node metastases of rectal cancer was elucidated in terms of the frequency of lateral lymph node metastases.[8,9] In Japanese patients, body mass indexes and the rates of atherosclerosis are generally lower than in Western patients; for such physical reasons, there was no increase in morbidity and mortality due to extended surgery. However, extended surgery was associated with severe urinary and sexual dysfunction, as it involved the resection of auto-