World Journal of Clinical Oncology

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DOI: 10.5306/wjco.v7.i2.155

World J Clin Oncol 2016 April 10; 7(2): 155-159
ISSN 2218-4333 (online)

EDITORIAL

Present laparoscopic surgery for colorectal cancer in Japan

Takeo Sato, Masahiko Watanabe

Takeo Sato, Masahiko Watanabe, Department of Surgery, Kitasato University School of Medicine, Sagamihara, Kanagawa 252-0374, Japan

Author contributions: Sato T and Watanabe M contributed equally to this work; Sato T drafted the manuscript; Watanabe M made significant edits of intellectual content; Sato T and Watanabe M approved the overall works.

Conflict-of-interest statement: Sato T and Watanabe M declare they have no conflict of interest or financial ties.

Correspondence to: Masahiko Watanabe, MD, PhD, Department of Surgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan. intl-aff@kitasato-u.ac.jp
Telephone: +81-42-7788111
Fax: +81-42-7789556

Received: July 1, 2015
Peer-review started: July 7, 2015
First decision: September 22, 2015
Revised: October 19, 2015
Accepted: December 17, 2015
Article in press: December 18, 2015
Published online: April 10, 2016

Abstract

In many clinical studies, laparoscopic surgery (LS) for colon cancer has been shown to be less invasive than open surgery (OS) while maintaining similar safety. Furthermore, there are no significant differences between LS and OS in long-term outcomes. Thus, LS has been accepted as one of the standard treatments for colon cancer. In the treatments of rectal cancer as well, LS has achieved favorable outcomes, with many reports showing long-term outcomes comparable to those of OS. Furthermore, the magnification in laparoscopy improves visualization in the pelvic cavity and facilitates precise manipulation, as well as providing excellent educational effects. For these reasons, rectal cancer has seemed to be well indicated for LS, as has been colon cancer. The indication for LS in the treatment of locally advanced rectal cancer, which is relatively unresectable (*e.g.*, cancer invading other organs), remains an open issue. In recent years, new techniques such as single-port and robotic surgery have begun to be introduced for LS. Presently, various clinical studies in our country as well as in most Western countries have demonstrated that LS, with these new techniques, are gradually showing long-term outcomes.

Key words: Laparoscopic surgery; Colorectal cancer; Colectomy; Total mesorectal excision; Randomized controlled trial; Robotic surgery; Single-port surgery

Core tip: Our findings describe the merits of laparoscopic surgery (LS) over open surgery. We present some new LS techniques. We conclude with an explanation of the safety and curability of LS for colorectal cancer.

Sato T, Watanabe M. Present laparoscopic surgery for colorectal cancer in Japan. *World J Clin Oncol* 2016; 7(2): 155-159 Available from: URL: http://www.wjgnet.com/2218-4333/full/v7/i2/155.htm DOI: http://dx.doi.org/10.5306/wjco.v7.i2.155

INTRODUCTION

Laparoscopic surgery (LS) 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 LS were gradually expanded to include colorectal cancer and inflammatory bowel diseases such as appendicitis and diverticulitis[3]. Around 1994, however, frequent port site recurrences (PSR) after LS for colon cancer were reported, resulting in LS temporarily being deemed to be contraindicated[4]. On the other hand, few reports on PSR were reported in Japan at that time. The reason LS had a very low incidence of PSR was that the indication of LS was limited to early stage cancer in Japan. PSR was, at that time, reported as arising from the spreading of cancer cells during LS due to inappropriate manipulations of the tumor. After this realization, the principles of surgical oncology were strictly followed resulting in decreased port site recurrence; and presently, there have been no such cases reported. As the use of LS spread, clinical studies began to be carried out comparing its short- and long-term outcomes with those of open surgery (OS)[5]. On the basis of these results, LS spread rapidly in Japan becoming another standard therapy for bowel diseases, in addition to the conventional OS. Herein, we outline the current status of LS for colorectal cancer in Japan and its perspectives for the future.

COLON CANCER

Regarding colon cancer, randomized controlled trials (RCTs) comparing LS with OS have been carried out, and numerous meta-analyses of data from such trials have been reported. These reports demonstrated the superiority of LS over OS in terms of short-term outcomes and the non-inferiority of LS to OS in terms of long-term outcomes. As LS has increasingly become a standard procedure, the difference in operative time *vs* OS has gradually been reduced. In Japan, a randomized controlled trial to confirm the non-inferiority of LS to OS in terms of overall survival was conducted. And the primary endpoint of 5-year overall survival was demonstrated in ASCO-GI 2014[6]. Eligibility criteria included: Colon cancer; tumor located in the cecum, ascending, sigmoid, or recto-sigmoid colon; T3 or T4 without involvement of other organs; N0-2; and M0. Patients were randomized preoperatively and underwent tumor resection with D3 dissection. A total of 1057 patients were randomized (OP 528, LAP 529) from October 2004 through March 2009. Conversion to OS was only needed for 29 patients (5.4%) in the LS arm. The low conversion rate indicated a high quality of surgeons in this study group. JCOG0404 and results of other large clinical trials are shown in Table 1. The 5-year OS was 90.4% (95%CI: 87.5%-92.6%) in the OS arm, and 91.8% (95%CI: 89.1%-93.8%) in the LS arm. The non-inferiority of laparoscopic complete mesocolic excision in overall survival was not demonstrated[4]. Additionally, patients assigned to LS had less blood loss ($P < 0.001$), although LS lasted 52 min longer ($P < 0.001$). The short-term results in this trial are shown in Table 2. LS was associated with a shorter time to the first flatus, decreased use of analgesics after 5 postoperative days, and a shorter hospital stay. Morbidity [14.3% (76/533) *vs* 22.3% (117/524), $P < 0.001$] was lower in the LS arm[7]. Unfortunately, the non-inferiority of laparoscopic complete mesocolic excision in overall survival was not demonstrated for stage Ⅱ, Ⅲ colorectal cancer, however, because the overall survival of both arms was relatively identical and better than expected. Furthermore, the safety of LS in elderly patients and those with Stage Ⅳ disease, for whom less invasive surgery is desirable, has been demonstrated retrospectively, and another RCT is now underway[8,9]. Therefore, during the two decades since its initial introduction, data unique to Japan, serving as evidence for the validity of LS as a standard therapy for colon cancer, have steadily been accumulated.

RECTAL CANCER

Standard treatment procedures for advanced rectal cancer have yet to be established in most Western countries and Japan. Control of local recurrence, a characteristic of advanced rectal cancer, is an important treatment goal, along with the improvement of overall survival. Total mesorectal excision (TME) 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, which is aggressively performed in Japan, patient enrollment in an RCT comparing this procedure with TME has been completed. The results of this trial are awaited.

Whether or not LS is an appropriate procedure for rectal cancer remains unclear. In many RCTs conducted in Western countries, LS is not indicated for the treatment of rectal cancer. The Medical Research Council CLASIC trial, an RCT of patients with colorectal cancer, reported a higher rate of tumor-positive circumferential resection margins after LS, despite no significant differences in the local recurrence rate or overall survival rate compared to LS. Oncologic safety was therefore not demonstrated.

Numerous clinical research investigations including RCTs comparing LS and OS in patients with rectal cancer, and meta-analyses have been conducted in recent years. COLOR Ⅱ (2004-2010) designed in the Netherlands and the COREAN trial (2006-2009) in South Korea exemplify RCTs focusing on advanced rectal cancer (cT3, T4)[10-13]. Both of these trials showed more significance of LS between groups in short-term outcome, and no significant differences were found in the complication rate. The long-term outcome of the CREAN trial reported no statistical differences in 3-year event-free survival rate at the primary end point, local recurrence rate at the secondary endpoint, overall survival rate, and quality of life. The same applies to the COLOR Ⅱ trial targeting 1044 cases of rectal cancer, where no statistical significances were shown between the two groups in 3-year local recurrence rate at the primary end point, and overall survival rate and event-free survival rate at the secondary end point.

In Japan, phase Ⅱ studies are being performed to

Table 1 Trial JCOG0404 and other large clinical trials

Trials	Cases Open:Laparoscopy	Conversion rate (%)	Overall survival (%) Open:Laparoscopy
COST	428:435	21	85:86
Braga	201:190	4	83:84
CLASIC C	268:526	16	68:67
COLOR	621:627	19	84.2:81.8
JCOG 0404	533:524	29 cases 5.40%	> 90

evaluate the safety and effectiveness of LS for clinical Stage 0/Ⅰ lower rectal cancer. As the first step, studies were designed to assess the technical safety of LS. 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 OS. The results of these clinical studies are very important for determining the future indications of LS for rectal cancer.

CERTIFICATION SYSTEM FOR SURGEONS

In 2005, the Japan Society for Endoscopic Surgery began a certification system for the fields of gastrointestinal and general surgery. This certification system initially focused on surgical technique. Accreditation in the fields of gastrointestinal and general surgery required experience as the head surgeon or an instructive assistant in at least 20 advanced operations, as well as the ability to independently perform advanced endoscopic surgery in a specialized field, and to provide "procedural guidance" on technique. Along with having the technical skills of a head surgeon, certification required that the candidate could act as a coordinator of LS. Certification is also based on a detailed review of unedited videotapes of the candidates' LSs. About 20%-40% of the applicants who apply receive accreditation. Review criteria are made public, and all reviews are conducted on an impartial basis.

Minimal invasiveness of laparoscopic colectomy

Compared with OS, LS offers many benefits, such as a small surgical wound, good esthetic results, less pain, decreased use of analgesics, early recovery of intestinal peristalsis, and a shorter hospital stay[14-23]. In terms of inflammatory cytokine levels, however, the minimal invasiveness of LS remains controversial. Some studies have reported significantly lower inflammatory cytokine levels after LS[15,16], whereas others have found no significant difference in such levels between LS and OS[17,24,25]. Further studies are needed to objectively evaluate the minimal invasiveness of LS for colorectal cancer.

Table 2 Short-term results in the JCOG0404 trial

Variables	Laparoscopic surgery	Open surgery	*P* value
Bleeding (mL)	50	85	< 0.001
Operation time (min)	211	159	< 0.001
Lymph node dissections	=		Not significant
First postoperative flatus	<		
Postoperative hospital stay	<		
Surgical site infection (superficial layer)	<		
Complications (anastomosis leakage/ileus)	=		

NEW OPERATIVE TECHNIQUES

New laparoscopic procedures such as natural orifice specimen extraction (NOSE), single-port surgery, and robotic surgery have begun to be attempted for colorectal cancer as well as other diseases covered by endoscopic surgery[26-28]. Regarding NOSE for colorectal disease, a procedure involving removal of the resected bowel *via* the vagina or anus 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 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 LS. In terms of short-term outcomes (*e.g.*, safety), it has been reported that NOSE is not inferior to LS. However, despite the complex manipulations required, the only significant advantage of NOSE is the esthetic outcome, according to the data collected to date.

In Japan, robotic surgery for colorectal cancer is not covered by the national health insurance, so patients receiving this surgery must pay all the related hospital expenses themselves. 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 erased electronically through the automation of the robot. The three-dimensional visual field and the manipulation of the forceps with a high degree of freedom can evidently shorten the learning curve for surgeons. However, a large-scale 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 mesenteric resection. On the other hand, smoothly dealing with accidental events during surgery (*e.g.*, bleeding) is anticipated to be difficult because this surgery requires such a large-scale system. Therefore, it would be desirable to clarify the features if in which robotic surgery is superior to LS.

CONCLUSION

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 of a laparoscopy allows high precision surgery in the narrow pelvic cavity. The colon and rectum can, therefore, be regarded as organs suitable for LS. If further efforts are made to achieve standardization of LS procedures and improvement of the LS educational system, LS will undoubtedly become a standard therapy for many bowel diseases. Furthermore, it is anticipated that new techniques such as reduced port surgery and robotic surgery will be proven safe in the near future. In any event, it is desirable to develop and advance operative procedures favorable from the viewpoints of low invasiveness, high safety, radical treatment capability, and cost effectiveness.

In Japan, the safety and curability of surgery for colorectal cancer are much better than in most Western countries, facilitating the rapid expansion of LS. LS is expected to gain further acceptance and progress even farther. However, daily efforts of colorectal surgeons to improve their surgical skills and to continuously collect and analyze data are considered most important.

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P- Reviewer: Golffier C, Ji W, Surlin V
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Li D

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