[Review]

An evidence-based medicine approach to the laparoscopic treatment of colorectal cancer

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Abstract

During the 1990s, laparoscopic resection was established as a treatment for gastrointestinal malignant tumors. A number of randomized controlled trials comparing laparoscopic-assisted colorectal surgery with conventional open colorectal surgery for colon cancer have been conducted. These trials have shown short-term benefits, and the vast majority demonstrated no significant difference in long-term outcomes. Laparoscopic-assisted colorectal surgery is widely performed for the treatment of colon cancer, whereas laparoscopic-assisted colorectal surgery for rectal cancer is less commonly performed. In recent years, there have been an increasing number of reports of laparoscopic-assisted colorectal surgery for rectal cancer, where improving short-term outcomes was shown, but no definitive effect on long-term survival has been shown to date. Randomized controlled trials focusing on long-term survival are currently ongoing.

Key words : colon cancer, rectal cancer, laparoscopic-assisted colorectal surgery

Introduction

Colorectal cancer is the fourth leading cause of cancer-specific mortality worldwide. Laparoscopic-assisted colorectal surgery (LAC) for colon cancer was first reported in 1991¹⁾. Several Randomized Controlled Trials (RCTs) have shown that LAC for colon cancer has short-term benefits and no difference in long-term outcomes, compared with conventional open colorectal surgery (OC)²⁻⁷⁾. In contrast, LAC for rectal cancer still remains controversial due to technical difficulties⁸⁾. With the ongoing development of medical devices as well as improvements in operative technique, however, the number of LAC performed for rectal cancer has gradually increased. Recent RCTs have provided evidence of LAC for rectal cancer as well^{3,9-12)}. In this article, we summarize the current evidence regarding the

treatment of CRC, especially laparoscopic surgery, focusing on multi-institutional RCTs.

Methods

To identify papers relevant to our study, we searched major medical databases including MEDLINE, EMBASE, Science Citation Index, and Cochrane Controlled Trial Register from 1990 till the present. The following search terms were used: "laparoscopic surgery" "colorectal cancer" "randomized controlled trial" and all related articles.

Laparoscopic Surgery for Colon Cancer

Short-term outcomes (Table 1)

A number of RCTs comparing LAC with OC for

Table 1. Randomized clinical trials of laparoscopic colon surgery (short-term outcomes)

Randomized Clinical Trial	Year	Participants	Number of Patients	Tumor Location	Conversion Rate (%)	Follow Up (Months)	Operative time [†] (min)	Blood loss [†] (ml)	Harvested nodes [†]	Leakage Rate (%)
Lacy ^{6,55)}	2002 2008	1 center	LAC: 111 OC: 108	C, A, D, S	11	95	LAC: 142 (52) [‡] OC: 118 (45)	LAC: 105 (99) [‡] OC: 193 (212)	LAC: 11.1 (7.9) ^φ OC: 11.1 (7.4)	LAC: 0 ^φ OC: 1.9
COST ^{4,54)}	2004 2007	48 centers 66 surgeons	LAC: 435 OC: 437	C, A, D, S	21	84	LAC: 150 (35-450) [‡] OC: 95 (27-435)	NA	LAC: 10 (3-20) ^φ OC: 10 (3-20)	NA
COLOR ^{8,50)}	2005 2009	29 centers	LAC: 627 OC: 621	C, A, D, S	17	53	LAC: 202 (50-540) [‡] OC: 170 (45-580)	LAC: 100 (0-2,700) [‡] OC: 175 (0-2,000)	NA	LAC: 3 ^φ OC: 2
Braga ⁵¹⁾	2010	1 center 1 team	LAC: 134 OC: 134	T, D, S	5.2	73	LAC: 213 (57) [‡] OC: 174 (77)	LAC: 46 (130) OC: 127 (265) [‡]	LAC: 14.5 (4.5) ^φ OC: 15.3 (6.3)	LAC: 3.7 ^φ OC: 4.5
CLASSIC ^{5,91)}	2005 2010	27 centers 32 surgeons	LAC: 273 OC: 140	C, A, D, S	25	56.3	LAC: 186 (135-220) [‡] OC: 135 (100-180)	NA	NA	LAC: 3 ^φ OC: 3

LAC, laparoscopic-assisted colorectal surgery ; OC, open colorectal surgery ; C, cecum ; A, ascending colon ; T, transverse colon ; D, descending colon ; S, sigmoid colon ; NA, not available ; ‡, values are mean (SD or Range) ; †, $p < 0.01$; φ, N.S.

colon cancer have been conducted around the world. Previous studies showed that LAC for CRC is associated with low morbidity, fast recovery, short hospital stay and a better quality of life compared to OC in the short-term^{4,6,13-16)}. Among those studies, the Lacy *et al.* trial⁴⁾, COST study group trial²⁾, COLOR trial⁶⁾ and MRC CLASICC trial³⁾ are particularly well-regarded. These trials all had a large sample size, demonstrating short-term benefits for LAC, compared to OC. In addition, patients undergoing LAC had significantly less blood loss and no significant differences in the number of harvested lymph nodes, anastomotic leak rate, or perioperative mortality and mortality. In spite of a significantly longer operative time, the safety and feasibility of LAC is similar to that of OC. The conversion rate was as high as 11-25% in previous reports, but approximately 5% in more recent studies¹⁷⁻¹⁹⁾. These improvements may be due to recent advances in technology as well as laparoscopic technique. Therefore, some recent studies report that LAC had an advantage in short-term outcomes not only for patients over age 75^{20,21)} but also for obese patients²²⁾.

Long-term outcomes (Table 2)

In 2007, the COST trial²³⁾ reported long-term outcomes for patients with CRC treated by LAC. Patients were followed for a median of seven years. The five-year disease-free survival (LAC 69.2%, OC 68.4%, $P = 0.94$), five-year overall survival (LAC 76.4%, OC 74.6%, $P = 0.93$) and overall recurrence rates (LAC 19.4%, OC 21.8%, $P = 0.25$) were similar between the two groups. In 2008, Lacy *et al.*²⁴⁾ also reported long-term outcomes. The median follow-up was 95 months. In the LAC group, there was a tendency toward higher cancer-related survival ($P = 0.07$, not significant) and overall survival ($P = 0.06$, not significant). Regression analysis showed that LAC was not independently associated with a reduced risk of tumor recurrence (hazard ratio 0.47, 95% CI : 0.23-0.94), death from a cancer-related cause (0.44, 0.21-0.92) or death from any cause (0.59, 0.35-0.98). In 2009, the COLOR trial²⁵⁾ reported long-term outcomes after LAC and OC. The median follow-up was 53 months. The combined 3-year disease-free survival (LAC 74.2%, OC 76.2%, $P = 0.70$) and combined 3-year overall survival (LAC 81.8%, OC 84.2%, $P = 0.45$) were similar in all stages of disease. These results suggest that the long-term oncological outcomes of LAC are similar to those of OC.

In 2013, a RCT (JCOG0404⁵⁵⁾) with a large co-

Table 2. Randomized clinical trials of laparoscopic colon surgery (long-term outcomes)

Randomized clinical trial	Year	5 year DFS (%)	<i>p</i> -value	5 year OS (%)	<i>p</i> -value
Lacy ⁵⁵⁾	2008	NA		NA	
COST ⁵⁴⁾	2007	LAC : 69.2 OC : 68.4	0.94	LAC : 76.4 OC : 74.6	0.93
COLOR ⁵⁹⁾	2009	*LAC : 74.2 *OC : 76.2	0.19	*LAC : 81.8 *OC : 84.2	0.21
Braga ⁵¹⁾	2010	NA		LAC : 72 OC : 66	0.321
CLASSIC ⁹¹⁾	2010	LAC : 57.6 OC : 64.0	0.399	LAC : 55.7 OC : 62.7	0.253

DFS, disease free survival ; OS, overall survival ; LAC, laparoscopic-assisted colorectal surgery ; OC, open colorectal surgery ; NA, not available ; *Data are 3 year.

hort (529 for LAC, 528 for OC, conversion rate 5.4%), was completed for patients with Stage II and III colon cancer at 30 tertiary centers in Japan. In an interim report, LAC showed impressive short-term outcomes and similar long-term oncological outcomes, compared to OC. LAC is clearly established as a reasonable alternative treatment to OC for patients with CRC.

Transverse colon cancer

Previous studies excluded transverse colon cancer, presumably because of the technical difficulty in laparoscopically resecting the cancers including an extended lymphadenectomy. There have been three reports of laparoscopic-assisted transverse cancer resection, supporting its feasibility, since 2007^{26,27)}. Kim *et al.*²⁷⁾ published a comparative study on the short-term clinico-pathologic outcomes of LAC ($n = 37$) vs. OC ($n = 50$) for transverse colon lesions. They reported that blood loss was significantly less, time to first flatus was shorter and the diet was started earlier in patients who underwent LAC. There were no intergroup differences in the number of harvested lymph nodes. In 2012, Hahn *et al.*²⁸⁾ published the long-term results for the laparoscopic-assisted resection of transverse colon cancer in 58 patients, which was the first study to demonstrate long-term oncologic outcomes after LAC for transverse colon cancer. One patient was converted to open surgery. The median follow-up was 40.5 months. There were no local recurrences during the follow-up period. Disease-free survival and overall survival for patients undergoing LAC at five years were 84.6% and 89.3%, respectively. A more recent report shows similar long-term outcomes comparing LAC and OC²⁹⁾. LAC for transverse colon cancer is expected to become an established treatment in the future.

Metastatic Colon Cancer

National Cancer Control Network guidelines recommend non-operative treatment for patients with incurable Stage IV CRC without symptoms. On the contrary, other reports advocate the benefits of primary tumor resection as treatment for patients with Stage IV CRC³⁰⁻³²⁾. At present, there is no consensus regarding the effectiveness of palliative primary tumor resection for patients with Stage IV disease. There are few comparative studies of LAC and OC for patients with Stage IV CRC. Law *et al.*³³⁾ reported a retrospective comparative study of LAC ($n = 77$) vs. OC ($n = 123$) in patients with metastatic colorectal cancer. In this study, the mortality rate was significantly lower in patients who underwent LAC (LAC 14%, OC 32%, $P = 0.007$) and the median hospital stay was significantly shorter (7 days for LAC vs. 8 days for OC, $P = 0.005$). The operative mortality rate and the survival were similar.

There have been four reports comparing LAC with OC for symptomatic or incurable stage IV CRC since 2012³⁴⁻³⁷⁾. These studies showed that patients who underwent LAC resumed oral intake significantly earlier and had significantly shorter hospital stays than patients undergoing OC. Two studies reported that LAC was associated with significantly less perioperative mortality^{35,37)} and other two studies reported shorter time intervals from surgery to chemotherapy compared to patients undergoing OC^{35,36)}. Among the four studies, Hida *et al.*³⁷⁾ reported that LAC had significantly better overall survival than that for OC ($P = 0.04$). These studies indicate that LAC has advantages in the short term and no disadvantages in the long term.

Recent Topics

Since aging is a significant risk factor for developing CRC, it is likely that we will see more patients with this disease in the future, due to the aging population³⁸⁾. Kennedy *et al.*³⁹⁾ analyzed data from the American College of Surgeons National Surgical Quality Improvement Program from 2005 to 2008 and evaluated patients over age 65 who underwent either LAC ($n = 2,113$) or OC ($n = 3,801$) for colon cancer. They concluded that patients undergoing LAC were generally at lower risk for developing postoperative complications (LAC 16.1% vs. OC 25.4%, $P < 0.005$). Statistical models controlling for preoperative and operative variables demonstrated that patients with an elevated body mass index (odds ratio [OR] = 1.26), history of chronic obstructive pulmonary disease (OR = 1.63), age over 85 (OR = 1.35), surgery lasting longer than four hours (OR = 1.48), or having undergone an OC (OR = 1.53), have an increased risk for developing postoperative complications.

In recent years, overall outcomes after colon cancer resection have not improved. High ligation with mesenteric lymph node dissection (Japanese D3 lymph node dissection)⁴⁰⁾ and European complete mesocolic excision⁴¹⁾ with high ligation are both based on sound oncologic principles and using both techniques report impressive outcomes as compared with standard operative techniques. West *et al.*⁴²⁾ reported, that compared with complete mesocolic excision, specimens resected using the Japanese D3 lymph node dissection technique were significantly shorter (162 vs. 324 mm, $P < 0.001$), resulting in a smaller number of lymph nodes (median, 18 vs. 32, $P < 0.001$). The distance from the high tie to the bowel wall (100 vs. 99 mm, $P = 0.605$) was equivalent, but did not decrease the number of tumor-involved nodes in patients undergoing OC. There was no difference in the number of lymph nodes but a greater distance from the high tie to the bowel wall in LAC specimens when compared with OC specimens. Follow up RCTs are now required to assess the benefit of high tie and extended bowel resection.

Sentinel lymph node mapping has been found to be diagnostically useful in patients with early stage CRC. Zaag *et al.*⁴³⁾ analyzed 57 reviews (3,934 patients) and reported that the sentinel lymph node in CRC has an overall sensitivity of 70%. The identification of the sentinel lymph node using infrared laparoscopy was five times better than that with conventional laparoscopy⁴⁴⁾. Regional lymphadenectomy is an integral part of the primary resection

in patients with CRC, but in contrast to breast cancer and melanoma, there are few secondary diseases after lymphadenectomy. Therefore, sentinel lymph node mapping has not become widely used in patients with CRC.

Laparoscopic Surgery for Rectal Cancer

Short-term Outcomes (Table 3)

Some trials report no difference in the rate of perioperative complications such as anastomotic leakage, wound infection, ileus, abscess, or bleeding comparing LAC and OC for rectal cancer, although anastomotic leakage has a slightly higher incidence than other complications. Since anastomotic leakage is a highly morbid complication in some patients, a protecting stoma is still recommended in low anterior resection regardless of the surgical procedure used, according to some studies^{9,45)}. Anastomotic leakage has a negative prognostic impact for local recurrence after restorative resection of rectal carcinoma. Therefore, if the anastomotic leakage rate in LAC for rectal cancer is higher than that for OC, LAC should be regarded as an unacceptable treatment⁴⁶⁾. The rate of anastomotic leakage in laparoscopic rectal cancer surgery ranged between 1 and 17% in the literature and was most commonly reported to be approximately 10%^{3,10,11,47-52)}. All comparative studies and RCTs reported no statistically significant difference in anastomotic leakage rate between LAC and OC for sphincter-saving rectal cancer resection^{3,10,11,47)}. Therefore, laparoscopic low anterior resection is considered as an acceptable therapeutic alternative.

Long-term Outcomes (Table 4)

The oncologic outcome of surgery for rectal cancer has substantially improved due to the introduction of total mesorectal excision in the Western world⁵³⁾. Whether LAC can allow the conduct of an adequate total mesorectal excision is an important concern in assessing the use of LAC in patients with rectal cancer. Accordingly, three multicenter trials (CLASSIC trial, COREAN trial and COLOR trial) have been conducted to examine this question.

Only the CLASICC trial has completed all analyses and reported five-year survival data^{3,54-56)} (Table 3). In this trial all participating surgeons (27 centers and 32 surgeons) were required to have completed 20 laparoscopic colorectal resections before enrolling in the study. The adequacy of this opera-

Table 3. Randomized clinical trials of laparoscopic rectal surgery (short-term outcomes)

Randomized Clinical Trial	Year	Participants	No. of Patients	Tumor Location	Conversion Rate (%)	Follow up (Months)	Operative time [†] (min)	Blood loss [‡] (ml)	Harvested nodes [†]	Leakage Rate (%)
CLASSIC ⁵⁾	2005	27 centers 32 surgeons	LAC : 253 OC : 128	Rs, Ra, Rb	34	56.3	LAC : 186 (135-220) [§] OC : 135 (100-180)	NA	NA	LAC : 10 ϕ OC : 7
Braga ¹³⁾	2007	1 center 1 team	LAC : 83 OC : 85	≤ 15 cm from AV	7.2	53.6	LAC : 262 (72) [§] OC : 209 (70)	LAC : 150 (50-1,600) [§] OC : 350 (50-1600)	LAC : 12.7 (7.3) ϕ OC : 13.6 (6.9)	LAC : 9.6 ϕ OC : 10.6
Lujan ¹⁴⁾	2009	1 center 1 team	LAC : 101 OC : 103	≤ 11 cm from AV	7.9	LAC : 32.8 OC : 34.1	LAC : 193.7 (45.1) [§] OC : 172.9 (59.4)	LAC : 127.8 (113.3) [§] OC : 234.2 (174.3)	NA	LAC : 5 ϕ OC : 10
COREAN ¹¹⁾	2010	3 centers 7 surgeons	LAC : 170 OC : 170	≤ 9 cm from AV	1.2	NA	LAC : 244.9 (75.4) [§] OC : 197.0 (62.9)	LAC : 200 (100-300) [§] OC : 217.5 (150-400)	LAC : 17 (12-22) ϕ OC : 18 (13-24)	LAC : 1.2 ϕ OC : 0
COLOR II ^{9,2)}	2013	30 centers	LAC : 739 OC : 364	≤ 15 cm from AV	17	NA	LAC : 240 (184-300) [§] OC : 188 (150-240)	LAC : 200 (100-400) [§] OC : 400 (200-700)	LAC : 13 (10-18) ϕ OC : 14 (10-19)	LAC : 13 ϕ OC : 10

LAC, laparoscopic-assisted colorectal surgery ; OC, open colorectal surgery ; Rs, rectosigmoid ; Ra, rectum above the peritoneal reflection ; Rb, rectum below the peritoneal reflection ; AV, anal verge ; NA, not available ; [†], values are mean (SD or Range) ; [‡], $p < 0.01$; ϕ , N.S.

tive experience may be a concern in the design of this trial. The data from this trial may be biased in an intention-to-treat analysis. The conversion rate was 45% in the initial phase and declined to 15% in the last year of the study³⁾. However, at five years of follow-up after surgery, local recurrence rates were similar in the two groups (LAC 9.4%, OC 7.6%)⁵⁷⁾. No differences were found between LAC and OC in terms of anastomotic leakage (LAC 7%, OC 10%), five-year disease-free survival (LAC 53.2%, OC 52.1%) and five-year OS (LAC 60.3%, OC 52.9%). Additionally, several other trials recruited a small number of patients, but found no statistically significant difference in the disease-free survival and overall survival rate in patients undergoing LAC and those undergoing OC^{3,54,56,58,59)}.

In 2013, the COLOR II study group⁶⁰⁾ published short-term outcomes of a phase three trial undertaken in 30 tertiary hospitals in eight countries. Patients with a single rectal cancer within 15 cm of the anal verge were recruited. This is the largest RCT to compare LAC ($n = 739$) with OC ($n = 364$). Similar to the results reported for colon cancer, LAC for rectal cancer is superior for short-term outcomes in comparison to OC. The morbidity (LAC 40%, OC 37%, $P = 0.424$) and mortality (LAC 1%, OC 2%, $P = 0.409$) within 28 days of surgery were also similar. The conversion rate was 16%, equivalent to the most recent data⁶¹⁾. Anastomotic leakage rates were similar between the two groups (LAC 13%, OC 10%, $P = 0.462$). These rates are in the same range as those reported from the CLASICC trial (7% and 10%, respectively) whereas lower rates were reported by Kang *et al.*⁹⁾ and Morino *et al.*⁶²⁾. This trial is still on-going. Locoregional recurrence rates, which is the primary endpoint, have not been reported as of early 2014. In 2010, the COREAN trial was published⁹⁾. It was the first RCT comparing LAC ($n = 170$) with OC ($n = 170$) for middle or lower rectal cancers after neoadjuvant chemo-radiotherapy. They reported a 1.2% conversion rate and a 1.2% anastomotic leakage rate (vs. OC 0% ; not significant). This trial included seven surgeons who treated more than 200 patients with rectal cancer annually. Diverting ileostomy was carried out in 91.4% of patients undergoing LAC and 88.4% undergoing OC. In contrast, Yamamoto *et al.*⁶³⁾ reported that 61 participating surgeons operated on 495 patients at 43 institutions. Splendid results, favorably comparable to the COREAN trial, were obtained, although the indications for LAC were limited. The conversion rate was 1.6%, sphincter-preserving rate was 97% and anastomotic

Table 4. Randomized clinical trials of laparoscopic rectal surgery (long-term outcomes)

Randomized clinical trial	Year	5 year DFS (%)	<i>p</i> -value	5 year OS (%)	<i>p</i> -value
CLASSIC ⁽⁹¹⁾	2010	LAC : 53.2 OC : 52.1	0.953	LAC : 60.3 OC : 52.9	0.123
Braga ⁽¹³⁾	2007	NA		NA	
Lujan ⁽¹⁴⁾	2009	LAC : 84.8 OC : 81.0	0.895	LAC : 72.1 OC : 75.3	0.98
COREAN ⁽¹¹⁾	2010	NA		NA	
COLOR II ⁽⁹²⁾	2013	NA		NA	

LAC, laparoscopic-assisted colorectal surgery ; OC, open colorectal surgery ; DFS, disease free survival ; OS, overall survival ; NA, not available.

leakage rate in patients who underwent anterior resection was 8.3%. However, we should pay attention to that these laparoscopic surgery were carried out by expert surgeons in high-volume centers and that high-risk patients were excluded in the study. In spite of this consideration, these data suggest that the outcomes are close to those expected in general clinical practice.

In recent years, there have been an increasing number of reports of LAC for rectal cancer, where short-term outcomes have improved. Lateral lymph node dissection by laparoscopic surgery might improve the long-term outcomes, but there is no report on this issue to date. Several large multi-center RCTs including the multinational COLOR II and American College of Surgeons Oncology Group Z6051 trial focusing on long-term survival, completely independent from the CLASSIC trials, are now under way. These studies will elucidate the short-term advantages and long-term oncologic outcomes of LAC for rectal cancer.

Conclusion

In this article, we have reviewed recent advancements in the field of laparoscopic treatment for CRC. LAC has demonstrated to have short-term benefits comparable to open surgery and also demonstrated to be as safe and efficacious as open surgery. Laparoscopic surgery for CRC is becoming more widely utilized, aiming at the use of less invasive techniques in the future. However, surgeons should be aware of that all clinical trials were performed in high-volume centers with experienced laparoscopic surgeons. Accordingly, super-expertise in laparoscopic surgery might be required to achieve these excellent outcomes. Further validation studies of the safety and oncological outcomes for laparoscopic surgery for CRC are warranted.

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Conflict of Interest Disclosure

Authors declare no conflict of interest in preparing this article.

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