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
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 1567 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.
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

<table>
<thead>
<tr>
<th>Author or trial name (reference number)</th>
<th>Number of patients</th>
<th>Mortality rate</th>
<th>Morbidity rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Laparoscopic</td>
<td>Open</td>
</tr>
<tr>
<td>Hewitt et al. (29)</td>
<td>16</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Milsom et al. (30)</td>
<td>80</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Schwenk et al. (31)</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Curet et al. (32)</td>
<td>43</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Braga et al. (33)</td>
<td>183</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>Lacy et al. (18)</td>
<td>219</td>
<td>111</td>
<td>108</td>
</tr>
<tr>
<td>Hasegawa et al. (28)</td>
<td>50</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>COST (19)</td>
<td>810</td>
<td>415</td>
<td>395</td>
</tr>
<tr>
<td>Kaiser et al. (34)</td>
<td>48</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Leung et al. (21)</td>
<td>403</td>
<td>203</td>
<td>200</td>
</tr>
<tr>
<td>CLASSICC UK (22)</td>
<td>413</td>
<td>273</td>
<td>140</td>
</tr>
<tr>
<td>COLOR (35)</td>
<td>1082</td>
<td>536</td>
<td>546</td>
</tr>
<tr>
<td>Liang et al. (36)</td>
<td>269</td>
<td>135</td>
<td>134</td>
</tr>
</tbody>
</table>
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. The 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 country. 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 open surgery (2.4% versus 0.7%) and positive rate of circumferential resection margin in laparoscopic group was higher than that in open surgical group (35% versus 33%). There are no many reports regarding complications between laparoscopic and open surgery in terms of long-term survival. However, there are some reports that there is no significant difference in terms of cancer-related mortality and recurrence rate in terms of cancer-related mortality and recurrence rate between laparoscopic and open surgery. Therefore, 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.

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

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

NS, not significant differences.
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.

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 rectal cancer.

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

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

NE, not evaluated.

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.

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.
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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