

療成績は良好であった。深達度とリンパ節転移に関する術前正診率は約90%であるが、拡大内視鏡やMDCTなどの新しいmodalityを用いて深達度診断とリンパ節診断能の向上に現在努めている。

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G. 知的財産権の出願・登録状況

1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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IV. 研究成果の刊行物・別刷

Review Article

Is laparoscopic surgery acceptable for advanced colon cancer?

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Laparoscopic surgery is widespread in the treatment of colorectal cancer. In Japan, a nationwide survey has shown that the rate of advanced colorectal cancer has increased gradually to 65% of total laparoscopic surgeries in 2007. Many randomized controlled trials have demonstrated that in the short term, laparoscopic surgery is feasible, safe, and has many benefits, including reduction of perioperative mortality. In terms of long-term outcomes, four randomized controlled trials suggest that there are no differences in laparoscopic and open surgery for colon cancer. However, important issues, including long-term oncological outcome, cost effectiveness, and the impact on the quality of life of patients, should be addressed in well-designed large-scale trials. In Japan, a retrospective multicenter study has demonstrated that the short-term outcomes of laparoscopic surgery are beneficial, and the long-term outcomes are the same as for open surgery. In 2004, a prospective large-scale randomized controlled trial (JCOG0404) to compare laparoscopic surgery with open surgery was started to evaluate oncological outcomes for advanced colon cancer. This trial is supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour, and Welfare. In the present study, laparoscopic surgery is found to be acceptable for stage I disease of colon cancer, whereas it is controversial for stage II/III disease because of inadequate clinical evidence. Whether laparoscopic surgery is acceptable for advanced colon cancer or not should be confirmed by the Japanese large-scale prospective randomized controlled trial (JCOG0404) in the near future. (*Cancer Sci* 2009; 100: 567–571)

Colorectal cancer is a major health problem in Western countries.⁽¹⁾ Recently in Japan, colorectal cancer has become the leading cause of death from all malignancies. Surgery is the mainstay of treatment, with or without chemotherapy and radiotherapy. Approximately 90–92% of patients with colon cancer and 84% of patients with cancer of the rectum are treated surgically.^(2,3) Conventional open surgery is associated with significant morbidity and long convalescence.

Laparoscopic surgery is the 'golden standard' in the treatment of benign gall bladder disease and has been widely used to treat diverse benign diseases.^(4,5) Jacobs *et al.* first reported the technical feasibility of laparoscopic colectomy in 1991.⁽⁶⁾ Since then, laparoscopic surgery has been used widely for various benign colorectal conditions such as polyps,⁽⁷⁾ diverticular disease,⁽⁸⁾ inflammatory bowel disease,⁽⁹⁾ rectal prolapse,⁽⁵⁾ and now increasingly for colorectal cancer.

The benefits of laparoscopic surgery in comparison to open surgery have been suggested with respect to decreased morbidity, decreased pain, faster recovery, shorter hospital stay, and possibly reduced immunosuppression.^(10–12) Laparoscopic colorectal surgery is technically complex as it involves laparoscopic mobilization of the colon over a wide area, intracorporeal division of major vessels, extraction of a specimen, and a bowel anastomosis (Fig. 1). There is a steep learning curve to achieve advanced

laparoscopic skills and specialized equipment is required.⁽¹³⁾ There are concerns with oncological outcomes and the safety of the laparoscopic procedure in colorectal cancer. There are also controversies with potential port site recurrence^(14–16) after curative resection of tumors, hospital costs,⁽¹⁷⁾ and the lack of data on long-term oncological outcome.

To address these concerns, several prospective randomized clinical trials have been undertaken with longer follow-up times and larger sample sizes.^(18–22) These provide a better quality of evidence regarding the efficacy and safety of the new procedure. In Japan, we designed a retrospective study to analyze the clinical outcomes in 12 surgical units from 2001 to 2003,⁽²³⁾ and a prospective randomized controlled trial (Japan Clinical Oncology Study Group 0404) in 27 institutes from 2004,⁽²⁴⁾ supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour, and Welfare.

In the present article, we have reviewed the clinical outcomes of laparoscopic colonic resection (LCR) versus open resection (OCR) for colon cancer based on multicenter studies in Japan and Western countries. We have addressed the important problem of whether laparoscopic surgery is acceptable for patients with advanced colon cancer.

Nationwide survey of laparoscopic surgery for colorectal cancer in Japan

In Japan, laparoscopic surgery for colorectal cancer was introduced in 1992. To date, individual institutions have reported decreased invasiveness, improved quality of life for patients, and satisfactory short-term oncological results.^(25–30) The education committee of the Japan Society of Endoscopic Surgery conducts a nationwide survey every 2 years. To the end of 2007, over 43 000 patients had undergone laparoscopic colorectal surgery, and for the year 2007, approximately 9000 operations were carried out in Japan.⁽³¹⁾ The rates of advanced colorectal cancer have increased gradually in Japan. In particular, in 2007 65% of the total number of colorectal cancer cases were advanced cancer. (Fig. 2).

Clinical outcomes of a retrospective multicenter study in Japan

We conducted a retrospective, multicenter study of a large series of patients in Japan to evaluate preliminary long-term results of laparoscopic surgery for colorectal cancer.⁽²³⁾ The study group included only expert surgeons who undertook laparoscopic resection for colorectal cancer in the 12 participating centers during the period April 1993 to August 2001. All participating surgeons were personally responsible for obtaining the written,

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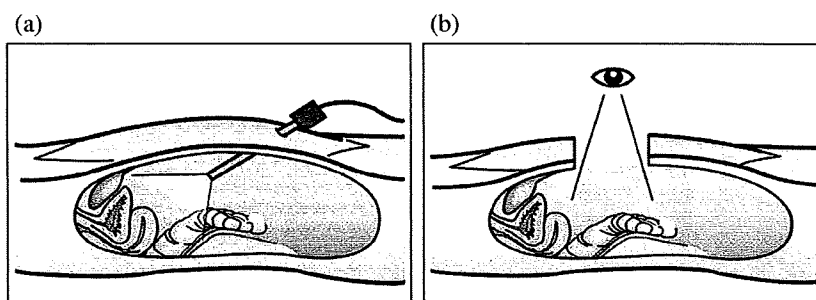


Fig. 1. (a) Laparoscopic and (b) open surgery for colon cancer. In laparoscopic surgery, surgical procedures are carried out through visualization of the laparoscope under CO₂ pneumoperitoneum.

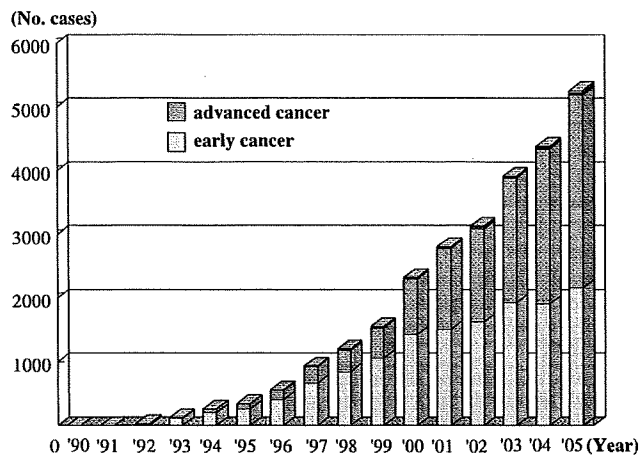


Fig. 2. Current status of laparoscopic colonic resection for colorectal cancer in Japan. A nationwide survey of 1373 Japanese institutes was conducted by the Japan Society of Endoscopic Surgery.

informed consent of their patients. Clinical data, including patient age, sex, surgical procedures, body mass index, conversion to open surgery, previous laparotomy, postoperative complications, postoperative oncological outcome, and histopathological data (including histological type, depth of tumor invasion, lymph node metastasis, and TNM stage (UICC)) were obtained for each patient. Two thousand and thirty-six patients (1145 men, 891 women) underwent laparoscopic colorectal resection during the study period, 1495 with colon cancer and 541 with rectal cancer. Sigmoid colectomy was the most common laparoscopic procedure among colon cancer patients and anterior resection was the most common among rectal cancer patients. The rate of conversion to open surgery was 4.8% of patients with colon cancer and 4.4% of patients with rectal cancer. Of the 1495 patients with colon cancer, 188 (12.6%) had postoperative complications. Complications occurred more frequently after transverse colectomy than after other surgical procedures ($P < 0.05$). The presence of complications was associated with body mass index, operative procedure, and previous laparotomy. Curative surgery was carried out in 1411 patients (94.4%) and was not carried out in 84 patients (5.6%) because of liver metastasis ($n = 46$), lung metastasis ($n = 13$), peritoneal dissemination ($n = 20$), and other metastases ($n = 5$). Cancer recurred in 61 (4.3%) of the 1411 curatively treated patients during a median follow-up period of 32 months (range 6–125 months). Recurrence was not associated with any surgical procedure or conversion to open colectomy. The 5-year survival rate was 96.6% in patients with stage I, 94.8% in those with stage II, and 79.6% in those with stage III disease (Fig. 3). The 5-year survival rates were not associated with any surgical procedure, presence of complications, or conversion to open colectomy. No port-site or abdominal wall

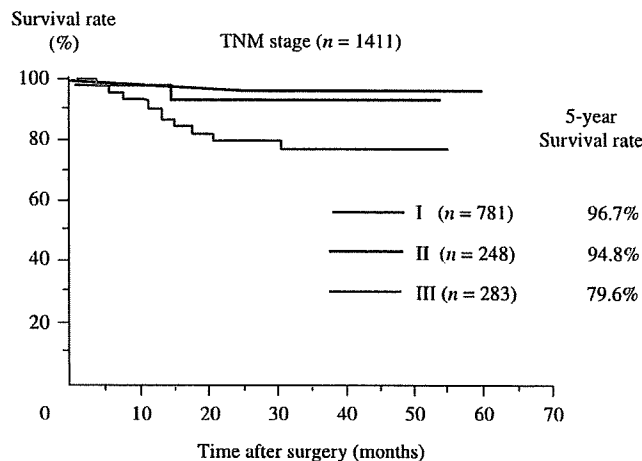


Fig. 3. Long-term outcomes of laparoscopic colonic resection for colon cancer in a Japanese retrospective multicenter study.⁽²³⁾ The 5-year survival rate in 1411 curatively treated patients was 96.7% for stage I, 94.8% for stage II, and 79.6% for stage III disease. The tumor staging system used was TNM stage (UICC).

recurrences were found in any of the 2036 patients. The Japanese retrospective multicenter study indicates that LCR for colon cancer yields an oncological outcome as good as that of conventional OCR in the Japanese Registry⁽³²⁾ for all disease stages.

Short-term outcomes in prospective randomized controlled trials

A literature search of all published randomized controlled trials in English from 1991 to 2007 gave 12 studies that compare LCR with OCR for colon and rectosigmoid cancer (Table 1).^(18,19,21,22,28,33-39) The rate of conversion to open surgery varied widely (0–46.4%) between studies. There were no significant differences in overall and surgical complication rates, anastomotic leakage rate, reoperation rate, or oncological clearance. However, LCR had a significantly lower preoperative mortality, lower wound complications, less blood loss, reduced postoperative pain scores, and reduced requirements for narcotic analgesia. After LCR, patients passed flatus earlier, had bowel movement earlier, and resumed oral diet sooner than patients after OCR. Prospective randomized controlled trials suggest that LCR for colon cancer is feasible, safe, and has many short-term benefits.

Long-term outcomes in prospective randomized controlled trials

Four randomized controlled trials have been reported to clarify the long-term outcomes of LCR for colon cancer (Table 2).⁽¹⁸⁻²²⁾ These trials evaluated the survival, mortality, and recurrence of

Table 1. Randomized clinical trials comparing laparoscopic colonic resection (LCR) with open colonic resection (OCR) for colon and rectosigmoid cancer in terms of short-term outcome

Author or trial name	Reference no.	Number of patients with cancer			Mortality rate		Morbidity rate	
		Total	LCR	OCR	LCR (%)	OCR (%)	LCR (%)	OCR (%)
Hewitt <i>et al.</i> 1998	33	16	8	8	0	0	0	0
Milsom <i>et al.</i> 1998	34	80	42	38	1.8	1.9	15	15
Schwenk <i>et al.</i> 2000	35	60	30	30	0	0	7	27
Curet <i>et al.</i> 2000	36	43	25	18	0	0	4	17
Braga <i>et al.</i> 2002	37	183	90	93	0	0	21	38
Lacy <i>et al.</i> 2002	18	219	111	108	0.9	2.8	11	29
Hasegawa <i>et al.</i> 2003	28	50	24	26	0	0	4	19
COST 2004	19	810	415	395	0.5	0.9	21	20
Kaiser <i>et al.</i> 2004	38	48	28	20	0	0	18	20
Leung <i>et al.</i> 2004	21	403	203	200	0.5	2.4	20	23
CLASICC UK 2005	22	413	273	140	0.4	4.9	33	35
COLOR 2005	39	1082	536	546	1.1	1.8	21	20

Table 2. Randomized controlled trials comparing laparoscopic colonic resection (LCR) with open colonic resection (OCR) in terms of long-term outcome

Author or trial name	Reference no.	Conversion rate (%)	Perioperative		Overall survival	Disease-free survival
			Morbidity (LCR vs OCR)	Mortality (LCR vs OCR)		
Lacy <i>et al.</i> (Spain)	18	11	$P = 0.001$ (11 vs 29%)	$P = 0.19$ (0.9 vs 2.8%)	NS	$P = 0.006$ (Stage III subgroup)
Leung <i>et al.</i> (Hong Kong)	21	23	NS (23 vs 20%)	$P = 0.97$ (2.4 vs 0.6%)	$P = 0.61$ (76 vs 73%)	$P = 0.45$ (75 vs 78%)
COST (USA)	20	21	$P = 0.64$ (21 vs 20%)	$P = 0.40$ (0.5 vs 0.9%)	$P = 0.51$ (86 vs 85%)	NS
CLASICC (UK)	22	16	NS (35 vs 33%)	$P = 0.65$ (0.4 vs 4.9%)	$P = 0.35$ (67 vs 68%)	$P = 0.70$ (66 vs 68%)

NS, no significant differences.

disease associated with the two types of surgical procedure, with follow-up periods of 3.6–5 years. These trials reported overall mortality rates of 17.9–32.0% for LCR and 22.2–61.0% for OCR. The Clinical Outcomes of Surgical Therapy group in the USA,^(19,20) Leung *et al.*,⁽²¹⁾ and MRC CLASSICC⁽²²⁾ demonstrated that overall survival and the rates of recurrent cancer were similar after LCR and OCR. Only Lacy *et al.* described significant differences between the two surgical methods.⁽¹⁸⁾ In this trial, cancer-related mortality was better in patients with stage III disease who underwent LCR, and no significant differences were found with respect to patients with stage I and II disease. Reza *et al.* reported that meta-analysis of four randomized controlled trials did not reveal any significant differences in terms of cancer-related mortality and recurrence rates between LCR and OCR.⁽⁴⁰⁾ Prospective randomized controlled trials and meta-analysis in terms of long-term outcomes suggest that there are no differences between the two surgical procedures. However, these randomized controlled trials in Western countries also have several problems, such as the criteria (including early-stage cancer and benign disease), undetermined levels of lymph node dissection, unclear indications for adjuvant chemoradiotherapy, and no description of quality control for the two surgical procedures.

Prospective randomized controlled trials in terms of long-term outcome in Japan

In Japan, we have conducted a randomized controlled trial to compare LCR with OCR to evaluate oncological outcomes for advanced colon and rectosigmoid cancer.⁽²⁴⁾ This study is supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour, and Welfare. The Clinical Trial Review

Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in September 2004, and the study (JCOG0404) was started in November 2004 to elucidate the optimal treatment for T3 or deeper colorectal cancer. Surgeons in 27 specialized institutions will recruit 1050 patients. The primary endpoint is overall survival. Secondary endpoints are relapse-free survival, short-term clinical outcomes, adverse events, and the rate of conversion from LCR to OCR. The short-term clinical outcomes are proportion of use of analgesics, duration from operation to flatus, highest body temperature during hospitalization, and highest body temperature during the 3 days after operation. In both arms, resection of the colon or rectum with D3 lymphadenectomy is carried out according to the Japanese Classification of Colorectal Carcinoma.⁽⁴¹⁾ In the LCR arm, pneumoperitoneal and intracorporeal approaches are used to explore the abdomen, mobilize the colon, identify critical structures, and ligate the vascular pedicle. Mobilization of the colon and identification of critical structures are carried out by laparoscopy only. Resection of the colon, ligation of the vascular pedicle, and reconstruction are carried out by laparoscopy or small (≤ 8 cm) incision. The patients are randomized by the minimization method for balancing the groups according to the location of the tumor and the institution (Fig. 4). This Japanese randomized controlled trial has a characteristic design comparable with other Western trials, such as inclusion criteria of only advanced cancer (T3, T4), lymph node dissection, adjuvant chemotherapy, and quality control. In cases of pathological stage III colorectal carcinoma, three cycles of adjuvant chemotherapy with fluorouracil and L-leucovorin are administered. To control the quality of operation, central review of the surgical procedure is carried out by photography in all patients. Registration of the patients in this trial will be accomplished in March 2009.

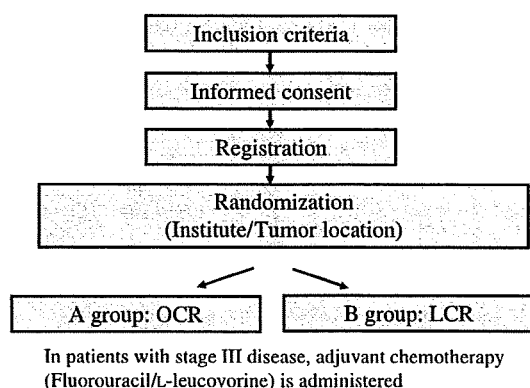


Fig. 4. The design protocol of the Japanese multicenter randomized controlled trial (Japan Clinical Oncology Group 0404) to compare laparoscopic colonic resection (LCR) with open colonic resection (OCR) to evaluate oncological outcomes for advanced colon and rectosigmoid cancer.

Conclusions and perspectives

Laparoscopic colonic resection has been used widely as a curative procedure for colorectal malignancies in Japan and Western

countries. A nationwide survey by the Japan Society of Endoscopic Surgery revealed that the rate of advanced colorectal cancer has increased gradually, reaching two-thirds of total colorectal cancer cases in 2007. Many randomized controlled trials demonstrate that LCR for colon and rectosigmoid cancer is feasible, safe, and has many short-term benefits, including reduction of peri-operative mortality. In addition to the beneficial short-term outcomes, important issues that need to be addressed include long-term oncological outcome, cost effectiveness, and the impact on the quality of life of patients. Although four randomized controlled trials in Western countries suggest that there are no differences in overall survival or rate of recurrence between LCR and OCR, it should be remembered that some large randomized controlled trials, including the Japanese trial, are yet to be completed. At present, LCR is acceptable for stage I disease of colon cancer, and is generally not acceptable for stage II and III disease of colon cancer. However, experienced and trained surgeons may do LCR for stage II/III colon cancer after accepting the informed consent of patients, because the clinical outcomes of laparoscopic surgery are equivalent or superior to open surgery in previous reports of randomized controlled trial reports. Further work is needed to assess the two surgical procedures for stage II/III colon cancer. The ongoing Japanese large-scale randomized controlled trial (JCOG0404) estimating oncological outcome will be beneficial to determine the role of LCR as a standard operation for advanced colon cancer. General surgeons expect the report of the clinical results of the JCOG0404 trial as soon as possible.

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Review Article

Clinical Evidences of Laparoscopic Versus Open Surgery for Colorectal Cancer

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Laparoscopic surgery has widely spread in the treatment of colorectal cancer. In Japan, a nation-wide survey has shown that a rate of advanced colorectal cancer has increased gradually and reached 65% of the total cases for colorectal cancer in 2007. For colon cancer, many randomized controlled trials regarding short-term outcome demonstrate that laparoscopic surgery is feasible, safe and has many benefits including reduction in a peri-operative mortality. In terms of long-term outcome, four randomized controlled trials insist that there are no differences in both laparoscopic and open surgeries. However, there are still more important issues including long-term oncological outcome for advanced colon cancer, cost effectiveness and the impact on quality of life of patients. Meanwhile, for rectal cancer, a controversy persists with regard to the appropriateness of laparoscopic surgery because of concerns over the safety of the procedure and a necessity of lateral lymph node dissection for lower rectal cancer. At present, laparoscopic surgery is acceptable for Stage I colon cancer, whereas there are controversies for Stage II/III colon cancer and each staged rectal cancer because of inadequate clinical evidences. Whether laparoscopic surgery further spreads to be applied for colorectal cancer or not, it would be confirmed by Japanese large-scale phase III trial (JCOG0404) estimating oncological outcome for Stage II/III colon cancer and a Phase II trial estimating the feasibility for Stage 0/I rectal cancer in near future.

Key words: laparoscopic surgery – colorectal cancer – randomized controlled trial – multicenter study

INTRODUCTION

Recently, colorectal cancer has been a significant leading cause of death from malignancies in Japan as one of the western countries. Surgery is the mainstay of the treatment, with or without chemotherapy and/or radiotherapy. About 90–92% and 84% of patients with cancer of colon and rectum, respectively, are treated surgically (1–3). Conventional open surgery is associated with significant morbidity and long convalescence. Laparoscopic surgery has been widely used as a minimally invasive surgery to treat diverse benign diseases such as benign gall bladder disease (4,5). Jacobs et al. (6) first reported the technical feasibility of laparoscopic colectomy in 1991. Since then, laparoscopic

surgery has been widely operated for various benign colorectal conditions such as polyps (7), diverticular disease (8), inflammatory bowel disease (9), rectal prolapse (5) and now colorectal cancer increasingly.

The benefits of laparoscopic surgery in comparison with open surgery have been suggested with respect to decreased morbidity, decreased pain, faster recovery, shorter hospital stay and possibly reduced immunosuppression (10–12). Laparoscopic colorectal surgery is technically complex as it involves laparoscopic mobilization of colon over a wide area, intracorporeal division of major vessels, extraction of specimen and a bowel anastomosis. There is a steep learning curve to achieve advanced laparoscopic skills, and specialized equipment is required (13). There are concerns with oncological outcome and safety of the laparoscopic procedure in colorectal cancer. There are also controversies with potential port site recurrence (14–16) after curative resection

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of tumor, hospital cost (17) and the lack of data on long-term oncological outcome.

To address these concerns, several prospective randomized clinical trials have been undertaken with longer follow-up time and larger sample size (18–22). In Japan, a retrospective multicenter study was performed to analyze the clinical outcomes for patients with colorectal cancer (23), and a prospective randomized controlled trial (Phase III) for advanced colon cancer (24) and a prospective feasible study (Phase II) for rectal cancer (25) have been conducted.

In this article, we have reviewed clinical studies of laparoscopic surgery versus open surgery for colorectal cancer. We have addressed the important problem whether laparoscopic surgery is acceptable or not for patients with colorectal cancer.

NATION-WIDE SURVEY OF LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER IN JAPAN

In Japan, laparoscopic surgery for colorectal cancer was introduced in 1992. The Education Committee of Japan Society of Endoscopic Surgery (JSES) conducts a nationwide survey every 2 years. Until the end of 2007, over 43 000 patients underwent laparoscopic colorectal surgery, and for the year 2007, ~9000 operations were carried out in Japan (26). A rate of advanced colorectal cancer has been increased gradually. Particularly, in 2007, 65% of the total cases were advanced cancer (Figure 1).

RETROSPECTIVE MULTICENTER STUDY OF LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER IN JAPAN

A retrospective multicenter study of a large series of patients has been conducted to evaluate long-term results of

laparoscopic surgery for colorectal cancer in Japan. The study group comprised 2036 patients undergoing laparoscopic colorectal resection during the period of April 1993–August 2002 in 12 participating surgical units (Japanese Laparoscopic Surgery Study Group). Of the 1495 patients with colon cancer, 781 (59%) had UICC Stage I, 248 (19%) had Stage II and 284 (22%) had Stage III disease. Cancer recurred in 61 (4.1%) of the 1367 curatively treated patients (median follow-up, 32 months; range 6–125 months). The 5-year survival rate was 96.7% for Stage I, 94.8% for Stage II and 79.6% for Stage III disease (Figure 2). Of the 541 patients with rectal cancer, 220 (56%) had Stage I, 62 (16%) had Stage II and 108 (28%) had Stage III disease. Cancer recurred in 30 (5.6%) of the 476 curatively treated patients (median follow-up, 25 months; range 6–102 months). The 5-year survival rate was 95.2% for Stage I, 85.2% for Stage II and 80.8% for Stage III disease. The Japanese data indicate that laparoscopic surgery for colorectal cancer yields an oncological outcome as well as that of conventional open surgery in Japanese Registry (27) for all disease stages.

CLINICAL EVIDENCES OF LAPAROSCOPIC VERSUS OPEN SURGERY FOR COLON CANCER

As searching for all published randomized controlled trials to compare laparoscopic surgery with open surgery for colon cancer, 13 studies were demonstrated in English from 1991 to 2007 (Table 1) (18,19,21,22,28–36). The rate of conversion to open surgery varied widely (0–46.4%) between those studies. There were no significant differences in overall and surgical complication rate, anastomotic leakage rate, re-operation rate and oncological clearance. However, laparoscopic surgery has a significantly lower preoperative mortality, lower wound complications, less blood loss,

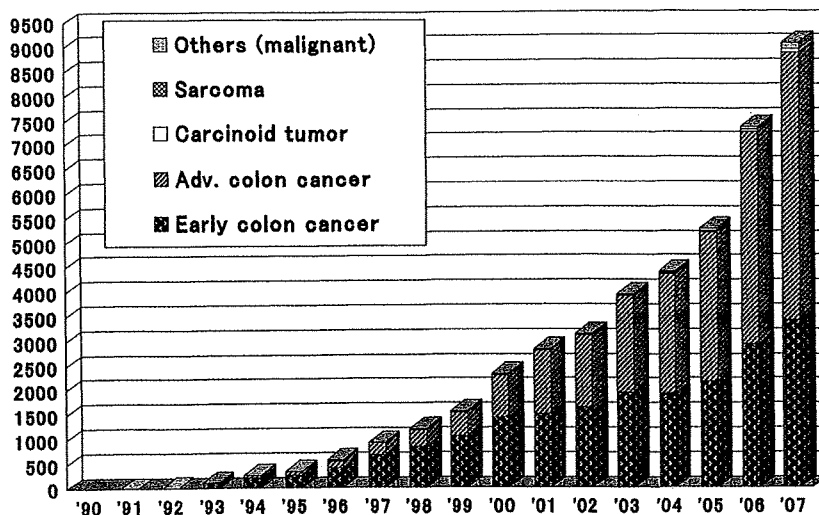


Figure 1. Current status of laparoscopic surgery for colorectal cancer in Japan. A nation-wide survey in 1373 institutes of Japan was conducted by Japan Society of Endoscopic Surgery.

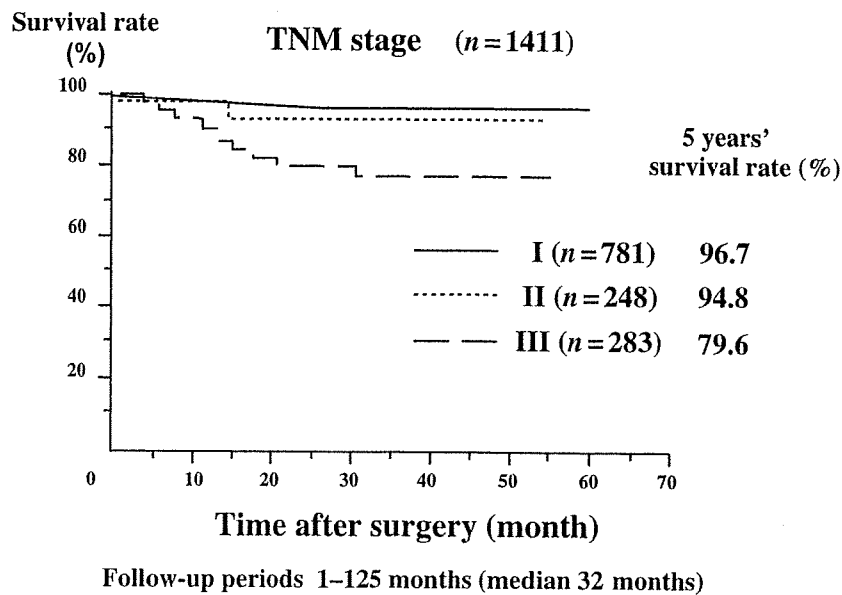


Figure 2. Long-term outcome of laparoscopic surgery for colon cancer in Japanese retrospective multicenter study. Tumor staging system is used with UICC-TNM staging.

reduced post-operative pain scores and reduced requirements for narcotic analgesia. After laparoscopic surgery, patients passed flatus earlier and had bowel movement earlier and resumed oral diet sooner than the patients did in open surgery. Prospective randomized controlled trials show that laparoscopic surgery for colon cancer is feasible, safe and has many short-term benefits.

Four randomized controlled trials have been reported to clarify long-term outcome of laparoscopic surgery for colon cancer (Table 2) (18–22). These trials were evaluated in the survival, mortality and recurrence of disease associated with

two types of surgical procedures with follow-up period of 3.6–5 years. These trials reported an overall mortality rate of 17.9–32% for laparoscopic surgery and 22.2–61% for open surgery. The Clinical Outcomes of Surgical Therapy (COST) Group in USA (19,20), Leung et al. (21) and MRC CLASSICC (22) demonstrated that overall survival rate and the recurrent cancer rate were similar after laparoscopic and open surgery. Only Lacy et al. (18) described significant differences between two surgical methods. In this trial, cancer-related mortality was lower in patients with Stage III disease who underwent LCR, and no significant differences

Table 1. Randomized controlled trials comparing laparoscopic surgery with open surgery for colon cancer with regard to short-term outcome

Author or trial name (reference number)	Number of patients			Mortality rate		Morbidity rate	
	Total	Laparoscopic	Open	Laparoscopic (%)	Open (%)	Laparoscopic (%)	Open (%)
Hewitt et al. (29)	16	8	8	0	0	0	0
Milsom et al. (30)	80	42	38	1.8	1.9	15	15
Schwenk et al. (31)	60	30	30	0	0	7	27
Curet et al. (32)	43	25	18	0	0	4	17
Braga et al. (33)	183	90	93	0	0	21	38
Lacy et al. (18)	219	111	108	0.9	2.8	11	29
Hasegawa et al. (28)	50	24	26	0	0	4	19
COST (19)	810	415	395	0.5	0.9	21	20
Kaiser et al. (34)	48	28	20	0	0	18	20
Leung et al. (21)	403	203	200	0.5	2.4	20	23
CLASICC UK (22)	413	273	140	0.4	4.9	23	35
COLOR (35)	1082	536	546	1.1	1.8	21	20
Liang et al. (36)	269	135	134	0	0	15	22

Table 2. Randomized controlled trials comparing laparoscopic surgery with open surgery for colon cancer with regard to long-term outcome

Author or trial name (reference number)	Number of patients (laparoscopic versus open)	Conversion rate	Morbidity (laparoscopic versus open)	Mortality (laparoscopic versus open)	Overall survival	Disease-free survival
Lacy et al. (Spain) (18)	206 (105 versus 101)	11%	$P = 0.001$ (11% versus 29%)	$P = 0.19$ (0.9% versus 2.8%)	NS	$P = 0.006$ (Stage III subgroup)
Leung et al. (Hong Kong) (21)	403 (203 versus 200)	23%	NS (23% versus 20%)	$P = 0.97$ (2.4% versus 0.6%)	$P = 0.61$ (76% versus 73%)	$P = 0.45$ (75% versus 78%)
COST (USA) (20)	863 (435 versus 428)	21%	$P = 0.64$ (21% versus 20%)	$P = 0.40$ (0.5% versus 0.9%)	$P = 0.51$ (86% versus 85%)	NS
CLASICC (UK) (22)	794 (526 versus 268)	16%	NS (35% versus 33%)	$P = 0.65$ (0.4% versus 4.9%)	$P = 0.35$ (67% versus 68%)	$P = 0.70$ (66% versus 68%)

NS, not significant differences.

were found with respect to patients with Stage I and II disease. Reza et al. (37) reported that meta-analysis of four randomized controlled trials had not revealed any significant difference in terms of cancer-related mortality and recurrence rates between laparoscopic and open surgery. Transatlantic laparoscopically assisted versus open-colectomy trials study group also reported that meta-analysis demonstrated no significant difference in terms of long-term survival between both surgical procedures (38). Prospective randomized controlled trials and meta-analysis in terms of long-term outcome states that there are no differences in the two surgical procedures. However, these randomized controlled trials in western countries also have several problems such as the criteria including early staged cancer and benign disease, undetermined level of lymph node dissection, unclear indication for adjuvant chemoradiotherapy and no description of quality control of the two surgical procedures.

CLINICAL EVIDENCES OF LAPAROSCOPIC VERSUS OPEN SURGERY FOR RECTAL CANCER

The results of multicenter randomized controlled trial to evaluate laparoscopic versus open surgery for rectal cancer have seldom been reported either in Japan or any other foreign countries, yet there is a report to present the fact that there is no significant difference between laparoscopic and open surgery in oncological short-term prognosis (22). There are not many reports regarding prognosis of laparoscopic surgery for advanced rectal cancer. However, there are some reports that an incidence of complications such as anastomotic leakage and pelvic abscess in laparoscopic surgery is the same as, or higher than that in open surgery (39–42). In 2007, CLASICC trial group targeted 794 patients with colon and rectal cancer in multicenter randomized clinical trial of laparoscopic versus open surgery (22). There was no significant difference in 3-years' local recurrence and overall survival rates after curative resection between both the groups. Though there was 5% in mortality rate in each group, a positive rate of circumferential resection margin in laparoscopic group was higher than that in open group. Short-term results of laparoscopic surgery for rectal cancer were shown in Table 3 (43–47). In retrospective studies, tumors were located at 0–15 cm away from the anal verge, and a conversion rate to open surgery was 3–12%. A rate of post-operative complications was 21–36%, and a rate of anastomotic leakage was 5.8–17.3%. In these reports from western countries, pre- or post-operative chemoradiotherapy was treated for 40% of patients with T3 or deeper rectal cancer. Because a standard treatment for advanced rectal cancer is different from the one in Japan, further detailed study would surely be required about the adaptation of laparoscopic surgery.

Table 3. Retrospective studies of laparoscopic surgery for rectal cancer with regard to short-term outcome

Author (reference number)	Number of patients	Conversion rate (%)	Leakage (%)	Complication (%)
Morino et al. 2003 (43)	100	12	17	36
Leroy et al. 2004 (45)	102	3	17	27
Zhou et al. (44)	82	NE	1	6
Dulucq et al. 2005 (46)	218	12	11	26
Kim et al. 2006 (47)	312	3	6	21

NE, not evaluated.

A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL FOR COLON CANCER IN JAPAN

In Japan, we have conducted a randomized controlled trial to compare laparoscopic surgery with open surgery to evaluate oncological outcome for advanced colon and recto-sigmoid cancer (24). This study has been supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labor and Welfare. The Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in September 2004, and the study (JCOG0404) has started in November 2004 to elucidate the optimal treatment for T3 or deeper colorectal cancer. Surgeons at 27 specialized institutions will recruit 1050 patients. The primary endpoint is the overall survival rate. Secondary endpoints are relapse-free survival rate, short-term clinical outcomes, adverse events and a rate of conversion from laparoscopic surgery to open surgery. The short-term clinical outcomes are the proportion of the use of analgesics, the duration from operation to flatus, the highest body temperature during hospitalization and the highest body temperature during 3 days after operation. In both arms, resection of colon or rectum with D3 lymphadenectomy is performed according to the Japanese Classification of Colorectal Carcinoma (48). The patients are randomized by the minimization method of balancing the groups according to the location of the tumor and the institution (Figure 3). This Japanese randomized controlled trial has characteristic designs comparing with other western trials such as inclusion criteria of only advanced cancer (T3, T4), lymph node dissection, adjuvant chemotherapy and the quality control. In the case of pathological Stage III colorectal carcinoma, three cycles of adjuvant chemotherapy with fluorouracil and L-leucovorin are administered. To control the quality of operation, central review of surgical procedure was done by using photographs of all patients. A registration of the patients in this trial will be accomplished in March 2009.

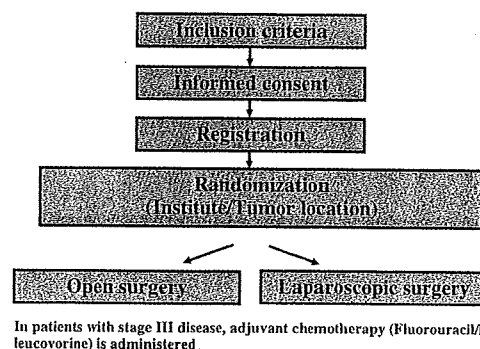


Figure 3. A protocol design of Japanese multicenter randomized controlled trial (Japan Clinical Oncology Group 0404) to compare laparoscopic surgery with open surgery to evaluate oncological outcome for advanced colon cancer.

A PROSPECTIVE STUDY FOR RECTAL CANCER IN JAPAN

To examine technical and oncological feasibility of laparoscopic surgery for rectal cancer, a Phase II trial (Lap-RC) started to be applied to patients with a preoperative diagnosis of Stage 0/I rectal cancer under the direction of the Japan Society of Laparoscopic Colorectal Surgery (26). Surgeons at 39 specialized institutions will recruit 350 patients. The primary endpoint at the first stage is an anastomotic leakage rate by double-stapling technique and the one at the second stage is an overall survival rate. Secondary endpoints are relapse-free survival rate, short-term clinical outcome, adverse events, the rate of histologically curative operation, the proportion of completion of laparoscopic and the conversion rate. To control the quality of operation, central review of surgical procedure was done by using photographs of all patients.

CONCLUSIONS AND PERSPECTIVES

Laparoscopic surgery has widely spread as a less invasive procedure for colorectal cancer in Japan and western countries. A nation-wide survey by JSES revealed that a rate of advanced colorectal cancer has increased gradually and reached two-thirds of total cases in 2007. Many randomized controlled trials demonstrate that laparoscopic surgery for colon cancer is feasible, safe and has many short-term benefits including reduction in peri-operative mortality. There are still more important issues including long-term oncological outcome for advanced colon cancer, cost-effectiveness and the impact on quality of life of patients with colon cancer. Meanwhile, a controversy persists with regard to the appropriateness of laparoscopic surgery for patients with rectal cancer because of concerns over the safety of the procedure, especially in low anterior resections for lower rectal carcinoma. Additionally, lateral lymph node dissection combined with total mesorectal excision remains the standard surgical procedure for patients with advanced

lower rectal carcinoma in Japan, but lateral lymph node dissection by laparoscopic surgery is still an unexplored frontier (49–51). At present, laparoscopic surgery is acceptable for Stage I disease of colon cancer, also it is generally not acceptable for Stage II/III colon cancer and each staged rectal cancer. However, experienced and trained surgeons may do laparoscopic surgery for Stage II/III colon cancer and early staged rectal cancer with accepting the informed consent from patients because clinical outcomes of laparoscopic surgery are equivalent or superior to open surgery in previous clinical trial reports. Further works are needed to estimate laparoscopic procedures for advanced colon and rectal cancer. Japanese on-going large-scale RCT (JCOG0404) estimating oncological outcome for Stage II/III colon cancer (24) and a prospective feasible study for Stage 0/I rectal cancer (25) would be beneficial to determine the role of laparoscopic surgery as a standard operation for colorectal cancer. General surgeons expect the report of clinical results of Japanese two trials to come out as soon as possible.

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Conflict of interest statement

None declared.

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