Original Investigation

Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer
The ALaCaRT Randomized Clinical Trial

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IMPORTANCE Laparoscopic procedures are generally thought to have better outcomes than open procedures. Because of anatomical constraints, laparoscopic rectal resection may not be better because of limitations in performing an adequate cancer resection.

OBJECTIVE To determine whether laparoscopic resection is noninferior to open rectal cancer resection for adequacy of cancer clearance.

DESIGN, SETTING, AND PARTICIPANTS Randomized, noninferiority, phase 3 trial (Australasian Laparoscopic Cancer of the Rectum; ALaCaRT) conducted between March 2010 and November 2014. Twenty-six accredited surgeons from 24 sites in Australia and New Zealand randomized 475 patients with T1-T3 rectal adenocarcinoma less than 15 cm from the anal verge.

INTERVENTIONS Open laparotomy and rectal resection (n = 237) or laparoscopic rectal resection (n = 238).

MAIN OUTCOMES AND MEASURES The primary end point was a composite of oncological factors indicating an adequate surgical resection, with a noninferiority boundary of Δ = −8%. Successful resection was defined as meeting all the following criteria: (1) complete total mesorectal excision, (2) a clear circumferential margin (≥1 mm), and (3) a clear distal resection margin (≥1 mm). Pathologists used standardized reporting and were blinded to the method of surgery.

RESULTS A successful resection was achieved in 194 patients (82%) in the laparoscopic surgery group and 208 patients (89%) in the open surgery group (risk difference of −7.0% [95% CI, −12.4% to ∞]; P = .38 for noninferiority). The circumferential resection margin was clear in 222 patients (93%) in the laparoscopic surgery group and in 228 patients (97%) in the open surgery group (risk difference of −3.7% [95% CI, −7.6% to 0.1%]; P = .06), the distal margin was clear in 236 patients (99%) in the laparoscopic surgery group and in 234 patients (99%) in the open surgery group (risk difference of −0.4% [95% CI, −1.8% to 1.0%]; P = .67), and total mesorectal excision was complete in 206 patients (87%) in the laparoscopic surgery group and 216 patients (92%) in the open surgery group (risk difference of −5.4% [95% CI, −10.9% to 0.2%]; P = .06). The conversion rate from laparoscopic to open surgery was 9%.

CONCLUSIONS AND RELEVANCE Among patients with T1-T3 rectal tumors, noninferiority of laparoscopic surgery compared with open surgery for successful resection was not established. Although the overall quality of surgery was high, these findings do not provide sufficient evidence for the routine use of laparoscopic surgery. Longer follow-up of recurrence and survival is currently being acquired.

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Surgical removal remains the primary treatment for rectal cancer. Results have improved substantially during the past 4 decades, largely owing to adherence to the principles of total mesorectal excision.[1] Removing all of the mesorectum containing the lymph nodes and tumor is paramount for a good outcome and minimal recurrence within the pelvis.[2] Involvement of the circumferential resection margin (CRM) or distal resection margin and the quality of total mesorectal excision are related to local recurrence and long-term survival.[3]

Advances in laparoscopic technology during the 1990s enabled a revolutionary change in the operative approach to diseases of the colon and rectum, but concerns about equivalence between laparoscopic and open approaches remained because large trials had yet to be performed. Subsequent large multicenter trials confirmed advantages of laparoscopic surgery in terms of morbidity and length of hospital stay.[4-7]

There were concerns about the applicability of minimally invasive surgery to rectal cancer, as highlighted by the high conversion rate of 34% for rectal tumors in the Conventional Versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial.[4] In that trial, the rates for 3-year overall survival, disease-free survival, and local recurrence were similar in the 2 technique groups; however, the laparoscopic group had a higher positive rate of CRM involvement.[8]

Proponents of the laparoscopic technique suggest that a similar tumor resection with better short-term outcomes can be achieved with minimal access surgery. The complex nature of pelvic surgery and the importance of local tumor control constitute an imperative for large randomized trials of patients with rectal cancer.

The aim of our trial was to determine whether laparoscopic rectal resection was noninferior to open rectal resection as a safe and effective oncological approach to the treatment of patients with rectal cancer.

Methods

Study Design and Oversight

The Australasian Laparoscopic Cancer of the Rectum Trial (ALaCaRT) was a multicenter randomized, noninferiority, phase 3 trial evaluating the safety and efficacy of laparoscopic resection vs open surgery for rectal cancer. The study protocol appears in Supplement 2.

The primary end point was a composite of pathological factors indicating adequate surgical resection. A successful resection was defined as meeting all the following criteria: (1) complete total mesorectal excision, (2) a clear CRM (≥1 mm), and (3) a clear distal resection margin (≥1 mm).

The secondary outcomes of late morbidity and mortality associated with the surgical intervention; disease-free survival; local pelvic recurrence at 2 years; overall survival at 5 years; quality of life; and sexual, bladder, and bowel function will be evaluated subsequently when longer-term follow-up data have accrued.

The trial management committee designed the study a priori in a similar fashion as the American College of Surgeons Oncology Group protocol Z6051 (clinicaltrials.gov Identifier: NCT00726622). A prospective meta-analysis of local recurrence and survival rates from these 2 trials was agreed to at inception. Central ethics approval was obtained by the Sydney Local Health District human research ethics committee. Individual sites not covered by the central approval obtained local approval. Patients gave written informed consent before randomization.

Patients

Eligible patients were aged 18 years or older, had a histological diagnosis of adenocarcinoma of the rectum within 15 cm of the anal verge, and had a life expectancy of at least 12 weeks. Patients were required to have adequate performance status (Eastern Cooperative Oncology Group Scale score of ≤2) and not have a comorbid illness or condition that would preclude the use of either form of surgery. Patients with T4 tumors or an involved CRM, which was determined by pretreatment pelvic magnetic resonance imaging (MRI), or endorectal ultrasound if MRI was contraindicated, were excluded. Patients with concurrent or previous invasive pelvic malignant tumors (cervical, uterine, or rectal; excluding the prostate) within 5 years before study enrollment also were excluded. Evidence of distant metastases was not an exclusion criterion.

Randomization

Patients were randomized to undergo laparoscopic or open surgery at the NHMRC Clinical Trials Centre via the Internet using the method of minimization and stratified by (1) the site of the tumor (measured by rigid sigmoidoscopy and defined by location from the anal verge: high, 10-15 cm; middle, 5-10 cm; low, <5 cm), (2) the registering surgeon, (3) the planned operative procedure (low anterior resection [sphincter preserving] or abdominoperineal resection [sphincter removal]), (4) body mass index (BMI [calculated as weight in kilograms divided by height in meters squared] of <30 or ≥30), (5) preoperative radiotherapy (yes vs no), and (6) distant metastases (yes vs no).

Surgical Procedure

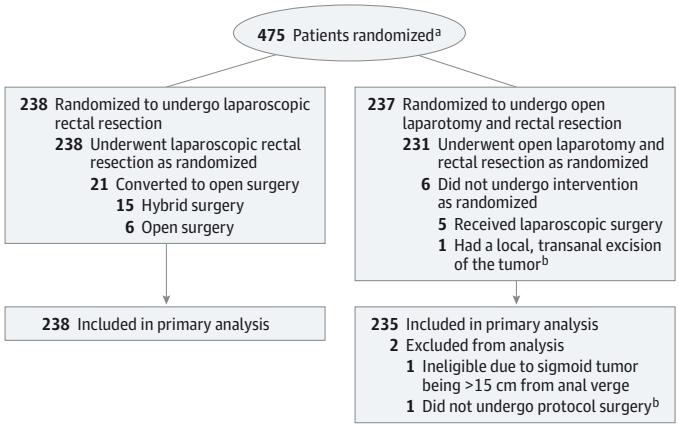
Open Surgery

A hybrid operation in which the abdominal component (splenic flexure mobilization and vessel division) could be performed laparoscopically; however, the rectal mobilization had to be performed as an open procedure under direct vision via a laparotomy. Laparoscopic-assisted procedures could include the use of a hand port, but robotic surgery was excluded. Transection of the anorectal junction could be performed transanally, laparoscopically with endoscopic staplers, or via the specimen extraction site using a transverse stapler.

Laparoscopic Surgery

For patients allocated to laparoscopic surgery, completion of any part of the pelvic dissection via the extraction site was considered a conversion. Extension of the tumor into adjacent organs (T4) required the surgeon to convert to an open procedure.

Figure 1. Flow of Patients in the ALaCaRT Trial



ALaCaRT indicates Australasian Laparoscopic Cancer of the Rectum.

[a] Screening log data from 2 selected sites that provided these data with a high completion rate through the duration of the trial identified 133 potentially eligible patients prior to randomization, of whom 80 (60%) were ineligible (34 advanced cancer, 24 recurrence, 3 sigmoid site, 9 other); 4 patients (3%) did not provide consent (2 patient decision, 2 physician decision); and 49 patients (37%) were randomized.

[b] This patient did not have protocol surgery and there was no pathological specimen suitable for the analysis.

Neoadjuvant Treatment

Usually neoadjuvant treatment included preoperative chemoradiotherapy and was planned according to the indications and preferences of the surgeon and the patient, independently of the randomized surgical approach.

Safety Monitoring

Patient safety and recruitment data (including conversion rates, postoperative complications, and surgical mortality for both laparoscopic and open surgery) were monitored regularly by an independent data and safety monitoring committee. The committee also reviewed an interim analysis for futility of noninferiority based on the first 240 patients enrolled.

Quality Assurance Measures

Surgeon Qualification

Strict eligibility criteria for including individual surgeons in the trial included evidence of laparoscopy expertise, which required more than 100 laparoscopic colon resections and more than 30 laparoscopic rectal dissections that were verified by operation and pathology reports. Surgeons were required to submit an unedited video of a laparoscopic total mesorectal excision in a male patient. These reports and video were independently audited by 2 of the study's senior surgeons.

Pathological Assessment

All excision specimens were processed and analyzed according to protocol recommendations of the Royal College of Pathologists of Australasia (RCPA) for structured reporting of colorectal cancer.[9] The primary outcome was based on assessment of the surgical specimen by a pathologist blinded to the mode of surgery. The specimens were photographed fresh and unopened to show the mesorectal dissection anteriorly and posteriorly before inking.

The pathologist assessed the distal margin in the fresh and unstretched specimen. Each pathologist was trained in assessing the mesorectal resection as complete, nearly complete, or incomplete.[10] After fixation, the specimens, including sections to assess circumferential and distal margins, were handled routinely according to guidelines from the RCPA.[11,12]

Audit

A sample of patients was selected for a comprehensive audit of surgical technique, pathological assessment, protocol compliance, and data quality at the participating hospitals. An audit pathologist also was blinded to the mode of surgery.

Statistical Analysis

With an expected surgical success rate of approximately 90% in the open surgery group, a sample size of 470 patients was calculated to be sufficient to declare laparoscopic resection noninferior to open resection with a margin of $\Delta = -8\%$ and 80% power. Noninferiority was to be declared if the lower bound of the 1-sided 95% confidence interval for the difference between the proportion of successful resections in the surgical group was greater than −8%. This margin was chosen to rule out a 10% worse surgical success rate for laparoscopic procedures, allowing for up to a 20% conversion rate to open surgery in this group. In addition, exploratory tests for superiority of laparoscopic vs open surgery were undertaken for the primary composite outcome and each of its components.

Between-treatment comparisons of continuous data were performed using the *t* test or the Wilcoxon rank sum test, depending on normality. Comparison of categorical data was performed using the χ^2 test or the conditional binomial exact test, depending on group numbers. Multivariable analyses used logistic regression. Subgroup analysis was performed according to stratification variables and other clinically relevant groups, with tests for interaction by logistic regression.

Primary analyses were based on the intention-to-treat principle according to randomized groups, with a secondary analysis according to the treatment received. Post hoc multivariable analyses compared the 2 groups with adjustment for baseline prognostic factors and then for these factors plus clinical pathological staging (nodal stage and histologi-

cal grade) after baseline. All analyses had a significance level of .05 and were performed using SAS version 9.3 (SAS Institute Inc).

Results

Between March 2010 and November 2014, 475 patients were enrolled into the study by 26 surgeons from 24 sites in Australia and New Zealand and randomized 1:1 to laparoscopic resection (n = 238) or open resection (n = 237). Two patients randomized to open resection were excluded after randomization (1 patient was ineligible owing to the sigmoid tumor being located >15 cm from the anal verge and the other patient did not receive the protocol surgery; **Figure 1**).

Five patients (1%) assigned to open rectal excision instead received laparoscopic surgery, and 21 patients (9%) assigned to laparoscopic rectal excision subsequently converted to open surgery (6 open and 15 hybrid). All were included in their allocated group for the intention-to-treat analysis.

The groups were well matched according to stratification variables (**Table 1**). Half the patients had received preoperative radiotherapy. Nearly 80% of tumors were located less than 10 cm from the anal verge. Nearly one-quarter of the patients were obese, with BMIs greater than 30 (median, 26; range, 17-47). Even though there was no difference in clinical staging at baseline, 16 patients were subsequently found to have T4 tumors on the final pathological assessment (most of these patients were in the laparoscopic group).

Pathological Outcomes

The primary outcome of a successful resection was achieved in 194 patients (82%) in the laparoscopic surgery group and in 208 patients (89%) in the open surgery group (risk difference of −7.0% [95% CI, −12.4 to ∞]; $P = .38$ for noninferiority) (**Table 2** and **Figure 2**). Hence, the margin of noninferiority of Δ = −8% was not excluded. A post hoc test for superiority favored the open surgery group (95% CI, −13.8% to −0.6%, $P = .03$). Multivariable analysis with adjustment for baseline prognostic factors, including pathological grade, did not materially change the overall treatment effect. The unadjusted odds ratio was 0.57 (95% CI, 0.34 to 0.96, $P = .03$) compared with an adjusted (for baseline factors and post-baseline pathological staging) odds ratio of 0.54 (95% CI, 0.30 to 0.96, $P = .04$; eTable in Supplement 1).

Furthermore, a test for noninferiority excluding patients with T4 tumors did not alter conclusions (successful resection: 83% for the laparoscopic surgery group [excluding 11 patients with T4 tumors] vs 89% for the open surgery group [excluding 5 patients with T4 tumors]; risk difference of −6.0% [95% CI, −11.2% to ∞]; $P = .26$ for noninferiority). In the analysis according to treatment received, the difference in proportions of successful resections was smaller at 4% (83% for the laparoscopic surgery group vs 87% for the open surgery group [95% CI for the risk difference, −9.4% to ∞]; $P = .11$).

In considering components of the primary outcome, there was a clear CRM (≥1 mm) in 93% of patients in the laparoscopic surgery group and in 97% of patients in the open surgery group (Table 2). There was a clear distal margin (≥1 mm) in 99% of patients in both groups. Complete total mesorectal excision was achieved in 87% of patients in the laparoscopic surgery group and 92% of patients in the open surgery group.

Differences in rates of pathological success between the 2 groups for the major subgroup characteristics appear in Figure 2. An apparent difference in treatment effect according to preoperative radiotherapy did not reach statistical significance (risk difference of −14% in those with prior radiotherapy vs 0% in those without prior radiotherapy; $P = .07$). Overall, there was not significant heterogeneity in risk differences for any subgroup characteristic ($P > .05$ for all interaction tests).

Table 1. Baseline Characteristics of Patients in the ALaCaRT Trial

	Laparoscopic Rectal Resection (n = 238)[a]	Open Laparotomy and Rectal Resection (n = 235)[a]
Age, median (IQR), y	65 (56-74)	65 (56-73)
Male sex	160 (67)	151 (64)
Body mass index[b]		
Median (IQR)	27 (24-30)	26 (24-30)
≥30	56 (24)	54 (23)
Performance status measured by Eastern Cooperative Oncology Group Scale score		
0	188 (79)	192 (82)
1	46 (19)	38 (16)
2	4 (2)	5 (2)
Preoperative radiotherapy	119 (50)	116 (49)
Planned operative procedure		
Low anterior resection	220 (92)	218 (93)
Abdominoperineal resection	18 (8)	17 (7)
Primary tumor location[c]		
High	53 (22)	50 (21)
Middle	103 (43)	102 (44)
Low	82 (35)	83 (35)
Tumor stage		
T1	18 (8)	11 (5)
T2	68 (29)	68 (29)
T3	151 (63)	155 (66)
Nodal status		
N0	107 (45)	125 (53)
N1	92 (39)	80 (34)
N2	37 (16)	30 (13)
Distant metastases	10 (4)	10 (4)

Abbreviations: ALaCaRT, Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial; IQR, interquartile range.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] High defined as 10-15 cm from the anal verge; middle, 5-10 cm; and low, less than 5 cm.

Surgical Outcomes

Surgical details and outcomes appear in **Table 3**. The operation duration was slightly less in the open surgery group

Table 2. Pathological Assessment of Patients in the ALaCaRT Trial

	Laparoscopic Rectal Resection (n = 238)	Open Laparotomy and Rectal Resection (n = 235)	Risk Difference, % (95% CI)	*P* Value
Primary Outcome				
No. (%) with negative circumferential and distal margins and complete total mesorectal excision	194 (82)	208 (89)	−7.0 (−12.4 to ∞)	.38[a]
Primary Outcome Components				
Circumferential resection margin, median (IQR), mm	10 (6-20)[b]	12 (6-20)[c]		.43[d]
No. (%) with negative margin (≥1 mm)	222 (93)	228 (97)	−3.7 (−7.6 to 0.1)	.06
Distal resection margin, median (IQR), mm	26 (15-45)[b]	30 (16-40)[c]		.50[d]
No. (%) with negative margin (≥1 mm)	236 (99)	234 (99)	−0.4 (−1.8 to 1.0)	.67
Total mesorectal excision, No. (%)				
Complete	206 (87)	216 (92)	−5.4 (−10.9 to 0.2)	
Nearly complete	24 (10)	17 (7)	2.8 (−2.2 to 7.9)	.06
Incomplete	8 (3)	2 (1)	2.5 (−0.06 to 5.1)	
Other Outcome Results				
Degree of histological differentiation, No. (%)				
Well	29 (14)[b,e]	28 (14)[c]	−0.2 (−6.9 to 6.5)	
Moderate	143 (68)[b,e]	149 (74)[c]	−6.4 (−15.1 to 2.4)	.52
Poor	32 (15)[b,e]	18 (9)[c]	6.2 (−0.03 to 12.5)	
Undifferentiated	3 (1)[b,e]	5 (3)[c]	−1.1 (−3.7 to 1.6)	
Tumor stage, No. (%)[e]				
T0 (or no residual cancer)	33 (14)	36 (15)	−1.4 (−7.8 to 4.9)	
T1	23 (10)	29 (12)	−2.7 (−8.3 to 3.0)	
T2	67 (28)	76 (32)	−4.2 (−12.5 to 4.0)	.07
T3	104 (44)	89 (38)	5.8 (−3.0 to 14.7)	
T4	11 (5)	5 (2)	2.5 (−0.7 to 5.7)	
Nodal status, No. (%)				
N0	148 (62)	168 (72)	−9.3 (−17.7 to −0.9)	
N1	67 (28)	48 (20)	7.7 (0.03 to 15.4)	.04
N2	23 (10)	19 (8)	1.6 (−3.5 to 6.7)	
Tumor size, median (IQR), mm	30 (20-40)[f]	30 (20-42)[c]		.77[d]
Lymphovascular invasion, No. (%)	74 (35)[b]	65 (32)[c]	2.7 (−6.4 to 11.9)	.56
Length of resected sample, median (IQR), mm	260 (205-310)	263 (230-330)		.01[d]

Abbreviations: ALaCaRT, Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial; IQR, interquartile range.

[a] Noninferiority *P* value.

[b] Data are from 211 patients.

[c] Data are from 201 patients.

[d] Calculated using the Wilcoxon rank sum test.

[e] Percentages do not equal 100 due to rounding.

[f] Data are from 209 patients.

(median of 210 minutes in the laparoscopic surgery group vs 190 minutes in the open surgery group; $P = .007$). There also was more blood loss in the open surgery group (median of 100 mL in the laparoscopic surgery group vs 150 mL in the open surgery group; $P = .002$) and a longer incision (median of 6.0 cm vs 13.0 cm, respectively; $P < .001$). There were no differences in surgical particulars between the 2 groups. Both groups had a high proportion of coloanal anastomoses (27%) and a relatively low rate of permanent stomata (10%), with 97% of planned sphincter preservations achieved.

There were no differences between the 2 groups in length of stay, intensive care unit stay, or analgesic requirement. There was an earlier return of bowel function in the laparoscopic group (median of 1 day vs 2 days in the open surgery group; $P = .04$). Overall, 30-day mortality was low (0.6%: 1 patient in the laparoscopy group vs 2 patients in the open surgery group). The overall clinical anastomotic leak rate was 7% (3% for clinically important grade 3 or 4 leaks). There were no significant differences in major complications.

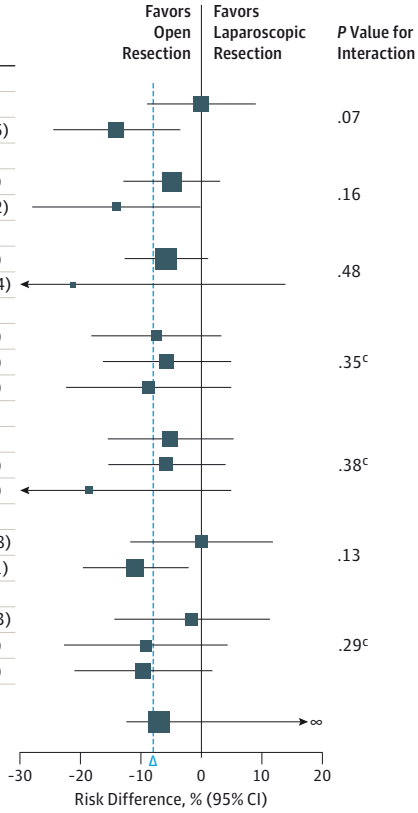
Discussion

We were unable to establish noninferiority of laparoscopic rectal cancer surgery in this large randomized trial. Four international trials of laparoscopic surgery for colon cancer have reported noninferiority in terms of safety and survival[4-7] and some advantages of laparoscopic surgery in terms of morbidity. We presumed similar benefits would occur when this surgery was extended to the more difficult treatment of rectal cancer. It was expected that improved pelvic visualization with laparoscopy would lead to better pelvic dissections and oncological outcomes. Our trial was conducted with an emphasis on quality assurance. There were strict criteria for surgeon eligibility and pathology assessment, a high proportion of tumors staged by MRI, and audits of surgery, pathology, and other hospital data.

The 85% overall rate of successful resection indicates that the quality of surgery was high. Even though we included pa-

Figure 2. Resection Rate for All Patients and Major Subgroups in the ALaCaRT Trial

	Total No. of Patients		Successful Resection, No. (%)			
	Laparoscopic Rectal Resection (n = 238)	Open Laparotomy and Rectal Resection (n = 235)	Laparoscopic Rectal Resection	Open Laparotomy and Rectal Resection	Risk Difference, % (95% CI)	*P* Value for Interaction
Preoperative radiotherapy						
No	119	119	105 (88)	105 (88)	0 (-9.0 to 9.0)	.07
Yes	119	116	89 (75)	103 (89)	-14.0 (-24.5 to -3.5)	
Body mass index[a]						
<30	182	181	149 (82)	157 (87)	-4.9 (-12.9 to 3.1)	.16
≥30	56	54	45 (80)	51 (94)	-14.1 (-28.0 to -0.2)	
Planned procedure						
Lower anterior resection	220	218	183 (83)	194 (89)	-5.8 (-12.7 to 1.1)	.48
Abdominoperineal resection	18	17	11 (61)	14 (82)	-21.2 (-55.9 to 13.4)	
Tumor location[b]						
High	53	50	48 (91)	49 (98)	-7.4 (-18.2 to 3.3)	.35[c]
Middle	103	102	85 (83)	90 (88)	-5.7 (-16.3 to 4.9)	
Low	82	83	61 (74)	69 (83)	-8.7 (-22.4 to 4.9)	
Nodal status						
N0	107	125	87 (81)	108 (86)	-5.1(-15.5 to 5.3)	.38[c]
N1	92	80	81 (88)	75 (94)	-5.7 (-15.4 to 4.0)	
N2	37	30	24 (65)	25 (83)	-18.5 (-41.8 to 4.9)	
T stage						
T1 or T2	86	79	74 (86)	68 (86)	0 (-11.8 to 11.8)	.13
T3	151	155	119 (79)	139 (90)	-10.9 (-19.6 to -2.1)	
Tumor size, cm						
≥0-3.0	79	66	67 (85)	57 (87)	-1.6 (-14.4 to 11.3)	.29[c]
3.1-4.9	67	77	53 (79)	68 (88)	-9.2 (-22.7 to 4.3)	
≥5.0	81	78	67 (83)	72 (92)	-9.6 (-21.0 to 1.8)	
All patients	238	235	194 (82)	208 (89)	-7.0 (-12.4 to ∞)	



Successful resection defined as negative circumferential and distal margins and complete total mesorectal excision. The 2-sided confidence limits are 95% CIs for each subgroup. The noninferiority boundary (dashed line, Δ = −8%) lies above the lower bound of the 95% CI for the group, all patients, so noninferiority has not been established. ALaCaRT indicates Australasian Laparoscopic Cancer of the Rectum.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] High defined as 10-15 cm from the anal verge; middle, 5-10 cm; and low, less than 5 cm.

[c] Test for linear trend used.

tients with high BMIs (range, 17-47), which is reflective of our typical patient population, there were very low rates of perioperative mortality, complications, and conversion to open or hybrid procedures (9%). Although 35% of the tumors were within 5 cm of the anal verge, a low rate of permanent stomata (10%) was achieved. This corresponds to a high rate of coloanal anastomoses and almost all planned sphincter preservations succeeding.

Earlier trials have reported operation and pathology results (some as primary and others as secondary outcomes). The first, the UK CLASICC colorectal cancer trial, included 242 patients with rectal cancer.[4,8] The results in this subgroup of patients with rectal cancer were concerning, with a conversion rate of 34% (82/242), high mortality (5%), and a high but nonsignificant positive CRM rate in the laparoscopic group of 12% compared with 6% in the open surgery group (95% CI, −2% to 14%). The rate of CRM involvement in the laparoscopic surgery group in our trial was 6.7%, which compares favorably with the rate in the CLASICC study. However, our open surgery group only had a rate of 3% for CRM involvement.

The results from the European Colon Carcinoma Laparoscopic or Open Resection (COLOR) II trial (n = 1044 included in the analysis) indicated technical improvements after the CLASICC trial (conversion rate of 17%) and pathological success (rate for CRM involvement of 10% with <2-mm margin and a complete total mesorectal excision rate of 90%).[13] However, there were some anomalies: a rate for CRM involvement of 22% for tumors located in the low rectal area in the open surgery group, a high permanent stoma rate of 29% in the laparoscopic surgery group, a low rate for coloanal anastomoses of 5.5%, and a high anastomosis leak rate (≤15% in tumors located in the middle rectal area). Patients with pT4 tumors (13/1103) were randomized but excluded from the final analysis.

Even though the patients were randomized and the groups appeared well balanced in our trial, there seemed to

Table 3. Surgical Details and Outcomes Within 30 Days for Patients in ALaCaRT

	Laparoscopic Rectal Resection (n = 238)	Open Laparotomy and Rectal Resection (n = 235)	Risk Difference, % (95% CI)	*P* Value
Time from randomization to surgery, median (IQR), d	5 (1-15)	6 (1-13)		.77[a]
Duration of operation, median (IQR), min	210 (163-253)	190 (160-240)		.007[a]
Estimated blood loss, median (IQR), mL	100 (50-200)	150 (55-300)		.002[a]
Final incision length, median (IQR), cm	6.0 (4.5-9.0)	13.0 (11.0-17.0)		<.001[a]
Surgical approach, No. (%)				
Low anterior resection	143 (60)	153 (65)	−5.0 (−13.7 to 3.7)	.72
Lower anterior resection and coloanal anastomosis	69 (29)	58 (25)	4.3 (−3.7 to 12.3)	
Abdominoperineal resection	25 (11)	23 (10)	0.7 (−4.7 to 6.2)	
Ostomy created at time of resection, No. (%)				
None	46 (19)	67 (29)	−9.2 (−16.8 to −1.5)	.06
Colostomy	30 (13)	27 (12)	1.1 (−4.7 to 7.0)	
Ileostomy	162 (68)	141 (60)	8.1 (−0.5 to 16.7)	
Sphincter preserved	211 (89)	210 (89)	−0.7 (−6.3 to 4.9)	.81
Distal margin measured by surgeon, median (IQR), mm	26 (20-45)	35 (20-50)		.02[a]
Postoperative recovery, median (IQR), d				
Length of hospital stay	8 (6-12)	8 (6-12)		.21[a]
Time requiring parenteral narcotics	2 (1-3)[b]	2 (1-3)[c]		.31[a]
Time to first flatus	1 (1-2)[c]	2 (1-2)[d]		.04[a]
Time to first bowel movement	2 (1-3)[c]	2 (1-4)[d]		.14[a]
Time to solid diet	3 (2-4)[e]	3 (2-5)[c]		.05[a]
No. (%) with grade 3-4 postoperative complications[f]				
Leak (including anastomotic)	7 (3)	8 (3)	−0.03 (−3.2 to 3.1)	.98
Hemorrhage or hematoma	10 (5)	4 (2)	2.9 (−0.2 to 6.0)	.06
Perforation	0	0		
Fever (in the absence of neutropenia)	7 (3)	11 (4)	−1.2 (−4.6 to 2.2)	.51
Ileus	11 (5)	24 (10)	−4.6 (−9.2 to 0.02)	.08
Thrombosis, thrombus, or embolism	0	1 (<1)	−0.4 (−1.2 to 0.4)	.73
Cardiac ischemia or infarction	1 (<1)[g]	3 (1)	−0.7 (−2.4 to 0.8)	.48
Urinary retention (including neurogenic bladder)	1 (<1)	2 (1)	−0.3 (−1.8 to 1.1)	.80
Infection	7 (3)	9 (4)	−0.4 (−3.7 to 2.8)	.80

Abbreviations: ALaCaRT, Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial; IQR, interquartile range.

[a] Calculated using the Wilcoxon rank sum test.

[b] Data are from 237 patients.

[c] Data are from 234 patients.

[d] Data are from 233 patients.

[e] Data are from 237 patients.

[f] Percentages are based on the treatment received. There were 222 patients in the laparoscopic group and 251 in the open surgery group for this variable.

[g] There was 1 case of grade 5 cardiac ischemia or infarction.

be some imbalance in the severity of disease (more node-positive and pT4 tumors in the laparoscopic group) identified at surgery. These more advanced pT4 tumors had not been classified on pretreatment MRI and hence were included in the intention-to-treat analysis. However, analyses adjusted for these factors did not alter the conclusions. The pT4 tumors accounted for 2 of the 21 patients who converted from laparoscopic to open surgery (9.5% of the 8.8% overall conversion rate).

The Comparison of Open Versus Laparoscopic Surgery for mid or low Rectal Cancer After Neoadjuvant Chemoradiotherapy (COREAN) trial (conducted in South Korea) had a conversion rate of only 1.5%,[14] and a low rate (3%) of CRM involvement, but a complete mesorectal excision rate of only 73% compared with 87% in our trial. The main point of difference in the COREAN trial was the mean (SD) BMI of 24 (3.2), which is lower than that of typical western populations. The US-based Z6051 trial was similar to our trial, with a similar combined pathological primary end point as an indicator of surgical quality and as a surrogate for the long-term oncological outcome. One potential difference is that the Z6051 trial included complete and nearly complete grades of total mesorectal excision as successful, whereas we regarded only a grade of complete as a successful excision.

Even though our trial was not designed to demonstrate whether one method of rectal dissection was superior to the other, the inability to establish noninferiority suggests that surgeons should be cautious when considering the suitability of a laparoscopic approach for a patient with rectal cancer. Subgroup analyses raise the possibility that laparoscopic surgery might be less successful than open surgery in patients who have received neoadjuvant therapy, have larger T3 tumors, or have higher BMIs. However, our study was underpowered to show significant differences in proportions of lower success rates for laparoscopic surgery vs open surgery

in any subgroup. Nevertheless, it raises the question that greater caution might be needed when considering laparoscopic pelvic dissection for such patients. Long-term follow-up on clinical outcomes and evidence from other trials is needed to confirm such considerations.

The short-term clinical benefits expected in the laparoscopic surgery group did not eventuate. This is probably because most patients in the open group would have had laparoscopic splenic flexure mobilization and lymphovascular ligation (the abdominal component of the surgery). Most of the open surgeries were hybrid procedures, with just the critical pelvic dissection performed as an open procedure through a transverse (Pfannenstiel) or lower midline incision.[15]

The low conversion rates in multicenter trials, such as ours and the COREAN trial, may reflect the stringent selection criteria set for surgeons to participate in these trials. Conversely, the high rates of conversion to open surgery in the CLASICC and COLOR II trials may be attributed to those trials commencing before sufficient experience beyond the learning curve had been gained by the surgeons. This may have implications for appropriate timing of future trials comparing novel techniques for rectal cancer, such as transanal total mesorectal excision and robotics with laparoscopic or open surgery.

The main criteria for considering laparoscopic surgery for rectal cancer should be based on long-term clinical outcomes of recurrence and overall survival. Further follow-up data from our trial are currently being acquired, along with data on other secondary end points, such as quality of life and cost-effectiveness.

Conclusions

Among patients with T1-T3 rectal tumors, noninferiority of laparoscopic surgery compared with open surgery for successful resection was not established. Although the overall quality of surgery was high, these findings do not provide sufficient evidence for the routine use of laparoscopic surgery. Longer follow-up of recurrence and survival is currently being acquired.

ARTICLE INFORMATION

Author Contributions: Drs Stevenson and Simes had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Stevenson, Solomon, Lumley, Hewett, Clouston, Gebski, Hague, Simes.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Stevenson, Gebski, Davies, Wilson, Hague, Simes.
Critical revision of the manuscript for important intellectual content: Stevenson, Solomon, Lumley, Hewett, Clouston, Gebski, Hague, Simes.
Statistical analysis: Solomon, Gebski, Davies, Simes.
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Administrative, technical, or material support: Stevenson, Solomon, Lumley, Hewett, Clouston, Wilson, Hague.
Study supervision: Stevenson, Solomon, Lumley, Gebski, Hague, Simes.

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