Long-term Oncologic Outcomes of Laparoscopic Versus Open Surgery for Rectal Cancer

A Pooled Analysis of 3 Randomized Controlled Trials

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Objective: To compare long-term oncologic outcomes between laparoscopic and open surgery for rectal cancer and to identify independent predictors of survival.

Background: Few randomized trials comparing laparoscopic and open surgery for rectal cancer have reported long-term survival data.

Methods: Data from the 3 randomized controlled trials comparing curative laparoscopic (n = 136) and open surgery (n = 142) for upper, mid, and low rectal cancer conducted at the Prince of Wales Hospital, Hong Kong, between September 1993 and August 2007 were pooled together for this analysis. Survival and disease status were updated to February 2012. Survival was calculated using the Kaplan-Meier method, and independent predictors of survival were determined using the Cox regression analysis.

Results: The demographic data of the 2 groups were comparable. The median follow-up time of living patients was 124.5 months in the laparoscopic group and 136.6 months in the open group. At 10 years, there were no significant differences in locoregional recurrence (5.5% vs. 9.3%; $P = 0.296$), cancer-specific survival (82.5% vs. 77.6%; $P = 0.443$), and overall survival (63.0% vs. 61.1%; $P = 0.505$) between the laparoscopic and open groups. There was a trend toward lower recurrence rate at 10 years in the laparoscopic group than in the open group among patients with stage III cancer ($P = 0.078$). The Cox regression analysis showed that stage III cancer, lymphovascular permeation, and blood transfusion, but not the operative approach, were independent predictors of poorer cancer-specific survival.

Conclusions: This pooled analysis with a follow-up of more than 10 years confirms the long-term oncologic safety of laparoscopic surgery for rectal cancer.

Keywords: laparoscopic surgery, oncologic outcomes, pooled analysis, randomized controlled trials, rectal cancer

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In recent years, accumulating evidence from single-center and multicenter randomized trials indicates that laparoscopic surgery for rectal cancer is associated with earlier postoperative recovery, lower morbidity, and better short-term quality of life than open surgery.[1–5] Oncologic clearance in terms of resection margins and number of lymph nodes removed are also similar between the laparoscopic and open groups.[1–5] However, none of the short-term benefits would be important if the incidence of recurrence and long-term survival are compromised. A detailed analysis of long-term oncologic outcomes is therefore mandatory to establish the role of laparoscopic surgery for rectal cancer.

To date, only a few randomized trials comparing laparoscopic and open surgery for rectal cancer have reported 5-year survival data.[4–6] However, none of these studies were specifically designed and powered to address long-term oncologic end points.[1,4–6] More recently, several meta-analyses comparing long-term oncologic outcomes between laparoscopic and open surgery for rectal cancer have been published, but a strong conclusion regarding long-term survival could not be drawn because of lack of good-quality evidence.[7–9] Furthermore, most of these meta-analyses on survival outcomes were performed using published data instead of raw trial data or individual patient data and hence their results might not be completely reliable.[10,11]

We have recently reported the 5-year and 10-year results of a randomized trial comparing laparoscopic-assisted (Lap) and conventional open (Open) resection for upper rectal cancer.[12,13] Our study confirmed that Lap anterior resection (AR) for upper rectal cancer is associated with fewer long-term complications and similar 10-year oncologic outcomes when compared with Open surgery. In another randomized trial, we have shown that Lap abdominoperineal resection (APR) improves postoperative recovery and seemingly does not jeopardize 5-year survival when compared with Open surgery for low rectal cancer located within 5 cm from the anal verge.[14] In a third randomized trial, we have demonstrated that Lap total mesorectal excision (TME) with anal sphincter preservation improves postoperative recovery, reduces short-term and long-term morbidity rate, and seemingly does not jeopardize 5-year survival when compared with Open surgery for mid and low rectal cancer.[15]

It is noteworthy that our 3 randomized trials were started at different times. The first trial was the Lap AR trial for upper rectal cancer, which was started in September 1993. We initially mainly focused on tumors located at the rectosigmoid region because it is the commonest site for colorectal cancer, and Lap AR is technically easier and straightforward to perform. The Lap APR trial was started in July 1994 to specifically investigate the safety and efficacy of laparoscopic surgery for low rectal cancer. Patients with mid rectal cancer who required sphincter-preserving TME were excluded from these early trials because Lap TME has been regarded as one of the most technically demanding operations in the field of laparoscopic colorectal surgery. However, with advancement in laparoscopic technology and accumulation of laparoscopic experience, we decided to embark on the third trial in 2001 that aimed to evaluate the role of Lap TME in patients with mid rectal cancer.

Although our randomized trials have consistently demonstrated similar 5-year survival between the Lap and Open groups, the relatively small sample sizes of these trials may not allow very firm conclusion regarding long-term survival to be drawn.[13,14] We therefore conducted this pooled or combined analysis of the

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3 randomized trials with updated survival data to compare (with greater statistical power) the long-term oncologic outcomes between laparoscopic and open surgery for rectal cancer and to identify independent predictors of survival after curative rectal cancer surgery.

PATIENTS AND METHODS

Between September 1993 and August 2007, 332 patients were enrolled into 3 separate randomized controlled trials comparing Lap and Open surgery for rectal cancer conducted at the Prince of Wales Hospital, Hong Kong. The first study randomized 153 patients with upper rectal cancer (located between 12 and 15 cm from the anal verge) between September 1993 and October 2002 to undergo either Lap or Open AR.[12,13] The second study randomized 99 patients with low rectal cancer within 5 cm from the anal verge between July 1994 and February 2005 to undergo either Lap or Open APR.[14] The third study randomized 80 patients with mid and low rectal cancer (located between 5 and 12 cm from the anal verge) between August 2001 and August 2007 to undergo either Lap or Open TME with anal sphincter preservation.[15] All 3 studies were approved by the local ethics committee. Operative techniques, perioperative management, definitions of study endpoints, and results of these studies have been reported previously.[12–16] Heterogeneity between the 3 trials was minimized by the same study design and methodology.

With the exception of tumor location, all 3 randomized controlled trials had similar inclusion and exclusion criteria. We excluded the following patients: patients with tumor larger than 6 cm or with tumor infiltration to the adjacent organs on computed tomography (CT), patients who presented with recurrent disease, patients with synchronous colorectal tumors, patients with intestinal obstruction or perforation, and patients who did not consent to randomization.

Patients who required neoadjuvant therapy were not included in our trials. During the early study period between early 1990s and early 2000s, neoadjuvant therapy was not offered to our patients, as its effectiveness was not yet proven, and there were concerns about higher risk of postoperative morbidity.[17] The standard treatment for locally advanced rectal cancer (pathologic stage T3, T4, and/or node-positive diseases, or tumors with close resection margins) at our institution at that time was surgery followed by adjuvant 5-fluorouracil–based chemoradiotherapy. Since 2006, with accumulation of new supporting evidence,[18,19] we began to offer long-course neoadjuvant chemoradiotherapy to selected patients with radiologic stage T3, T4, and/or node-positive diseases at our institution. However, as neoadjuvant therapy might have an impact on the short-term clinical outcomes after rectal cancer surgery, we decided to continue the exclusion of those patients who required neoadjuvant therapy to avoid "contamination" of the earlier cohort of patients (recruited before 2006) who did not receive such treatment. During the study period, all patients with high-risk stage II and stage III disease were offered adjuvant chemoradiotherapy.

Patients were eligible for this pooled analysis if they had undergone curative resection, which was defined as a resection in which the surgeon believed that all macroscopic tumors (both primary and metastatic if present) had been removed at the time of surgery. Pathologic evaluation of all resected specimens was performed according to standardized protocol.[20] All patients underwent the same perioperative management and follow-up protocol. The short-term clinical outcomes and long-term survival were recorded and compared between the Lap and Open groups.

Follow-up

After surgery, the patients were followed up regularly at 3-monthly intervals in the first 2 years and then every 6 months until year 5. Thereafter, patients were seen annually. Clinical examination, rigid sigmoidoscopy, and serum carcinoembryonic antigen (CEA) testing were done at each visit. Colonoscopy was performed at 1 year after surgery and, thereafter, every 3 years. If recurrence was suspected clinically, CT or positron emission tomography would be performed. Annual surveillance CT for 3 years was also offered to selected patients who were at high risk of recurrence (eg, stage T4 or N2 diseases, poorly differentiated tumors, or presence of lymphovascular permeation). Data regarding recurrence and survival were prospectively recorded. Locoregional recurrence was defined as the presence of radiologically confirmed or histologically proven tumor restricted to the anastomosis or in the pelvis within the region of the primary surgery. The last follow-up was in February 2012. The survival status was cross-checked with the networked computer database of the local hospital authority.

Statistical Analysis

Data were analyzed by the intention-to-treat principle. The χ^2 test (or the Fisher exact test when appropriate), Student t test, and Mann-Whitney U test were used to compare categorical, parametric, and nonparametric data, respectively. Recurrence and survival were calculated by the Kaplan-Meier method, and differences between groups were compared by the log-rank test. For the calculation of cancer-specific survival, patients who died from causes other than rectal cancer were censored at the time of death. For the calculation of disease-free interval, patients who died without having disease recurrence were censored at the time of death.

Analysis of predictive factors of long-term survival was performed. Clinicopathologic variables analyzed were age, sex, surgical approach (Lap vs. Open), surgical procedure [AR/low anterior resection (LAR) vs. APR], preoperative serum CEA level (the normal cutoff value is 4.7 μg/L at our institution), presence of medical comorbidities, perioperative blood transfusion, postoperative complications, tumor staging, tumor differentiation, lymphovascular permeation, number of lymph nodes harvested (<12 vs. ≥ 12), and adjuvant therapy. Circumferential resection margin (CRM) involvement was not analyzed because the event rate was low.[12–15] Only variables associated with $P \leq 0.15$ in the univariate analysis were used for multivariate analysis using a Cox proportional hazards regression model to identify independent predictors of survival. A P value of less than 0.05 was taken as significant.

RESULTS

Of the 332 originally randomized patients, 278 were eligible for inclusion in this pooled analysis: 130 from the AR trial, 76 from the APR trial, and 72 from the TME trial. One hundred thirty-six patients were assigned to the Lap group, and 142 patients were assigned to the Open group. The 2 groups of patients had comparable demographic data (Table 1), with 1 patient lost to follow-up in each group. In the Lap group, 21 patients (15.4%) required conversion to open surgery because of bulky tumor ($n = 5$), narrow pelvis ($n = 5$), dilated small bowel obscuring view ($n = 1$), failure to identify the left ureter ($n = 1$), dense adhesions ($n = 3$), bleeding ($n = 3$), rectal perforation ($n = 1$), and anastomotic failure ($n = 2$). All patients were available for analysis of long-term survival, whereas the lost patients were censored at the date last known to be alive during survival analysis. The median follow-up time of living patients was 124.5 months (range, 52.2–218.2 months) in the Lap group and 136.6 months (range, 55.8–210.3 months) in the Open group.

Perioperative Outcomes

Perioperative outcomes are summarized in Table 2. The operative time was significantly longer in the Lap group than that in the Open group. Although the operative blood loss in the Lap group was significantly less, the number of patients who required postoperative blood transfusion was similar between the 2 groups. Measures

TABLE 1. Demographic Data

	Lap Group	Open Group	*P*
No. patients	136	142	—
Age (yr, mean ± SD)	63.9 ± 11.8	64.9 ± 12.5	0.491*
Sex (male/female)	74/62	87/55	0.247†
Preoperative hemoglobin (g/dL, mean ± SD)	12.2 ± 2.2	12.6 ± 2.1	0.125*
Preoperative CEA (μg/L, median and range)	3 (0.2–157)	4.2 (0.7–1050)	0.048‡
No. patient with comorbidities (%)	48 (35.3)	49 (34.5)	0.891†
Surgical procedure (AR/LAR/APR)	60/36/40	70/36/36	0.654†
AJCC staging (I/II/III)	26/57/53	27/48/67	0.317†
Adjuvant chemotherapy (%)	48 (35.3)	58 (40.8)	0.341†
Adjuvant radiotherapy (%)	47 (34.6)	50 (35.2)	0.909†
Follow-up time of all patients (mo, median and range)	101.6 (0.3–218.2)	106.5 (0.1–210.3)	0.217‡
Follow-up time of living patients (mo, median and range)	124.5 (52.2–218.2)	136.6 (55.8–210.3)	0.707‡

*Student *t* test.
†χ^2 test.
‡Mann-Whitney *U* test.
AJCC indicates American Joint Committee on Cancer; SD, standard deviation.

TABLE 2. Perioperative Outcomes and Pathologic Data

	Lap Group (n = 136)	Open Group (n = 142)	*P*
Conversion (%)	21 (15.4)	—	—
Operative time (min, mean ± SD)	213.7 ± 53.1	158.8 ± 58.9	< 0.001*
Blood loss (mL, mean and range)	200 (0–2000)	420.3 (0–4720)	0.001†
No. patients requiring blood transfusion (%)	18 (13.2)	26 (18.3)	0.247‡
Postoperative analgesic requirement (no. injections, mean and range)	4.7 (0–22)	11.2 (0–52)	<0.001†
Time of first bowel motion (d, mean and range)	3.8 (1–22)	4.7 (1–14)	<0.001†
Time to resume normal diet (d, mean and range)	4.7 (2–25)	5.5 (3–18)	<0.001†
Hospital stay (d, mean and range)	9.7 (4–32)	13.3 (3–167)	0.002†
Total no. patients with complications (%)	45 (33.1)	61 (43.0)	0.090‡
Operative death (%)	2 (1.5)	4 (2.8)	0.685‡
Tumor differentiation (well/moderate/poor)	2/122/12	2/127/13	0.995‡
Lymphovascular permeation (%)	24 (17.6)	22 (15.5)	0.629‡
Circumferential resection margin involvement (%)	2 (1.5)	2 (1.4)	1.000‡
Lymph nodes removed (mean and range)	12.4 (0–45)	12.7 (0–35)	0.346†

*Student *t* test.
†Mann-Whitney *U* test.
‡χ^2 test or Fisher exact test.

of postoperative recovery, including analgesic requirement, return of bowel function, mobilization, and duration of hospital stay, were all significantly better in the Lap group.

There was no difference in short-term or 30-day morbidity rates between the Lap and Open groups. Six patients died within 30 days after the primary surgery: 2 in the Lap group and 4 in the Open group. In the Lap group, a patient who required conversion died on the next day after reoperation for anastomotic leak. Another patient in the Lap group who also required conversion because of bulky tumor died of chest infection 27 days after the operation. In the Open group, a patient committed suicide 24 days after the operation because of social reasons. Other causes of operative mortality in the Open group were anastomotic leak (n = 1), acute coronary syndrome (n = 1), and chest infection (n = 1).

Oncologic Clearance and Long-term Survival

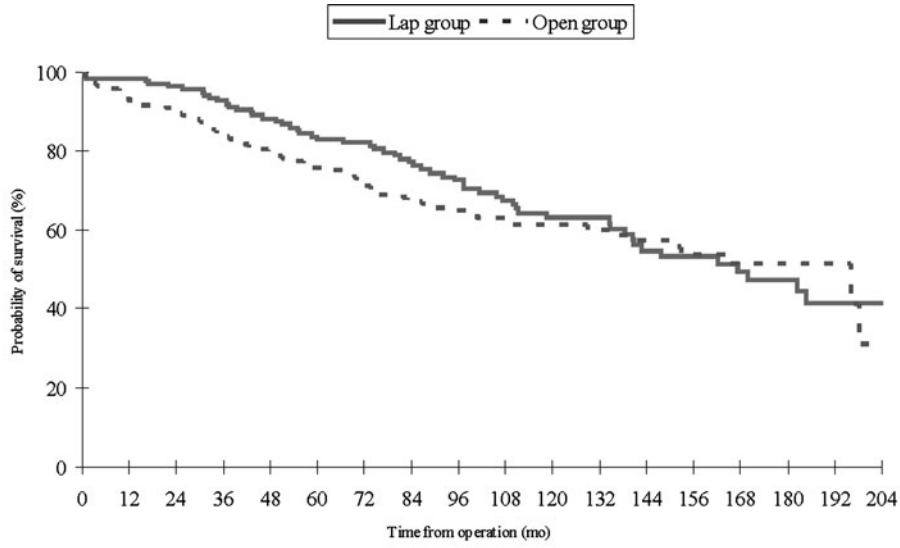
The oncologic clearance in terms of CRM involvement and the mean number of lymph nodes removed were similar between the Lap and Open groups (Table 2).

After curative resection, the probabilities of overall survival at 10 and 15 years were 63.0% [standard error (SE) = 4.6%] and 47.4% (SE = 5.6%), respectively, for the Lap group, and 61.1% (SE = 4.3%) and 51.4% (SE = 5.2%), respectively, for the Open group ($P = 0.505$, log-rank test; Fig. 1). The probabilities of cancer-specific survival at 10 and 15 years were 82.5% (SE = 3.6%) and 79.3% (SE = 4.6%), respectively, for the Lap group, and 77.6% (SE = 3.9%) and 75.9% (SE = 4.2%), respectively, for the Open group ($P = 0.443$, log-rank test; Fig. 2). No significant difference in overall survival or cancer-specific survival according to tumor stage was observed between the 2 groups.

The pattern of recurrence is shown in Table 3. There was no port-site recurrence in this study. The probabilities of being recurrence-free at 10 years were 79.0% (SE = 3.7%) for the Lap group and 72.9% (SE = 4.0%) for the Open group ($P = 0.218$, log-rank test; Fig. 3). The locoregional and distant recurrence rates at 10 years were also not different between the Lap and Open groups. However, there was a trend toward lower overall cancer recurrence rate at 10 years in the Lap group than in the Open group among patients with stage III rectal cancer [25.8% (SE 6.2%) vs. 43.2% (SE 6.6%); $P = 0.078$, log-rank test; Fig. 4].

Predictive Factors for Survival

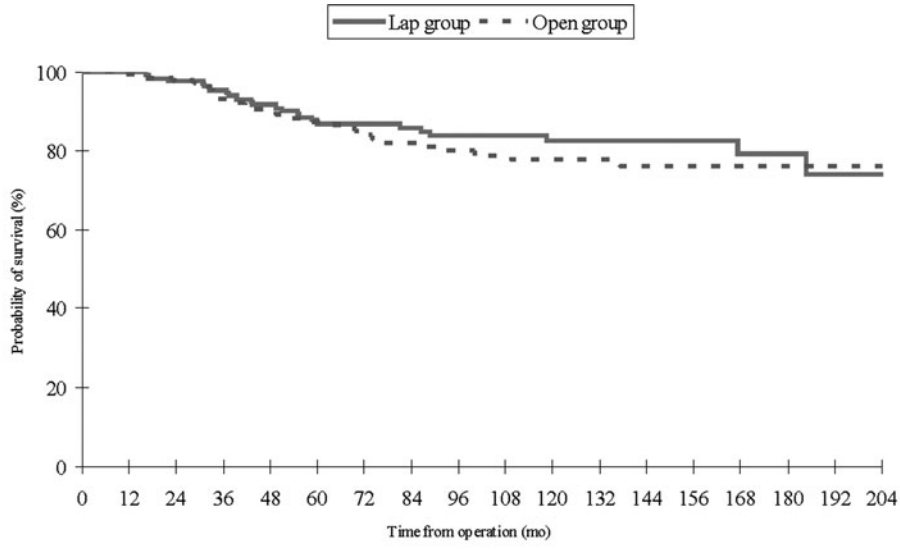
Results of univariate and multivariate analyses for predictive factors of survival are summarized in Tables 4 and 5. Predictive



Time from operation (mo)

No. at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204
Lap group	136	134	131	126	119	109	102	90	75	63	55	46	38	32	24	20	12	9
Open group	142	131	127	119	111	101	92	82	75	67	59	53	37	28	21	14	5	2

FIGURE 1. Overall survival for all patients ($P = 0.505$, log-rank test).



Time from operation (mo)

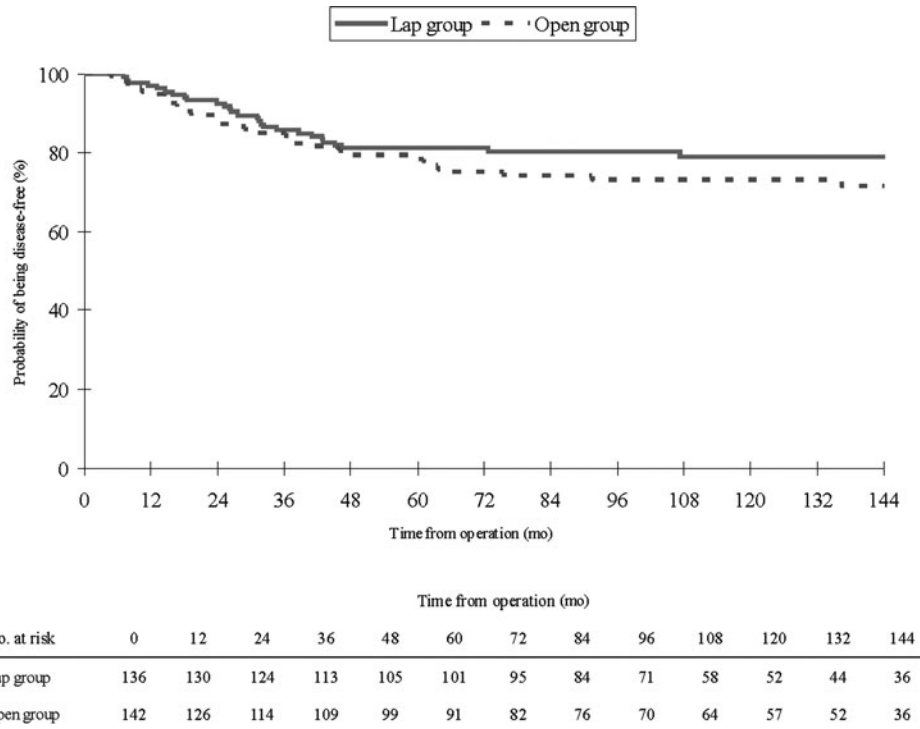
No. at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204
Lap group	136	136	131	126	119	109	102	90	75	63	55	46	38	32	24	20	12	9
Open group	142	131	127	119	111	101	92	82	75	67	59	53	37	28	21	14	5	2

FIGURE 2. Cancer-specific survival for all patients ($P = 0.443$, log-rank test).

TABLE 3. Survival and Recurrence

	Lap Group (n = 136)	Open Group (n = 142)	Difference (95% CI)	*P*
Probability of overall survival at 10 yr	63.0% (SE 4.6%)	61.1% (SE 4.3%)	–1.9% (–9.3% to 5.5%)	0.505*
Probability of overall survival at 15 yr	47.4% (SE 5.6%)	51.4% (SE 5.2%)	4.0% (–7.8% to 15.8%)	
Probability of cancer-specific survival at 10 yr	82.5% (SE 3.6%)	77.6% (SE 3.9%)	–4.9% (–14.3% to 4.5%)	0.443*
Probability of cancer-specific survival at 15 yr	79.3% (SE 4.6%)	75.9% (SE 4.2%)	–3.4% (–10.8% to 4.0%)	
Crude recurrence rate	27 (19.9%)	35 (24.6%)	—	0.337†
Locoregional alone	5 (3.7%)	3 (2.1%)		
Distant alone	20 (14.7%)	24 (16.9%)		
Both locoregional and distant	2 (1.5%)	8 (5.6%)		
Port site	0	—		
Probability of being disease-free at 10 yr	79.0% (SE 3.7%)	72.9% (SE 4.0%)	–6.1% (–16.1% to 3.9%)	0.218*
Probability of being disease-free at 15 yr	79.0% (SE 3.7%)	71.4% (SE 4.2%)	–7.6% (–17.7% to 2.5%)	
Overall locoregional recurrence rate at 10 yr	5.5% (SE 2.0%)	9.3% (SE 2.7%)	3.8% (–2.3% to 9.9%)	0.296*
Overall distant recurrence rate at 10 yr	17.7% (SE 3.5%)	25.3% (SE 4%)	7.6% (–2.0% to 17.2%)	0.117*

*Log-rank test.
†χ^2 test.



Time from operation (mo)

No. at risk	0	12	24	36	48	60	72	84	96	108	120	132	144
Lap group	136	130	124	113	105	101	95	84	71	58	52	44	36
Open group	142	126	114	109	99	91	82	76	70	64	57	52	36

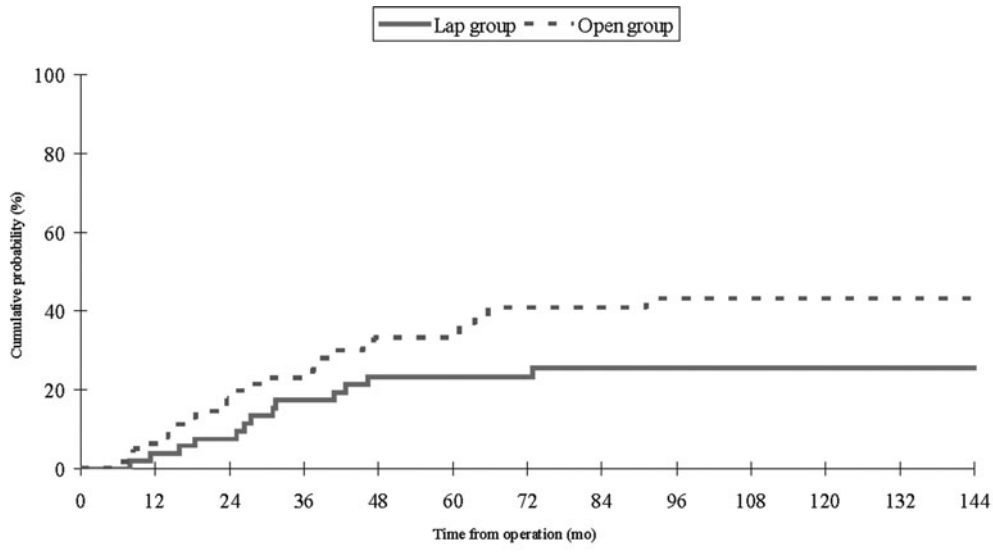
FIGURE 3. Probability of being disease-free for all patients ($P = 0.218$, log-rank test).

factors of poorer overall survival were age 65 years or older, stage III cancer, poor differentiation of tumor, and postoperative blood transfusion. Predictors of poorer cancer-specific survival were stage III cancer, lymphovascular permeation, and postoperative blood transfusion; stage III cancer and lymphovascular permeation were also predictors of shorter disease-free interval. The laparoscopic approach was not a predictor of survival.

DISCUSSION

This study pooled the data from 3 separate randomized controlled trials with similar inclusion criteria and treatment, and the same follow-up protocol, thus increasing the power to evaluate the long-term oncologic outcomes of laparoscopic surgery for rectal cancer in comparison with the open approach. The survival and disease status were updated to February 2012, and only 2 patients were lost to follow-up. The median follow-up of living patients was more than 10 years, which is believed to be the longest of any published randomized trial of laparoscopic versus open surgery for colorectal cancer to date.

Few randomized trials comparing laparoscopic and open surgery for rectal cancer have reported 5-year survival data. The first randomized study describing long-term oncologic outcomes was reported by Braga et al,[4] who found no difference in 5-year overall and disease-free survivals between the 2 approaches. Lujan et al[5] reported similar 5-year overall survival rates between laparoscopic and open surgery for rectal cancer (72.1% vs. 75.3%; $P = 0.980$, log-rank test). For the rectal cancer patients in the United Kingdom Medical Research Council trial of Conventional versus Laparoscopic-Assisted



Time from operation (mo)

No. at risk	0	12	24	36	48	60	72	84	96	108	120	132	144
Lap group	53	50	48	42	38	35	33	30	22	18	14	14	12
Open group	67	57	49	46	39	36	29	27	24	22	20	19	13

FIGURE 4. Cumulative incidence of recurrence in patients with stage III rectal cancer ($P = 0.078$, log-rank test).

Surgery In Colorectal Cancer (CLASICC), the 5-year overall survival rates were also not different statistically between the laparoscopic and open groups (60.3% vs. 52.9%; $P = 0.132$, log-rank test).[6] However, all these studies were not specifically designed and powered to address long-term oncologic end points.

In this pooled analysis, 278 patients who had undergone curative rectal resection were enrolled. Our sample size for survival analysis (after curative resection) was larger than that in the studies by Braga et al[4] (n = 144) and Lujan et al[5] (n = 193), but comparable with that in the CLASICC trial (n = 326).[6] We demonstrated similar 10-year and 15-year overall and cancer-specific survivals between the Lap and Open groups. Stage-for-stage comparison for the 2 groups also showed no significant differences. A post hoc analysis revealed that with a sample size of about 300, our study would have a power of 80% to establish noninferiority of Lap to Open surgery regarding survival with 1-sided type I error of 2.5%, assuming a noninferiority margin of 15% and a survival rate of 75% in the Open group. The sample size of the COREAN trial (n = 340) was also calculated on the basis of similar assumptions and noninferiority margin.[2] In our study, the 10-year cancer-specific survival was 82.5% [95% confidence interval (CI): 75.4–89.6] in the Lap group and 77.6% (95% CI: 70.0–85.2) in the Open group; the difference was –4.9% (95% CI: –14.3 to 4.5). As the upper limit of the 95% CI for the difference (Open minus Lap surgery) did not exceed the noninferiority margin, we may safely declare that the 10-year cancer-specific survival of Lap surgery is not inferior to that of Open surgery for rectal cancer.

We also observed a similar probability of being recurrence-free at 10 years between the Lap (79.0%) and Open groups (72.9%). Notably, a trend toward lower overall recurrence rate at 10 years was found in the Lap group than in the Open group among patients with stage III cancer. However, this difference did not translate into any survival advantage in this subgroup of patients. On the contrary, 2 non-randomized studies have reported better survival among patients with stage III disease undergoing laparoscopic than among patients undergoing open surgery for rectal cancer.[21,22] In the Barcelona randomized trial, Lacy et al[23,24] reported significantly higher probabilities of survival and being recurrence-free in the laparoscopic colectomy group than in the open colectomy group only for patients with stage III colonic cancer. It has been postulated that better preservation of cellular immunity and attenuation of systemic inflammatory response associated with the laparoscopic approach may explain the better survival observed after laparoscopic colorectal surgery.[25,26] However, the reason why this advantage is limited to stage III cancer only is unclear.[24] Furthermore, it is generally recognized that subgroup analyses of randomized trials can produce spurious results and are prone to biases.[6,27,28] To date, no randomized trials comparing laparoscopic and open surgery for rectal cancer have yet reported similar survival benefit among patients with node-positive disease.

In our study, oncologic clearance in terms of resection margins and number of lymph nodes removed was comparable between the Lap and Open groups. In particular, very low rates of CRM involvement were observed in the Lap (1.5%) and Open (1.4%) groups. In this study, only patients who had undergone curative resection were included. If patients with stage IV disease from the original trials were also included, the CRM involvement rates would become 4.8% for the Lap group and 3.0% for the Open group ($P = 0.573$, Fisher exact test). One of the reasons for our lower CRM involvement rates might be partly explained by the single-center nature of our study, with standardized surgical techniques performed by experienced surgeons. In fact, other published single-center randomized trials that did not use neoadjuvant therapy have also reported low CRM involvement rates: Zhou et al[3] reported no CRM involvement in both the Lap and Open groups, whereas Braga et al[4] reported CRM involvement rates of 1.2% in the Lap group and 2.4% in the Open group.

Owing to our low rates of CRM involvement, we had reasonably low 10-year locoregional recurrence rates, with no significant

TABLE 4. Prognostic Factors of 10-Year Survival and Disease-Free Interval: Univariate Analysis (Log-Rank Test)

	Overall Survival	*P*	Cancer-Specific Survival	*P*	Disease-Free Interval	*P*
Age (yr)						
<65	74.6% (SE 4.3%)	<0.001	81.4% (SE 3.9%)	0.548	77.6% (SE 3.9%)	0.577
≥65	52.9% (SE 4.2%)		79.0% (SE 3.6%)		74.8% (SE 3.7%)	
Sex						
Male	59.5% (SE 4.1%)	0.216	80.9% (SE 3.4%)	0.964	75.5% (SE 3.6%)	0.741
Female	66.1% (SE 4.7%)		79.4% (SE 4.1%)		77.2% (SE 4.1%)	
Surgical approach						
Laparoscopy	63.0% (SE 4.6%)	0.505	82.5% (SE 3.6%)	0.443	79.0% (SE 3.7%)	0.218
Open	61.1% (SE 4.3%)		77.6% (SE 3.9%)		72.9% (SE 4.0%)	
Surgical procedure						
AR/LAR	63.6% (SE 3.7%)	0.339	80.3% (SE 3.2%)	0.484	76.7% (SE 3.2%)	0.472
APR	58.8% (SE 5.8%)		79.3% (SE 4.9%)		74.1% (SE 5.3%)	
Preoperative CEA (μg/L)						
<4.7	66.9% (SE 3.8%)	0.122	85.6% (SE 3.0%)	0.028	81.3% (SE 3.2%)	0.026
≥4.7	54.8% (SE 5.2%)		71.2% (SE 4.9%)		67.8% (SE 4.7%)	
Presence of comorbidities						
Yes	61.3% (SE 5.4%)	0.576	77.6% (SE 4.6%)	0.151	70.6% (SE 4.8%)	0.041
No	63.1% (SE 3.8%)		81.7% (SE 3.2%)		79.2% (SE 3.2%)	
Blood transfusion						
Yes	48.9% (SE 8.0%)	0.006	72.0% (SE 7.6%)	0.094	68.8% (SE 7.5%)	0.099
No	64.8% (SE 3.3%)		81.5% (SE 2.8%)		77.3% (SE 2.9%)	
Postoperative complications						
Yes	55.8% (SE 5.2%)	0.208	81.6% (SE 4.4%)	0.432	75.8% (SE 4.6%)	0.958
No	66.0% (SE 3.8%)		79.2% (SE 3.3%)		76.2% (SE 3.4%)	
AJCC staging						
I	77.0% (SE 6.2%)	0.005	87.2% (SE 5.0%)	0.001	86.6% (SE 4.7%)	0.002
II	69.4% (SE 4.7%)		88.8% (SE 3.4%)		83.2% (SE 3.9%)	
III	48.7% (SE 5.0%)		68.4% (SE 4.8%)		64.7% (SE 4.7%)	
Tumor differentiation						
Well/moderate	63.9% (SE 3.2%)	0.009	81.5% (SE 2.7%)	0.067	77.0% (SE 2.8%)	0.294
Poor	45.1% (SE 10.3%)		65.2% (SE 10.7%)		65.8% (SE 10.5%)	
Lymphovascular permeation						
Yes	45.2% (SE 8.0%)	0.017	63.0% (SE 7.8%)	<0.001	56.2% (SE 7.6%)	<0.001
No	65.6% (SE 3.3%)		83.5% (SE 2.7%)		80.1% (SE 2.8%)	
No. lymph nodes						
<12	61.6% (SE 4.3%)	0.621	82.4% (SE 3.5%)	0.367	76.6% (SE 3.8%)	0.692
≥12	63.4% (SE 4.5%)		77.8% (SE 3.9%)		75.6% (SE 3.9%)	
Adjuvant chemotherapy						
Yes	65.6% (SE 5.1%)	0.421	73.1% (SE 4.9%)	0.090	68.1% (SE 4.8%)	0.035
No	60.8% (SE 3.9%)		84.3% (SE 3.1%)		80.9% (SE 3.1%)	
Adjuvant radiotherapy						
Yes	61.0% (SE 5.4%)	0.480	72.1% (SE 5.2%)	0.085	66.8% (SE 5.0%)	0.016
No	62.7% (SE 3.8%)		84.4% (SE 3.0%)		81.1% (SE 3.1%)	

difference between the Lap (5.5%) and Open (9.3%) groups. In our study, routine surveillance CT was not offered to all patients with stage III disease because of financial reason, and there might be concerns about underestimation of the recurrence rates. We admit that this might be one of the limitations of this study. However, we believe that the recurrence and survival data presented in this study were still clinically important and meaningful, as the median follow-up of all living patients was more than 10 years, with only 2 patients lost to follow-up. Most recurrences would have manifested clinically during the long-term follow-up, and the risk of underestimation would be small. In fact, our locoregional recurrence rates compared favorably with those reported by Lujan et al[5] (5-year local recurrence rates: Lap 4.8% vs. Open 5.3%, $P = 0.781$, log-rank test) and the CLASICC trial (5-year local recurrence rates after AR: Lap 9.4% vs. Open 7.6%, $P = 0.740$, log-rank test).[6] Remarkably, we also found a lower 10-year distant recurrence rate in the Lap group (17.7%) than in the Open group (25.3%), but the difference did not reach statistical significance ($P = 0.117$, log-rank test). Our findings support the concept that laparoscopic surgery for rectal cancer is a safe oncologic procedure when performed by experienced surgeons.

Regarding prognostic implication, the laparoscopic approach has been demonstrated by 1 randomized[24] and 2 nonrandomized studies[29,30] to be an independent predictor of better survival after colorectal surgery. However, more than half of the patients in these studies were colonic cancer patients and hence their results may not be applicable to rectal cancer. In another study by Laurent et al,[22] laparoscopic surgery was found to be an independent predictor of better overall but not cancer-specific survival for rectal cancer, and the authors concluded that the type of surgery did not influence cancer outcome. In our study, the laparoscopic approach was also not found to be a predictor of better survival. Indeed, it is not essential to demonstrate a survival benefit of laparoscopic surgery over the open approach to justify its role in treating rectal cancer; the long-term oncologic safety of laparoscopic for rectal cancer can be confirmed if its oncologic clearance and survival are no worse than that of the open approach, as clearly indicated in our study.

TABLE 5. Prognostic Factors of 10-Year Survival and Disease-Free Interval: Multivariate Analysis

	Hazard Ratio (95% CI)	P*
Overall survival		
Age ≥65 yr	2.57 (1.71–3.87)	<0.001
AJCC stage III	1.94 (1.34–2.82)	0.001
Poor differentiation of tumor	1.84 (1.06–3.19)	0.029
Postoperative blood transfusion	1.72 (1.09–2.72)	0.020
Cancer-specific survival		
AJCC stage III	2.57 (1.40–4.71)	0.002
Lymphovascular permeation	2.07 (1.11–3.86)	0.021
Postoperative blood transfusion	2.01 (1.02–3.96)	0.045
Disease-free interval		
AJCC stage III	2.10 (1.24–3.56)	0.006
Lymphovascular permeation	2.06 (1.18–3.59)	0.012

*Cox proportional hazards regression analysis.

One of the aims of this study was to identify independent predictors of survival after rectal cancer surgery. The results of our Cox regression analysis suggested that stage III or node-positive disease and the presence of lymphovascular permeation on histologic examination were independent predictors of higher recurrence rate and poorer cancer-specific survival after rectal cancer surgery. These adverse pathologic features are well-recognized poor prognostic factors for colorectal cancer.[22–24,29–31]

The other clinical factor that was found by our multivariate analysis to be an independent predictor of poorer overall and cancer-specific survivals was postoperative blood transfusion. There are data suggesting an increased rate of recurrence and reduced survival after perioperative blood transfusions in patients undergoing colorectal cancer surgery; the underlying mechanism has been proposed to be related to the immunosuppression effects induced by the blood components.[32,33] One of the benefits of laparoscopic surgery is less operative blood loss, and, theoretically, the need for blood transfusion would be lower. Although our study did not show a significantly lower blood transfusion requirement despite less blood loss in the Lap group than in the Open group, we still believe that the survival benefits of laparoscopic surgery for colorectal cancer that were demonstrated by other studies may be partly explained by less blood loss and blood transfusion associated with the laparoscopic approach.[23,24,30]

CONCLUSIONS

In conclusion, this pooled analysis of 3 randomized controlled trials with a follow-up of more than 10 years demonstrates that laparoscopic surgery for rectal cancer is associated with similar long-term recurrence and survival rates when compared with open surgery. The oncologic safety of laparoscopic surgery for rectal cancer is therefore confirmed.

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