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Article:
Jayne, D, Pigazzi, A, Marshall, H et al. (2017) 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. Journal of the American Medical Association, 318 (16). pp. 1569-1580. ISSN: 0098-7484

https://doi.org/10.1001/jama.2017.7219

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EFFECT OF ROBOTIC-ASSISTED VS CONVENTIONAL LAPAROSCOPIC SURGERY ON RISK OFCONVERSION TO OPEN LAPAROTOMY AMNG PATIENTS UNDERGOING RESECTION FOR RECTAL CANCER. THE ROLARR RANDOMIZED CLINICAL TRIAL.

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Subtitle: The ROLARR clinical trial.

Word count: 4119

KEY POINTS

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

Findings: In this randomised 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, a non-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.

ABSTRACT

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

Objective: To compare robotic-assisted with conventional laparoscopic surgery for risk of conversion to laparotomy among patients undergoing resection rectal cancer resection.

Design, setting, and participants: Multicentre, randomised, clinical trial comparing robotic-assisted surgery versus conventional laparoscopic surgery among 471 patients with rectal adenocarcinoma suitable for curative resection conducted at 26 sites across 10 countries and including 40 surgeons. Recruitment of patients was from 07/01/11 to 30/09/14 with 30 day and 6 month follow-up, and final follow-up on16/06/2015.

Intervention: Robotic-assisted and conventional laparoscopic rectal cancer resections were performed by either high (upper rectum) or low (total rectum) anterior resection or abdominoperineal resection (rectum and perineum). 237 patients were randomised to robotic-assisted and 234 to conventional laparoscopic surgery. Follow-up was at 30-days and 6-months post-operation.

Main Outcome and Measure: The primary outcome was conversion to laparotomy. Secondary endpoints included intra- and post-operative complications, cicumferential resection margin positivity

(CRM+) and other pathological outcomes, quality of life (36-Item Short Form Survery (SF-36), Multidimensional Fatigue Inventory (MFI-20)), bladder and sexual dysfunction (International Prostate Symptom Score (I-PSS), International Index of Erectile Function (IIEF), Female Sexual Function Index (FSFI)), and oncological outcomes. Of 11 pre-specified short-term secondary endpoints, 9 are reported.

Results: Among 471 randomised patients (mean age 64.9 years (s.d. 11.0); 320 (67.9%) men), 466 (98.9%) completed the study. The overall rate of conversion to laparotomy was 10.1%: 19 (8.1%) patients in the robotic-assisted group and in 28 (12.2%) of patients in the conventional laparoscopic group - unadjusted risk difference 4.12% (95% CI: -1.35%, 9.59%), adjusted odds ratio 0.61 (95% CI: 0.31-1.21; p=0.16). Overall CRM+ rate was 5.7%, and occurred in 14 (6.3%) in the laparoscopic group and 12 (5.1%) in the robotic group – unadjusted risk difference 1.14% (95% CI: -3.10%, 5.38%), adjusted odds ratio 0.785 (95% CI: 0.350, 1.762); p=0.56). Of the other 8 pre-specified secondary endpoints, including intra-operative complications, post-operative complications, plane of surgery, 30-day mortality and bladder and sexual dysfunction, none showed a statistically significant difference between groups.

Conclusions and Relevance: Among patients with rectal adenocarcinoma suitable for curative resection, robotic-assisted laparoscopic surgery, 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.

www.isrctn.com ISRCTN80500123 Robotic versus laparoscopic resection for rectal cancer

INTRODUCTION

Laparoscopic surgery is increasingly used for the treatment of colon cancer, but its use for rectal cancer is more controversial with two recent, large, multicentre, randomised trials[1 2] supportive of laparoscopic

surgery and two other major trials[3 4] reporting evidence that does not allow a designation of "non-inferior" as compared to 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, non-randomised studies have supported its safety and efficacy in rectal cancer surgery[5 6]. Meta-analyses have failed to show superiority for robotic over laparoscopic surgery in terms of short-term patient and pathological outcomes, and have consistently reported longer operating times, but a reduced need to convert to open surgery with the robot[7 8]. A few non-randomised studies have suggested the robot may offer an advantage in terms of 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 analysed the costs of robotic rectal cancer surgery, reporting higher total hospital costs than laparoscopic surgery [11 12]. In spite of 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 (EME) programme, funded the Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial to undertake an evaluation of the safety, efficacy, and short- and long-term outcomes of robotic as compared to laparoscopic rectal cancer surgery. This trial was designed as a multicentre, international clinical trial to accommodate the limited adoption of the robotic system at that time. This manuscript presents the short-term results to 6-months follow-up.

METHODS

This is an international, multicentre, randomised, unblinded, parallel-group trial [13] comparing robotic versus laparoscopic surgery for the curative treatment of rectal adenocarcinoma (distal extent at or within

15cm of the anal margin) either by high anterior resection, low anterior resection, or abdominoperineal resection. Participating surgeons had to perform a minimum of 30 minimally invasive (laparoscopic or robotic) rectal cancer resections before taking part in the trial, of which at least 10 had to be laparoscopic and at least 10 robotic resections [14]. The trial received national ethical approval in the UK or either local ethical committee/institutional review board approval at international centres. An independent Trial Steering Committee and Data Monitoring & Ethics Committee oversaw the trial conduct. All participants provided written, informed consent.

The trial design has been reported previously [13]. To be included, patients 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 multi-visceral resection or with synchronous colorectal tumours requiring multi-segment surgical resection were not eligible.

Randomisation (minimisation incorporating a random element) was on a 1:1 basis. The stratification factors were treating surgeon, patient, sex, preoperative radio- or chemoradiotherapy, intended procedure and body mass index (BMI) classified according to WHO 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 and sexual function was measured at baseline and 6 months following surgery with the International Prostate Symptom Score (I-PSS), International Index of Erectile Function (IIEF) and the Female Sexual Function Index (FSFI). The I-PSS[17] is a standardised, patient self-reported measure of the subjective problems that the patient experiences with urinating, with scores ranging from 0-35 and greater scores indicating more severe symptoms. The IIIEF[18] is a patient self-reported measure developed for the assessment of erectile function, with scores ranging from 5-75 and lower scores indicating higher severity of dysfunction. The FSFI[19] is a patient self-reported measure of sexual function in women, with scores

ranging from 2-36 and greater scores indicating greater function. Patients underwent clinical review at 30 days and 6 months post-operation. Annual follow-up is continuing.

The primary endpoint was 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 endpoints were all pre-specified and included pathological circumferential resection margin positivity (CRM+, defined as tumour ≤ 1mm), intra-operative and post-operative (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 plane of surgery was judged according to the method of Quirke *et al* [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 pre-specified secondary endpoints, not reported here, include central pathology review with photo documentation of resection specimens, and a full quality of life analysis. A full health economic evaluation was undertaken separately. Longer-term endpoints (local recurrence rates, disease-free survival and overall survival) will be reported at 3 years after the last patient randomisation.

The target sample size was 400 patients, which provides 80% power at the 5% (2-sided) level of significance to detect a reduction in conversion rate from 25% in the laparoscopic group to 12.5% in the robotic group allowing for 16% attrition [13]. The anticipated conversion rate in the laparoscopic group was based upon the MRC CLASICC Trial which was the best available evidence at that time. The MRC CLASICC trial reported a conversion rate of 34% for 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 maximise the power of the study. This decision was made in consultation with the independent Trial Steering

Committee and Data Monitoring Committee without review of data or an interim analysis being performed.

All analyses were pre-specified and were conducted on the intention-to-treat (ITT) population i.e. all randomised patients were accounted for in the analyses, and patients were categorised into treatment groups based on their randomisation regardless of what they subsequently received. Complete case analyses were performed for all pre-specified endpoints. 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 endpoint, patient characteristics were compared between those with and without missing data and multi-level logistic regression models were used to identify any associations between prognostic variables and whether or not a patient had missing data to inform whether data was missing at random. All hypothesis tests were two-sided and conducted at the 5% level of significance. Estimates and their corresponding 95% confidence intervals (CIs) and p-values are presented for fixed effects. For the (random) surgeon effect, the intra-cluster correlation coefficient (ICC), estimated via the ANOVA method along with bias-corrected bootstrapped 95% confidence intervals is reported[22 23]. Analyses were carried out in SAS v9.4.

Multi-level logistic regression was used to estimate the odds ratios for conversion to laparotomy, CRM+, intra-operative complications and post-operative complications between treatment groups adjusting for the stratification factors, where operating surgeon was modelled as a random effect. Generalised 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 and laparoscopic experience and the

treatment effect. Subgroup analyses relating to the primary endpoint across sex, BMI class and procedure received were performed as well as relating to CRM+ across sex, BMI class and T-stage. 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 pre-specified.

Cost analysis was undertaken from the perspective of a public (i.e. NHS UK) health care provider for all patients. Resource utilisation data for 190 UK and US patients were collected at baseline, intra-operative, 30 days and 6-months post-operatively using study forms. Costs were computed in £ 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 (PSSRU) costs of health and social care and British National Formulary. For reporting purposes, costs are converted with 2015 OECD purchasing power parity (0.866 GBP/USD) and reported here as 2015 US dollars. Multiple imputation methods were used for missing data. Sensitivity analysis was undertaken to account for uncertainty (see Supplemental data). Given wide variation in costs due to contractual arrangements, acquisition and maintenance costs for the robotic and laparoscopic systems were excluded.

RESULTS

Between 07/01/2011 and 30/09/2014, 1276 patients were assessed for eligibility by 40 surgeons from 26 sites across 10 countries (UK, Italy, Denmark, USA, Finland, South Korea, Germany, France, Australia and Singapore). Recruitment by country (number of sites) was 131 (6) UK, 105 (5) Italy, 92 (3) Denmark, 59 (9) USA, 35 (1) Finland, 18 (1) S. Korea, 16 (1) Germany, 11 (1) France, 2 (1) Australia, 2 (1) Singapore. 471 (36.9%) of these patients were randomised; 234 to laparoscopic and 237 to robotic surgery (Figure 1). 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 16/06/2015.

The two treatment groups were well balanced with respect to baseline characteristics and operative procedures (Table 1). Low anterior resection was performed in 317/466 (68.0%) cases with an abdominoperineal rate of 97/466 (20.8%). Mean operative time was 37.5 minutes longer in the robotic group. The length of hospital stay was similar between groups.

Participating surgeons had a wide range of previous laparoscopic and robotic experience. On average, patients received an operation performed by a surgeon with experience of around 91 (Median. IQR: 45, 180) previous laparoscopic and 50 (Median. IQR: 30, 101) previous robotic operations.

219/471 (46.5%) patients received preoperative radio- or chemoradiotherapy, with no difference between the two treatment groups (see Supplemental data). 222/471 (47.6%) patients received postoperative chemotherapy, with no difference between the two treatment groups (see Supplemental data).

Conversion rate

The rate of conversion to open surgery was 47/466 (10.1%) patients overall, 28/230 (12.2%) in the laparoscopic group, and 19/236 (8.1%) in the robotic group – unadjusted difference in proportions 4.12% (95% CI: -1.35%, 9.59%). There was no statistically significant difference between robotic surgery and conventional laparoscopic surgery with respect to odds of conversion – adjusted odds ratio (OR) 0.614 (95% CI: 0.311, 1.211. p=0.16). Table 2 presents results from the multi-level logistic regression model and shows significantly increased odds of conversion in obese patients vs. underweight/normal patients – adjusted OR 4.691 (95% CI: 2.080, 10.581. p<0.01) and in males vs. females - adjusted OR 2.444 (95% CI: 1.047, 5.708. p=0.04). Patients whose intended procedure was a low anterior resection had a significantly higher rate of conversion as compared to patients whose intended procedure was abdominoperineal resection – adjusted OR 5.435 (95% CI: 1.595, 18.519. p=0.007). Operating surgeon had a mild-to-moderate effect on odds of conversion, as reflected by the ICC estimate of 0.05 (95% CI: 0.007, 0.056).

Results from the sensitivity analysis that extended the primary analysis model to account for potential learning effects suggest that the benefit of robotic surgery compared to conventional laparoscopic (with respect to conversion rate) is greater under surgeons who have more robotic experience, regardless of their level of laparoscopic experience. For further information, see Supplemental data.

None of the pre-specified subgroup analyses were statistically significant. Regarding the sex subgroup analysis, 39/317 (12.3%) male patients underwent conversion to laparotomy, 25/156 (16.0%) in the laparoscopic group and 14/161 (8.7%) in the robotic group – unadjusted difference in proportions 7.3% (95% CI: 0.1%, 14.6%). 8/149 (5.4%) female patients underwent conversion to laparotomy, 3/74 (4.1%) in the laparoscopic group and 5/75 (6.7%) in the robotic group – unadjusted difference in proportions -2.6% (95% CI: -9.8%, 4.6%). A Wald test of interaction between treatment effect and sex in the adjusted model yielded p=0.09, and the estimated adjusted OR for conversion to laparotomy (robotic vs. conventional laparoscopic) in males given by the model is 0.455 (95% CI: 0.209, 0.987; p=0.04). Further details on all subgroup analyses are given in the Supplemental data.

Pathology outcomes

The pathological outcomes are shown in Table 1. The majority, 356/466 (76.4%), of tumours were pT-stage 2 or 3. The total number of lymph nodes retrieved at pathology (lymph node yield) were high in both groups, with means of 24.1 (SD 12.91) in the laparoscopic group and 23.2 (SD 11.97) in the robotic group. 459 (98.5%) patients of the 466 who had an operation had complete pathology data available. 26/459 (5.7%) were CRM+, 14/224 (6.25%) in the laparoscopic group and 12/235 (5.11%) in the robotic group – unadjusted difference in proportions 1.14% (95% CI: -3.10%, 5.38%). There was no statistically significant difference in the odds of CRM+ between the groups - adjusted OR 0.785 (95% CI: 0.350, 1.762); p=0.56 (Table 3). Subgroup analyses were largely uninformative due to the low overall CRM+ rate. Proximal margin involvement was not observed in any patients, and distal margin involvement in only one patient in the laparoscopic group. Pathological assessment of the quality of the plane of surgery

for the mesorectal area was captured for 456/466 (97.9%) patients and was of the highest standard (mesorectal plane) in 351/456 (76.97%) cases, 173/223 (77.58%) in the laparoscopic group and 178/233 (76.39%) in the robotic group – unadjusted difference in proportions 1.18% (95% CI: -6.54%, 8.91%). There was no statistically significant difference in the odds of achieving the highest standard plane of surgery (mesorectal plane) between the groups – adjusted OR 0.943 (95% CI: 0.565, 1.572); p=0.14 (Table 3).

Complications

Table 4 shows the complication rates up to 6 months post-operative. 70/466 (15.0%) patients had an intra-operative complication, 34/230 (14.8%) in the laparoscopic group and 36/236 (15.3%) in the robotic group – unadjusted RD -0.5% (95% CI: -6.0%, 7.0%). There was no significant difference between the groups – adjusted OR 1.020 (95% CI: 0.599, 1.736. p=0.94). The most common intra-operative complications were damage to an organ/structure, significant haemorrhage, and surgical equipment failure. 151/466 (32.4%) patients reported a complication within 30 days, 73/230 (31.7%) in the laparoscopic group and 78/236 (33.1%) in the robotic group – unadjusted RD -1.3% (95% CI: -9.8%, 7.2%). There was no significant difference between the groups - adjusted OR 1.043 (95% CI: 0.689, 1.581. p=0.84). 72/466 (15.5%) patients reported a complication after 30 days and within 6 months, 38/230 (16.5%) in the laparoscopic group and 34/236 (14.4%) in the robotic group – unadjusted RD 2.1% (95% CI: -4.5%, 8.7%). There was no significant difference between the groups - adjusted OR 0.719 (95% CI: 0.411, 1.258. p=0.25). The occurrence of anastomotic leak was determined by the surgeon and reported under “Gastrointestinal complication”. Of the 361 patients with an anastomosis 40 (11.1%) reported an anastomotic leak within 6 months - 18/181 (9.9%) laparoscopic and 22/180 (12.2%) robotic.

Mortality (within 30 days post-operation)

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

Post-operative Bladder and Sexual function

Patient self-reported assessment of bladder function between baseline and 6 months was complete in 351/466 (75.3%) cases. Patient self-reported assessment of sexual function was complete in 181/320 (56.6%) males and 108/151 (71.5%) females. Exploratory analyses comparing prognostic factors between patients with and without complete data and also between the two treatment groups showed that the conclusions of the complete case analyses are robust to any potential effect of the missing data.

I-PSS scores – relating to bladder function, with higher scores indicating worse function on a scale of 0-35 - for laparoscopic and robotic surgery at baseline and 6 months are presented in Figure 2. The adjusted analysis comparing 6-month scores yielded an estimated difference (laparoscopic – robotic) of 0.743 (95% CI: -0.587, 2.072. p=0.27), indicating there was no statistically significant difference between the groups.

IIEF - relating to male sexual function, with higher scores indicating worse function on a scale of 5-75 - and FSFI - relating to female sexual function, with higher scores indicating better function on a scale of 2-36 - scores for laparoscopic and robotic surgery at baseline and 6 months are also presented in Figure 2. Adjusted analyses comparing the 6 month scores yielded estimated IIEF total score difference (laparoscopic – robotic) of 0.802 (95% CI: -4.100, 5.704. p=0.75) and estimated FSFI total score difference (laparoscopic – robotic) of 0.332 (95% CI: -2.474, 3.138. p=0.81), 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 and these data are reported here. The health care costs in the robotic group (mean £11,853 or $13 668 (95% CI: $13 025, 14 350) were higher than in the laparoscopic group (mean £10,874 or $12 556 (95% CI: $11 889, 13 223)), and this difference was significant (mean $1 132 (95% CI: $191-2 072. p = 0.019).. The main drivers of higher operative costs were longer usage of the operating theatre (robotic – laparoscopic) of 50.88

minutes (95% CI: 20.26, 81.56. p = 0.001) and the cost of instruments (robotic – laparoscopic) of £513 or ($593, 95% CI: $493, 693. p < 0.001)..

Health care resource allocation data was complete in 47/95 patients receiving laparoscopic surgery and 52/95 patients receiving robotic surgery. Amongst the patients with complete data, the mean cost for patients receiving laparoscopic surgery was slightly lower than the imputed analysis ($12 341 vs $12 556) and was almost identical for those patients receiving robotic surgery ($13 691 vs. $13 688).

DISCUSSION

In this study, to our knowledge the largest randomised trial of robotic-assisted surgery for patients with rectal adenocarcinoma suitable for curative resection, there were no statistically significant differences in the rates of conversion to 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 resection margin positivity, 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 laparotomy when performed by surgeons of varying experience with robotic 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, and included the largest randomised clinical trial of laparoscopic rectal cancer surgery, the MRC CLASICC trial, which reported a 34% conversion rate to open surgery[21]. A 25% conversion rate from laparoscopic to open surgery was assumed, giving a sample size of 400 patients to demonstrate a 50% relative reduction in conversion rate with robotic surgery. The actual overall conversion rate turned out to be much lower at 10.1%. A similar reduction in conversion rates with time has been reported in other laparoscopic rectal cancer trials: COLOR II 16%[24], ACOSOG Z6501 11%[4], ALaCaRT 9%[3]. In our

trial, a difference in conversion rate between laparoscopic (12.2%) and robotic (8.1%) surgery was not statistically significant. The statistically significant lower overall conversion in patients undergoing low anterior resection, as compared to abdominoperineal resection, probably reflects that the majority of the oncological component of the operation is performed from the perineum in the abdomino-perineal approach and is less affected by the laparoscopic approach. Similarly, the higher overall conversion rates for males, as compared to females, and obese, as compared to underweight/normal, probably reflects 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 experience, regardless of their level of laparoscopic experience. This suggests that the majority of participating surgeons were experts in laparoscopic surgery, but still in their learning phases for robotic surgery, and that at the higher end of the spectrum of experience in robotic surgery there is evidence of a benefit (in terms of conversion rate) over standard 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 laparoscopic and robotic groups in males, with robotic surgery appearing to offer a benefit. Whilst 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 males and the clinical plausibility of the robot facilitating dissections in the narrower male pelvis with more operator-controlled retraction, better optics, and instrument precision all warrants further investigation into the potential benefit of robotic 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 laparoscopic rectal cancer trials: COLOR II 10%, ACOSOG Z6501

12.1%, 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 Z5601 (72.9%), and is probably due to the recognised variation in reporting between pathologists. In our trial, reporting of pathological plane of surgery was standardised to the method described by Quirke[25].

In accordance with other studies, robotic surgery was associated with longer operating times, and with no benefit over laparoscopic surgery in terms of length of hospital stay[7 26]. A full healthcare economics analysis will be reported separately.

The complication rates following laparoscopic and robotic 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 intra-operative morbidity were iatrogenic damage to an organ/structure and significant haemorrhage. In contrast to other studies, haemorrhage was not more frequently associated with robotic surgery[27]. Rectal cancer surgery is a high-risk intervention with 32.4% of patients experiencing a complication within 30 days and after that 15.5% of the patients had complications between 30 days and 6 months.

Previous studies have shown that both laparoscopic and robotic rectal cancer surgery can result in bladder and sexual dysfunction, but suggest that recovery is earlier for robotic surgery[28 29]. 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 any of the I-PSS, IIEF and FSFI scores between baseline and 6-month, 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 rectal cancer surgery is unlikely to be cost-saving. The mean difference per operation, excluding the acquisition and maintenance costs, was

£980 ($1 132) and driven by longer operating theatre time and increased costs for robotic instruments. When considering robotic 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 utilisation of the robot per year for all robotic procedures. Estimates of acquisition costs in 2017 vary between $0.6-$2.5 million with maintenance costs between $0.08-$0.17 million per year (30). Assuming a mid-point acquisition cost of $1.55 million and mid-point maintenance cost of $0.125 million per year, with an operational life/amortisation period of 7 years (31, 32), the total cost of a robot would be around $2.425 million. Estimates for total utilisation 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 (30). This gives the total fixed costs 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 needs to be positive, and the whole set of cost-effective procedures needs to have an average net benefit of at least $1611. On average all robot procedures combined must exceed this figure with all procedures making at least some positive contribution. On the basis of the evidence presented here, robotic rectal cancer surgery 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 had several limitations. The much lower than anticipated rate of conversion to laparotomy limits the ability to provide conclusive evidence about our primary question of how robotic surgery compares to conventional laparoscopic surgery in terms of the odds of conversion. However, the fact that no statistically significant differences between the treatment groups were seen in any of the endpoints does suggest that robotic surgery, when performed by surgeons with varying robotic experience, does not confer a clinically important benefit over laparoscopic surgery in the short term.

No blinding to treatment allocation was incorporated into this trial. Our primary endpoint and the measure of mortality with certainly be unaffected by this, as objective endpoint. However, there is the potential for endpoints which are not completely objective to have been affected. In our pathology endpoints, 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 their learning phase for robotic surgery. The pre-specified sensitivity analysis of learning effects addresses this by extending the primary analysis model to analyse the interaction between operating surgeon experience and the treatment effect (see Supplemental data).

The primary analysis adjusted only for stratification factors (including operating surgeon), and thus in particular did not include an adjustment for treating site. A (pre-specified) 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, 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

Acknowledgements

We are indebted to the patients who participated in this trial. We would also like to thank the Trial Steering Committee (Michael Parker MS, Lynn Faulds Wood, Gareth Griffiths PhD, Hamish Macdonald MD), the Data Monitoring & Ethics Committee (Azad Najmaldin MS, Nigel Scott MD, Craig Ramsay

PhD), additional members of the Trial Management Group (Jennifer Barrie PhD, Sarah Perry BSc, Christopher Garbett MSc, Helen Howard PhD, Fiona Collinson PhD) and the Clinical Trials Research Unit Project Team for their important contributions.

The following institutions and surgeons participated in the trial:

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This project was funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D Division, Public Health Agency in Northern Ireland. The funders of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript or the decision to submit for publication. PQ and NW were supported by Yorkshire Cancer Research Campaign and the MRC Bioinformatics initiative. DGJ was supported by NIHR.

Professor DG Jayne and Mr N Corrigan had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

DGJ, AP, JC, NC, HM, JC, and JMB designed the study and were involved in study coordination. DGJ, AP, TR, NT, HT, MG, and PPB made major contributions to patient recruitment. NC, HM, and JMB were responsible for the statistical analysis. PQ and NW designed the pathology protocol, provided training to other centres, reviewed the pathology, and interpreted the pathology data. RE and CH conducted the cost analysis and reporting. All authors contributed to data interpretation and the writing and review of the manuscript.

Potential conflicts of interest

A Piagzzi is a consultant and proctor for Intuitive Surgical Inc. D Jayne, N Thomassen, T Rautio, PP Bianci, and M Gudgeon are proctors for Intuitive Surgical Inc.

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TABLE LEGENDS

Table 1: Patient baseline characteristics, operative details, and pathological outcomes.

Table 2: Conversion rates by treatment group, conversion rates within all stratification factor groups, unadjusted risk differences of conversion between treatment groups and between all stratification subgroups, and multi-level logistic regression model of odds of conversion including estimated surgeon effect (ICC).

Table 3: Circumferential resection margin positivity (secondary end point) by treatment group.

Table 4: Number of patients with intra-operative and post-operative complications

FIGURE LEGENDS

Figure 1. Diagram showing the flow of participants.

Figure 2. Bladder (I-PSS) and sexual (IIEF and FSFI) function at baseline (prior to randomization) and 6 months postoperative following laparoscopic and robotic surgery.

Table 1

Variable	Laparoscopic surgery	Robotic surgery
BASELINE	**(n=234)**	**(n=237)**
Age (years, mean (SD))	65.5 (11.93)	64.4 (10.98)
ASA classification		
I: A normal healthy patient	52 (22.2%)	39 (16.5%)
II: A patient with mild systemic disease	124 (53.0%)	150 (63.3%)
III: A patient with severe systemic disease	52 (22.2%)	46 (19.4%)
IV: A patient with severe systemic disease that is a constant threat to life	1 (0.4%)	0 (0.0%)
Missing	5 (2.1%)	2 (0.8%)
Sex		
Male	159 (67.9%)	161 (67.9%)
Female	75 (32.1%)	76 (32.1%)
BMI classification*		
Underweight or normal (0-24.9)	87 (37.2%)	93 (39.2%)
Overweight (25-29.9)	92 (39.3%)	90 (38.0%)
Obese (≥30)	55 (23.5%)	54 (22.8%)
Class I (30-34.9)	38 (16.2%)	41 (17.3%)
Class II (35-39.9)	10 (4.3%)	9 (3.8%)
Class III (≥40)	7 (3.0%)	4 (1.7%)
Preoperative radio- or chemoradiotherapy		
Yes	108 (46.2%)	111 (46.8%)
No	126 (53.8%)	126 (53.2%)
Prior abdominal surgery		
Yes	67 (28.6%)	62 (26.2%)
No	162 (69.2%)	174 (73.4%)
Missing	5 (2.2%)	1 (0.4%)
Intended operation		
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	**(n=230)**	**(n=236)**
Operation performed		
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**	1 (0.4%)	4 (1.7%)
Height of tumour (cm from anal verge)***		
11 - 15	69 (30.0%)	71 (30.1%0
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 (mins)		
Mean (SD)	261 (83.24)	298.5 (88.71)

Missing	4	1
Stoma formation		
Temporary	157 (68.3%)	142 (60.2%)
Permanent	49 (21.3%)	53 (22.5%)
No	24 (10.4%)	41 (17.4%)
Length of stay (days)		
Mean (SD)	8.2 (6.03)	8.0 (5.85)
Missing	13	14
PATHOLOGY	**(n=230)**	**(n=236)**
T-stage		
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		
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)	24.1 (12.91)	23.2 (11.97)
Missing	9	1
Plane of surgery		
Mesorectal area (all specimens)		
Mesorectal plane		
Intramesorectal plane	173 (75.2%)	178 (75.4%)
Muscularis propria plane	38 (16.5%)	33 (14.0%)
Missing	12 (5.2%)	22 (9.3%)
	7 (3.1%)	3 (1.3%)
Sphincter area (abdominoperineal resections only)	**(n=45)**	**(n=52)**
Levator plane	18 (40.0%)	18 (34.6%)
Sphincteric plane	19 (42.2%)	22 (42.3%)
Intrasphincteric or submucosal plane	5 (11%)	9 (17.3%)
Missing	3 (6.7%)	3 (5.8%)

*derived from WHO classification of obesity based on BMI (kg/m^2): overweight 25.0-29.9, obese ≥30.
**"Other" operations: Laparoscopic group – "Laparoscopic biopsy of peritoneum". Robotic group – "Dorsal pelvic exenteration, ureter resection distally right sided", "Hartmann's procedure" (x2), "High anterior resection + subtotal colectomy".
*** Height of tumour determined by the lower border of the tumour from the anal verge at examination under anaesthesia.
Lymph node yield refers to the number of lymph nodes retrieved from the specimen for histological analysis.
Plane of surgery was categorized according to the method of Quirke et al [20] by grading the pathological specimen in terms of completeness of surgical resection. Mesorectal refers to an intact mesorectal envelope, intramesorectal has small defects in the mesorectal envelop, and muscularis propria has defects in the mesorectal envelop 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 extra-rectal tissue.

Table 2

Effect: Comparator group (vs reference group)	Reference group (No. conversions/ No. patients (%))	Comparator group (No. conversions/ No. patients (%))	Risk difference and 95% confidence interval (unadjusted)	Odds Ratio (adjusted)	95% Confidence interval for Odds Ratio (adjusted)		p-value
					Lower limit	Upper limit	
Treatment: Robotic surgery (vs laparoscopic)	28/230 (12.2)	19/236 (8.1)	4.1 (-1.4, 9.6)	0.614	0.311	1.211	0.16
Sex: Male (vs Female)	39/317 (12.3)	8/149 (5.4)	6.9 (1.8, 12.1)	2.444	1.047	5.708	0.04
BMI Class*: Overweight (vs Underweight/Normal)	13/179 (7.3)	9/180 (5.0)	2.3 (-2.7, 7.2)	0.538	0.210	1.374	0.19
BMI Class*: Obese (vs Underweight/Normal)	13/179 (7.3)	25/107 (23.4)	-16.1 (-25.0, -7.2)	4.691	2.080	10.581	0.0002
Previous radio- or chemoradiotherapy therapy: Yes (vs No)	27/262 (10.3)	20/204 (9.8)	0.5 (-5.0, 6.0)	1.069	0.504	2.265	0.86
Intended procedure**: High AR (vs Low AR)	37/312 (11.9)	6/68 (8.8)	3.0 (-4.6, 10.7)	0.551	0.194	1.563	0.26
Intended Procedure**: APR (vs Low AR)	37/312 (11.9)	4/86 (4.7)	7.2 (1.5, 12.9)	0.184	0.054	0.627	0.007

Effect	Intra-cluster correlation coefficient (ICC)***	95% Confidence interval	
		Lower limit	Upper limit
Operating surgeon (random effect)	0.050	0.007	0.056

AR= anterior resection
APR= abdominoperineal resection
The variables in column 1 are all of the variables included in the model. All variables were included as fixed effects unless stated otherwise.
Risk differences are unadjusted estimates. Odds ratios are adjusted estimates yielded by the model.

* derived from WHO classification of obesity based on BMI (kg/m^2): overweight 25.0-29.9, obese ≥30.
**Note: Intended procedure, rather than actual procedure, is included in the model. The intended procedure was collected at randomisation 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 APR vs. LAR, which was less pronounced (adjusted OR: 0.433, 95% CI: 0.165, 1.134; p=0.09).
***The ICC is a measure of the proportion of variance in the outcome which is explained by the operating surgeon (e.g. an ICC of 0 would indicate that the odds of conversion for a given patient would not be affected at all if they received surgery from a different operating surgeon). ICCs for a range of outcomes across a number of surgical trials are reported in the ICC database (22).

Table 3

Endpoint	Laparoscopic surgery (No./Total No. (%))	Robotic surgery (No./Total No. (%))	Risk difference and 95% confidence interval (unadjusted)	Odds ratio and 95% confidence interval (adjusted)*	p-value
CRM+	14/224 (6.3)	12/235 (5.1)	1.2 (-3.1, 5.4)	0.785 (0.350, 1.762)	0.560
Mesorectal area = Mesorectal plane	173/223 (77.6)	178/233 (76.4)	1.2 (-6.5, 8.9)	0.943 (0.565, 1.572)	0.135
Intra-operative complication	34/230 (14.8)	36/236 (15.3)	-0.5 (-6.0, 7.0)	1.020 (0.599, 1.736)	0.940
Post-operative complication within 30 days of operation	73/230 (31.7)	78/236 (33.1)	-1.3 (-9.8, 7.2)	1.043 (0.689, 1.581)	0.840
Post-operative complication within 6 months of operation (after 30 days)	38/230 (16.5)	34/236 (14.4)	2.1 (-4.5, 8.7)	0.719 (0.411, 1.258)	0.250
Mortality within 30 days of operation	2/230 (0.87)	2/236 (0.85)	0.02 (-1.7, 1.7)	-	-

*adjusted for sex, BMI class, preoperative radiotherapy, intended procedure and operating surgeon.
CRM+ defined as tumour cells within 1mm of circumferential resection margin on histological analysis
Adjusted analysis was not performed for Mortality within 30 days of operation due to the small number of events.

Table 4

	Laparoscopic surgery (n=230)	**Robotic surgery (n=236)**
Intra-operative complications	**n (%)**	**n (%)**
Overall	**34 (14.8)**	**36 (15.3)**
Damage to organ/structure	5 (2.2)	11 (4.7)
Significant haemorrhage	11 (4.8)	4 (1.7)
Equipment failure	6 (2.6)	8 (3.4)
Faecal contamination	6 (2.6)	7 (3.0)
Anastomotic complication	6 (2.6)	7 (3.0)
Iatrogenic tumour perforation	3 (1.3)	2 (0.8)
Inadequate tumour localization/clearance	2 (0.9)	2 (0.8)
Respiratory event	2 (0.9)	1 (0.4)
Cardiac event	1 (0.4)	1 (0.4)
30 day complications	**n (%)**	**n (%)**
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)
6 month complications (after 30 days)	**n (%)**	**n (%)**
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 (0.0)
Cerebrovascular complication	1 (0.4)	0 (0.0)
Other	12 (5.2)	7 (3.0)

Note: the categories are not mutually exclusive.