

Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer The ROLARR Randomized Clinical Trial

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IMPORTANCE Robotic rectal cancer surgery is gaining popularity, but limited data are available regarding safety and efficacy.

OBJECTIVE To compare robotic-assisted vs conventional laparoscopic surgery for risk of conversion to open laparotomy among patients undergoing resection for rectal cancer.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial comparing robotic-assisted vs conventional laparoscopic surgery among 471 patients with rectal adenocarcinoma suitable for curative resection conducted at 29 sites across 10 countries, including 40 surgeons. Recruitment of patients was from January 7, 2011, to September 30, 2014, follow-up was conducted at 30 days and 6 months, and final follow-up was on June 16, 2015.

INTERVENTIONS Patients were randomized to robotic-assisted (n = 237) or conventional (n = 234) laparoscopic rectal cancer resection, performed by either high (upper rectum) or low (total rectum) anterior resection or abdominoperineal resection (rectum and perineum).

MAIN OUTCOMES AND MEASURES The primary outcome was conversion to open laparotomy. Secondary end points included intraoperative and postoperative complications, circumferential resection margin positivity (CRM+) and other pathological outcomes, quality of life (36-Item Short Form Survey and 20-item Multidimensional Fatigue Inventory), bladder and sexual dysfunction (International Prostate Symptom Score, International Index of Erectile Function, and Female Sexual Function Index), and oncological outcomes.

RESULTS Among 471 randomized patients (mean [SD] age, 64.9 [11.0] years; 320 [67.9%] men), 466 (98.9%) completed the study. The overall rate of conversion to open laparotomy was 10.1%. The overall CRM+ rate was 5.7%. Of the other 8 reported prespecified secondary end points, including intraoperative complications, postoperative complications, plane of surgery, 30-day mortality, bladder dysfunction, and sexual dysfunction, none showed a statistically significant difference between groups.

End Point	No. With Outcome/Total No. (%)		Unadjusted Risk Difference (95% CI), %	Adjusted Odds Ratio (95% CI)	P Value
	Conventional Laparoscopy	Robotic-Assisted Laparoscopy			
Conversion to open laparotomy	28/230 (12.2)	19/236 (8.1)	4.1 (-1.4 to 9.6)	0.61 (0.31-1.21)	.16
CRM+	14/224 (6.3)	12/235 (5.1)	1.1 (-3.1 to 5.4)	0.78 (0.35-1.76)	.56

CONCLUSIONS AND RELEVANCE Among patients with rectal adenocarcinoma suitable for curative resection, robotic-assisted laparoscopic surgery, as compared with conventional laparoscopic surgery, did not significantly reduce the risk of conversion to open laparotomy. These findings suggest that robotic-assisted laparoscopic surgery, when performed by surgeons with varying experience with robotic surgery, does not confer an advantage in rectal cancer resection.

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Laparoscopic surgery is increasingly used for the treatment of colon cancer, but its use for rectal cancer is more controversial. Two recent, large, multicenter randomized clinical trials^{1,2} support laparoscopic surgery, and 2 other major trials^{3,4} report evidence that does not allow a designation of noninferior as compared with open surgery.

Robotic assistance has the potential to overcome some of the limitations of laparoscopic rectal cancer surgery, providing an immersive 3-dimensional depth of field, articulating instruments, and a stable camera platform. Several small, nonrandomized studies have supported its safety and efficacy in rectal cancer surgery.^{5,6} Meta-analyses have failed to show superiority for robotic-assisted laparoscopic surgery over conventional laparoscopic surgery in short-term patient and pathological outcomes and have consistently reported longer operating times, but they have also shown a reduced need to convert to open surgery with the robot.^{7,8} A few nonrandomized studies have suggested that the robot may offer better preservation of bladder and sexual function.^{9,10}

The main concern about robotic surgery is the cost, including the capital and ongoing maintenance charges. A few studies have analyzed the costs of robotic rectal cancer surgery, reporting higher total hospital costs than for conventional laparoscopic surgery.^{11,12} Despite this, robotic rectal cancer surgery has continued to gain global utilization.

In 2009, the UK Medical Research Council and National Institute of Health Research, through the Efficacy and Mechanism Evaluation Programme, funded the Robotic vs Laparoscopic Resection for Rectal Cancer (ROLARR) trial to undertake an evaluation of the safety, efficacy, and short- and long-term outcomes of robotic-assisted vs conventional laparoscopic rectal cancer surgery. This trial was designed as a multicenter, international randomized clinical trial to accommodate the limited adoption of the robotic system at that time. This article presents the short-term results to 6-month follow-up.

Methods

This is an international, multicenter, randomized, unblinded, parallel-group trial¹³ comparing robotic-assisted vs conventional laparoscopic surgery for the curative treatment of rectal adenocarcinoma (distal extent ≤ 15 cm of the anal margin) by high anterior resection, low anterior resection, or abdominoperineal resection. Participating surgeons had to perform at least 30 minimally invasive (conventional laparoscopic or robotic-assisted laparoscopic) rectal cancer resections before taking part in the trial, of which at least 10 had to be conventional laparoscopic resections and at least 10 had to be robotic-assisted laparoscopic resections.¹⁴ The trial received national ethical approval in the United Kingdom or either local ethical committee or institutional review board approval at international centers. An independent trial steering committee and data monitoring and ethics committee oversaw the trial conduct. All participants provided written informed consent.

Key Points

Question Does robotic-assisted laparoscopic surgery, as compared with conventional laparoscopic surgery, reduce the risk of conversion to laparotomy among patients undergoing surgery for rectal cancer?

Findings In this randomized clinical trial that included 471 patients undergoing surgery for rectal cancer, the conversion rate was 8.1% for robotic surgery and 12.2% for laparoscopic surgery, not a statistically significant difference.

Meaning Among patients undergoing resection for rectal cancer, robotic-assisted laparoscopic surgery performed by surgeons with varying experience with robotic surgery did not confer an advantage compared with laparoscopic surgery for reducing the odds of conversion to laparotomy.

The trial design has been reported previously,¹³ and the full trial protocol is included in [Supplement 1](#). For patients to be included, they had to be fit for resectional surgery with a diagnosis of adenocarcinoma of the rectum. Patients with benign lesions of the rectum, cancers of the anal canal, locally advanced cancers not amenable to curative surgery or requiring en bloc multivisceral resection, or synchronous colorectal tumors requiring multisegment surgical resection were not eligible.

Randomization (minimization incorporating a random element) was on a 1:1 basis. The stratification factors were treating surgeon, patient, sex, preoperative radiotherapy or chemoradiotherapy, intended procedure, and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) classified according to World Health Organization criteria.¹⁵

The specifics of each operation were at the discretion of the operating surgeon. The only absolute requirement under robotic surgery was that the robot had to be used for mesorectal resection. Pathology reporting was according to internationally agreed criteria.¹⁶ Patient self-reported bladder function and sexual function were measured at baseline and 6 months following surgery with the International Prostate Symptom Score (I-PSS), International Index of Erectile Function (IIEF), and Female Sexual Function Index (FSFI). The I-PSS¹⁷ is a standardized, patient self-reported measure of the subjective problems that the patient experiences with urinating, with scores ranging from 0 to 35 and higher scores indicating more severe symptoms. The IIEF¹⁸ is a patient self-reported measure developed for the assessment of erectile function, with scores ranging from 5 to 75 and lower scores indicating greater severity of dysfunction. The FSFI¹⁹ is a patient self-reported measure of sexual function in women, with scores ranging from 2 to 36 and higher scores indicating greater function. Patients underwent clinical review at 30 days and 6 months postoperatively. Annual follow-up is continuing.

The primary end point was the rate of conversion to open surgery, defined as the use of a laparotomy wound for any part of the mesorectal dissection. The use of a small abdominal wound to facilitate a low, stapled anastomosis and/or

specimen extraction was permissible and not defined as an open conversion. Secondary end points were all prespecified and included pathological circumferential resection margin positivity (CRM+; defined as tumor ≤ 1 mm), intraoperative complications, postoperative (30-day and 6-month) complications, 30-day operative mortality, patient-reported bladder and sexual function, and pathological assessment of the quality of the plane of surgery. Quality of the plane of surgery was judged according to the method of Quirke and Dixon,²⁰ grading the pathology specimen in terms of completeness of surgical resection. For high and low anterior resection, this was defined as mesorectal (best), intramesorectal (intermediate), and muscularis propria (worst). For abdominoperineal excision, this was defined as levator (best), sphincteric (intermediate), and intrasphincteric (worst). Other prespecified secondary end points, not reported herein, include central pathology review with photographic documentation of resection specimens, and a full quality-of-life analysis. A full health economic evaluation was undertaken separately. Longer-term end points (local recurrence rates, disease-free survival, and overall survival) will be reported at 3 years after the last patient randomization.

The target sample size was 400 patients, which provides 80% power at the 5% (2-sided) level of significance to detect a reduction in the conversion rate from 25% in the conventional laparoscopic group to 12.5% in the robotic-assisted laparoscopic group, allowing for 16% attrition.¹³ The anticipated conversion rate in the conventional laparoscopic group was based on the MRC CLASICC Trial, which was the best available evidence at that time. The MRC CLASICC trial reported a conversion rate of 34% for conventional laparoscopic rectal cancer resection,²¹ which was reduced to 25% to account for advances in surgical technique. Sufficient funding was available to extend recruitment to 471 patients to take advantage of excellent patient recruitment and maximize the power of the study. This decision was made in consultation with the independent trial steering committee and data monitoring and ethics committee without review of data or an interim analysis being performed.

All analyses were prespecified and were conducted on the intention-to-treat population, ie, all randomized patients were accounted for in the analyses, and patients were categorized into treatment groups based on their randomization regardless of what treatment they subsequently received. Complete case analyses were performed for all prespecified end points. When the complete case analysis excluded more than 3% of patients due to missing data, exploratory analyses to investigate the effect of missing data were performed. Specifically, to explore the mechanism of the missing data and the validity of a complete case analysis for each end point, patient characteristics were compared between those with and without missing data and multilevel logistic regression models were used to identify any associations between prognostic variables and whether a patient had missing data, to inform whether data were missing at random. All hypothesis tests were 2-sided and conducted at the 5% level of significance. Estimates and their corresponding 95% confidence intervals and *P* values are presented for fixed effects. For the

(random) surgeon effect, the intraclass correlation coefficient, estimated via the analysis-of-variance method, and bias-corrected bootstrapped 95% confidence intervals are reported.^{22,23} Analyses were carried out in SAS version 9.4 statistical software (SAS Institute Inc).

Multilevel logistic regression was used to estimate the odds ratios (ORs) for conversion to laparotomy, CRM+, intraoperative complications, and postoperative complications between treatment groups, adjusting for the stratification factors, where operating surgeon was modeled as a random effect. Generalized linear mixed models were used to compare 6-month bladder and sexual function scores, adjusting for baseline scores and the stratification factors.

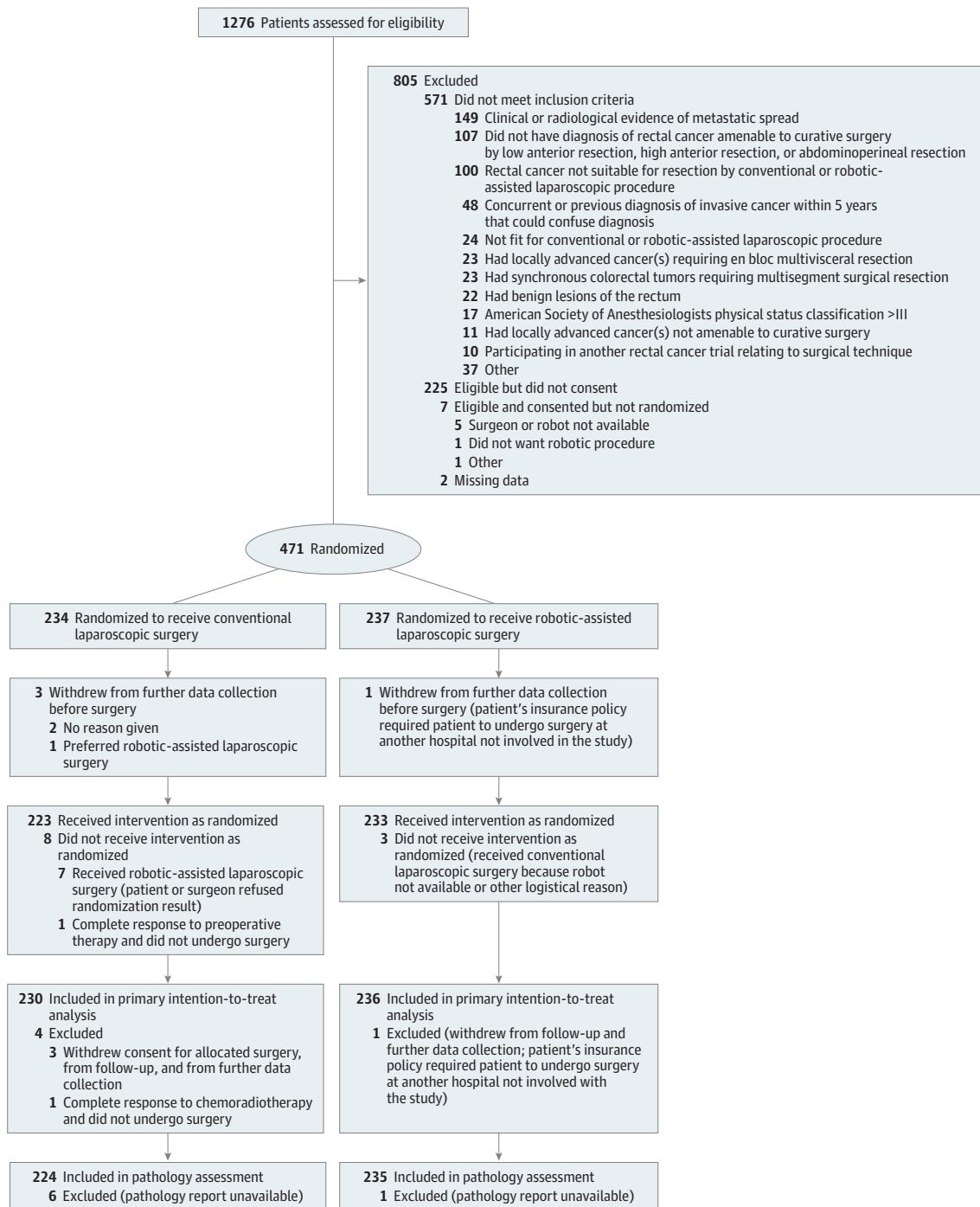
Sensitivity analyses were performed to determine the robustness of the findings from the primary analysis, including extension of the primary analysis to account for potential learning effects by including interaction terms for the operating surgeon's level of relevant robotic-assisted and conventional laparoscopic experience and the treatment effect. Subgroup analyses relating to the primary end point across sex, BMI class, and procedure received as well as relating to CRM+ across sex, BMI class, and T stage were performed. All subgroup analyses tested heterogeneity of the treatment effect across the subgroups and also estimated the treatment effect within each subgroup, via the inclusion of an appropriate interaction term. All sensitivity analyses and subgroup analyses were prespecified.

Cost analysis was undertaken from the perspective of a public (ie, UK National Health Service [NHS]) health care professional for all patients (eAppendix 1 and eTable 1 in Supplement 2). Resource utilization data for 190 UK and US patients were collected at baseline, intraoperatively, 30 days postoperatively, and 6 months postoperatively using study forms. Costs were computed in British pounds using a price year of 2015 and estimated using UK NHS unit costs from national data sources including the NHS Reference Costs database, Personal Social Services Research Unit costs of health and social care, and British National Formulary. For reporting purposes, costs are converted with 2015 Organisation for Economic Co-operation and Development purchasing power parity (0.866 British pound per 1 US dollar) and reported herein as 2015 US dollars. Multiple imputation methods were used for missing data. Sensitivity analysis was undertaken to account for uncertainty (eAppendix 2, eTables 2 and 3, and eFigure in Supplement 2). Given wide variation in costs due to contractual arrangements, acquisition and maintenance costs for the robotic-assisted and conventional laparoscopic systems were excluded.

Results

Between January 7, 2011, and September 30, 2014, 1276 patients were assessed for eligibility by 40 surgeons from 29 sites across 10 countries (United Kingdom, Italy, Denmark, United States, Finland, South Korea, Germany, France, Australia, and Singapore). Recruitment by country was 131 patients (6 sites) in the United Kingdom, 105 patients (5 sites)

Figure 1. Diagram of the Flow of Participants



in Italy, 92 patients (3 sites) in Denmark, 59 patients (9 sites) in the United States, 35 patients (1 site) in Finland, 18 patients (1 site) in South Korea, 16 patients (1 site) in Germany, 11 patients (1 site) in France, 2 patients (1 site) in Australia, and 2 patients (1 site) in Singapore. A total of 471 patients (36.9%) were randomized: 234 to conventional laparoscopic surgery and 237 to robotic-assisted laparoscopic surgery (Figure 1). A total of 466 patients underwent an operation, with 456

(97.9%) undergoing the allocated treatment. Follow-up for analysis was at 30 days and 6 months, with a final follow-up date of June 16, 2015.

The 2 treatment groups were well balanced with respect to baseline characteristics and operative procedures (Table 1). Of the 466 cases included in the primary intention-to-treat analysis, low anterior resection was performed in 317 (68.0%) and abdominoperineal resection was performed in 97

Table 1. Patient Baseline Characteristics, Operative Details, and Pathology Outcomes

Variable	Conventional Laparoscopic Surgery (n = 234)	Robotic-Assisted Laparoscopic Surgery (n = 237)
Baseline	(n = 234)	(n = 237)
Age, mean (SD), y	65.5 (11.93)	64.4 (10.98)
ASA classification, No. (%)		
I, Normal healthy patient	52 (22.2)	39 (16.5)
II, Patient with mild systemic disease	124 (53.0)	150 (63.3)
III, Patient with severe systemic disease	52 (22.2)	46 (19.4)
IV, Patient with severe systemic disease that is a constant threat to life	1 (0.4)	0
Missing	5 (2.1)	2 (0.8)
Sex, No. (%)		
Male	159 (67.9)	161 (67.9)
Female	75 (32.1)	76 (32.1)
BMI classification, No. (%) ^a		
Underweight or normal, 0-24.9	87 (37.2)	93 (39.2)
Overweight, 25.0-29.9	92 (39.3)	90 (38.0)
Obese, ≥30.0	55 (23.5)	54 (22.8)
Class I, 30.0-34.9	38 (16.2)	41 (17.3)
Class II, 35.0-39.9	10 (4.3)	9 (3.8)
Class III, ≥40.0	7 (3.0)	4 (1.7)
Preoperative radiotherapy or chemoradiotherapy, No. (%)		
Yes	108 (46.2)	111 (46.8)
No	126 (53.8)	126 (53.2)
Missing	14 (5.9)	6 (2.5)
Prior abdominal surgery, No. (%)		
Yes	67 (28.6)	62 (26.2)
No	162 (69.2)	174 (73.4)
Missing	5 (2.2)	1 (0.4)
Intended operation, No. (%)		
High anterior resection	34 (14.5)	35 (14.8)
Low anterior resection	158 (67.5)	159 (67.1)
Abdominoperineal resection	42 (17.9)	43 (18.1)
Operative details	(n = 230)	(n = 236)
Operation performed, No. (%)		
High anterior resection	19 (8.3)	28 (11.9)
Low anterior resection	165 (71.7)	152 (64.4)
Abdominoperineal resection	45 (19.6)	52 (22.0)
Other ^b	1 (0.4)	4 (1.7)
Height of tumor, cm from anal verge, No. (%) ^c		
11-15	69 (30.0)	71 (30.1)
6-10	99 (43.0)	107 (45.3)
0-5	61 (26.5)	57 (24.2)
Missing	1 (0.4)	1 (0.4)
Operative time		
Mean (SD), min	261.0 (83.24)	298.5 (88.71)
Missing, No. (%)	4 (1.7)	1 (0.4)
Stoma formation, No. (%)		
Temporary	157 (68.3)	142 (60.2)
Permanent	49 (21.3)	53 (22.5)
No	24 (10.4)	41 (17.4)
Length of stay		
Mean (SD), d	8.2 (6.03)	8.0 (5.85)
Missing, No. (%)	13 (5.7)	14 (5.9)

(continued)

Table 1. Patient Baseline Characteristics, Operative Details, and Pathology Outcomes (continued)

Variable	Conventional Laparoscopic Surgery (n = 230)	Robotic-Assisted Laparoscopic Surgery (n = 236)
Pathology outcomes	(n = 230)	(n = 236)
T stage, No. (%)		
0	24 (10.4)	22 (9.3)
1	20 (8.7)	24 (10.2)
2	61 (26.5)	64 (27.1)
3	114 (49.6)	117 (49.6)
4	8 (3.5)	5 (2.1)
Tx or missing	3 (1.3)	4 (1.7)
N stage, No. (%)		
0	150 (65.2)	146 (61.9)
1	58 (25.2)	63 (26.7)
2	21 (9.1)	25 (10.6)
Missing	1 (0.4)	2 (0.8)
Lymph node yield		
Mean (SD), No. ^d	24.1 (12.91)	23.2 (11.97)
Missing, No. (%)	9 (3.9)	1 (0.4)
Plane of surgery, No. (%) ^e		
Mesorectal area, all specimens		
Mesorectal	173 (75.2)	178 (75.4)
Intramesorectal	38 (16.5)	33 (14.0)
Muscularis propria	12 (5.2)	22 (9.3)
Missing	7 (3.1)	3 (1.3)
Sphincter area, abdominoperineal resections only	(n = 45)	(n = 52)
Levator	18 (40.0)	18 (34.6)
Sphincteric	19 (42.2)	22 (42.3)
Intrasphincteric or submucosal	5 (11.1)	9 (17.3)
Missing	3 (6.7)	3 (5.8)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a Derived from World Health Organization classification of obesity based on BMI, with a BMI of 25.0 to 29.9 indicating overweight and a BMI of 30.0 or greater indicating obese.

^b For the conventional laparoscopic group, this included laparoscopic biopsy of the peritoneum. For the robotic-assisted laparoscopic group, this included dorsal pelvic exenteration, ureter resection distally right-sided; Hartmann procedure (2 patients); and high anterior resection plus subtotal colectomy.

^c Height of tumor was determined by the lower border of the tumor from the anal verge at examination under anesthesia.

^d Lymph node yield refers to the number of lymph nodes retrieved from the specimen for histological analysis.

^e Plane of surgery was categorized according to the method of Quirke and Dixon²⁰ by grading the pathological specimen for completeness of surgical resection. Mesorectal refers to an intact mesorectal envelope; intramesorectal has small defects in the mesorectal envelope; and muscularis propria has defects in the mesorectal envelope down to the muscular bowel wall. Levator plane refers to complete surgical resection without wasting of the specimen at the level of the levators; sphincteric plane incorporates the anal sphincter muscles but with wasting at the level of the levators; and intersphincteric or submucosal refers to inadequate extent of resection in terms of extrarectal tissue.

(20.8%). The mean operative time was 37.5 minutes longer in the robotic-assisted laparoscopic group than in the conventional laparoscopic group (mean [SD] operative time, 298.5 [88.71] vs 261.0 [83.24] minutes, respectively). The length of hospital stay was similar between groups.

Table 2. Rates, Unadjusted Risk Differences, and Multilevel Logistic Regression Model of Odds of Conversion to Open Laparotomy^a

Effect ^b	No. With Conversion to Open Laparotomy/Total No. (%)	Unadjusted Risk Difference (95% CI), % ^c	Adjusted Odds Ratio (95% CI) ^d	P Value
Treatment				
Conventional laparoscopic surgery	28/230 (12.2)		1 [Reference]	
Robotic-assisted laparoscopic surgery	19/236 (8.1)	4.1 (-1.4 to 9.6)	0.61 (0.31-1.21)	.16
Sex				
Male	39/317 (12.3)		1 [Reference]	
Female	8/149 (5.4)	6.9 (1.8 to 12.1)	2.44 (1.05-5.71)	.04
BMI class, overweight vs underweight or normal^e				
Underweight or normal	13/179 (7.3)		1 [Reference]	
Overweight	9/180 (5.0)	2.3 (-2.7 to 7.2)	0.54 (0.21-1.37)	.19
BMI class, obese vs underweight or normal^e				
Underweight or normal	13/179 (7.3)		1 [Reference]	
Obese	25/107 (23.4)	-16.1 (-25.0 to -7.2)	4.69 (2.08-10.58)	<.001
Previous radiotherapy or chemoradiotherapy				
No	27/262 (10.3)		1 [Reference]	
Yes	20/204 (9.8)	0.5 (-5.0 to 6.0)	1.07 (0.50-2.26)	.86
Intended procedure, high vs low anterior resection^f				
Low anterior resection	37/312 (11.9)		1 [Reference]	
High anterior resection	6/68 (8.8)	3.0 (-4.6 to 10.7)	0.55 (0.19-1.56)	.26
Intended procedure, abdominoperineal resection vs low anterior resection^f				
Low anterior resection	37/312 (11.9)		1 [Reference]	
Abdominoperineal resection	4/86 (4.7)	7.2 (1.5 to 12.9)	0.18 (0.05-0.63)	.007

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a The intracluster correlation coefficient (ICC) for operating surgeon as a random effect was 0.05 (95% CI, 0.01-0.06). The ICC is a measure of the proportion of variance in the outcome that is explained by the operating surgeon (eg, an ICC of 0 would indicate that the odds of conversion for a given patient would not be affected at all if he or she underwent surgery by a different operating surgeon). The ICCs for a range of outcomes across a number of surgical trials are reported in the ICC database.²²

^b The variables in this column were included in the model as fixed effects, and operating surgeon was included in the model as a random effect; these are all of the variables included in the model.

^c Risk differences are unadjusted estimates.

^d Odds ratios are adjusted estimates yielded by the model.

^e Derived from World Health Organization classification of obesity based on BMI, with a BMI of 25.0 to 29.9 indicating overweight and a BMI of 30.0 or greater indicating obese.

^f Intended procedure, rather than actual procedure, is included in the model. The intended procedure was collected at randomization and used for stratification. A sensitivity analysis adjusting for actual procedure instead of intended procedure showed no notable changes to the effect estimates, with the exception of the odds ratio comparing abdominoperineal resection vs low anterior resection, which was less pronounced (adjusted odds ratio = 0.43 [95% CI, 0.16-1.13]; *P* = .09).

Participating surgeons had a wide range of previous experience with conventional and robotic-assisted laparoscopic surgery. On average, patients received an operation performed by a surgeon with experience of a median 91 (interquartile range, 45-180) previous conventional laparoscopic operations and a median 50 (interquartile range, 30-101) previous robotic-assisted laparoscopic operations.

Of the 471 patients who were randomized, 219 (46.5%) received preoperative radiotherapy or chemoradiotherapy, with no difference between the 2 treatment groups (Table 1). Also among these 471 patients, 222 (47.1%) received postoperative chemotherapy, with no difference between the 2 treatment groups.

Conversion Rate

Conversion to open surgery occurred in 47 of 466 patients (10.1%) overall: 28 of 230 patients (12.2%) in the conventional

laparoscopic group and 19 of 236 patients (8.1%) in the robotic-assisted laparoscopic group (unadjusted difference in proportions, 4.1% [95% CI, -1.4% to 9.6%]). There was no statistically significant difference between robotic-assisted and conventional laparoscopic surgery with respect to odds of conversion (adjusted OR = 0.61 [95% CI, 0.31 to 1.21]; *P* = .16). **Table 2** presents results from the multilevel logistic regression model and shows significantly increased odds of conversion in obese patients as compared with underweight or normal-weight patients (adjusted OR = 4.69 [95% CI, 2.08 to 10.58]; *P* < .001) and in men as compared with women (adjusted OR = 2.44 [95% CI, 1.05 to 5.71]; *P* = .04). Patients whose intended procedure was a low anterior resection had a significantly higher rate of conversion as compared with patients whose intended procedure was abdominoperineal resection (adjusted OR = 5.44 [95% CI, 1.60 to 18.52]; *P* = .007). Operating surgeon had a mild-to-moderate effect on odds of

Table 3. Secondary End Points by Treatment Group

End Point	No./Total No. (%)		Unadjusted Risk Difference (95% CI), %	Adjusted Odds Ratio (95% CI) ^a	P Value
	Conventional Laparoscopic Surgery	Robotic-Assisted Laparoscopic Surgery			
CRM ⁺ ^b	14/224 (6.3)	12/235 (5.1)	1.2 (-3.1 to 5.4)	0.78 (0.35 to 1.76)	.56
Mesorectal area = mesorectal plane	173/223 (77.6)	178/233 (76.4)	1.2 (-6.5 to 8.9)	0.94 (0.56 to 1.57)	.14
Intraoperative complication	34/230 (14.8)	36/236 (15.3)	-0.5 (-6.0 to 7.0)	1.02 (0.60 to 1.74)	.94
Postoperative complication within 30 d of operation	73/230 (31.7)	78/236 (33.1)	-1.3 (-9.8 to 7.2)	1.04 (0.69 to 1.58)	.84
Postoperative complication >30 d and ≤6 mo after operation	38/230 (16.5)	34/236 (14.4)	2.1 (-4.5 to 8.7)	0.72 (0.41 to 1.26)	.25
Mortality within 30 d of operation ^c	2/230 (0.9)	2/236 (0.8)	0.02 (-1.7 to 1.7)	NA	NA

Abbreviations: CRM+, circumferential resection margin positivity; NA, not applicable.

^a Adjusted for sex, body mass index class, preoperative radiotherapy, intended procedure, and operating surgeon.

^b Defined as tumor cells within 1 mm of the circumferential resection margin on histological analysis.

^c Adjusted analysis was not performed for mortality within 30 days of operation due to the small number of events.

conversion, as reflected by the intracluster correlation coefficient estimate of 0.05 (95% CI, 0.01 to 0.06).

Results from the sensitivity analysis that extended the primary analysis model to account for potential learning effects suggest that the benefit of robotic-assisted laparoscopic surgery compared with conventional laparoscopic surgery (with respect to conversion rate) is greater under surgeons who have more robotic-assisted laparoscopic experience, regardless of their level of conventional laparoscopic experience (eAppendix 2, eTables 2 and 3, and eFigure in Supplement 2).

No results from the prespecified subgroup analyses were statistically significant. Regarding the sex subgroup analysis, 39 of 317 men (12.3%) underwent conversion to laparotomy, 25 of 156 (16.0%) in the conventional laparoscopic group and 14 of 161 (8.7%) in the robotic-assisted laparoscopic group (unadjusted difference in proportions = 7.3% [95% CI, 0.1% to 14.6%]); 8 of 149 women (5.4%) underwent conversion to laparotomy, 3 of 74 (4.1%) in the conventional laparoscopic group and 5 of 75 (6.7%) in the robotic-assisted laparoscopic group (unadjusted difference in proportions = -2.6% [95% CI, -9.8% to 4.6%]). A Wald test of interaction between treatment effect and sex in the adjusted model yielded *P* = .09, and the estimated adjusted OR for conversion to laparotomy (robotic-assisted vs conventional laparoscopic surgery) in men given by the model was 0.46 (95% CI, 0.21 to 0.99; *P* = .04). Further details on all subgroup analyses are given in eAppendix 3 and eTables 4, 5, and 6 in Supplement 2.

Pathology Outcomes

The pathological outcomes are shown in Table 1. The majority of tumors, 356 of 466 (76.4%), were pT2 or pT3. The total number of lymph nodes retrieved at pathology (lymph node yield) was high in both the conventional and robotic-assisted laparoscopic groups (mean [SD], 24.1 [12.91] vs 23.2 [11.97] lymph nodes, respectively). Of 466 patients who had an operation, 459 (98.5%) had complete pathology data available. Of these 459 patients, 26 (5.7%) had CRM+: 14 of 224 (6.2%) in the conventional laparoscopic group and 12 of 235 (5.1%) in the robotic-assisted laparoscopic group (unadjusted difference in proportions = 1.1% [95% CI, -3.1% to 5.4%]). There was no statistically significant difference in the odds of CRM+ between the groups (adjusted OR = 0.78 [95% CI, 0.35 to 1.76]; *P* = .56) (Table 3). Subgroup analyses were largely

uninformative owing to the low overall CRM+ rate. Proximal margin involvement was not observed in any patients, and distal margin involvement was observed in only 1 patient in the conventional laparoscopic group. Pathological assessment of the quality of the plane of surgery for the mesorectal area was captured for 456 of 466 patients (97.9%), and the quality of the plane was of the highest standard (mesorectal plane) in 351 of 456 cases (77.0%): 173 of 223 (77.6%) in the conventional laparoscopic group and 178 of 233 (76.4%) in the robotic-assisted laparoscopic group (unadjusted difference in proportions = 1.2% [95% CI, -6.5% to 8.9%]). There was no statistically significant difference in the odds of achieving the highest-standard plane of surgery (mesorectal plane) between the groups (adjusted OR = 0.94 [95% CI, 0.56 to 1.57]; *P* = .14) (Table 3).

Complications

Table 4 shows the complication rates up to 6 months postoperatively. Of 466 patients, 70 (15.0%) had an intraoperative complication: 34 of 230 (14.8%) in the conventional laparoscopic group and 36 of 236 (15.3%) in the robotic-assisted laparoscopic group (unadjusted risk difference = -0.5% [95% CI, -6.0% to 7.0%]). There was no significant difference between the groups (adjusted OR = 1.02 [95% CI, 0.60 to 1.74]; *P* = .94). The most common intraoperative complications were damage to an organ or structure, significant hemorrhage, and surgical equipment failure. Overall, 151 patients (32.4%) reported a complication within 30 days: 73 of 230 patients (31.7%) in the conventional laparoscopic group and 78 of 236 (33.1%) in the robotic-assisted laparoscopic group (unadjusted risk difference = -1.3% [95% CI, -9.8% to 7.2%]). There was no significant difference between the groups (adjusted OR = 1.04 [95% CI, 0.69 to 1.58]; *P* = .84). Seventy-two patients (15.5%) reported a complication after 30 days and within 6 months: 38 of 230 patients (16.5%) in the conventional laparoscopic group and 34 of 236 (14.4%) in the robotic-assisted laparoscopic group (unadjusted risk difference = 2.1% [95% CI, -4.5% to 8.7%]). There was no significant difference between the groups (adjusted OR = 0.72 [95% CI, 0.41 to 1.26]; *P* = .25). The occurrence of anastomotic leak was determined by the surgeon and reported as gastrointestinal complication. Of the 361 patients with an anastomosis, 40 (11.1%) reported an anastomotic leak within 6 months: 18 of 181 patients (9.9%) in the

Table 4. Number of Patients With Intraoperative and Postoperative Complications

Complication ^a	No. (%)	
	Conventional Laparoscopic Surgery (n = 230)	Robotic-Assisted Laparoscopic Surgery (n = 236)
Intraoperative		
Overall	34 (14.8)	36 (15.3)
Damage to organ or structure	5 (2.2)	11 (4.7)
Significant hemorrhage	11 (4.8)	4 (1.7)
Equipment failure	6 (2.6)	8 (3.4)
Fecal contamination	6 (2.6)	7 (3.0)
Anastomotic complication	6 (2.6)	7 (3.0)
Iatrogenic tumor perforation	3 (1.3)	2 (0.8)
Inadequate tumor localization or clearance	2 (0.9)	2 (0.8)
Respiratory event	2 (0.9)	1 (0.4)
Cardiac event	1 (0.4)	1 (0.4)
Within 30 d postoperatively		
Overall	73 (31.7)	78 (33.1)
Gastrointestinal complication	40 (17.4)	35 (14.8)
Surgical site infection	19 (8.3)	21 (8.9)
Urinary complication	14 (6.1)	17 (7.2)
Respiratory complication	6 (2.6)	4 (1.7)
Cardiac complication	6 (2.6)	3 (1.3)
Other	12 (5.2)	17 (7.2)
>30 d and ≤6 mo postoperatively		
Overall	38 (16.5)	34 (14.4)
Gastrointestinal complication	18 (7.8)	20 (8.5)
Urinary complication	6 (2.6)	7 (3.0)
Surgical site infection	8 (3.5)	4 (1.7)
Respiratory complication	3 (1.3)	2 (0.8)
Cardiac complication	1 (0.4)	0
Cerebrovascular complication	1 (0.4)	0
Other	12 (5.2)	7 (3.0)

^a The categories (intraoperative, within 30 days postoperatively, and within 6 months [after 30 days]) are not mutually exclusive.

conventional laparoscopic group and 22 of 180 (12.2%) in the robotic-assisted laparoscopic group.

Mortality Within 30 Days Postoperatively

Mortality was a rare event, with 4 deaths (0.9%) among 466 patients (2 in each group). All deaths were related to the surgical intervention and involved a septic complication.

Postoperative Bladder and Sexual Function

Patient self-reported assessment of bladder function between baseline and 6 months was complete in 351 of 466 cases (75.3%). Patient self-reported assessment of sexual function was complete in 181 of 320 men (56.6%) and 54 of 151 women (35.8%). Exploratory analyses comparing prognostic factors between patients with and without complete data and also between the 2 treatment groups showed that the conclusions of the complete case analyses are robust to any potential effect of the missing data.

The I-PSS scores for bladder function (with higher scores indicating worse function on a scale of 0-35) for conventional and robotic-assisted laparoscopic surgery at baseline and 6 months are presented in **Figure 2**. The adjusted analysis comparing 6-month scores yielded an estimated difference (conventional laparoscopic group minus robotic-assisted laparoscopic group) of 0.743 (95% CI, -0.587 to 2.072; $P = .27$), indicating there was no statistically significant difference between the groups.

The IIEF scores for male sexual function (with higher scores indicating worse function on a scale of 5-75) and FSFI scores for female sexual function (with higher scores indicating better function on a scale of 2-36) for conventional and robotic-assisted laparoscopic surgery at baseline and 6 months are also presented in **Figure 2**. Adjusted analyses comparing the 6-month scores yielded an estimated IIEF total score difference (conventional laparoscopic group minus robotic-assisted laparoscopic group) of 0.802 (95% CI, -4.100 to 5.704; $P = .75$) and an estimated FSFI total score difference (conventional laparoscopic group minus robotic-assisted laparoscopic group) of 1.231 (95% CI, -3.541 to 6.003; $P = .60$), indicating there was no difference between the groups.

Health Economic Analysis

Multiple imputation was used to provide data for all 190 US and UK patients. The health care costs in the robotic-assisted laparoscopic group (mean of £11 853 or \$13 668 [95% CI, \$13 025-\$14 350]) were higher than in the conventional laparoscopic group (mean of £10 874 or \$12 556 [95% CI, \$11 889-\$13 223]), and this difference was statistically significant (mean difference = £980 or \$1132 [95% CI, \$191-\$2072]; $P = .02$). The main drivers of higher operative costs were longer mean use of the operating theater (robotic-assisted laparoscopic group minus conventional laparoscopic group, difference = 50.88 minutes [95% CI, 20.26-81.56]; $P = .001$) and the mean cost of instruments (robotic-assisted laparoscopic group minus conventional laparoscopic group, difference = £513 or \$593 [95% CI, \$493-\$693]; $P < .001$).

Health care resource allocation data were complete in 47 of 95 patients receiving conventional laparoscopic surgery and 52 of 95 patients receiving robotic-assisted laparoscopic surgery. Among the patients with complete data, the mean cost for patients receiving conventional laparoscopic surgery was slightly lower than the imputed analysis (\$12 341 vs \$12 556, respectively) and was almost identical to the mean cost for patients receiving robotic-assisted laparoscopic surgery (\$13 691 vs \$13 688, respectively).

Discussion

In this study, to our knowledge the largest randomized clinical trial of robotic-assisted laparoscopic surgery for patients with rectal adenocarcinoma suitable for curative resection, there were no statistically significant differences in the rates of conversion to open laparotomy for robotic-assisted laparoscopic surgery compared with conventional laparoscopic

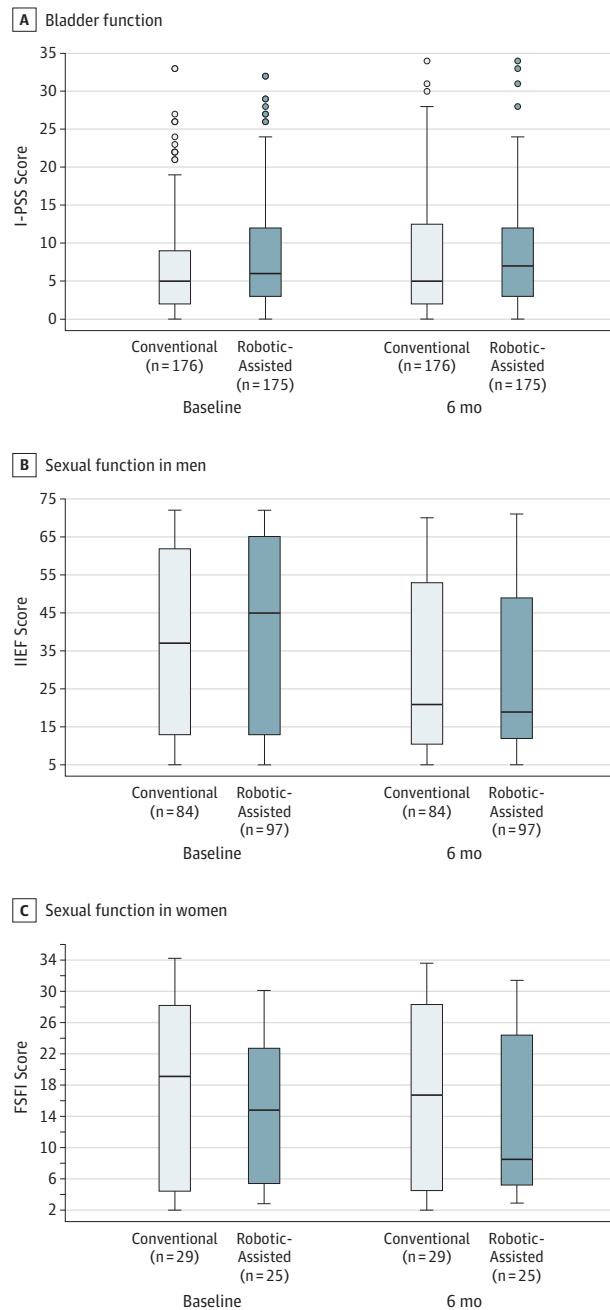
surgery (8.1% vs 12.2%, respectively), and there were no statistically significant differences in CRM+, complication rates, or quality of life at 6 months. There is insufficient evidence to conclude that robotic-assisted laparoscopic surgery, compared with conventional laparoscopic surgery, reduces the risk of conversion to open laparotomy when performed by surgeons of varying experience with robotic-assisted surgery.

The primary outcome measure was conversion to open surgery, based on the hypothesis that the technological advantages of the robot should facilitate rectal cancer resection and avoid the need to convert to an open operation. The sample size calculations were based on best available evidence in 2009, including the largest randomized clinical trial of conventional laparoscopic rectal cancer surgery, the MRC CLASICC trial, which reported a 34% conversion rate to open surgery.²¹ A 25% conversion rate from conventional laparoscopic to open surgery was assumed, giving a sample size of 400 patients to demonstrate a 50% relative reduction in the conversion rate with robotic-assisted surgery. The actual overall conversion rate was much lower, 10.1%. A similar reduction in conversion rates with time has been reported in other conventional laparoscopic rectal cancer trials: COLOR II, 16%²⁴; ACOSOG Z6051, 11%⁴; and ALaCaRT, 9%.³ In our trial, the difference in conversion rates between conventional laparoscopic surgery (12.2%) and robotic-assisted laparoscopic surgery (8.1%) was not statistically significant. The statistically significant lower overall conversion in patients undergoing low anterior resection, as compared with abdominoperineal resection, probably reflects that the majority of the oncological component of the operation is performed from the perineum in the abdominoperineal approach and is less affected by the laparoscopic approach. Similarly, the higher overall conversion rates for men (as compared with women) and obese patients (as compared with underweight or normal-weight patients) probably reflect the increasing technical difficulty in these patients.

The sensitivity analysis exploring learning effects suggested a potential benefit of robotic surgery when performed by surgeons with substantial prior robotic-assisted laparoscopic experience, regardless of their level of conventional laparoscopic experience. This suggests that most participating surgeons were experts in conventional laparoscopic surgery but still in their learning phases for robotic-assisted laparoscopic surgery and that at the higher end of the spectrum of experience in robotic-assisted laparoscopic surgery there is evidence of a benefit (in terms of conversion rate) over conventional laparoscopic surgery.

In almost all of the subgroup analyses, there were insufficient numbers of patients to produce statistically meaningful comparisons between the groups regarding the need to convert to an open operation. However, differences were apparent in the conversion rates for the conventional and robotic-assisted laparoscopic groups in men, with robotic-assisted laparoscopic surgery appearing to offer a benefit. While results yielded by a subgroup analysis must be interpreted with caution, the moderate evidence of interaction between sex and treatment effect, evidence of a difference between treatments in men, and the clinical plausibility of the robot faci-

Figure 2. Bladder and Sexual Function at Baseline and 6 Months Postoperatively Following Conventional or Robotic-Assisted Laparoscopic Surgery



Bladder function was assessed with the International Prostate Symptom Score (I-PSS; scores range from 0-35, with higher scores indicating worse function) (A), sexual function in men with the International Index of Erectile Function (IIEF; scores range from 5-75, with higher scores indicating worse function) (B), and sexual function in women with the Female Sexual Function Index (FSFI; scores range from 2-36, with higher scores indicating better function) (C). Horizontal line in the middle of each box indicates median; lower and upper borders of each box, 25th and 75th percentiles, respectively; whiskers, 1.5 times the interquartile range; and circles, extreme outliers.

tating dissections in the narrower male pelvis with more operator-controlled retraction, better optics, and instrument precision all warrant further investigation into the potential

benefit of robotic-assisted laparoscopic surgery in this subgroup of technically challenging patients.

The experience of the participating surgeons was also evident in the low CRM+ rate (overall, 5.7%), which was lower than previous trials studying conventional laparoscopy for rectal cancer: COLOR II, 10%; ACOSOG Z6051, 12.1%; and ALaCaRT, 7%. Pathological grading of the plane of surgery showed a good standard, with mesorectal plane surgery observed in 75.3% overall. This is lower than reported in COLOR II (88%) and ALaCaRT (87%), but similar to ACOSOG Z6051 (72.9%), and is probably due to the recognized variation in reporting between pathologists. In our trial, reporting of the pathological plane of surgery was standardized to the method described by Nagtegaal and Quirke.²⁵

In accordance with other studies, robotic-assisted laparoscopic surgery was associated with longer operating times and no benefit over conventional laparoscopic surgery in length of hospital stay.^{7,26} A full health care economics analysis will be reported separately.

The complication rates following conventional and robotic-assisted laparoscopic surgery were similar, and there were no safety issues attributable to the robotic system. Overall 30-day mortality was low at 0.9%, in keeping with the results of meta-analyses.⁷ The leading causes of intraoperative morbidity were iatrogenic damage to an organ or structure and significant hemorrhage. In contrast to other studies, hemorrhage was not more frequently associated with robotic-assisted laparoscopic surgery.²⁷ Rectal cancer surgery is a high-risk intervention, with 32.4% of patients experiencing a complication within 30 days and 15.5% of patients having complications between 30 days and 6 months.

Previous studies have shown that both conventional and robotic-assisted laparoscopic surgery for rectal cancer can result in bladder and sexual dysfunction, but the studies suggest that recovery is earlier for robotic-assisted laparoscopic surgery.^{10,28} This analysis of bladder and sexual function, at the same time points and using the same research questionnaires, does not support previous findings. There was little change in the I-PSS, IIEF, and FSFI scores between baseline and 6 months postoperatively, suggesting that the surgeons were accomplished in autonomic nerve preservation and that clinically relevant bladder and sexual dysfunction were an infrequent event.

Results from the health economics analysis suggest that robotic-assisted laparoscopic surgery for rectal cancer is unlikely to be cost-saving. The mean difference per operation, excluding the acquisition and maintenance costs, was £980 (\$1132) and driven by longer operating theater time and increased costs for robotic instruments. When considering robotic-assisted laparoscopic surgery as a whole, rather than just rectal cancer surgery, one has to consider the cost of purchase and maintenance of the system, the operational life, and the total utilization of the robot per year for all robotic procedures. Estimates of acquisition costs in 2017 vary between \$0.6 million and \$2.5 million, with maintenance costs between \$0.08 million and \$0.17 million per year.²⁹ Assuming a midpoint acquisition cost of \$1.55 million and

midpoint maintenance cost of \$0.125 million per year, with an operational life and amortization period of 7 years,^{30,31} the total cost of a robot would be approximately \$2.425 million. Estimates for total utilization of the robot per year in 2017 vary between 819 000 and 843 000 procedures across 3919 installed systems, or 1505 procedures per robot over 7 years.²⁹ This gives the total fixed cost of around \$1611 per procedure, in addition to the variable costs.

Alternatively stated, the net benefits (excluding fixed costs) of any robotic procedure included in a set of cost-effective procedures need to be positive, and the entire set of cost-effective procedures needs to have an average net benefit of at least \$1611. On average, all robotic procedures combined must exceed this figure, with all procedures making at least some positive contribution. On the basis of the evidence presented here, robotic-assisted laparoscopic surgery for rectal cancer does not appear to provide a positive contribution and does not appear to be justified given the extra costs and equivalency of clinical outcomes.

Limitations

This study has several limitations. The much lower than anticipated rate of conversion to open laparotomy limits the ability to provide conclusive evidence about our primary question of how robotic-assisted laparoscopic surgery compares with conventional laparoscopic surgery in odds of conversion. However, the fact that no statistically significant differences between the treatment groups were seen in any of the end points does suggest that robotic-assisted laparoscopic surgery, when performed by surgeons with varying robotic experience, does not confer a clinically important benefit over conventional laparoscopic surgery in the short term.

No blinding to treatment allocation was incorporated into this trial. The primary end point and the measure of mortality were certainly unaffected by this as objective end points. However, there is the potential for end points that are not completely objective to have been affected. In our pathology end points, including CRM+, we have guarded against this by carrying out a blinded central review of pathology assessments.

Despite enforcing a mandatory minimum experience level for surgeon participation, operations in this trial were performed, on average, by a surgeon considered to be an expert in conventional laparoscopic surgery and who may still have been in his or her learning phase for robotic-assisted laparoscopic surgery. The prespecified sensitivity analysis of learning effects addresses this by extending the primary analysis model to analyze the interaction between operating surgeon experience and the treatment effect (eAppendix 2, eTables 2 and 3, and eFigure in Supplement 2).

The primary analysis adjusted only for stratification factors (including operating surgeon) and thus did not include an adjustment for treating site. A (prespecified) adjustment for treating site was considered in a sensitivity analysis, but model estimation issues were caused by the small sizes of the resulting strata, resulting in no meaningful output.

Conclusions

Among patients with rectal adenocarcinoma suitable for curative resection, robotic-assisted laparoscopic surgery, as compared

with conventional laparoscopic surgery, did not significantly reduce the risk of conversion to open laparotomy. These findings suggest that robotic-assisted laparoscopic surgery, when performed by surgeons with varying experience with robotic surgery, does not confer an advantage in rectal cancer resection.

ARTICLE INFORMATION

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