



The Short- and Long-Term Feasibility of Laparoscopic Surgery in Colon Cancer Patients with Bulky Tumors

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Abstract

Background Compared to open surgery for colon cancer, randomized controlled trials have shown that laparoscopic approaches have equivalent short- and long-term outcomes. However, the feasibility of laparoscopy for removal of bulky tumors has not been evaluated. The aim of our study was to determine the short- and long-term feasibility of laparoscopic surgery for bulky (> 8 cm) colon cancer.

Methods A total of 80 patients with bulky tumors (defined as greater than 8 cm in diameter) underwent curative resection from July 2004 to July 2014. Short- and long-term outcomes were compared between patients undergoing laparoscopic ($n = 48$) and open ($n = 32$) resection.

Results Compared to open, the operative time was significantly longer (213 vs. 148 min, $p < 0.001$), return of bowel function quicker (time to oral intake; 2 vs. 5 days, $p < 0.001$), and length of stay shorter (10 vs. 13 days, $p < 0.001$) in the laparoscopic group. Five-year cancer-specific and relapse-free survival was similar with no patients developing local recurrence in either group.

Conclusions Laparoscopic resection of colon cancers greater than 8 cm in diameter is feasible and oncologically safe with better short-term and equivalent long-term outcomes compared to open surgery.

Keywords Laparoscopic surgery · Bulky tumor · Colon cancer

Introduction

Laparoscopic surgery (LS) for patients with colon cancer (CC) has been widely accepted, and several randomized controlled trials (RCTs) have demonstrated the short-term benefits of LS over the open approach, including reduced postoperative pain, earlier recovery of bowel function, decreased operative blood loss, and shorter hospital stay.^{1–5} Compared to open, laparoscopic surgery has also been shown to have equivalent oncologic and long-term outcomes.^{6–9}

Previous RCTs did not include patients with bulky colon cancers defined as having a diameter > 8 cm,^{4, 10, 11} because atraumatic laparoscopic manipulation of bulky tumors is technically demanding and requires a larger skin incision to remove specimens. The guidelines from the European Association of Endoscopic Surgery (EAES) has noted that adequate laparoscopic manipulation of bulky tumors is difficult, and the size of the tumor is an important factor in considering the indication for LS in CC patients.¹² Furthermore, bulky tumor is a predictor of conversion in laparoscopic CC surgery,^{13, 14} and previous reports have demonstrated that conversion was associated with adverse short- and long-term outcomes.^{13–17} To the best of our knowledge, no previous study has evaluated the feasibility of LS for CC patients with bulky tumors.

The aim of the present study was to assess the feasibility of LS for CC patients with bulky tumors, in terms not only of postoperative outcomes, but also of long-term outcomes.

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Materials and Methods

From July 2004 to July 2014, consecutive patients were retrospectively reviewed if they had undergone curative resection for pathological stage II/III primary colon adenocarcinoma by a laparoscopic or open approach in our institution. Tumors originating from the cecum to recto-sigmoid colon were defined as colon cancer in the study. Patients with preoperative chemoradiotherapy or chemotherapy, synchronous tumors including multiple colorectal carcinomas, appendiceal cancer, rectal cancer, colitic cancer, familial adenomatous polyposis, and Lynch syndrome were excluded. Patients who underwent synchronous pelvic exenteration ($n = 2$) and pancreaticoduodenectomy ($n = 2$) were excluded from this study, because these procedures are associated with longer operating time, a large amount of blood loss, and high morbidity and were performed only by laparotomy during this study period. Furthermore, we excluded 32 patients who underwent combined resection of the adjacent structures because this procedure was more frequent in the open than in the laparoscopic group (19 vs. 13). Finally, 80 patients were eligible for this analysis. This retrospective analysis was approved by our institutional review board.

Laparoscopic colectomy for primary CC was adopted at our institution in July 2005. At the beginning, bulky tumors, tumors invading adjacent structures, and lymph node metastases in the root of a feeding artery were considered contraindications to LS.¹⁸ However, with our increased experience, the indications for LS were gradually expanded.^{19–22} Patients with bulky CC underwent complex LS by consultant surgeons who had each completed over 300 LS for common CC within 8 cm in diameter. There are no specific exclusion criteria for LS at present, except patients with tumor infiltrating the duodenum or major vessels (e.g., iliac vessels). The presence of abdominal adhesions was not a contraindication to LS, but the expectation of severe adhesions might affect the decision to perform LS. The final indication for LS was determined in our team meeting and at the surgeon's discretion, which was greatly affected by each surgeon's learning curve at that time.

Laparoscopic procedures were performed by highly experienced laparoscopic surgeons using the five-trocar technique. We did not use a hand-assisted approach. Our laparoscopic procedures involved ligating the root of the main feeding artery and mobilizing consecutive bowel segments. During sigmoidectomy or anterior resection for sigmoid colon or recto-sigmoid colon cancer, the recto-sigmoid colon or rectum was intracorporeally transected using a linear stapler, and intracorporeal anastomosis proceeded using a circular stapler. For other procedures, including ileocecal resection, right hemicolectomy, transverse colectomy, and left hemicolectomy, a stapled side-to-side functional end-to-end extracorporeal anastomosis was created. To extract the bulky tumor and complete the bowel reconstruction

safely, broad mobilization of consecutive bowel segments was performed. We mobilized bulky tumors by bluntly and sharply dissecting tissue surrounding the target lesion without grasping the tumor itself. Under adequate traction, the laparoscopic magnified view allows more meticulous dissection along the areolar layer in the deep abdominal area and around the bulky tumors (especially the dorsal side).

The clinical parameters, including sex, age at surgery, body mass index (BMI; kg/m^2), serum carcinoembryonic antigen (CEA; ng/ml), and location of tumor, were collected from our prospectively maintained database. The location of primary tumors was classified as right-sided colon (cecum to splenic flexure) and left-sided colon (splenic flexure to recto-sigmoid colon). Surgical outcomes and pathological tumor characteristics were investigated, including operative procedure, lengths of the extended umbilical port sites and laparotomy incisions, operation time, estimated blood loss, with or without blood transfusion, number of lymph nodes harvested, number of metastatic lymph nodes, rate of conversion to open surgery, tumor size, pathological T status, pathological N status, histological type, status of lymphovascular invasion, and pathological margin status. The pathological stage was determined according to the classification of the Union for International Cancer Control (UICC). Conversion to open surgery was defined as the need for an abdominal incision greater in size than originally planned to accomplish bowel mobilization or vessel ligation. Postoperative outcomes within 30 days of the index operation were also collected, including time to first flatus passage, time to first stool, time to oral intake of semisolid food, the number and duration of intravenous pain-relieving drugs, rate of postoperative complications, rate of reoperation, postoperative hospital stay, and administration of adjuvant chemotherapy. The data were compared between CC patients with bulky tumors who underwent laparoscopic ($n = 48$) and open ($n = 32$) approaches.

Different clinical pathways were used for laparoscopic and open surgeries. Epidural analgesia and intravenous pain-relieving agents, including pentazocine and non-steroidal anti-inflammatory drugs, were administered as needed for postoperative pain control in both groups. Epidural analgesia was removed on the second postoperative day in the laparoscopic group and on the third day in the open group. Clear liquid was started on the first postoperative day in the laparoscopic group and on the second day in the open group. Oral intake of semisolid food was started on the second postoperative day in the laparoscopic group and on the third day in the open group if the patients had no clinical problems during their postoperative course. With regard to the day of discharge, clinical pathways assumed it to be the seventh postoperative day in both groups.

Statistical analysis was performed using BellCurve for Excel software, version 2.02 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Quantitative data are presented as median values with ranges. Categorical variables

were analyzed using the chi-squared test or Fisher's exact test, as appropriate, and continuous variables were compared using the Mann-Whitney *U* test. Long-term outcomes, including 5-year cancer-specific survival (CSS), relapse-free survival (RFS), and the local recurrence (LR) rate, were analyzed using the Kaplan-Meier method with the log-rank test. All *p* values less than 0.05 were considered significant. LR was defined as recurrence in the original tumor bed, regional lymph nodes, or the anastomotic site.

Results

The study group consisted of 39 (48.8%) men and 41 (51.2%) women; pT3 and T4 were identified in 54 (67.5%) and 26 (32.5%) patients, respectively. We harvested a median of 22.5 (range, 9–58) lymph nodes in the present study. Two patients had < 12 harvested lymph nodes. We harvested nine and 10 lymph nodes from one patient each with recto-sigmoid colon cancer in the open and laparoscopic groups, respectively. In total, 49 (61.3%) patients were diagnosed with pathological stage II, and 31 (38.7%) were diagnosed with pathological stage III.

The clinical characteristics of the patients are summarized in Table 1. The differences between the laparoscopic and open groups in sex distribution, age at operation, BMI, serum CEA, and location of tumor were not significant.

Surgical and pathological outcomes are summarized in Table 2. With respect to the length of the laparotomy incisions, data of 29 (60.4%) patients in the laparoscopic group and 30 (93.8%) patients in the open group were collected. The median length of the laparotomy incision was significantly shorter in patients in the laparoscopic group than in the open group (6.0

vs. 22.0 cm, $p < 0.001$). Operation time was significantly longer in the laparoscopic group than in the open group (213 vs. 148 min, $p < 0.001$). The estimated blood loss and the requirement for blood transfusion were similar between the groups. The number of harvested lymph nodes (23.5 vs. 20) and the number of metastatic lymph nodes were not significantly different. One patient (1.6%), who was 93 years old at surgery and had a history of laparotomy for gastric cancer, was immediately converted to open surgery due to dense adhesions. Tumor size, pathological T status, pathological N status, histological type, and the status of lymphovascular invasion were not significantly different between the groups. The final pathological findings showed that there were no patients with positive resection margins in both groups.

The differences between the groups in postoperative outcomes are summarized in Table 3. Time to first flatus (2 vs. 3 days, $p < 0.001$), time to first stool (3 vs. 4 days, $p < 0.001$), and time to oral intake (2 vs. 5 days, $p < 0.001$) were significantly shorter in the laparoscopic group than in the open group. The number (2 vs. 4, $p = 0.0087$) and period (1 vs. 3 days, $p < 0.001$) of using intravenous pain-relieving drugs were significantly lower in the laparoscopic group than in the open group. There was not significant difference in the rate of postoperative complications (4.2% vs. 6.3%, $p = 0.9999$). None of the patients in either group required re-operation. The postoperative hospital stay was significantly shorter in the laparoscopic group than in the open group (10 vs. 13 days, $p < 0.001$). The rate of adjuvant chemotherapy administration did not differ significantly between the groups.

The 5-year CSS, RFS, and LR rates of all patients in this study were 93.3%, 88.2%, and 0.0%, respectively. The median follow-up of all surviving patients was 5.0 years (range 2.0–10.8 years), and the follow-up period of the laparoscopic and the open group were also calculated separately. The median follow-up period of the laparoscopic group was significantly shorter than that of the open group (4.6 vs. 5.4 years, $p < 0.001$). The survival curves by pathological stage are shown in Figs. 1 and 2. Five-year CSS (92.3% vs. 100%, $p = 0.0699$) and RFS (87.9% vs. 100%, $p = 0.1263$) in patients with stage II tumors were not significantly different between the laparoscopic and open groups (Fig. 1). Five-year CSS (86.3% vs. 92.3%, $p = 0.6987$) and RFS (83.0% vs. 76.9%, $p = 0.6956$) in patients with stage III were also not significantly different between the groups (Fig. 2). The site of recurrence is listed by the surgical approach in Table 4, and patterns of relapse were similar between the groups.

Discussion

The results of the present study found feasible short- and long-term outcomes of LS for patients with bulky (> 8 cm) colon cancer compared with laparotomy. Even though LS for bulky

Table 1 Clinical characteristics

	Laparoscopic (<i>n</i> = 48)	Open (<i>n</i> = 32)	<i>p</i> value
Sex			0.6155
Male	25	14	
Female	23	18	
Age, <i>y</i> (range)	70 (32–93)	71 (35–87)	0.7983
Body mass index (kg/m ²) (range)	21.7 (14.7–31.4)	21.7 (13.0–32.1)	0.6338
Serum level of CEA* ^a (ng/ml)			0.4365
< 5.0	28	15	
≥ 5.0	20	17	
Location of tumor			0.9603
Right-sided colon* ^b	33	23	
Left-sided colon* ^c	15	9	

*^a carcinoembryonic antigen, *^b cecum to splenic flexure, *^c splenic flexure to recto-sigmoid colon

Table 2 Surgical and pathological outcomes

	Laparoscopic (n = 48)	Open (n = 32)	p value
Operative procedure			
Ileocecal resection	7	5	
Right hemicolectomy	22	18	
Transverse colectomy	4	0	
Left hemicolectomy	1	0	
Sigmoidectomy	6	3	
Anterior resection	8	6	
Length of laparotomy incisions (cm) (range)*	6.0 (5.0–10.0)	22.0 (15.7–34.2)	< 0.001
Operation time (min) (range)	212.5 (115–330)	147.5 (60–296)	< 0.001
Blood loss (ml) (range)	20 (0–200)	30 (0–600)	0.1170
Blood transfusion	1	0	0.9999
Number of lymph nodes harvested	23.5 (10–45)	20 (9–58)	0.7307
Number of metastatic lymph nodes	2 (1–6)	2 (1–18)	0.8847
Conversion to open surgery	1	–	–
Tumor size (mm) (range)	85 (80–130)	90 (80–130)	0.4098
Pathological T status			0.1576
T3	29	25	
T4	19	7	
Pathological N status			0.9626
Negative	30	19	
Positive	18	13	
Histological type			0.2110
Adenocarcinoma	46	28	
(Well/moderate/poor)	9/30/7	11/13/4	
Mucinous adenocarcinoma	2	4	
Lymphovascular invasion			0.6788
Absent	3	3	
Present	45	29	
Pathological margin positive	0	0	

*Data were collected in 29 (60.4%) patients in the laparoscopic group and 30 (93.8%) in the open group

tumors is technically demanding, and abundant experience for LS would be absolutely essential, the present study clearly showed that the well-known benefits of LS could be observed in CC patients with bulky tumors.

Laparoscopic colectomy for CC patients has already been accepted worldwide, and the indication for LS has gradually been extended to locally advanced colorectal cancer.^{19–26} However, the feasibility of LS for CC patients with bulky tumors has remained controversial. For highly experienced laparoscopic surgeons, laparoscopic manipulation of bulky tumor without direct compression of the tumor itself should be technically possible by mobilizing consecutive bowel segments with grasping and withdrawing the soft tissues apart from the primary lesion. Moreover, the laparoscopic magnified vision may allow sharp dissection through the specific layer around the tumor under adequate traction. With an increased number of cases of LS for CC, we gradually broadened the indications for LS and realized the usefulness of LS for bulky CCs after sufficient preoperative evaluation

and careful case selection. In this study, short-term outcomes of LS for bulky tumors were better than those of laparotomy and similar to those of previous RCTs.^{1–5}

Previous reports demonstrated that the major reasons for conversion to laparotomy were invasion to adjacent organs, adhesions, and bulky tumor.^{13, 14} Biondi et al. showed that tumor size was an independent predictor for conversion and found that those converted had worse short- and long-term outcomes than patients who completed LS.¹³ In this study, only one case (1.6%) needed to be converted to open surgery due to dense adhesions after open gastrectomy. The conversion rate of the present study was similar to that of our previous report about LS for primary CC, which considered bulky tumor as a contraindication to LS,¹⁸ and lower than that of former RCTs (5.4–24.8%).^{1–5} To safely complete LS for bulky tumor, substantial experience with laparoscopic procedures appears indispensable. However, surgeons should not hesitate to convert to an open procedure if difficulties arise.

Table 3 Postoperative outcomes

	Laparoscopic (n = 48)	Open (n = 32)	p value
Time to first flatus passage (days) (range)	2 (1–4)	3 (1–4)	< 0.001
Time to first stool (days) (range)	3 (0–8)	4 (1–10)	< 0.001
Time to oral intake (days) (range)	2 (1–8)	5 (2–7)	< 0.001
Number of times using pain-relieving drugs (range)	2 (0–7)	4 (0–9)	0.0087
Period of using pain-relieving drugs, days (range)	1 (0–4)	3 (0–6)	< 0.001
Postoperative complications	3 (4.2%)	2 (6.3%)	0.9999
Surgical site infection	3	0	
Bleeding from duodenal ulcer	0	1	
Ascites	0	1	
Re-operation	0	0	
Postoperative hospital stay (days) (range)	10 (7–37)	13 (9–33)	< 0.001
Adjuvant chemotherapy			0.4306
No	26	21	
Yes	22	11	

Some surgeons might worry about the oncological safety of LS for bulky CC and the risk of tumor spread during laparoscopic manipulation. It has been noted that tumor size is related to the depth of tumor invasion,²⁷ and therefore, bulky tumors would penetrate serosa (T4). Previous reports demonstrated the oncological safety and the equivalence of long-term survival of LS for T4 CC compared with open surgery.^{23–26} In this study, all patients underwent R0 resection, all patients were free from LR, and the long-term prognosis of the laparoscopic group was very good, though the target of this study was stage II/III CC patients. Moreover, the long-term survival and patterns of relapse were not different between the groups. The present study showed that the oncological and long-term outcomes of LS for CC patients with bulky tumors were equivalent to those of the open approach.

It is clear that the one advantage of LS is the smaller incision compared with laparotomy. On the other hand, the same or larger size of incision was needed to remove bulky tumors, and a minimally invasive approach for these patients was believed to be meaningless.¹² In fact, some RCTs excluded

patients with bulky tumors from their analyses,^{4, 10, 11} and conversion was defined as the need for an abdominal incision greater than 8 to 10 cm.^{10, 11, 28} However, the merit of LS is not only the smaller skin incision, but also less direct manipulation by the operator’s hands. One of the important effects of LS is less direct manipulation of abdominal organs and reduced adhesions.²⁹ Moreover, the closed abdominal cavity reduces direct exposure of organs to the air, causing them to dry, and foreign substances, such as operator’s gloves and textile materials (swab, gauze, and towel), which may induce adhesion formation.³⁰ In this study, faster recovery of gastrointestinal function in LS was maintained for CC patients with bulky tumors, and the outcomes of bowel recovery were similar to those of previous RCTs.^{1–5} The present report is the first to demonstrate the merit of LS for CC patients with bulky tumors in terms of earlier recovery of bowel function compared with the open approach.

The present study had some limitations. First, it was a retrospective, single-center analysis with a small number of patients. Second, the background characteristics of the patients

Fig. 1 Five-year cancer-specific survival (a) and relapse-free survival (b) of stage II patients who underwent laparoscopic and open surgery for bulky colon cancers

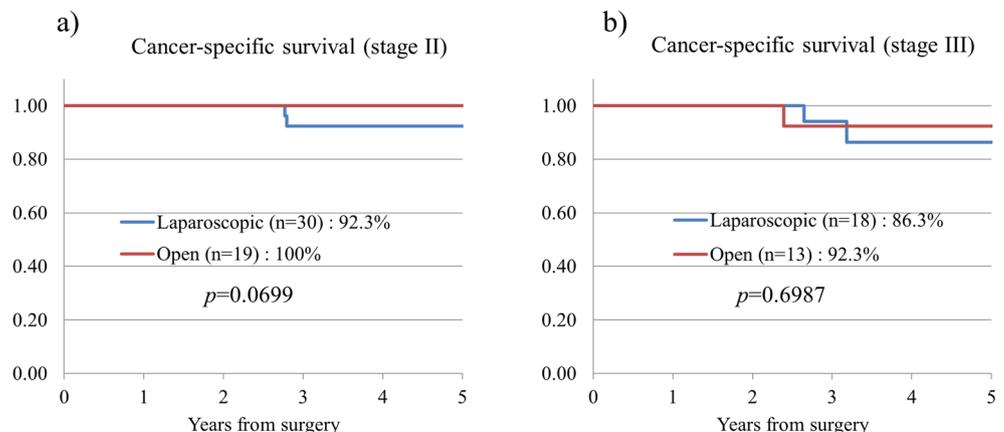
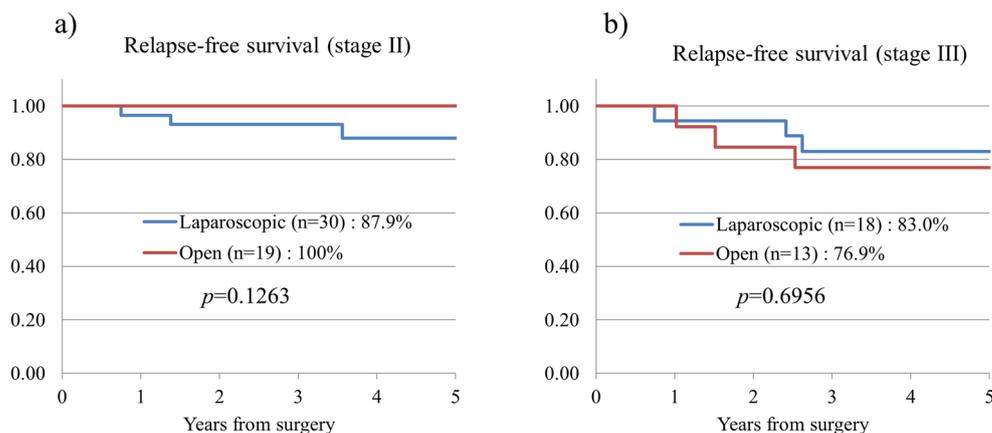


Fig. 2 Five-year cancer-specific survival (a) and relapse-free survival (b) of stage III patients who underwent laparoscopic and open surgery for bulky colon cancers



were potentially different between the laparoscopic and open groups, and the groups were not matched. In this study, 30 (93.8%) patients in the open group were operated in 2004–2010, and 38 (79.2%) patients in the laparoscopic group were operated in 2011–2014. The follow-up periods were different between the two groups, and the historical background characteristics of the two groups may have been different. In this study, the two groups were followed postoperatively by different clinical pathways, and the first day of eating tended to be earlier in the laparoscopic group than in the open group. However, the median time to oral intake of semisolid food was 2 days in the laparoscopic group and 5 days in the open group. Therefore, the differences in time to oral intake between the groups were greater than would be expected based on using different clinical pathways. Third, the differences between the laparoscopic and open groups in the postoperative pain score and degree of inflammatory reaction were not evaluated. Regarding the length of the laparotomy incision, the median wound length in the laparoscopic group was less than 8 cm. These results might be explained by the compliance of the skin and that a vertically long tumor could be extracted from a wound with length less than 8 cm. On the other hand, operation time was significantly longer in the laparoscopic group than in the open group, and prolonged operative time might have contributed to the complications and increased the overall medical costs. However, the present study showed the feasibility of LS for CC patients with bulky tumors, including smaller skin incision, improved pain control, earlier recovery of bowel function, and shorter hospitalization compared with

open surgery. Moreover, oncological safety and the long-term prognosis of LS for CC patients with bulky tumors were very good, equivalent to those of the open approach.

Conclusions

Compared to open surgery, laparoscopic resection of colon cancers greater than 8 cm in diameter is feasible and oncologically safe with better short-term and equivalent long-term outcomes. Therefore, LS could be considered a treatment option for CC patients with bulky tumors if technically possible.

Author Contribution Toshiya Nagasaki mainly designed the study and analyzed the data. All coauthors contributed substantially to the study and fulfilled the requirements for authorship as per the guidelines of the International Committee of Medical Journal Editors. All authors have read and approved the final version of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Table 4 Patterns of relapse by surgical approach

	Laparoscopic (n = 6)	Open (n = 4)	p value
Liver	2	1	0.9999
Lung	1	2	0.5607
Peritoneal dissemination	1	1	0.9999
Para-aortic lymph node	1	0	0.9999
Brain	1	0	0.9999

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