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REVIEW ARTICLE

The present status and developments of laparoscopic surgery for colorectal cancer

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Abstract:

Laparoscopic surgery for colorectal cancer has been shown to be less invasive than open surgery, while maintaining a similar safety level in many clinical trials. Furthermore, there are no significant differences between laparoscopic surgery and open surgery with respect to the long-term outcomes in colon cancer. Thus, laparoscopic surgery has been accepted as one of the standard treatments for colon cancer. In addition, laparoscopic surgery has also achieved favorable outcomes in the treatments of rectal cancer, with many reports showing long-term outcomes comparable to those of open surgery. Furthermore, the magnification in laparoscopy improves visualization in the pelvic cavity and facilitates precise manipulation, as well as providing an excellent educational opportunity. Laparoscopic surgery may be an ideal approach for the treatment of rectal cancer and colon cancer. Recently, two trials showed that, among patients with advanced rectal cancer, the use of laparoscopic surgery as compared with open surgery confirmed to meet the criterion for non-inferiority for long-term outcomes. In addition, new techniques such as single-port and robotic surgery have been introduced for laparoscopic surgery in recent years.

Keywords:

laparoscopic surgery, colorectal cancer, total mesorectal excision, randomized controlled trial, robotic surgery, single-port surgery

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Introduction

Laparoscopic surgery for bowel disease was first reported in 1991 in the United States[1]. In Japan, the first such surgery was performed in 1992 for a patient with cecal cancer[2]. Subsequently, the indications for laparoscopic surgery were gradually expanded to include colorectal cancer and inflammatory bowel diseases such as appendicitis and diverticulitis[3]. Around 1994, however, frequent port site recurrences following laparoscopic surgery for colon cancer were reported, resulting in laparoscopic surgery temporarily being considered contraindicated[4]. On the other hand, in Japan, laparoscopic surgery had a very low incidence of port site recurrences because the indication of laparoscopic surgery was limited to early stage cancer. Port site recurrences were, at that time, reported as arising from the spreading of cancer cells during laparoscopic surgery due to the inappropriate manipulation of the tumor. After this realization, the principles of surgical oncology were more strictly followed, resulting in decreased port site recurrences; and to date, there have been no such cases reported. With the spread of laparoscopic surgery, clinical studies began to be carried out comparing its short- and long-term outcomes with those of open surgery[5]. With the increase in the use of laparoscopic surgery, and laparoscopic surgery spread rapidly in Japan, becoming another standard treatment for diseases of the anus, rectum, and colon, in addition to conventional open surgery. Herein, we outline the current status of laparoscopic surgery for colorectal cancer in Japan and its perspectives for the future.

Colon Cancer

Regarding colon cancer, randomized controlled trials comparing laparoscopic surgery with open surgery have been carried out, and numerous meta-analyses of data from such trials have been reported. These reports demonstrated the superiority of laparoscopic surgery over open surgery in both

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Table 1. Trial JCOG 0404 and Other Large Clinical Trials.

Trials	JCOG0404	COST	Braga	CLASICC	COLOR
Cases	533:524	428:435	201:190	268:526	621:627
Open:Laparoscopy					
Conversion rate (%)	5.4	21	4	16	19
Overall survival (%)	90.4:91.8	85:86	83:84	68:67	84.2:81.8
Open:Laparoscopy					

Table 2. Short-term Results in the JCOG 0404 Trial.

Variables	Laparoscopic Surgery	Open Surgery	P value
Bleeding (ml)			
Median	30	85	<0.001
IQR	10-70	50-180	
Operation time (minutes)			
Median	211	159	<0.001
IQR	179-256	130-189	
First postoperative flatus (days)			
Median	2	2	<0.0001
IQR	1-2	2-3	
Postoperative hospital stay (days)			
Median	10	11	<0.0001
IQR	8-13	9-14	
Wound complications (%)	28 (5.3)	51 (9.7)	0.007
Anastomosis leakage	19 (3.6)	19 (3.6)	N.S.

short- and long-term outcomes As laparoscopic surgery has increasingly become a standard procedure, the difference in operative time, when compared to open surgery, has gradually been reduced. In Japan, a randomized, controlled trial was conducted to confirm the non-inferiority of laparoscopic surgery to open surgery in terms of overall survival. The primary endpoint of the 5-year overall survival was demonstrated in the paper[6]. Eligibility criteria included: colon cancer; tumor located in the cecum, ascending, sigmoid, or rectosigmoid colon; T3 or T4 in TMN classification without involvement of other organs; N0-2; and M0. Patients were randomized preoperatively and underwent bowel resection with D3 dissection. A total of 1,057 patients were randomized (Open surgery 528, Laparoscopy 529) from October 2004 through to March 2009. Conversion to open surgery was only needed for 29 patients (5.4%) in the laparoscopic surgery arm. The low conversion rate could have been an indication of the higher quality of surgeons in this study group. Japan Clinical Oncology Group (JCOG) 0404 and the results of other large clinical trials are shown in Table 1. The 5-year overall survival was 90.4% in the open surgery arm, and 91.8% in the laparoscopic surgery arm. The non-inferiority of laparoscopic D3 dissection in overall survival was not demonstrated[6]. Additionally, patients assigned to laparoscopic surgery had less blood loss (P<0.001), although laparoscopic surgery lasted 52 minutes longer (P<0.001). The short-term results in this trial are shown in Table 2. Laparoscopic surgery was associated with a shorter time to the first flatus, decreased use of analgesics after 5 days post operation, and a shorter hospital stay. Morbidity was lower in the laparoscopic surgery arm[7]. Unfortunately, the non-inferiority of laparoscopic D3 dissection in overall survival was not demonstrated for stage II and III colorectal cancer, because the overall survival of both arms was unexpectedly similar. Furthermore, the safety of laparoscopic surgery in elderly patients and in those with Stage IV disease for whom less invasive surgery is desirable, has been demonstrated retrospectively, and another randomized controlled trial is now underway[8,9]. Therefore, during the two decades since its initial introduction, data unique to Japan have steadily been accumulated and serves as evidence for the validity of laparoscopic surgery as a standard treatment for colon cancer.

Compared with open surgery, laparoscopic surgery offers many benefits, such as smaller surgical wounds, good esthetic results, less pain, decreased use of analgesics, early recovery of intestinal peristalsis, and a shorter hospital stay[10-19]. In terms of inflammatory cytokine levels, however, the minimal invasiveness of laparoscopic surgery remains controversial. Some studies have reported significantly lower inflammatory cytokine levels after laparoscopic surgery[12,20], whereas others have found no significant differences in such levels between laparoscopic surgery and open surgery[13,21,22]. Further studies are warranted to objectively evaluate the minimal invasiveness of laparoscopic surgery for colorectal cancer.

Rectal cancer

Total mesorectal excision has been accepted as a standard procedure for the reduction of local recurrence throughout the world. As for the clinical significance of prophylactic lateral lymph node dissection (LLND), which is aggressively performed in Japan, patient enrollment in a randomized controlled trial comparing this procedure with total mesorectal excision has been completed. The 5-year relapse free survival was 73.4% and 73.3% in the mesorectal excision + LLND group and the mesorectal excision group, respectively. The non-inferiority of mesorectal excision was not confirmed. The 5-year overall survival was "not significantly different from both groups. The numbers of patients with local recurrence were 25 (7.1%) and 44 (12.6%) in the mesorectal excision + LLND group and the mesorectal excision group, respectively (p=0.02)[23].

Whether or not laparoscopic surgery is an appropriate procedure for rectal cancer remains unclear. In many randomized, controlled trials conducted in Western countries, laparoscopic surgery is not indicated for the treatment of rectal cancer. The MRC (Medical Research Council) trial, a randomized, controlled trial of patients with colorectal cancer, reported a higher rate of tumor-positive circumferential resection margins after laparoscopic surgery, despite no significant differences in the local recurrence rate or overall survival rate as compared to laparoscopic surgery. Therefore, oncologic safety was not demonstrated.

Numerous clinical research investigations, including randomized controlled trials comparing laparoscopic surgery and open surgery in patients with rectal cancer, and meta-analyses, have been conducted in recent years. COLOR II (2004-2010), conducted in the Netherlands, and the COREAN trial (2006-2009) in Korea exemplify randomized, controlled trials focusing on advanced rectal cancer (cT3, T4)[24-27]. The COREAN trial showed more significance of laparoscopic surgery between groups with regard to the short-term outcome. Three year disease-free survival was 72.5% for the open surgery group and 79.2% for the laparoscopic surgery group, with a difference that was lower than the prespecified non-inferiority margin. 25 (15%) patients died in the open group and 20 (12%) died in the laparoscopic group. No deaths were treatment related. These results show that laparoscopic surgery for locally advanced rectal cancer after preoperative chemoradiotherapy provides similar outcomes for disease-free survival as compared to open surgery[25]. The same applies to the COLOR II trial targeting 1,044 cases of rectal cancer. At 3 years, the locoregional recurrence rate was 5.0% in the two groups. Disease-free survival rates were 74.8% in the laparoscopic surgery group and 70.8% in the open surgery group. Overall survival rates were 86.7% in the laparoscopic surgery group and 83.6% in the open surgery group[27]. Therefore, two large scale randomized controlled trial demonstrated that laparoscopic surgery is safe and short-term benefit compared with open surgery. In addition, those results show that laparoscopic surgery provides similar long-term outcome as open surgery.

The ACOSOG Z6051 randomized controlled trial was expected to determine whether or not laparoscopic surgery is non - inferior to open surgery, as determined by gross pathologic and histologic evaluation of the resected specimen. The primary outcome assessing efficacy was a composite of circumferential radial margin greater than 1 mm, distal margin without tumor, and completeness of total mesorectal excision. Successful resection occurred in 81.7% of laparoscopic surgery cases and 86.9% of open surgery cases and did not support non-inferiority. Negative circumferential radial margin was observed in 90% of the overall group (87.9% laparoscopic surgery and 92.3% open surgery; P= 0.11). Distal margin result was negative in more than 98% of patients, irrespective of type of surgery (P=0.91)[28].

The ALaCaRT trial was conducted between March 2010 and November 2014. Twenty-six accredited surgeons from 24 sites in Australia and New Zealand randomized 475 patients with T1-T3 rectal adenocarcinoma less than 15 cm from the anal verge. The primary end point was a composite of oncological factors indicating an adequate surgical resection, with a non-inferiority boundary of −8%. This trial showed that, among patients with T1-T3 rectal tumors, non-inferiority of laparoscopic surgery compared with open surgery for successful resection was not established[29].

These data demonstrated that laparoscopic surgery, as compared with open surgery, could not confirm for pathological outcomes.

In Japan, phase II trials are being performed to evaluate the safety and efficacy of laparoscopic surgery for clinical Stage 0/I lower rectal cancer. Accredited surgeons from 43 institutions in Japan participated in the trial. For the first step, studies were designed to assess the technical safety of laparoscopic surgery. The primary endpoint was the incidence of adverse events. If the safety is confirmed, the second step will focus on oncologic outcomes, with overall survival as the primary endpoint. Secondary endpoints in both the first and second steps included recurrence-free survival, operative mortality, the rate of histologically curative surgery, and the rate of conversion to open surgery. A total of 495 patients were registered between February 2008 and August 2010. Sphincter-preserving procedures were performed in 477 (97%) patients. The positive resection margin rate was 0.4% (2/490), and 68.6% (336/490) of the patients were graded stage 0/I. There were no perioperative mortalities. Twenty-four intraoperative and 160 postoperative complications occurred, and the morbidity rate was 23.9% (117/490). The anastomotic leakage rate in patients who underwent anterior resection was 8.3% (33/400), and 9.1% (7/77) in patients who underwent intersphincteric resection. Nineteen (3.9%) patients underwent reoperation[30].

In Japan, a large multicenter cohort study with more than 1000 cases of low rectal cancer was planned to settle this issue. The data of patients with clinical stage II-III low rectal cancer below the peritoneal reflection were collected and analyzed retrospectively. The operations were performed

from 2010 to 2011 and the cases were followed up until 2015. A total of 1608 cases were collected from 69 institutes, and 1500 cases were eligible for analysis. The cases were matched using propensity scores (482 open cases and 482 laparoscopic cases). The conversion rate from laparoscopic to open surgery was 5.2%. Estimated blood loss during laparoscopic surgery was significantly less than that during open surgery (90 ml vs 625 ml, p<0.001). Overall, the occurrence of complications after laparoscopic surgeries was less than that after open surgeries (30.3% vs 39.2%, p= 0.005), and the proportion of anal preservation was higher in the laparoscopic group than in the open group (60.0% vs 53.3%, p=0.037). Three-year overall survival rates of R0 surgery cases were 91.7% and 92.0% in the laparoscopic and open groups, respectively, and no significant difference was shown between the two groups. No significant difference was observed in relapse-free survival between the two groups (72.1% vs 75.1%). Even for advanced, very low rectal cancer below the peritoneal reflection, laparoscopic surgery could be considered a useful option based on the short- and long-term results of our large cohort trial[31].

New Operative Techniques

Recently, we observed reports of laparoscopic surgery with new surgical techniques and instruments. New laparoscopic procedures such as natural orifice specimen extraction (NOSE), single-port surgery, and robotic surgery are being attempted for colorectal cancer as well as for other diseases ordinarily taken care of by endoscopic surgery[32-34]. In addition, Trans anal-Total Mesorectal Excision (Ta-TME) has been tested to seek improvement of short- and long-term results for rectal cancer.

Regarding NOSE for colorectal disease, a procedure involving removal of the resected bowel via the vagina or anus, it has frequently been reported. The procedure performed via the vagina is applicable to all bowel resection techniques, including right hemicolectomy, but the procedure via the anus is applicable only to the resection of rectal cancers located at low levels. NOSE requires resection and anastomosis within the peritoneal cavity and is, therefore, more difficult and time consuming than laparoscopic surgery. In terms of short-term outcomes (e.g., safety), NOSE is reportedly not inferior to laparoscopic surgery. However, despite the complex manipulations required, the only significant advantage of NOSE is the esthetic outcome, according to the data collected to date.

With regard to Single Port Surgery, we could not only research retrospective papers, but also systematic reviews. Accordingly, a systematic review was performed by Hirano et al. from 2008 to December 2014[35]. The aim was to determine the effect of single-incision laparoscopic colectomy for colorectal cancer on short-term clinical and oncological outcomes by comparison with multiport conventional laparoscopic colectomy. A total of 15 trials with 589 patients who underwent single-incision laparoscopic colectomy for colorectal cancer were conducted. No significant differences between the groups were noted in terms of mortality or morbidity. The benefit of the single-incision laparoscopic colectomy approach included a reduction in conversion rate to laparotomy, but there were no significant differences in other short-term clinical outcomes between the groups. Satisfactory oncological surgical quality was also demonstrated for single-incision laparoscopic colectomy for the treatment of colorectal cancer, with a similar average lymph node harvest and proximal and distal resection margin length as multiport conventional laparoscopic colectomy.

During robotic surgery, the surgeon remotely controls the robot three-dimensionally from a console, with the use of a binocular magnifier. Physiological tremor of the surgeon is eliminated electronically through the automation of the robot. The three-dimensional visual field and the manipulation of the forceps, with a high degree of freedom and maneuverability, can evidently shorten the learning curve for surgeons. However, a large system is needed, preoperative manipulations are complex, and the devices and materials are expensive. Robotic surgery has been reported to be excellent as a means of preserving nerves during pelvic surgery and improving the precision of total mesorectal resection. We identified a systemic review of robotic surgery for rectal cancer. The systematic review was performed to identify relevant articles from January 2007 to November 2013[36]. After the initial screen of 380 articles, 20 papers were selected for review:

In this review, median anastomotic leak rate was found to be similar with mean of 6.4% in the robotic group compared to 7.4% in the laparoscopic group. The quality of the total mesorectal excision was also assessed. Recurrence of cancer from 6 trials ranged from no recorded recurrence to 5.5%. Three-year disease-free survival ranges from 77.6 to 100% with overall survival between 90%-97%. A review of the selected articles found four trials which explored the cost of robotic surgery. In two of the trials, the cost of robotic rectal surgery was estimated to be three times more expensive than laparoscopic rectal surgery. Also, the remaining two trials found robotic rectal surgery to be more expensive when compared to laparoscopic and open rectal surgery.

In Japan, robotic surgery for colorectal cancer is not covered by the national health insurance, so patients undergoing this surgery must pay all the related hospital expenses themselves. Therefore, it would be desirable to clarify the features in which robotic surgery is superior to laparoscopic surgery.

Conclusions

The colon and rectum are rich in elasticity, and their resection and anastomosis are possible, leaving only a small surgical wound and enabling segments to easily be exposed for surgery. The visual field magnification during a laparoscopic surgery allows a high degree of surgical precision in the narrow pelvic cavity. The colon and rectum are, there-

fore, suitable for laparoscopic surgery. If further efforts are made to achieve the standardization of laparoscopic surgical procedures and the improvement of the laparoscopic surgery educational system, laparoscopic surgery will undoubtedly become a standard treatment for many diseases of the anus, rectum, and colon. Furthermore, it is anticipated that new techniques such as robotic surgery will be proven even safer in the near future. Moreover, it will be desirable to develop and improve the operative procedures in terms of low invasiveness, high safety, radical treatment capability, and cost-effectiveness.

Conflicts of Interest

The authors declare that there are no conflict of interest.

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