Robotic-assisted surgery compared with laparoscopic resection surgery for rectal cancer: the ROLARR RCT

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Scientific summary

The ROLARR RCT

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Scientific summary

Background

Total mesorectal excision is the standard of care in rectal cancer surgery, involving complete removal of the tumour along with the draining lymphatics within an intact mesorectal envelope. The feasibility and safety of laparoscopic surgery have been established for colon cancer, but the case for rectal cancer is less clear. At the time of the study's design in 2010, the MRC CLASICC trial [Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, *et al.* Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;**365**:1718–26] was the only randomised study, to our knowledge, to include an evaluation of laparoscopic compared with open rectal cancer surgery. Concern was expressed about the higher rate of circumferential resection margin (CRM) involvement in the laparoscopic group (12.4%) than in the open group (6.3%) for patients undergoing anterior resection. This, however, did not translate into a difference in local recurrence at either 3-year follow-up or 5-year follow-up. The difference in CRM involvement was felt to reflect the increased technical difficulties associated with the laparoscopic technique in the rectal cancer group.

Since completion of the CLASICC trial, the COLOR II [van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ, COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013;**14**:210–18] and COREAN studies [Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, *et al.* Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol* 2010;**11**:637–45] compared laparoscopic with open surgery for rectal cancer. Both studies reported better short-term outcomes following laparoscopic rectal cancer resection than open surgery, and similar pathological outcomes compared with open surgery. In contrast, there have been two large randomised trials, AlaCarte (Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, *et al.* Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *JAMA* 2015;**314**:1356–63) and ACOSOG (Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, *et al.* Effect of laparoscopic-assisted resection vs open resection of stage II or III Rectal Cancer on Pathologic Outcomes: the ACOSOG Z6051 randomized clinical trial. *JAMA* 2015;**314**:1346–55), that have cast doubt on the benefits of laparoscopic compared with open rectal cancer surgery.

Robotic-assisted laparoscopic surgery was introduced with the promise to eliminate many of the technical difficulties inherent in laparoscopic surgery, providing intuitive manipulation of the laparoscopic instruments with 7 degrees of freedom of movement, a three-dimensional field of view, a stable camera platform with zoom magnification, dexterity enhancement and an ergonomic operating environment.

There have been numerous reports from single centres, analyses of national databases and several systematic reviews and meta-analyses, but no large randomised comparison with laparoscopic or open rectal cancer surgery. Results from the meta-analyses tell a broadly similar story, with no clear advantage of robotic over laparoscopic surgery in terms of short-term outcomes, with the exception of lower conversion rates and a suggestion of improved postoperative bladder and sexual function. The main disadvantage of robotic, compared with laparoscopic, surgery is the increased hospital costs.

Objectives

The purpose of the trial was to perform a rigorous evaluation of robotic-assisted rectal cancer surgery compared with laparoscopic rectal cancer surgery by means of a randomised controlled trial. The key short-term outcomes included assessment of technical ease of the operation, as determined by the clinical indicator of low conversion rate to open operation, and clear pathological resection margins as an indicator of surgical accuracy and improved oncological outcome. In addition, quality-of-life (QoL) assessment and analysis of cost-effectiveness were performed. Longer-term outcomes concentrated on oncological aspects of the surgery with analysis of disease-free survival (DFS) and overall survival (OS) and local recurrence rates at the 3-year follow-up.

Methods

The ROLARR trial was an international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial comparing robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer. Participating surgeons had to have previously performed a minimum of 30 minimally invasive (laparoscopic or robotic) rectal cancer resections (at least 10 laparoscopic and at least 10 robotic). The trial received national ethics approval in the UK and either ethics committee approval or institutional review board (IRB) approval as required at the location of each of the international centres; all participants gave written informed consent.

Patients were eligible if they were aged ≥ 18 years with a diagnosis of rectal adenocarcinoma amenable to curative surgery by low anterior resection, high anterior resection (HAR) or abdominoperineal resection (APR). Patients had to be suitable and fit for robotic-assisted or standard laparoscopic rectal resection. Exclusion criteria included locally advanced cancers not amenable to curative surgery or requiring en bloc multivisceral resection, synchronous colorectal tumours, coexistent inflammatory bowel disease, malignancy within the past 5 years, or pregnancy.

Preoperative investigation and preparation was as per institutional protocol. Laparoscopic mesorectal resection was performed in accordance with each surgeon's usual practice. Robotic surgery involved either a totally robotic approach or a hybrid approach; the only absolute requirement was that the robot had to be used for mesorectal resection. The specifics of each operation were at the discretion of the operating surgeon, as was the decision to convert to an open operation. Detailed guidance was provided to ensure consistent histopathological analysis and reporting of the rectal dissection specimens according to internationally agreed criteria. Digital photographs of the specimen and sequential cross-sectional views were collected to allow blinded assessment of the quality of the plane of surgery. To enable a central pathology review, the tissue slides (or high-quality digital slide images) were submitted.

Postoperative care was as per institutional protocol; however, the protocol required that patients underwent a clinical assessment at 30 days and at 6 months post operation. Follow-up data were collected on an annual basis until the last participant reached 3 years post randomisation.

Participants completed questionnaires prior to randomisation (baseline) and at 30 days and at 6 months postoperatively. General QoL [Short Form questionnaire-36 items version 2 (SF-36v2)] and fatigue [Multidimensional Fatigue Inventory-20 (MFI-20)] data were collected at baseline and at 30 days and at 6 months postoperatively. In addition, patient-reported bladder and sexual function questionnaires [International Prostatic Symptom Score (I-PSS) and International Index of Erectile Function/ Female Sexual Function Index (IIEF/FSFI)] were completed at baseline and at 6 months post operation. Participants in the UK and USA also completed the EuroQol-5 Dimensions (EQ-5D) at baseline, at 30 days and at 6 months post operation, and a resource utilisation questionnaire at 30 days and at 6 months post operation for the health economic component of the trial.

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Results

Between 7 January 2011 and 30 September 2014, 1276 patients were assessed for eligibility by 40 surgeons from 26 sites across 10 countries (i.e. UK, Italy, Denmark, USA, Finland, South Korea, Germany, France, Australia and Singapore). The numbers of patients recruited in each country (together with the number of sites in the country) were as follows: UK, $n = 131$ (6); Italy, $n = 105$ (5); Denmark, $n = 92$ (3); USA, $n = 59$ (9); Finland, $n = 35$ (1); South Korea, $n = 18$ (1); Germany, $n = 16$ (1); France, $n = 11$ (1); Australia, $n = 2$ (1); and Singapore, $n = 2$ (1). Four hundred and seventy-one (36.9%) of these patients were randomised: 234 to laparoscopic and 237 to robotic surgery. From this group, 466 patients underwent an operation, with 456 (97.9%) undergoing the allocated treatment. The final follow-up date was 16 June 2015.

The two treatment groups were well balanced with respect to baseline characteristics and operative procedures. On average, patients received an operation performed by a surgeon with experience of around a median of 91 [interquartile range (IQR) 45–180] previous laparoscopic and a median of 50 (IQR 30–101) previous robotic operations.

The rate of conversion to open surgery was 47 out of 466 (10.1%) patients overall, 28 out of 230 (12.2%) in the laparoscopic group and 19 out of 236 (8.1%) in the robotic group (unadjusted difference in proportions 4.12%, 95% CI –1.35% to 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 to 1.211; $p = 0.16$].

Of the 466 patients who had an operation, 459 (98.5%) had complete pathology data available. Furthermore, 26 out of 459 (5.7%) patients had a positive CRM: 14 out of 224 (6.25%) in the laparoscopic group and 12 out of 235 (5.11%) in the robotic group (unadjusted difference in proportions 1.14%, 95% CI –3.10% to 5.38%). There was no statistically significant difference in the odds of CRM positivity between the groups (adjusted OR 0.785, 95% CI 0.350 to 1.762; $p = 0.56$).

There were 70 out of 466 (15.0%) patients who had an intraoperative complication, 34 out of 230 (14.8%) in the laparoscopic group and 36 out of 236 (15.3%) in the robotic group (unadjusted risk difference –0.5%, 95% CI –6.0% to 7.0%). There was no significant difference between the groups (adjusted OR 1.020, 95% CI 0.599 to 1.736; $p = 0.94$). There was a significant difference in the odds of having an intraoperative complication between males and females (adjusted OR 3.083, 95% CI 1.543 to 6.158; $p = 0.0015$).

There were 151 out of 466 (32.4%) patients who had a postoperative complication within 30 days of their operation, 73 out of 230 (31.7%) in the laparoscopic group and 78 out of 236 (33.1%) in the robotic group (unadjusted risk difference –1.3%, 95% CI –9.8% to 7.2%). There was no significant difference between the treatment groups (adjusted OR 1.043, 95% CI 0.689 to 1.581; $p = 0.84$). There was a significant difference in the odds of having a postoperative complication within 30 days of operation between males and females (adjusted OR 3.083, 95% CI 1.573 to 4.183; $p = 0.0002$).

There were 72 out of 466 (15.5%) patients who had a postoperative complication after 30 days and within 6 months of their operation, 38 out of 230 (16.5%) in the laparoscopic group and 34 out of 236 (14.4%) in the robotic group (unadjusted risk difference 2.1%, 95% CI –4.5% to 8.7%). There was no significant difference between the groups (adjusted OR 0.719, 95% CI 0.411 to 1.258; $p = 0.25$).

Bladder function scores, as measured by the I-PSS, were similar between the groups at baseline and at 6 months. The adjusted estimated difference in mean I-PSS (robotic minus standard) was –0.7426 (95% CI –2.0722 to 0.5870; $p = 0.2726$). The estimated difference in mean I-PSS between patients with a difference in baseline score of 10 points, all else being equal, was 4.20 (95% CI 3.23 to 5.17; $p < 0.0001$).

The distribution of sexual function scores, as measured by the IIEF, was very similar between the treatment groups at baseline and at 6 months. Median IIEF scores at 6 months were notably lower than at baseline in both groups; the estimated difference in mean IIEF (robotic minus standard) was –0.8020 (95% CI –5.7039 to 4.1000; $p = 0.7468$).

The female sexual function score, as measured by the FSFI, at baseline was marginally lower in the robotic group. The distribution of scores was very similar between the treatment groups at 6 months; the estimated difference in mean FSFI (robotic minus standard) was –1.2309 (95% CI –6.0030 to 3.5413; $p = 0.6010$).

Patient-reported generic health was measured using the SF-36v2, providing a physical component score (PCS) and a mental component score (MCS). The baseline PCS and MCS were similar in the two treatment groups at all time points. At the 6-month follow-up, the adjusted estimated difference in mean PCS between the groups (robotic vs. laparoscopic) was –0.1220 (95% CI –1.6281 to 1.3840; $p = 0.8737$). The adjusted estimated difference in MCS between the groups (robotic vs. laparoscopic) was –0.4875 (95% CI –2.6008 to 1.6258; $p = 0.6508$).

The Multidimensional Fatigue Inventory is a self-report instrument consisting of five scales of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The distribution of scores was similar between the two treatment groups at all time points for all five scales. At the 6-month follow-up, the estimated adjusted difference in mean general fatigue between the groups (robotic vs. laparoscopic) was –0.2517 (95% CI –0.5965 to 1.0999; $p = 0.5603$), the difference in physical fatigue was 0.3964 (95% CI –0.4404 to 1.2332; $p = 0.3527$), the difference in reduced activity was –0.1634 (95% CI –0.9777 to 0.6510; $p = 0.6938$), the difference in reduced motivation was –0.03917 (95% CI –0.7324 to 0.6540; $p = 0.9117$) and the difference in mental fatigue was 0.1374 (95% CI –0.6626 to 0.9374; $p = 0.7360$).

A total of 351 out of 456 (77.0%) patients' specimens were graded by pathological assessment of the plane of surgery. There were 178 out of 233 (76.4%) in the laparoscopic group and 173 out of 223 (77.6%) in the robotic group who had best-quality surgery (mesorectal plane) (unadjusted risk difference 1.2%, 95% CI –6.5% to 8.9%). There was no significant difference of the odds of a mesorectal plane surgery between the groups (adjusted OR 0.943, 95% CI 0.565 to 1.572; $p = 0.821$).

Local recurrence was observed in 30 out of 471 (6.4%) patients, 14 out of 234 (6.0%) in the laparoscopic group and 16 out of 237 (6.8%) in the robotic group. There was no difference between the treatment groups in local recurrence rates at the 3-year follow-up; the estimated difference in cumulative incidence of local recurrence was 0.002 (95% CI –0.041 to 0.046). There was a difference in the probability of local recurrence between males and females, with males being more likely to experience local recurrence [adjusted hazard ratio (HR) 3.184, 95% CI 1.109 to 9.174; $p = 0.031$].

No difference was observed between the treatment groups in DFS at the 3-year follow-up, estimated adjusted HR (robotic vs. laparoscopic) of 1.030 (95% CI 0.713 to 1.489; $p = 0.874$). Disease recurrence was more common following APR and least common following HAR.

Death was observed for 46 out of 471 (9.8%) patients, 23 out of 234 (9.8%) in the laparoscopic group and 23 out of 237 (9.7%) in the robotic group, estimated HR (robotic vs. laparoscopic) 0.945 (95% CI 0.530 to 1.686; $p = 0.848$). Males were 2.187 (95% CI 1.017 to 4.700; $p = 0.045$) times more likely to die than females at 3 years' follow-up.

Quality-of-life scores were very similar between the treatment groups, with a difference in favour of robotic surgery of 0.013 quality-adjusted life-years (QALYs) at 6 months' follow-up. The overall cost difference was £980, with higher costs associated with robotic surgery, driven by longer operating times and higher instrument costs. The estimated incremental cost-effectiveness ratio (ICER) for robotic surgery was £69,837 per QALY, which is well in excess of the standard threshold of £20,000–30,000 per QALY.

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Conclusions

Robotic rectal cancer surgery results in comparable outcomes to laparoscopic surgery. There is no statistical benefit in terms of conversion to open surgery, bladder or sexual function, pathological outcomes, or DFS and OS. The observed trend to reduced conversion in male patients requires further confirmation. Robotic rectal cancer surgery is not cost-effective compared with laparoscopic rectal cancer surgery because the increased costs far outweigh any marginal benefit in QoL.

Trial registration

This trial is registered as ISRCTN80500123.

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