

Open versus Laparoscopic Surgery for Advanced Low Rectal Cancer

A Large, Multicenter, Propensity Score Matched Cohort Study in Japan

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 on behalf of Japan Society of Laparoscopic Colorectal Surgery

Background: Laparoscopic surgery for rectal cancer is widely performed all over the world and several randomized controlled trials have been reported. However, the usefulness of laparoscopic surgery compared with open surgery has not been demonstrated sufficiently, especially for the low rectal area.

Objective: The aim of this study was to investigate the hypothesis that laparoscopic primary tumor resection is safe and effective when compared with the open approach for locally advanced low rectal cancer.

Patients and Methods: Data from patients with clinical stage II to III low rectal cancer below the peritoneal reflection were collected and analyzed. The operations were performed from 2010 to 2011. Short-term outcomes and long-term prognosis were analyzed with propensity score matching.

Results: Of 1608 cases collated from 69 institutes, 1500 cases were eligible for analysis. The cases were matched into 482 laparoscopic and 482 open cases. The mean height of the tumor from the anal verge was 4.6 cm. Preoperative treatment

was performed in 35% of the patients. 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 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%, $P = 0.005$). Three-year overall survival rates were 89.9% [95% confidence interval (95% CI) 86.7–92.4] and 90.4% (95% CI 87.4–92.8) in the laparoscopic and open groups, respectively, and no significant difference was seen between the 2 groups. No significant difference was observed in recurrence-free survival (RFS) between the 2 groups (3-year RFS: 70.9%, 68.4 to 74.2 vs 71.8%, 67.5 to 75.7).

Conclusion: Laparoscopic surgery could be considered as a treatment option for advanced, low rectal cancer below the peritoneal reflection, based on the short-term and long-term results of this large cohort study (UMIN-ID: UMIN00013919).

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Rectal cancer is a major cause of death worldwide, and the number of patients has significantly increased. The treatment strategy for rectal cancer, especially low rectal cancer, has changed dramatically in the last century. First described around 1900, abdominoperineal resection subsequently became the standard surgical treatment for rectal cancer, but the attendant risk of operative mortality was very high.¹ Preservation of the anal sphincter is a long-running theme that still exists today. Anterior resection and the pull-through technique were developed, and progress has been made in these procedures. In the 1980s, total mesorectal excision was advocated, and laparoscopic surgery was introduced.^{2,3} In Japan, conducting an ideal randomized controlled study for rectal cancer patients is quite difficult because several treatment options exist, such as the open approach, the laparoscopic approach, lateral lymph node dissection, and preoperative chemoradiotherapy determined by the surgeon's preference and/or institutional policy. In 2009, a total of 1057 cases of laparoscopic rectal surgery were reported by Miyajima et al.⁴ They concluded that laparoscopic surgery is feasible and safe in selected patients with rectal cancer, with favorable short-term and mid-term outcomes. Laparoscopic surgery for rectal cancer was reported to be more difficult than that for colon cancer, so rectal cancer had been eliminated from clinical trials in the early 2000s.^{5–8} Several large-scale clinical trials proved the usefulness of laparoscopic surgery for colon cancer compared with open surgery with regard to short-term outcomes, and long-term noninferiority has also been demonstrated. However, only a few clinical trials demonstrated the benefit of laparoscopic surgery for rectal cancer compared with open surgery,^{9,10} whereas other clinical trials did not show the noninferiority of laparoscopic surgery.^{11,12} To the best of our knowledge, there is no large-scale study on low rectal cancer only.

Therefore, we planned this large retrospective cohort study of laparoscopic and open surgery for locally advanced “low” rectal cancer. Patient data from 69 institutes were collected and analyzed. Propensity score matching was used for protocol analysis.

PATIENTS AND METHODS

This study involved patients with clinical stage II and III low rectal cancer who underwent open or laparoscopic surgery at 69 institutes participating in the Japan Society of Laparoscopic Colorectal Surgery from January 2010 to December 2011. This cohort study and the associated protocol were registered in UMIN in 2014 (UMIN000013919). After approval from each institutional ethical committee, patient data were collected from clinical report forms. Most of the surgeons (86%) had experience of more than 100 open surgeries and 100 laparoscopic surgeries. All the surgeons had experience of at least 50 open surgeries and almost all (97%) had experience of at least 30 laparoscopic surgeries. Eligibility criteria were 1) clinical stage II/III low rectal cancer (tumor below the peritoneal reflection) and 2) having undergone primary rectal cancer resection. The exclusion criteria were 1) multiple primary cancers, 2) a history of treatment for other pelvic malignancy, and 3) robotic surgery cases. Emergent cases were excluded from the analysis. The peritoneal reflection was identified by barium or gastrografin enema and/or pelvic magnetic resonance imaging (MRI). The demographic and clinicopathological data of consecutive patients were collected retrospectively, including the American Society of Anesthesiologists physical status classification, preoperative chemoradiotherapy, operative time, blood loss, conversion, intraoperative complications, tumor pathology, length of hospital stay, postoperative

complications, recurrence-free survival (RFS), and overall survival (OS) periods. A positive circumferential resection margin (CRM) was defined according to the Japanese classification of colorectal carcinoma as a pathological positive resection margin (tumor identified at the radial margin).¹³

The primary endpoint of this study was postoperative complications. Secondary endpoints were RFS, OS, local recurrence rate, operative time, blood loss, length of hospital stay, and anastomotic leakage. The proportion of patients requiring reoperation, oral intake on the day after the operation, and increases in C-reactive protein (CRP) and white blood cell count (WBC) on the first postoperative day (POD) were also evaluated.

The sample size was based on the Chi-squared test with a significance level of 0.05 and a power of 0.80. The required sample size for comparison of the proportion of postoperative complications was estimated to be 521 in each matched group. In the calculation, based on the previous findings,¹⁴ the proportions of postoperative complications of laparoscopic and open surgery were expected to be 17% and 24%, respectively.

Statistical Analysis

Case matching was performed using the propensity score of 8 factors: age, body mass index (BMI), sex, history of abdominal operations, tumor distance from the anal verge, tumor depth, lymph node metastasis, and preoperative therapy as prescribed in the protocol. Nearest-neighbor matching without replacement within a caliper was used. According to the suggestion of Austin,¹⁵ the size of the caliper was set as 0.2 of the standard deviation of the logit of the estimated propensity score. Patients who were found to be outside the caliper were excluded. Unmatched patients were also excluded. Although the proportion of patients who underwent laparoscopic surgery in each institute was also prescribed in the protocol, it varied considerably and the use of propensity score matching for the factor was judged to be difficult. All statistical analyses for primary and secondary endpoints were performed on all matched-paired patients. OS was calculated from the date of operation until death from any cause or the date of the last follow-up. RFS was calculated from the date of the operation until the date of confirmed recurrence or any cause of death. Survival curves were estimated using the Kaplan-Meier method, and a comparison was performed with the log-rank test. Categorical variables were analyzed with Fisher exact test. Continuous variables were analyzed using the *t* test. All *P* values were 2-sided and values less than 0.05 were considered statistically significant. Propensity score matching was performed using R software version 3.2.1 (R Core Team, Vienna, Austria). All other analyses, including Lap analysis, were performed using JMP pro 12.0.1 (SAS Institute, Cary, NC).

RESULTS

Data from a total of 1608 patients were collected from 69 institutes, and 108 cases were excluded. Among the remaining 1500 cases, laparoscopic surgery was performed in 574 cases, and open surgery was performed in 926 cases. Using the propensity score, the patients were matched into an open group of 482 and a laparoscopic group of 482 (Fig. 1). The median follow-up period was 3.3 years.

Table 1 summarizes the background data of the overall cohort and matched cases. Before matching, the clinical tumor depth was deeper, the proportion of patients with clinical lymph node metastasis was higher, and the proportion of patients who received preoperative treatment was much lower in the group of open cases. After matching, these results became more balanced: mean age was 63.4 years, mean BMI was 22.4, and mean height of the tumor was 4.6 cm.

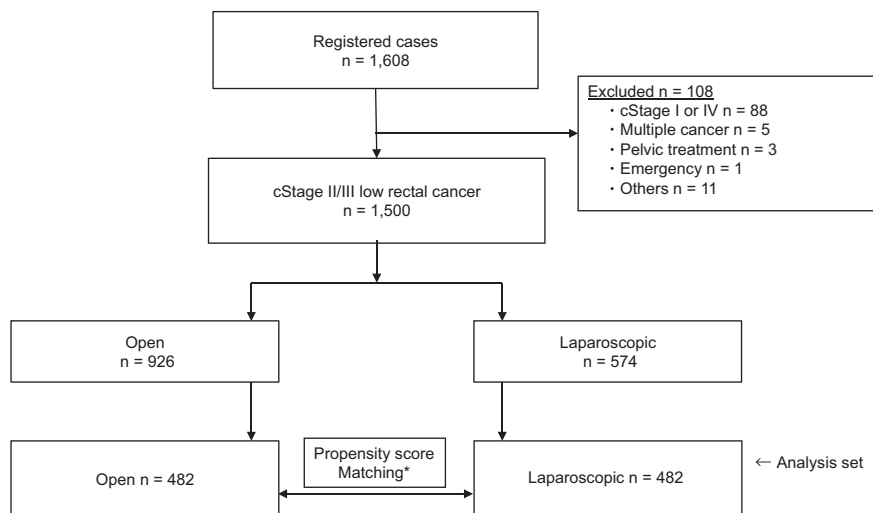


FIGURE 1. Flow diagram of patient disposition. *For propensity score: age, sex, BMI, history of laparotomy, cT, cN, distance from AV, preoperative Tx.

The surgical results are summarized in Table 2. The percentages of laparoscopic low anterior resection and inter-sphincteric resection were 49.2% and 17.8%, respectively, and those of open surgery were slightly lower ($P = 0.042$). The proportion of patients who underwent lateral lymph node dissection was significantly lower in the laparoscopic group, especially for patients without clinically detectable metastasis. The proportion of patients who underwent simultaneous resection of other organs was lower in the laparoscopic group. The operative times in each group were not different, but the operative time of the laparoscopic group was longer than that of the open group when stratified by lateral lymph node dissection. Intraoperative blood loss was significantly lower in the laparoscopic surgery group. The left colic artery was less frequently preserved

in the laparoscopic group, and there were fewer harvested lymph nodes in the laparoscopic group. There were fewer pathologically diagnosed Stage IV cases in the laparoscopic group. Pathologically diagnosed Stage IV disease is liver metastasis, peritoneal metastasis, ovarian metastasis, or distant lymph node metastasis diagnosed intraoperatively. The proportion of cases with a positive circumferential margin was not different between the groups (laparoscopic: 4.53%; open: 4.47%). The proportion of patients with anal sphincteric preservation was higher in the laparoscopic group (60.0%) than in the open group (53.3%) ($P = 0.037$).

The short-term results are summarized in Table 3. Overall, postoperative complications (Clavien-Dindo Classification, \geq grade II) occurred less frequently in the laparoscopic group (30.3%)

TABLE 1. Patient and Tumor Characteristics

Characteristic	Overall Cohort			After Matching		
	Open (n = 926)	Laparoscopic (n = 574)	Absolute Standardized Difference	Open (n = 482)	Laparoscopic (n = 482)	Absolute Standardized Difference
Age, yrs*	63.8 ± 11.1	63.3 ± 12.8	0.042	63.4 ± 10.9	63.4 ± 13.1	0.002
Male sex*	69.4	68.1	0.028	69.5	67.8	0.036
BMI, kg/m ² *	22.2 ± 3.5	22.6 ± 3.6	0.113	22.4 ± 3.4	22.5 ± 3.6	0.015
History of laparotomy*	24.8	25.3	0.012	24.7	25.7	0.024
ASA-PS (≥ 3)	6.5	4.4	0.093	5.6	5.0	0.028
Distance from AV, cm*	4.4 ± 2.2	4.6 ± 2.3	0.089	4.6 ± 2.2	4.6 ± 2.3	0.036
cT*						
cT1/2	5.5	10.8	0.195	10.2	7.9	0.080
cT3	72.7	78.3	0.130	75.7	79.7	0.095
cT4	21.8	10.8	0.301	14.1	12.5	0.049
cN*						
cN +	64.5	56.8	0.158	57.9	56.2	0.034
cLLN +	20.6	19.1	0.038	21.5	20.0	0.038
Preoperative Tx*	20.7	40.2	0.434	34.7	35.1	0.009
CRT	13.5	33.8	0.492	23.2	28.2	0.114
CT	6.4	3.7	0.124	10.0	4.2	0.228
RT	0.9	2.8	0.141	1.5	2.7	0.088

Absolute standardized difference is defined as the difference in means, scaled by the square root of the average of the 2 within-group variances: $d = (\bar{x}_1 - \bar{x}_2) / \sqrt{(s_1^2 + s_2^2) / 2}$, where \bar{x}_1, \bar{x}_2 are group means, and s_1^2, s_2^2 are group variances.

ASA-PS indicates American Society of Anesthesiologists Physical Status; AV, anal verge; BMI, body mass index; CRT, chemoradiotherapy; CT, chemotherapy; LPLN, lateral lymph node; Tx, treatment; RT, radiotherapy.

*Used for propensity score matching. Data presented as % or mean ± standard deviation.

TABLE 2. Operative Outcomes

Characteristic	Open (n = 482)	Laparoscopic (n = 482)	P
Procedure			
LAR	46.7	49.2	0.042
APR	31.5	30.3	
ISR	14.3	17.8	
Hartmann	5.6	2.5	
TPE	1.9	0.2	
Sphincter preserving	61.0	67.2	0.044
Diverting stoma	39.4	45.0	0.703
Lateral lymph node dissection	59.3	25.1	<0.001
cN (+)	12.7	10.6	0.366
cN (−)	46.7	14.5	<0.001
bilateral	52.9	15.6	<0.001
unilateral	6.4	9.5	
Resection of other organs	11.4	7.7	0.049
Autonomic nerve preserving	89.7	93.2	0.063
LCA preserving	56.2	48.7	0.020
Number of lymph nodes examined			
Along IMA	17, 10–26	14, 10–22	0.001
Lateral N w bilateral LLND	17, 10–24	14, 9–22	0.081
w unilateral LLND	8, 4–13	6, 4–10	0.210
Time, min	326, 248–415	330, 259–427	0.124
w LLND	371	460	<0.001
w/o LLND	250	295	<0.001
Blood loss, mL	603, 312–1100	90, 25–210	<0.001
Blood transfusion	21.6	5.6	<0.001
Intraoperative complications \geq Grade 2 CTCAE 4.0	1.0	1.2	1.000
Pathological Stage 0 (pCR)	1.9	1.9	0.200
I	15.2	18.7	
II	39.0	35.3	
III	42.5	43.9	
IV	1.4	0.2	
Circumferential margin (+)	4.47	4.53	1.000

Data presented as % or median, interquartile range.

APR indicates abdominoperineal resection; CTCAE, Common Terminology Criteria for Adverse Events; IMA, inferior mesenteric artery; ISR, intersphincteric resection; LAR, low anterior resection; LCA, left colic artery; LLND, lateral lymph node dissection; pCR, pathological complete response; TPE, total pelvic exenteration.

compared with the open resection group (39.2%; $P = 0.005$), and the relative risk was 0.77 (95% confidence interval: 0.65–0.92). The anastomotic leak rate was not significantly different between the 2 surgical approaches (laparoscopic, 10.8%; open, 11.9%; $P = 0.704$).

When stratified by lateral lymph node dissection (LLND), the complication rate tended to be higher after open surgery than after laparoscopic surgery, but the difference was not statistically significant. The observed proportions after open and laparoscopic surgery

TABLE 3. Short-term Results

	Procedure		RR	95% CI	P
	Open (n = 482)	Laparoscopic (n = 482)			
Postoperative complications	39.2	30.3	0.77	0.65–0.92	0.005
\geq Grade II CD classification					
Wound infection	7.9	5.8	0.74	0.46–1.18	0.251
Leakage/anastomotic cases	11.9	10.8	0.91	0.58–1.41	0.704
Ileus	8.5	6.4	0.76	0.48–1.18	0.270
Urinary dysfunction	6.6	3.7	0.56	0.32–1.00	0.058
Others	14.3	11.8	0.83	0.60–1.16	0.293
w LLND	42.0	38.0	0.91	0.69–1.18	0.508
w/o LLND	35.2	27.7	0.79	0.61–1.01	0.068
Reoperation <30 d	4.6	3.5	0.77	0.42–1.44	0.514
Postoperative blood transfusion	3.7	1.7	0.44	0.19–1.00	0.049
Fasting period (POD)	3, 2–5	2, 1–3			<0.001
Length of hospital stay (POD)	19, 13–26	19, 13–27			0.902
Residual tumor R1/R2	5.8	3.7	0.64	0.36–1.15	0.130
Postoperative chemotherapy	38.9	41.9	1.08	0.92–1.26	0.358

Data presented as % or median, interquartile range.

CD indicates Clavian Dindo; CI, confidence interval; LLND, lateral lymph node dissection; POD, postoperative date; RR, relative risk.

without LLND were 34.8% and 28.1%, respectively, and those after open and laparoscopic surgery with LLND were 41.9% and 36.5%, respectively.

In the laparoscopic group, postoperative blood transfusion was given less frequently after laparoscopic surgery, and the postoperative fasting period was shorter. Length of postoperative hospital stay did not differ between the 2 groups.

OS and RFS did not differ between the laparoscopic and open surgery groups (Figs. 2 and 3). The 3-year estimated OS for patients in the laparoscopic and open surgery groups was 89.9% and 90.4% ($P = 0.128$), respectively, and the 3-year estimated RFS was 70.9% and 71.8% ($P = 0.855$), respectively.

In terms of recurrence site, there was no difference between the laparoscopic and open surgery groups (Supplemental data 1, <http://links.lww.com/SLA/B249>). The 3-year local recurrence rate of the open and laparoscopic group was 8.5% and 10.1%, respectively ($P = 0.410$).

DISCUSSION

Laparoscopic surgery has been one of the optional treatments for rectal cancer in many countries. However, the evidence for laparoscopic resection of rectal cancer, especially low rectal cancer, is insufficient. This study focused on locally advanced low rectal cancer, and is the largest study to date.

In this study, propensity score matching was performed to make the background patient data uniform, because the treatment strategy for rectal cancer seemed to vary widely. The 8 factors of age, BMI, sex, history of abdominal operations, tumor distance from the anal verge, tumor depth, lymph node metastasis, and preoperative therapy were used as described in the protocol. The surgical procedure was not used as a matching factor and was used as one of the surgical results because it is considered to be related to the surgical approach (open or laparoscopic). Patient background was ideally balanced in the groups by matching, and the comparison of open and laparoscopic surgery was considered reliable.

Postoperative complications, the primary endpoint of this study, were observed less frequently after laparoscopic surgeries than after open surgeries. Intraoperative complications occurred in very few cases (1.2% during laparoscopic surgery and 1.0% during open surgery) and there were no differences between the groups. Several studies of rectal cancer have also reported the lower rate of postoperative complications after laparoscopic surgery,^{16–18} and

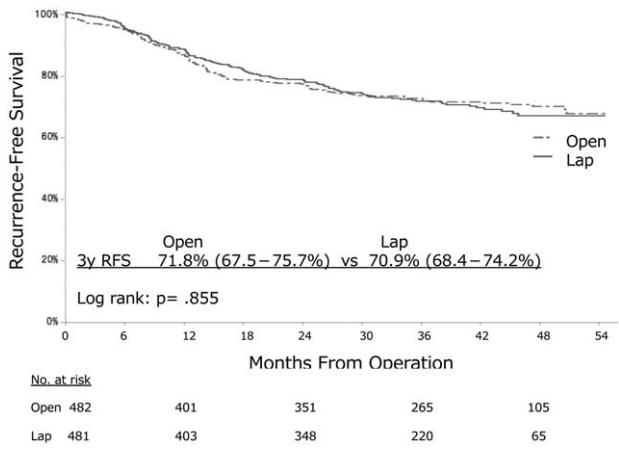


FIGURE 3. Kaplan-Meier plots of recurrence-free survival.

other studies reported that perioperative morbidity and mortality were similar in the laparoscopic and open surgery groups.^{9–12}

There was less blood loss and a lower blood transfusion requirement in the laparoscopic surgery group than in the open surgery group. The difference was statistically significant even when stratified by lateral lymph node dissection, and when stratified by the surgical approach, LLND was correlated with a higher amount of blood loss and longer operative time (Supplemental data 2, <http://links.lww.com/SLA/B250>) as reported by Fujita et al.¹⁹ Less blood loss in laparoscopic surgery for rectal cancer or colon cancer has often been reported as a superior feature of laparoscopic surgery.^{9–11,12}

The longer operative time is a well-known disadvantage of laparoscopic surgery according to several reports.²⁰ In this study, the overall operative time was not different between the groups, but the result is affected by the difference in the proportion of patients who had lateral lymph node dissection. Lateral lymph node dissection takes about 1 hour per side, directly prolonging operative time if performed. In the open surgery group, the proportion of cases that had lateral lymph node dissection was significantly higher than that in the laparoscopic surgery group, and subgroup analysis using lateral lymph node dissection as a factor showed that the operative time of laparoscopic surgery was longer than in open surgery.

Although the postoperative complications were less frequent, WBC and CRP were lower, and blood transfusion was not as frequently required in the laparoscopic group. The length of postoperative hospital stay was not different between the open and laparoscopic groups. This could be because the Japanese health insurance system covers the entire in-hospital fee. In the COREAN trial, the ALaCaRT trial, and ACOSOG Z6051 trial, postoperative hospital stays were not significantly different between the laparoscopic and open groups.^{9,11,12} On the contrary, in the COLOR II trial, hospital stay was significantly shorter after laparoscopic surgery than after open surgery.¹⁰

In this study, there were fewer dissected lymph nodes in the laparoscopic group. All operations were performed according to the Japanese Classification of Colorectal Carcinoma, that is, pericolic lymph nodes within 10 cm of the tumor were removed by lymphadenectomy as part of the colorectal surgery and more than 10 cm of proximal colon was dissected according to the surgeon's definition.¹³ In laparoscopic surgery when an anastomosis is planned, the proximal resection length is limited by the tension-free anastomosis. On the contrary, in open surgery, anastomotic tension is easily checked before the anastomosis, so that proximal additional resection beyond

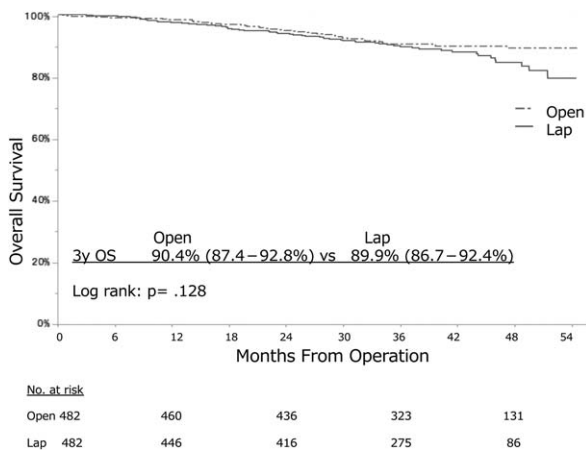


FIGURE 2. Kaplan-Meier plots of overall survival.

the oncological safety margin is often performed. This might explain the difference in the number of resected lymph nodes. In a previous randomized study, the proximal margin was shorter and there tended to be fewer dissected lymph nodes in laparoscopic surgery than in open surgery.¹⁰ According to previous reports, patients who receive CRT tend to have fewer lymph nodes harvested. In our study, the median number of lymph nodes harvested in patients who had received CRT was lower than that in patients who did not (12 vs 18, respectively). This may be one reason why significantly fewer lymph nodes were harvested in the laparoscopic group. When stratified by CRT, there was a tendency for fewer lymph nodes to be harvested in laparoscopic surgery than in open surgery without preoperative treatment (16 vs 20, respectively) and for more lymph nodes to be harvested in laparoscopic surgery than in open surgery with CRT (12 vs 11; Supplemental data 3, <http://links.lww.com/SLA/B250>).

With regard to anal sphincter preservation, in a retrospective observational study of 263 patients with rectal cancer by Park et al,²¹ the sphincter preservation rate was lower in the open surgery group than in the laparoscopic and robotic groups. In our study, the proportion of patients with anal sphincter preservation was significantly higher in the laparoscopic group than in the open group after propensity score matched analysis. The reason for this finding is unclear, but may reflect factors that were not controlled for in this study.

In Japan, lymph nodes in the mesorectum are usually sent for pathological examination just after surgery, so if the tumor does not invade the perirectal fatty tissue, the radial edge of the CRM is reduced. Although there were limited data, the positive CRM rate between the 2 groups was not different. In some previous studies, CRM was not different between the laparoscopic and open surgery groups, and positive CRM rates were higher after laparoscopic surgery than after open surgery in other studies.^{8–11,12} CRM between laparoscopic and open surgery is still an unresolved issue.

With regard to OS, RFS, and local RFS, there are no large studies showing a significant difference between laparoscopic and open surgery for rectal cancer. In the COLOR II study, similar locoregional recurrence after laparoscopic surgery to that after open surgery was demonstrated. Similarly, the COREAN study showed the non-inferiority of disease-free survival after laparoscopic surgery compared with that after open surgery. In the other 2 studies, the ALaCaRT trial and the ACOSOG Z6051 trial, the noninferiority of a positive CRM rate could not be shown after laparoscopic surgery compared with open surgery, and long-term results are awaited. Our study included only low rectal cancer (median tumor distance 4.5 cm from the anal verge), so the recurrence rate seemed high (3-year RFS: laparoscopic group, 71.8%; open surgery group, 70.9%). However, the 3-year-RFS rates for pathological stage III disease were 64.6% and 57.9%, respectively (Supplemental data 4, <http://links.lww.com/SLA/B250>). These data are comparable with those reported by the COREAN trial (around 50% from the graph) and COLOR-II trial (laparoscopic group, 64.9%; open surgery group, 52.0%).^{22,23} In this study, there was no significant difference in OS and RFS between the 2 groups; however, we acknowledge that our study might be somewhat underpowered and our OS and DFS results should be interpreted with caution, particularly given that we only had 3.3 years of follow-up data available. Further study is needed to clarify the long-term outcomes.

The strengths of our study are the number of patients analyzed, the large number of participating institutes, the meticulous selection of patients with rectal cancer located below the peritoneal reflection only, and the validated populations matched by propensity score. In addition, the period during which the patients underwent rectal cancer surgery was very short, at only 2 years. Although some limitations exist such as selection bias due to retrospective cohort in our study, this was reduced as much as possible using propensity

score matching. Although TME is known to be important, the quality of TME was not assessed in this study. The difference between the groups in the number of lateral lymph node dissections performed may have contributed to the difference in complication rates. The conceivable bias was reduced as much as possible using propensity score matching. Thus, we believe that this study offers the highest level of evidence currently available for patients with locally advanced low rectal cancer.

CONCLUSIONS

Laparoscopic surgeries for low rectal cancer were safely performed in the 69 participating institutes. The occurrence of postoperative complications was significantly lower after laparoscopic surgery than after open surgery. The RFS and OS rates were not significantly different between the laparoscopic and open surgery groups during the limited follow-up duration (median 3.3 years) possible in this study. Even for advanced very low rectal cancer below the peritoneal reflection, laparoscopic surgery could be considered as a useful option based on the results of this large cohort study.

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