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Oncologic Outcome of Stages II/III Colon Cancer Treated via Minilaparotomy

Hideyuki Ishida, Toru Ishiguro, Tomonori Ohsawa, Norimichi Okada, Kensuke Kumamoto, Keiichiro Ishibashi, Norihiro Haga, Masaru Yokoyama, Hiroshi Nakada, Tsuyoshi Gonda

Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

We analyzed clinicopathologic, surgical, and survival data on consecutive series of patients with stages II/III colon cancer for whom curative resection via minilaparotomy (skin incision, ≤7 cm) was attempted between September 2002 and March 2009 to clarify the oncologic safety of this type of surgery. There were 64 men and 55 women; the median age was 70 years (range, 25–91 years). The median body mass index was 21.7 kg/m^2 (range, 15.1–28.9 kg/m^2). The minilaparotomy approach was successful in 115 cases (96.6%). The cumulative 5-year disease-free and overall survival rates were 89.7% and 82.4%, respectively, in patients with stage II disease (n = 62) and were 68.4% and 82.4%, respectively, in patients with stage III disease (n = 57), all of which were compatible with those of the historical control patients who underwent conventional open surgery. Minilaparotomy approach for stages II/III colon cancer seems to be oncologically equivalent to conventional open surgery.

Key words: Minilaparotomy – Colon cancer – Laparoscopy – Prognosis

Laparoscopic-assisted colectomy usually requires a small incision to retrieve the specimen and perform anastomosis. In addition, keeping the incision small is believed to facilitate early recovery of patients undergoing laparoscopic-assisted colectomy.[1] The report by Fleshman *et al*[1] and the subsequent work by several investigators,[2–4] including ourselves,[5] have demonstrated favorable results when using the minilaparotomy approach without laparoscopic assistance for resection of colon cancer and have suggested that this approach could be a useful alternative to laparoscopic-assisted surgery. On the basis of our favorable results in the initial 54 cases,[5] we continued to employ this approach, adding some modifications, and we have extended the indications for this procedure.[6] Meanwhile,

Reprint requests: Hideyuki Ishida, MD, PhD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama, Japan 350-8550.
Tel: +81 49 228 3619; Fax: +81 49 222 8865; E-mail: 05hishi@saitama-med.ac.jp

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laparoscopic-assisted surgery for colon cancer has continued to predominate during this decade.

Despite the fact that the feasibility, safety, and minimal invasiveness of the minilaparotomy approach for treatment of benign and malignant colorectal diseases have been well described in the literature,[3–12] little is known about the oncologic efficacy of this type of surgery in the treatment of locally advanced colon cancer. Therefore, we conducted this retrospective study to evaluate the oncologic outcome of stages II/III colon cancer treated by using the minilaparotomy approach.

Patients and Methods

Patients

From September 2002 to March 2009, 230 patients with colon cancer underwent attempted curative colectomy via minilaparotomy (skin incision ≤7 cm) approach at our institution. Of these, 119 patients with pathologically confirmed stages II/III colon cancer, classified according to Union for International Cancer Control (UICC)-TNM staging,[13] were included in this study. For comparison of the survival data, we examined a control group comprising 119 patients matched for age (±10 years), body mass index (BMI; ±2.0 kg/m^2), maximal tumor diameter (±25 mm) and pathologic stage (stage II or stage III) who underwent elective conventional open surgery for colon cancer between January 1997 and August 2002.

Patient selection

Excluded from the study were patients who did not consent to the procedure, those with a tumor located within 10 cm proximal or distal to the splenic flexure, those with a tumor diameter larger than 7 cm as estimated by barium enema study or abdominal computed tomography (CT), those with a tumor infiltrating the adjacent organs (T4b)[13] as detected by abdominal CT, those suspected of severe adhesions after previous major abdominal surgery on the basis of the CT findings, those who had intestinal obstruction, those with synchronous cancers, and those who had metastases to the liver, para-aortic lymph nodes, or distant organs. In principle, patients with a BMI greater than 25.0 kg/m^2 were also excluded. However, patients whose tumors were located in the midtransverse or sigmoid colon were selectively indicated for the procedure even if their BMI was greater than 25.0 kg/m^2 (<30.0 kg/m^2) from September 2005.

Surgical procedure

The surgical procedure was described in detail elsewhere.[5,6] In brief, the patient was placed in a supine position. All the steps of minilaparotomy procedure were performed by using conventional instruments via a small skin incision (≤7 cm). The site of minilaparotomy incision was determined in a manner intended to facilitate the most straightforward resection. A wound retractor (Alexis, medium size, Applied Medical, California) was applied to the edge of the wound. If necessary, 1 to 4 gauze swabs were placed intraperitoneally to retract the small bowel and omentum away from the operative field. The small bowel was kept *in situ* during the entire surgical procedure. This technique was useful not only to perform colectomy and lymph node dissection more easily but also to keep the bowel warm and moist. The wound was slid cephalad, caudally or laterally, by using the North-bridge retractor system (Takasago, Tokyo, Japan) or conventional retractors. Lymph node dissection was performed according to the therapeutic guidelines for colorectal carcinoma in Japan.[14] Specifically, for T3 and T4 (T4a) tumors, lymph node dissection, including the epicolic, paracolic, intermediate, and main lymph nodes (*i.e.*, D3-level lymph node dissection), was routinely performed. For T1 and T2 tumors, limited lymph node dissection, including the epicolic, paracolic and intermediate lymph nodes (*i.e.*, D2-level), was performed, although standard lymph node dissection (*i.e.*, D3-level) was also performed in selected cases with T2 tumors. The bowel resection was extended at least 10 cm proximally and 10 cm distally from T2/T3/T4a cancer and at least 5 cm proximally and 5 cm distally from T1 cancer. The depth of invasion (*i.e.*, T category)[13] was evaluated comprehensively on the basis of findings of the barium enema, abdominal CT, and colonoscopy. In principle, the median approach was adopted to dissect lymph nodes and to mobilize the bowel. All anastomoses were stapled extracorporeally.

Postoperative care

Oral intake was resumed after operation as soon as the bowel function returned clinically. Analgesia (pentazocine, 15 mg/body, intramuscular injection) was administered as required. The patients were discharged from the hospital when they became fully ambulatory. In principle, 5-fluorouracil–based adjuvant chemotherapy was started within 4 weeks of the surgery and was administered for 6 months in

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patients age 75 years or younger who had stage III disease and in those with stage II disease whose tumor was histopathogically confirmed to penetrate the serosa.

Short-term outcomes

Information on the incidences/types of postoperative complications and the postoperative length of hospital stay was collected from the medical charts.

Histologic examination

Information on the histologic findings of the removed specimen, such as the extent of the primary tumor, regional lymph node metastasis, and the pathologic stage according to the UICC-TNM classification,[13] was also collected from medical charts.

Follow-up

Postoperative evaluation for tumor recurrence was performed every 3 to 6 months during the first 2 years and every 6 months thereafter. The evaluation routinely included general physical check-up, measurement of serum carcinoembryonic antigen, chest X-ray or chest CT, and abdominal CT. Information on the site and date of detection of recurrence, occurrence of death, and the cause of death was collected from medical charts.

Statistical analysis

A statistical software package (Statview, version 5.0, SAS Institute, Cary, North Carolina) running on a Windows personal computer was used to conduct the analysis. Continuous data were expressed as median and range and were analyzed by the Mann-Whitney *U* test. Categoric data were analyzed by the χ^2 test or Fisher's exact probability test. Survival rates were calculated by the Kaplan-Meier method, and the differences between the survival curves were tested by the log-rank test. Patients lost to follow-up were censored at the date last known to be alive and recurrence free for calculating the overall and disease-free survival rates, respectively. Patients without evidence of recurrence at death were also censored at the date of death for calculating the disease-free survival rate.

All the tests were two tailed and $P < 0.05$ was considered to denote significance. Because this study was performed on an intention-to-treat basis, even patients with failed minilaparotomy were included in this study.

Table 1 Patient characteristics

Age, years, median (range)	70 (25–91)
Male:female	64:55
Body mass index, kg/m^2, median (range)	21.7 (15.1–28.9)
Site of tumor	
Cecum	13
Ascending colon	34
Transverse colon	12
Descending colon	4
Sigmoid colon	56
ASA classification	
I:I:III	50:59:10
Prior abdominal surgery, No. (%)	33 (27.7)

ASA, American Society of Anesthesiology.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. The median age was 70 years (range, 25–91 years), and the male:female ratio was 64:55. The median BMI was 21.7 kg/m^2 (range, 15.1–28.9 kg/m^2). Of the patients enrolled, 33 patients (27.7%) had undergone prior abdominal surgery on one or two occasions. In accordance with the American Society of Anesthesiology classification, there were 50 patients in class I, 59 in class II, and 10 in class III. Overall, 13 tumors were located in the cecum, 34 were in the ascending colon, 12 were in the transverse colon, 4 were in the descending colon, and 56 were in the sigmoid colon.

Operative results

The operative results are shown in Table 2. The minilaparotomy approach was successful in 115 (96.6%) of the 119 cases. Four patients required extension of the minilaparotomy wound to as long as 11 to 20 cm. The reasons for unsuccessful minilaparotomy were intra-abdominal adhesions after appendectomy in 2 patients and suspected tumorous invasion to the retroperitoneum in 2 patients. The types of operation performed were ileocecal resection in 3 patients, right (hemi) colectomy in 48 patients, transverse colectomy in 8 patients, left hemicolectomy in 4 patients, sigmoidectomy in 54 patients, and other segmental resection in 2 patients. The level of lymph node dissection was D2 in 16 patients, and it was D3 in 103 patients. The median duration of operation was 125 minutes (range, 72–255 minutes). The median estimated blood loss was 80 mL (range, 5–700 mL). There were no intraoperative complications.

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Table 2 Operative results

Successful cases of minilaparotomy, No. (%)	115 (96.6)
Type of operation	
Ileocecal resection	3
Right (hemi) colectomy	48
Transverse colectomy	8
Left hemicolectomy	4
Sigmoidectomy	54
Other segmental colectomy	2
Level of lymph node dissection[a]	
D2	16
D3	103
Operation time, min, median (range)	125 (72–255)
Blood loss, mL, median (range)	80 (5–700)

[a]According to the therapeutic guidelines for colorectal carcinoma in Japan.[14]

Postoperative complications and postoperative length of hospital stay

A total of 15 patients (12.6%) developed postoperative complications, which included intestinal obstruction (n = 7), enteritis (n = 2), wound infection (n = 2), atelectasis (n = 2), intra-abdominal abscess (n = 1), anastomotic bleeding (n = 1), and bleeding gastric ulcer (n = 1). Of these, 2 patients (1.7%) required reoperation because of intra-abdominal abscess (n = 1) and anastomotic bleeding (n = 1). The median postoperative length of hospital stay was 11 days (range, 7–159 days; Table 3).

Histopathologic examination

The median maximal diameter of the tumor was 39.5 mm (range, 8–110 mm). Overall, 55 patients had well-differentiated adenocarcinoma, 60 patients had moderately differentiated adenocarcinoma, and 4 patients had poorly differentiated adenocarcinoma. Ten patients had T1 tumors, 6 patients had T2 tumors, 74 patients had T3 tumors, and 29 patients had T4 (T4a) tumors. The median number of harvested lymph nodes was 15 (range, 4–51). Thus, 48 patients were classified as stage IIA; 14, as stage IIB; 10, as stage IIIA; 30, as stage IIIB; and 17, as stage IIIC (Table 4).

Table 3 Postoperative complications

Intestinal obstruction	7 (5.9%)
Enteritis	2 (1.7%)
Wound infection	2 (1.7%)
Atelectasis	2 (1.7%)
Intra-abdominal abscess	1 (0.8%)
Anastomotic bleeding	1 (0.8%)
Bleeding gastric ulcer	1 (0.8%)

Table 4 Histologic examinations

Maximal tumor diameter, mm, median (range)	39.5 (8–110)
Histologic differentiation	
Well differentiated	55
Moderately differentiated	60
Poorly differentiated	4
Depth of invasion	
pT1	10
pT2	6
pT3	74
pT4	29
Pathologic stage	
IIA	48
IIB	14
IIIA	10
IIIB	30
IIIC	17

Adjuvant chemotherapy

Eighteen patients (29.0%) with stage II disease and 48 patients (84.2%) with stage III disease received adjuvant chemotherapy. Two patients (1.7%) were lost to follow-up. As of August 2010, the median follow-up period for all the patients was 39 months (range, 2–96 months). The initial sites of recurrence are summarized in Table 5. Nineteen of the 115 patients in whom the minilaparotomy approach was successful and 1 of the 4 patients who required extension of the minilaparotomy wound developed recurrence (7 with stage II disease, and 13 with stage III disease). The most frequent site of recurrence was liver, followed by lung. There was no case of recurrence in the minilaparotomy wound. Of the patients who developed recurrence, peritoneal, pulmonary, and hepatic metastatectomy were performed in 1, 2, and 3 patients, respectively. Eight patients (2 with stage II disease, and 6 with stage III disease) died as a result of colon cancer, 2 with stage III disease died as a result of malignant disease other than colorectal cancer, and 9 (7 stage II disease, and

Table 5 Initial sites of recurrence

Site of recurrence	Stage II (n = 62)	Stage III (n = 57)
Liver	2	3
Lung	4	2
Liver + lung		2
Liver + lymph node		1
Liver + peritoneum		1
Lymph node		2
Peritoneum	1	1
Ovary		1
Total	7	13

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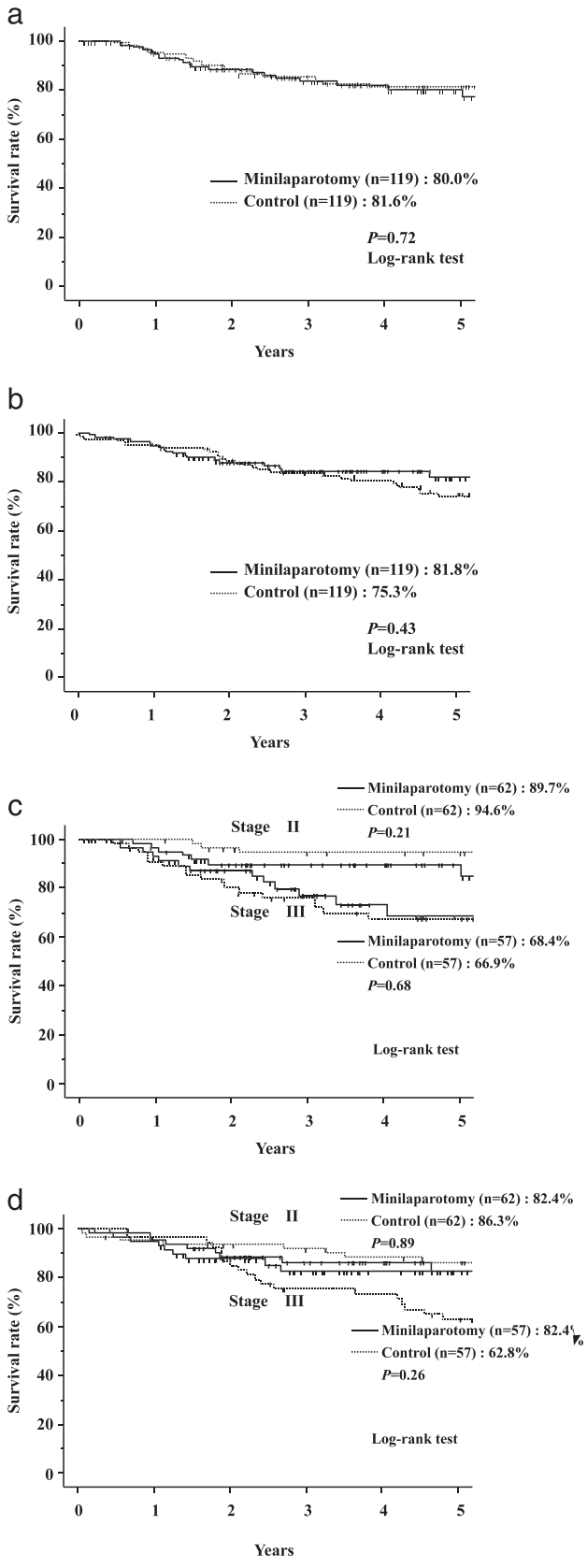

2 stage III disease) died as a result of benign diseases during the follow-up period. The cumulative 5-year disease-free survival rate was 80.0% in the minilaparotomy group, and it was 81.6% in the historical control group (Fig. 1a). The disease-free survival period did not significantly differ between the 2 groups ($P = 0.72$). The cumulative 5-year overall survival rate was 81.8% in the minilaparotomy group, and it was 75.3% in the control group (Fig. 1b). The overall survival period also did not differ significantly between the groups ($P = 0.43$). When the results of the analysis were stratified by stage, the cumulative 5-year disease-free and overall survival rates of the minilaparotomy group were 89.7% and 82.4%, respectively, in patients with stage II disease (n = 62) and were 68.4% and 82.4%, respectively, in patients with stage III disease (n = 57), all of which were compatible with those of the historical control patients (Fig. 1c and 1d). The rate of introducing postoperative 5-fluorouracil–based chemotherapy for the historical control group (39.9% for stage II disease, and 82.5% for stage III disease) was identical to that of the patients in the minilaparotomy group.

Discussion

The feasibility, safety, and minimal invasiveness of the minilaparotomy approach have been well documented in the surgical treatment of benign and malignant colorectal diseases. However, to the best of our knowledge, there are no data on the oncologic outcome of patients undergoing curative colectomy via minilaparotomy, except for the report by Nakagoe *et al*.[3] They reported recurrence in 6 (8%) of their 72 patients (32 patients with stage I disease, 24 with stage II disease, and 16 with stage III disease) within a median follow-up period of 24.8 months. This is the first report, to our

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Fig. 1 (a) Disease-free survival curves in patients undergoing minilaparotomy and matched control patients undergoing conventional open surgery. (b) Overall survival curves in patients undergoing minilaparatomy and historical control patients undergoing conventional open surgery. (c) Disease-free survival curves in patients undergoing minilaparatomy and historical control patients undergoing conventional open surgery according to stage. (d) Overall survival curves in patients undergoing minilaparotomy and historical control patients undergoing conventional open surgery according to stage.

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knowledge, to closely describe the pattern of recurrence and survival after resection of locally advanced (stages II/III) colon cancer via minilaparotomy approach. In this study, we found acceptable results in terms of operating time, blood loss, and occurrence of postoperative complications in curative resection of stages II/III colon cancer via minilaparotomy. However, there may be objections from some surgeons that local recurrence and lymph node metastasis would increase owing to limited operative field in minilaparotomy. From our investigations, we found that the most common form of metastasis was hematogenous; therefore, such concepts appear unnecessary. Furthermore, there was not even a single case of wound recurrence, which was the focus of much attention during the early days of laparoscopic-assisted surgery. It is well known that the number of such case reports has diminished as laparoscopic technique has advanced. In addition, the minilaparotomy appears to be identical to conventional open surgery in terms of both disease-free and overall survivals, although the length of follow-up is not sufficiently long to provide an accurate prediction of the 5-year survival. Our results suggest that it is safe to perform minilaparotomy in patients with stages II/III colon cancer. However, we must continue to observe our patients closely to evaluate the long-term oncologic outcome in order to confirm the validity of this procedure.

The definition of minilaparotomy is a matter of personal opinion. Some authors,[3,4] including ourselves,[5,6] considered 7 cm to be the maximal incision length, whereas Fleshman *et al*[1] reported a median incision length of 12 cm (range, 7–18 cm), and Fürstenberg *et al*[2] reported a maximal incision length of 10 cm. In practice, 6 to 7 cm is the shortest length of incision that would allow the surgeon to insert his or her hand into the operative field, not only for palpation of the intra-abdominal organs but also for prompt control of any unexpected bleeding. Importantly, we should note that a curative colectomy can be safely performed through an incision smaller than is generally believed.

The main purpose of this study was to evaluate the oncologic outcomes of minilaparotomy; therefore, we did not compare the results in terms of postoperative pain and hospital stay. The length of our minilaparotomy incision (<7cm) is considered to be no longer than the incision used for standard laparoscopic-assisted colectomy, when multiple incisions made for inserting trocars are added to the main incision length. Therefore, postoperative pain after the minilaparotomy approach may be expected to be comparable to that after a laparoscopic-assisted approach. Such comparisons were not performed in our series and deserve further investigation. The degree of invasiveness of minilaparotomy has been reported to be identical to that of the laparoscopic approach.[7] In addition, compared with conventional open surgery, minilaparotomy approach has been shown to be less invasive in terms of postoperative recovery and various laboratory parameters.[8,9] Provided that minilaparotomy is recognized as minimally invasive surgery, one of its benefits of the minilaparotomy is a shorter postoperative hospital stay than for conventional open surgery. Japanese patients usually demand longer hospital stays than recommended by their surgeons, which consequently results in longer hospitalizations than required for recovery to their preoperative status. Moreover, patients' family members tend to strongly support a longer stay. These factors resulted in a relatively long postoperative hospital stay (median, 11 days) in this series.

In terms of indications for our minilaparotomy approach, there are several factors to consider. Because minilaparotomy approach is most suitable for straightfoward resection, patients with tumors located within 10 cm proximal or distal to the splenic flexure were excluded. This is because of the long distance between the skin incision and the tumor and because of the requirement of lymph node dissections at the roots of inferior mesenteric artery and left branch of middle colic artery. During the study period, we have come across 4 such cases and actually performed the curative surgeries under laparoscopic assistance. Recently, laparoscopic-assisted colectomy for transverse colon cancer has been reported to be feasible and safe from institutions quite adept in laparoscopic skills. However, from 4 randomized controlled trials comparing laparoscopy to conventional open surgery, transverse colon cancer was considered to be a contraindication for laparoscopic-assisted colectomy. Owing to the difficulty in performing lymph node dissection around the root of middle colic vessels, it is believed that laparoscopic-assisted colectomy of transverse colon cancer jeopardizes the safety of the patient to an extent that is generally considered unacceptable. Although we had not specifically considered this factor, performing colectomy by minilaparotomy approach on transverse colon cancer did not pose any technical difficulties compared with that for tumors at other locations.[15] Many reports[16–18] described that the conversion rate was reported to be relatively high in laparoscopic-

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assisted colectomy because of high BMI, although several researchers[19,20] claimed that obesity did not have an adverse impact on the technical difficulties in laparoscopic techniques. Except for the tumors of midsigmoid and midtranverse colon, we have also limited the selection of patients to nonoverweight persons (BMI < 25.0 kg/m^2). It is still unknown whether minilaparotomy could be performed safely in more obese patients, which calls for further investigation in the future. Nakagoe *et al*[21] investigated 141 cases of colorectal cancer via minilaparotomy and reported that being a man, having a BMI of >25.5 kg/m^2, and tumor site (splenic flexure and rectum) were significant independent factors for failure of minilaparotomy. Because the incidence of overweight status (BMI > 25.0 kg/m^2) or morbidly obese patients (BMI > 30.0 kg/m^2) in East Asian countries, including Japan, is considered to be lower than that in Western countries,[22] minilaparotomy approach may be suitable for the majority of patients with colon cancer in East Asian countries.

The publication of well-designed prospective randomized trials[23–26] and a meta-analysis[27] of these trials paved the way for widespread acknowledgement that laparoscopic-assisted resection of colon cancer is oncologically safe, because a 5-year survival equivalence was demonstrated between the laparoscopic and open approaches, even in patients with locally advanced disease (stages II and III disease). The short-term benefits and the absence of oncologic risk appear to counterbalance the longer operative time and higher cost of laparoscopic-assisted colectomy. Our results do not suggest the need for any restrictions against laparoscopic-assisted colectomy. However, unlike the laparoscopic-assisted approach, the minilaparotomy approach does not require extraordinary surgical skills, have a steep learning curve, or generate high costs. In addition, our results suggest that the oncologic risk of the minilaparotomy approach seems to be equivalent to that of conventional open surgery. Although the oncologic merit of minilaparotomy approach needs to be addressed in comparison to that of laparoscopic-assisted approach, we believe that the minilaparotomy approach should continue to be used in selected patients as a useful alternative to the laparoscopic approach for curative colectomy.

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