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Laparoscopic-Assisted Versus Open Abdominoperineal Resection for Low Rectal Cancer: A Prospective Randomized Trial

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Background: Laparoscopic resection of colonic cancer has been shown to improve postoperative recovery without jeopardizing tumor clearance and survival, but information on low rectal cancer is scarce. The aim of this randomized trial was to compare postoperative recovery between laparoscopic-assisted versus open abdominoperineal resection (APR) in patients with low rectal cancer. Recurrence and survival data were also recorded and compared between the two groups.

Methods: Between September 1994 and February 2005, 99 patients with low rectal cancer were randomized to receive either laparoscopic-assisted (51 patients) or conventional open (48 patients) APR. The median follow-up time of living patients was about 90 months for both groups. The primary and secondary endpoints of the study were postoperative recovery and survival, respectively. Data were analyzed by intention-to-treat principle.

Results: The demographic data of the two groups were comparable. Postoperative recovery was better after laparoscopic surgery, with earlier return of bowel function ($P < .001$) and mobilization ($P = .005$), and less analgesic requirement ($P = .007$). This was at the expense of longer operative time and higher direct cost. There were no differences in morbidity and operative mortality rates between the two groups. After curative resection, the probabilities of survival at 5 years of the laparoscopic-assisted and open groups were 75.2% and 76.5% respectively ($P = .20$). The respective probabilities of being disease-free were 78.1% and 73.6% ($P = .55$).

Conclusions: Laparoscopic-assisted APR improves postoperative recovery and seemingly does not jeopardize survival when compared with open surgery for low rectal cancer. A larger sample size is needed to fully assess oncological outcomes.

Key Words: Laparoscopy—Laparoscopic-assisted—Abdominoperineal resection—Rectal cancer—Randomized trial.

Laparoscopic surgery is increasingly being performed worldwide for colorectal cancer. In recent years, the results of a few large randomized trials were published that confirmed that postoperative recovery was better after laparoscopic resection of colonic cancer than that after conventional open surgery, without jeopardizing the disease control and survival of patients.[1–4] However, patients with rectal cancer were not included in most of these trials.

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Further good-quality studies are thus necessary to better define the role of laparoscopic surgery in treating patients with rectal cancer, especially among those with mid and low rectal cancer.

In our previous nonrandomized comparative study, laparoscopic-assisted abdominoperineal resection (APR) has been shown to improve postoperative recovery, with equivalent oncological clearance and survival when compared with conventional open surgery for patients with low rectal cancer.[5] Since then better evidence was scarce.[6] To date, only a small randomized trial specifically designed to compare laparoscopic-assisted and open APR for low rectal cancer was found in the literature.[7] Unfortunately, this study was unable to demonstrate any benefits in terms of postoperative recovery and survival in the laparoscopic group because of its small sample size ($n = 28$) and short duration of follow-up.

The aim of this single-center prospective randomized trial was to compare postoperative recovery between laparoscopic-assisted versus open APR in patients with low rectal cancer. Recurrence and survival data were also recorded and compared between the two groups.

METHODS

Patient Selection and Randomization

Between July 1994 and February 2005, patients diagnosed with low rectal cancer within 5 cm from the anal verge were enrolled into the study and randomized to receive either laparoscopic-assisted (Lap) or conventional open (Open) APR. All patients provided written informed consent. We excluded the following patients: patients with tumor larger than 6 cm or with tumor infiltration to the adjacent organs on ultrasonography and/or computed tomography, patients who presented with recurrent disease, patients who did not consent to the randomization, and patients with intestinal obstruction or perforation. Randomization was performed on the day before surgery according to a computer-generated random sequence kept concealed by an independent operating theater coordinator. The study was approved by the local ethics committee, and registered with ClinicalTrials.gov (NCT00485316).

Preoperative Management

All patients underwent preoperative colonoscopy and biopsy of the tumor. Computed tomography was performed to look for evidence of local infiltration and/or distant metastasis. Neoadjuvant therapy was not offered, as its effectiveness was not yet proven during the early period of this study. Mechanical bowel preparation was carried out on the day before operation with sodium phosphates oral solution. Systemic prophylactic antibiotics consisting of Cefuroxime 1500 mg and Metronidazole 500 mg were administered intravenously at induction of anesthesia. Urinary catheter was routinely used.

Operative Techniques

All operations were performed or supervised directly by surgeons experienced in both laparoscopic and colorectal surgery. Our laparoscopic techniques have been described previously.[5] In short, the patient was put in the Lloyd-Davies position. Pneumoperitoneum was created by the open technique. Three 12-mm working ports were inserted under direct vision: at the right midclavicular line at the level of the umbilicus, at the right midclavicular line at the level of the anterior superior iliac spine, and at the left midclavicular line at the level of the anterior superior iliac spine. In the later cases, we inserted the left lower quadrant port at the intended site of colostomy. The sigmoid colon and rectum were mobilized down to the pelvic floor. The ureters, the hypogastric nerves, and the pelvic parasympathetic plexus were safeguarded. The lymphovascular pedicle, the sigmoid mesentery, and the sigmoid colon were transected with laparoscopic linear staplers. With the help of the perineal surgeon, the rectum together with the whole mesorectum was fully mobilized and the specimen was retrieved through the perineal wound. The perineal wound was closed primarily with a drain put in the pelvic cavity via a separate stab wound. An end colostomy was fashioned at the left lower quadrant port site after a 2-cm disk of skin was excised.

Postoperative Care and Data Collection

Postoperatively, diet was resumed as soon as bowel function returned clinically. Pethidine 1 mg/kg or morphine .1 mg/kg was given every 4 hours on demand. The patients were discharged if manageable at home.

The following parameters were measured prospectively: demographic data, operative time, disposable instruments used, blood loss and transfusion, postoperative analgesic requirement, pain score on a visual analog scale, time first passing flatus and opening bowel, time to resume normal diet, time to

walk independently, duration of hospital stay, morbidity, and operative mortality. The specimens were fixed unpinned, examined for margin clearance and staged according to the fifth edition of the American Joint Committee on Cancer (AJCC) manual.[8] All patients were followed up regularly at 3-month intervals in the first 2 years and then every 6 months thereafter for clinical examination and carcinoembryonic antigen (CEA) testing. The last follow-up date was in February 2007. The survival status was cross-checked with the networked computer database of local hospital authority.

Statistical Analysis

The primary endpoints of the study were analgesic requirement and postoperative recovery. According to our previous study,[5] if the difference in analgesic requirement was 6 doses with a pooled standard deviation of 9, then 47 patients in each limb were required to show the difference at 5% significance level ($\alpha = .05$) with 90% probability ($\beta = .1$). The secondary endpoints of the study were survival and disease-free interval. If survival is used as primary endpoint, the required sample size is much larger and is not achievable in a single-center study.

Data were analyzed by intention-to-treat principle. The χ^2 test, *t* test, and Mann-Whitney *U* test were used to compare categorical, parametric, and nonparametric data, respectively. The direct cost of operation was estimated according to the present market value of theater time, the disposable instrument, and the hospital in-patient service.[9] Survival and disease-free interval were calculated by the Kaplan-Meier method, and differences between groups were compared with the log-rank test. For the calculation of disease-free interval, patients who died without having disease recurrence were censored at the time of death. A *P*-value of less than .05 was taken as significant.

RESULTS

Between July 1994 and February 2005, 153 consecutive patients diagnosed with low rectal cancer within 5 cm from the anal verge were assessed for eligibility; of these 54 did not meet the inclusion criteria. A total of 99 patients were subsequently enrolled into the study and randomized to either Lap ($n = 51$) or Open ($n = 48$) APR (Fig. 1). The two groups of patients had comparable demographic data (Table 1), with one patient lost to follow-up in each group. In the Lap group, five patients (9.8%) required conversion to open surgery because of failure to identify the left ureter ($n = 1$), bleeding ($n = 1$), unexpected pelvic side wall invasion ($n = 2$), and bulky tumor ($n = 1$). All patients were available for analysis of the primary endpoints, while 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 87.2 months (range, 22.8–150.0 months) for the Lap group and 90.1 months (range, 27.0–145.5 months) for the Open group.

Perioperative Outcomes

Complications of the two groups are summarized in Table 2. There was one postoperative death in each group. In the Lap group, a patient who 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. Reoperation was necessary in one patient in the Lap group due to small bowel obstruction. In the Open group, four patients required reoperation because of reactionary bleeding ($n = 1$), wound dehiscence ($n = 1$), pelvic abscess ($n = 1$), and small bowel obstruction ($n = 1$). Perineal wound infection and urinary tract problems accounted for the majority of complications in both groups. The differences between the groups were not statistically significant.

The operative time was significantly shorter in the Open group. The postoperative analgesic requirement, the time for return of bowel function, and the time to mobilization were significantly less in the Lap group. However, there were no differences in operative blood loss, pain score, and duration of hospital stay between the two groups (Table 3). The direct cost of the Lap group was about US $2000 more expensive than the Open group.

Oncological Clearance and Long-Term Survival

The oncological clearance in terms of mean number of lymph nodes removed was comparable in both groups: 12.4 ± 6.7 in the Lap group and 13.0 ± 7.0 in the Open group. In the Lap group, three patients were found to have circumferential resection margin (CRM) involvement; in two of them conversion was required because the tumor was found to have invaded the pelvic side wall intraoperatively. In the third patient the tumor was found to have invaded the prostate and was mobilized through the perineal wound. In the Open group, two patients with tumor invasion of the pelvic side wall also had CRM involvement. These five patients with unsuspected

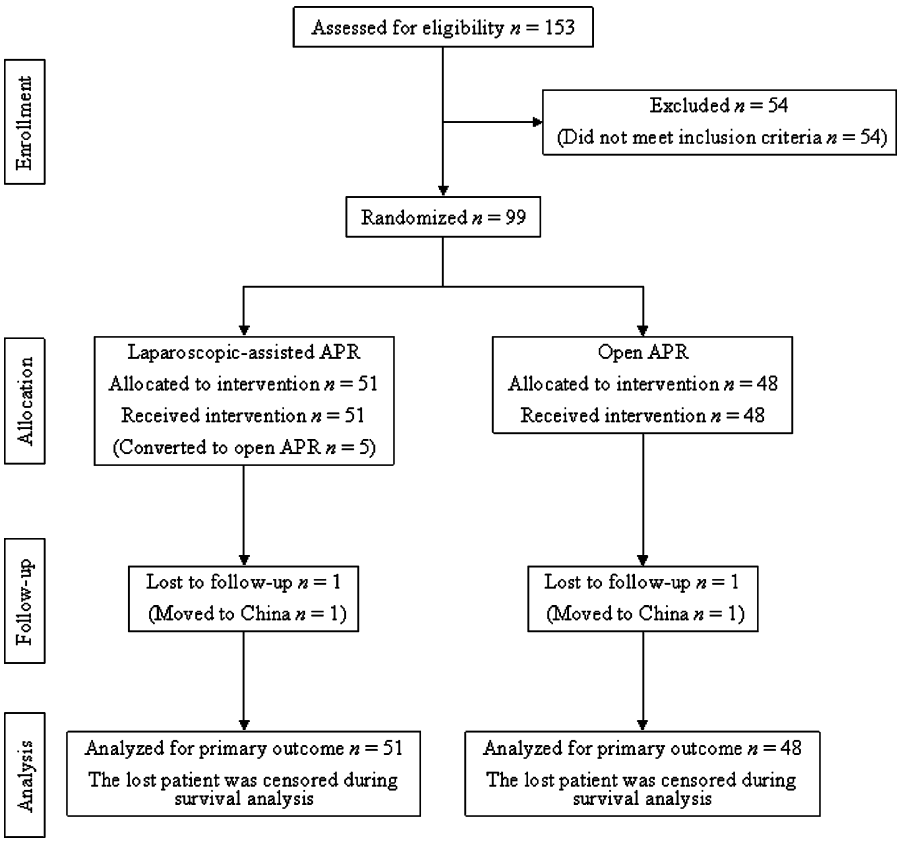


FIG. 1. Trial profile.

TABLE 1. *Demographic data*

	Lap group	Open group
Number of patients	51	48
Sex (male/female)	31/20	30/18
Age (years, mean ± SD)	63.7 ± 11.8	63.5 ± 12.6
Preoperative hemoglobin (g/dL, mean ± SD)	11.9 ± 2.4	12.8 ± 2.4
Preoperative CEA (μg/L, range and median)	.7–112 (4.3)	.7–1,050 (7.4)
AJCC staging (I/II/III/IV)	10/13/17/11	8/8/20/12
Follow-up time of living patients (months, range and median)	22.8–150.0 (87.2)	27.0–145.5 (90.1)

SD, standard deviation; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

tumor invasion of the adjacent structures all had a normal preoperative computed tomography.

After curative resection (stages I–III), the probabilities of survival at 5 years were 75.2% (standard error [SE] 7.2%) for the Lap group and 76.5% (SE 7.3%) for the Open group (log-rank test, $P = .20$). Stage-by-stage comparison for the two groups also showed no significant differences. The respective probabilities of being disease-free at 5 years were 78.1% (SE 6.9%) and 73.6% (SE 8.1%) (log-rank test, $P = .55$). The survival plots are shown in Figs. 2 and 3. The pattern of recurrence is shown in Table 4. The overall recurrence rates were not significantly different between the two groups (Lap 20% vs Open 25%, $P = .60$). Local recurrence was observed in two patients (5%) in the Lap group and four patients (11.1%) in the Open group. There was no port site recurrence in this study, but perineal wound metastasis, as part of systemic carcinomatosis, was noticed in a patient in the Open group. For patients with stage IV disease, the respective mean survival rates were 32.6 months (SE 6.0 months) and 13.9 months (SE 4.3 months); the Lap group was significantly better than the Open group (log-rank test, $P = .049$).

DISCUSSION

Laparoscopic resection of colorectal cancer has been the focus in the surgical field in the past decade.

TABLE 2. *Complications*

	Lap group	Open group
Reactionary bleeding	–	1
Abdominal abscess	1	1
Chest infection	2	2
Arrhythmia	–	1
Transient ischemic attack/confusion	–	2
Surgical emphysema	1	–
Urinary tract infection	8	9
Urinary retention	9	8
Urinary fistula	–	1
Epididymoorchitis	1	–
Paralytic ileus	1	2
Small bowel obstruction	1	1
Gastrointestinal bleeding	–	1
Chylous ascites	1	–
Wound dehiscence	–	1
Abdominal wound infection	–	4
Perineal wound infection	10	6
Sacral sore	1	–
Deep vein thrombosis	–	3
Gouty attack	2	–
Reoperation	1	4
Operative death	1	1
Total number of patients with complications	23 (45.1%)	25 (52.1%)

Researchers are eager to know if the laparoscopic technique will truly improve patients' recovery and achieve adequate tumor clearance. A few authoritative randomized trials comparing laparoscopic and open surgery for colorectal cancer have been recently published.[1–4] Lacy et al. found that patients with colonic cancer recovered faster, had less morbidity, and enjoyed better chance of cancer-related survival after laparoscopy-assisted colectomy.[1] The Clinical Outcomes of Surgical Therapy (COST) Study Group showed that perioperative recovery was faster in the laparoscopic-surgery group, but the morbidity and survival rates were not different.[2] The COlon cancer Laparoscopic or Open Resection (COLOR) Study Group also showed better postoperative recovery after laparoscopic colectomy, but survival data were not yet provided.[3] All the three studies did not recruit patients with rectal or transverse colon cancer or with metastatic disease.

Good data comparing laparoscopic and open resection for rectal cancer are relatively scarce. A recent meta-analysis on rectal cancer surgery, which comprised mostly nonrandomized studies, showed a faster recovery in terms of bowel function and hospital stay among patients who underwent laparoscopic surgery; in the subgroup of patients who underwent APR, wound infection and analgesic requirement were also significantly reduced after laparoscopic surgery.[6] The UK Medical Research Council trial of Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (CLASICC) was the only multicenter randomized study to include rectal lesions.[4] This study essentially did not show any differences in short-term outcomes between laparoscopic and open surgery for colorectal cancer. Specifically for rectal cancer, the authors emphasized that among patients who underwent anterior resection (AR), a nonsignificant difference in CRM positivity rates favoring open surgery was recorded; no difference in CRM positivity rates had been shown among patients who underwent APR.

We have previously reported that patients with rectosigmoid or upper rectal cancer recovered better after laparoscopic surgery, while long-term survival was not jeopardized.[10] In a subgroup analysis on upper rectal cancer, similar findings were achieved.[11] However, tumor at the lower rectum warrants a separate study because of difference in disease behavior and treatment options.

The results of this study demonstrated that for patients who required APR, the laparoscopic-assisted approach could allow faster return of bowel function, earlier mobilization, and less analgesic requirement when compared with the open approach. However, unlike the previous studies on colonic cancer, we were unable to show any significant differences in blood loss, pain score, hospital stay, and morbidity between the two groups. APR is different from other colorectal resection in having a higher complication rate because of the perineal wound.[12] Although a midline laparotomy wound is avoided, the perineal wound and its related complications may not be altered by the use of laparoscopic approach. As a result, the sample size of this study may not be big enough to show significant benefits in all the parameters measured.

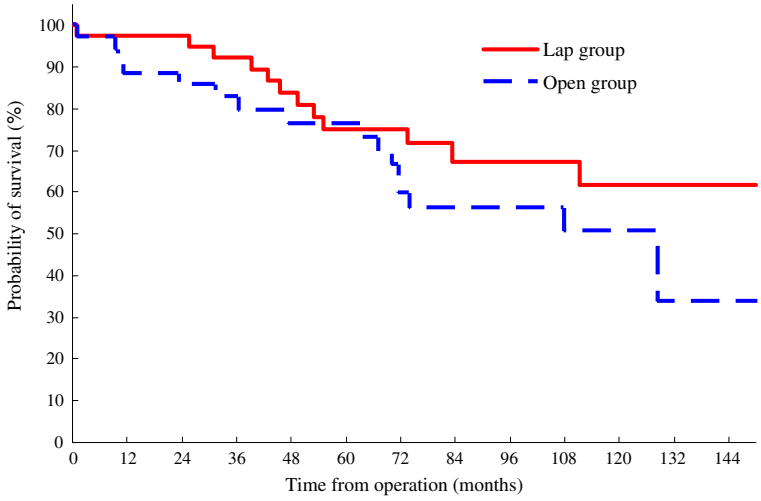
It is also proposed that the observation of clinical parameters may be biased by the surgeons' enthusiasm and patients' perception, as they were not blinded to the surgical approach. Similar benefits may be achieved with fast-track programs.[13] Yet a recent randomized study showed that, despite perioperative optimization of open surgery for colorectal cancer, short-term outcomes were still better following laparoscopic surgery.[14]

Neoadjuvant therapy was not offered to our patients, as its effectiveness was not yet proven during the early period of the study. Advocates would argue that the downsizing and downstaging of low rectal cancer induced by either preoperative radiotherapy or chemoradiotherapy would increase the likelihood of sphincter preservation and obviate the need of a permanent stoma.[15,16] However, in a recent systematic review of 10 randomized studies encompassing

TABLE 3. *Perioperative outcomes*

	Lap group	Open group	*P*-value
Operative time (minutes, mean ± SD)	213.5 ± 46.2	163.7 ± 43.4	<.001*
Blood loss (mL, mean ± SD)	321.7 (0–3000)	555.6 (0–4720)	.093†
Postoperative analgesic requirement (No. of injections, mean and range)	6.0 (0–47)	11.4 (0–49)	.007†
Visual analogue pain score on postoperative day 1 (mean ± SD)	4.5 ± 2.1	4.9 ± 1.9	.41*
Time first passing flatus (days, mean and range)	3.1 (1–22)	4.6 (1–14)	<.001†
Time of first bowel motion (days, mean and range)	4.3 (1–22)	6.3 (3–14)	<.001†
Time to resume normal diet (days, mean and range)	4.3 (2–25)	5.1 (3–16)	.001†
Time to walk independently (days, mean and range)	4.4 (1–10)	5.9 (2–20)	.005†
Hospital stay (days, mean and range)	10.8 (5–27)	11.5 (5–38)	.55†
Lymph nodes removed (mean ± SD)	12.4 ± 6.7	13.0 ± 7.0	.72*
Direct cost (US$, mean ± SD)	9588 ± 1683	7517 ± 1693	<.001*

SD, standard deviation.
* *t*-test.
† Mann–Whitney *U*-test.

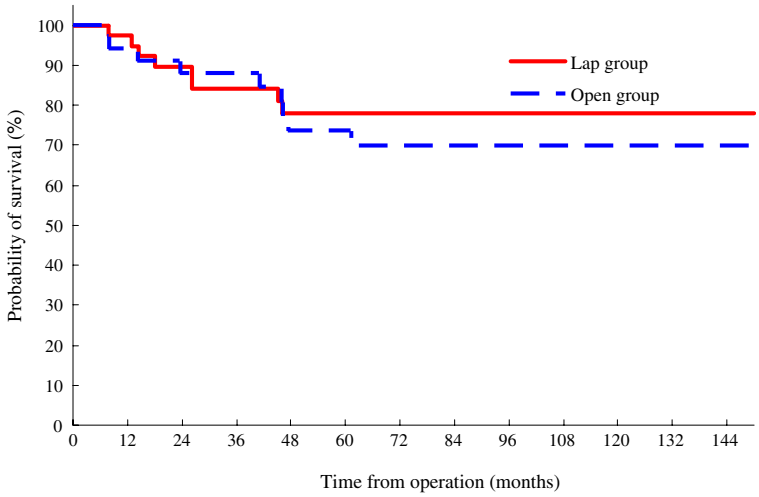


	Time from operation (months)												
Numbers at risk	0	12	24	36	48	60	72	84	96	108	120	132	144
Lap group	40	39	38	34	29	24	22	15	13	12	9	7	3
Open group	36	31	30	27	24	23	18	14	12	9	6	2	2

FIG. 2. Overall survival after curative resection (log-rank test, $P = .20$).

more than 4000 patients with rectal cancer, the sphincter preservation rate was not significantly higher among patients who received preoperative radiotherapy or chemoradiotherapy in the experimental arm as compared with the control arm.[17] Ultimately, the decision to perform sphincter-preserving surgery is not related to preoperative treatment, but is dependent on the technical skill and attitude of the surgeon along with tumor and patient characteristics. For patients with low rectal cancer within 5 cm from the anal verge, APR is still regarded by most colorectal surgeons to be the standard surgical option.

Disease control and long-term survival are the major concerns of tumor surgery. While surgeons have accepted that the laparoscopic approach does not jeopardize tumor clearance for colonic cancer, its role in rectal cancer is still uncertain. Recently, the long-term oncologcial outcomes of the CLASICC trial were reported.[18] For patients with rectal cancer, the 3-year overall and disease-free survival after laparoscopic surgery (AR or APR) were found to be no



	Time from operation (months)												
Numbers at risk	0	12	24	36	48	60	72	84	96	108	120	132	144
Lap group	40	38	34	29	26	23	21	14	12	11	9	7	3
Open group	36	30	28	26	20	19	17	13	11	8	5	2	2

FIG. 3. Disease-free survival after curative resection (log-rank test, $P = .55$).

TABLE 4. *Survival and recurrence (stage I–III diseases)*

	Lap group ($n = 40$)	Open group ($n = 36$)	*P*-value
Mortality	12 (30.0%)	17 (47.2%)	.12‡
Operative	1 (2.5%)	1 (2.8%)	
Cancer-related	6 (15.0%)	8 (22.2%)	
Others	5 (12.5%)	8 (22.2%)	
Probability of survival at 5 years	75.2% (SE 7.2%)	76.5% (SE 7.3%)	.20*
Recurrence	8 (20.0%)	9 (25.0%)	.60‡
Distant	6 (15.0%)	9 (25.0%)	
Local/peritoneal	2 (5.0%)	4 (11.1%)	
Port site/wound	0	1 (2.8%)	
Probability of being disease free at 5 years	78.1% (SE 6.9%)	73.6% (SE 8.1%)	.55*

SE, standard error.
* Log-rank test.
‡ χ^2 test.

worse than open surgery. Similarly, our study also confirmed that the oncological clearance in terms of number of lymph nodes removed and CRM was not adversely affected by the laparoscopic-assisted approach. Besides, disease control and survival among patients with stages I–III low rectal cancer were seemingly not jeopardized. The CLASICC trial reported a local recurrence rate of 15.1% and a 3-year disease-free survival rate of 49.8% among the subgroup of patients undergoing laparoscopic APR.[18] For our study, the local recurrence rate was only 5% after laparoscopic surgery, and the probability of being disease-free at 5 years was 78.1%. The more favorable oncological results achieved in our randomized trial may be partly explained by the single-center nature of our study with standardized operative techniques. Finally, a marginal survival benefit favoring the laparoscopic-assisted group was also observed for our patients with stage IV disease. However, the very small number of patients involved may render this conclusion invalid because of type 2 error. Admittedly, the sample size of this study was not adequate for comparing survival. Based on our data, approximately 4000 patients will be required to

show a difference in disease-free survival, which will be a challenging target for a future trial.

In conclusion, this prospective randomized trial demonstrated that laparoscopic-assisted APR offers better immediate outcomes in terms of faster return of bowel function, earlier mobilization, and less analgesic requirement when compared with open surgery for low rectal cancer, but at the expense of longer operative time and higher direct cost. The presence of a perineal wound may negate some of the benefits of minimally invasive surgery. Oncological clearance and long-term survival are seemingly not jeopardized by the laparoscopic-assisted approach. A larger sample size is needed to fully assess oncological outcomes.

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