

Project Title:	ROLARR: Robotic versus Laproscopic Resection for Rectal Cancer
Project Ref:	08-52-01
Cost:	£1,013,404
Lead Applicant & Institution:	Mr David Jayne Academic Surgical Unit University of Leeds
Start Date:	1 March 2010
Plain English Summary:	<p>The last fifteen years has seen a revolution in general surgical practice with the development of laparoscopic (key-hole) surgery. This has benefited patients and healthcare providers; patients benefit from reduced pain, earlier return to normal activity and improved cosmesis, whilst healthcare providers benefit from shortened hospital stay and more efficient working.</p> <p>In cancer surgery, the benefits of laparoscopic surgery must also be considered alongside the oncological outcomes. Despite the enthusiasm for laparoscopic colorectal surgery, it is technically demanding with a long learning curve. In great part this is due to the current limitations of laparoscopy: the operative field is viewed on a 2-dimensional display unit with no depth perception; movements are limited because instruments must pass through a "port" in the abdominal wall; the instruments are limited to 4-degrees of freedom of movement; and there is a dependency on the skills of a cameraman.</p> <p>The benefits of the robotic surgical systems have been established in some surgical subspecialties, most notably in radical prostatectomy, and it is apparent that it is most useful when accurate surgical dissection is required within a restricted field. This is the situation for rectal cancer surgery, where accurate dissection is needed to achieve best cancer outcomes with preservation of normal function.</p> <p>It is hypothesised that robotic-assistance will overcome some of the technical difficulties of laparoscopic rectal cancer surgery, leading to a reduction in the need to resort to open surgery and should lead to improved cancer outcomes and preservation of normal function. To test this hypothesis we propose a prospective, randomised, controlled trial comparing laparoscopic with robotic-assisted rectal cancer surgery. As the number of robots in clinical practice and the necessary expertise is as yet limited in the UK, the trial will need to be an international collaboration.</p> <p>The primary aim of the study is to determine whether robotic-assistance facilitates rectal cancer resection, as measured by the need to convert to open surgery. Secondary aims include an analysis of the surgical accuracy (the margin around the dissected cancer specimen & local recurrence</p>

	<p>rates), safety profile of the two techniques, assessment of quality of life and preservation of pelvic organ function, and an analysis of the associated health economics.</p> <p>It is planned to recruit 400 patients (200 laparoscopic, 200 robotic-assistance) from 20 centres to detect a clinically relevant difference in the primary endpoint of conversion rates to open surgery. This sample size is also adequate to rule out clinically significant differences in the other key endpoints which include a specific cancer resection margin and local disease recurrence.</p> <p>A study duration of 66 months is proposed, including 18-month patient recruitment and 3-year follow-up data collection. Primary and other short-term outcomes will be reported following planned analysis at 33 months and longer-term outcomes at 3 years follow-up. This trial addresses an important question which has emerged with the advent of advanced surgical technology.</p>
<p>Abstract:</p>	<p><u>Design:</u> Multicentre, prospective, randomised, controlled, parallel-group trial of robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer. The setup is designed on a "hub-spoke-site" basis with regional spokes in USA, Singapore, and Leeds feeding into the central CTRU. Patients will be randomised on an equal basis to either laparoscopic or robotic-assisted surgery. Randomisation will be stratified according to participating surgeon, patient sex, neoadjuvant therapy (yes or no), and nature of proposed procedure (high or low anterior resection or abdominoperineal resection).</p> <p><u>Setting:</u> Teaching Hospital (or their equivalent) with expertise in laparoscopic and robotic rectal cancer surgery and clinical trial involvement, and can guarantee ~15 patients/year.</p> <p><u>Target population:</u> Male or female aged 18+ years and able to provide written informed consent, with diagnosis of rectal cancer amenable to curative surgery either by anterior resection or abdominoperineal resection.</p> <p><u>Interventions being evaluated:</u> Pre- and post-operative care will be as per institutional protocol. Robotic surgery may be by a totally robotic or a hybrid approach; the only absolute requirement is for robotic TME rectal resection. The specifics of each operation will be at the discretion of the surgeon, as will the decision to convert to open operation. Laparoscopic TME will be performed in accordance with each surgeon's usual practice.</p> <p><u>Measurement of outcomes and duration of follow up:</u> The treatment period constitutes the surgical period only. Clinical follow-up data will be collected by review at 30 days, 6 & 12 months post-operatively & annually thereafter until 3-years post-randomisation. Bladder and sexual function and QoL data will be measured at baseline and 6 months (and at 30 days for the Euroqol-5D (EQ-5D)).</p> <p><u>Primary outcome:</u> Conversion rates: conversion to open surgery (as an indicator of technical difficulty). Conversion is defined as the need to use a laparotomy wound for any reason other than specimen retrieval.</p> <p><u>Sample size:</u> The primary endpoint is conversion to open rectal resection; the sample size has been calculated to address this single endpoint. Assuming the</p>

	<p>conversion rate for laparoscopic rectal cancer resection is 25% and a relative reduction of 50% (12.5% in the robotic arm) is clinically relevant, with 80% power and a 5% (2-sided) significance level, 336 patients are required using a two-group continuity corrected chi-squared test of equal proportions. 400 patients (200 per arm) will be recruited to allow for early withdrawals, protocol violations and missing data. The sample size is based on the single primary endpoint; although it is not a requirement to ensure sufficient power for the secondary outcomes, the sample size of 400 patients will be adequate to obtain meaningful conclusions regarding the key secondary endpoints of CRM positivity rate and 3-year local recurrence rate.</p> <p><u>Planned analyses:</u> Analysis will be performed on an ITT basis, by actual treatment group and by using a per-protocol population. Analysis will adjust for the stratification factors. The proportion of patients who are converted, have positive resection margins, have complications, and have died within 30 days will be compared using logistic regression. CIs of the differences in proportions will be reported. Overall and disease-free survival and local recurrence rates at 3 years will be compared using Cox's proportional hazards model. CIs of the differences in 3-year outcomes will be reported. Bladder and sexual function and SF-36 at 6 months will be summarised using adjusted for baseline mean scores and 95% CIs. The GOALS score and its five component items will be summarised descriptively. No formal interim analyses are planned. Final analysis will take place in 2 stages when each patient has completed 1) 6-months and 2) 3-years of follow-up.</p> <p><u>Project timetables including recruitment rate:</u> Duration of study is 66 months. It is planned to recruit 400 patients over 18 months, with 20 centres each recruiting ~20 patients. Primary and other short-term outcomes will be reported at 33 months (9-months set-up, 18-months recruitment + 6-months follow-up). A final analysis of 3-year data will be reported at 66 months (9-months set-up, 18-months recruitment, 36-months follow-up + 3-months analysis/publication).</p>
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