



# Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial

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## Summary

**Background** Laparoscopic-assisted surgery for colorectal cancer has been widely adopted without data from large-scale randomised trials to support its use. We compared short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer to predict long-term outcomes.

**Methods** Between July, 1996, and July, 2002, we undertook a multicentre, randomised clinical trial in 794 patients with colorectal cancer from 27 UK centres. Patients were allocated to receive laparoscopic-assisted (n=526) or open surgery (n=268). Primary short-term endpoints were positivity rates of circumferential and longitudinal resection margins, proportion of Dukes' C2 tumours, and in-hospital mortality. Analysis was by intention to treat. This trial has been assigned the International Standard Randomised Controlled Trial Number ISRCTN74883561.

**Findings** Six patients (two [open], four [laparoscopic]) had no surgery, and 23 had missing surgical data (nine, 14). 253 and 484 patients actually received open and laparoscopic-assisted treatment, respectively. 143 (29%) patients underwent conversion from laparoscopic to open surgery. Proportion of Dukes' C2 tumours did not differ between treatments (18 [7%] patients, open vs 34 [6%], laparoscopic; difference  $-0.3\%$ , 95% CI  $-3.9$  to  $3.4\%$ ,  $p=0.89$ ), and neither did in-hospital mortality (13 [5%] vs 21 [4%];  $-0.9\%$ ,  $-3.9$  to  $2.2\%$ ,  $p=0.57$ ). Apart from patients undergoing laparoscopic anterior resection for rectal cancer, rates of positive resection margins were similar between treatment groups. Patients with converted treatment had raised complication rates.

**Interpretation** Laparoscopic-assisted surgery for cancer of the colon is as effective as open surgery in the short term and is likely to produce similar long-term outcomes. However, impaired short-term outcomes after laparoscopic-assisted anterior resection for cancer of the rectum do not yet justify its routine use.

## Introduction

The past two decades have witnessed substantial improvements in the survival from colorectal cancer resulting from earlier diagnosis, improved efficiency and delivery of chemotherapy and radiotherapy, and advances in surgical techniques such as total mesorectal excision.<sup>1</sup> However, the mainstay of cure remains adequate surgical excision of the primary tumour. Since its initial use more than a decade ago<sup>2–4</sup> curative colorectal resection may now be achieved with laparoscopic assistance, bringing advantages to patients such as more rapid recovery, fewer complications, and shorter duration of hospital stay than for those with standard treatment. Of the many non-randomised studies of laparoscopic resections,<sup>5–8</sup> most have concluded that the procedure is safe, despite previous concerns about atypical patterns of tumour recurrence, such as in the port sites.<sup>9,10</sup> However, randomised trials of colon cancer<sup>11–14</sup> have provided data for survival and disease-free intervals that do not show any reduced survival in laparoscopic-assisted treatment.

Results of large-scale randomised trials should be available and should address the concerns that laparoscopic surgery compromises surgical principles.<sup>15–18</sup> The UK Medical Research Council (MRC) trial of conventional versus laparoscopic-assisted surgery

in colorectal cancer (CLASICC) was designed as a pragmatic trial to incorporate the standard clinical endpoints of survival and disease-free intervals, and to provide a detailed pathological analysis of all resected samples.<sup>19</sup> We used these short-term endpoints as surrogates to predict long-term clinical outcomes<sup>20</sup> and also assess the quality of surgery in not only cancer of the colon but also cancer of the rectum.

## Methods

### Patients

Between July, 1996, and July, 2002, we undertook a randomised, controlled, open, parallel-group trial comparing laparoscopic-assisted surgery with conventional open surgery in patients with cancer of the colon or rectum from 27 UK centres. These patients were suitable for right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection, or abdominoperineal resection. Exclusion criteria were adenocarcinoma of the transverse colon, contraindications to pneumoperitoneum (chronic cardiac or pulmonary disease), acute intestinal obstruction, malignant disease in the past 5 years, synchronous adenocarcinomas, pregnancy, and associated gastrointestinal disease needing surgical intervention.

Written informed consent was obtained from all patients. Patients were randomly allocated to receive either laparoscopic or open surgery at a two-to-one ratio, to allow for anticipated conversions (ie, from laparoscopic to open surgery) and to provide as much information as possible on laparoscopic surgery. Randomisation was stratified by surgeon, proposed site of operation, presence of liver metastases, and preoperative radiotherapy administration; this process was done by telephone by the trial coordinator at the Clinical Trials Research Unit, University of Leeds, Leeds, UK. The trial received approval from multicentre and local research ethics committees.

### Procedures

Laparoscopic-assisted resection consisted of the laparoscopic mobilisation of the diseased segment of bowel together with (where possible) the division of blood vessels and bowel, although a small incision was still needed to remove the resected specimen from the abdominal cavity. Surgical resection was undertaken according to every surgeon's specific current practice. Poorly differentiated, very low rectal lesions (<5 cm from the anal verge) were treated by abdominoperineal resection. Conversion to an open operation was defined as a vertical abdominal incision greater in size than that needed for specimen retrieval. Quality of life was measured with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire<sup>21</sup> and the colorectal-cancer module QLQ-CR38 (currently being validated for use in colorectal patients, webappendix).

Follow-up visits were at 1 and 3 months after surgery, then every 3 months for the first year, every 4 months for the second year, and every 6 months afterwards. The trial design required that every surgeon had undertaken at least 20 laparoscopic-assisted resections.<sup>22</sup> In every centre, a gastrointestinal pathologist ensured consistent reporting of resection specimens according to an agreed and established technique that focused on the completeness of resection and extent of the circumferential resection margin (CRM).<sup>20</sup> Tumour histology was reviewed centrally. A trial steering committee and data monitoring and ethics committee were responsible for overseeing the undertaking of the trial.

Primary short-term endpoints were positivity rates of circumferential and longitudinal resection margins, proportion of Dukes' C2 tumours (ie, those detected by central pathology review that go through the bowel wall with apical nodal metastases), and in-hospital mortality. Secondary short-term endpoints were complication rates measured during surgery and 30 days and 3 months after surgery, quality of life measured up to 3 months after surgery, and transfusion requirements. We will report long-term endpoints (survival, recurrence, and quality of life) at 3 and 5 years.

### Statistical analysis

We decided that 1000 patients was the maximum achievable sample size in a reasonable time period. This decision was based on practical constraints due to the number of UK surgeons who were experienced in the laparoscopic technique when the MRC CLASICC trial was proposed, urgency of data collection in a trial of laparoscopic surgery, and possible data combination with those for the COST trial (which compared open surgery for colon cancer with laparoscopic-assisted surgery).<sup>11</sup> This sample size did not have enough statistical power to detect whether the procedures were equivalent with respect to short-term or long-term main endpoints, and thus examination of the absolute difference between the two procedures for every endpoint was proposed.<sup>23</sup> 1000 patients would establish CIs of 10% around differences (regarded as clinically significant).

At the end of funding, 794 patients had been recruited and the trial was stopped because extension would not increase precision of the estimated differences. The data monitoring and ethics committee endorsed this decision.

We compared the proportion of patients with positive resection margins, in-hospital mortality, and complication rates between groups using the Pearson's  $\chi^2$  test or Fisher's exact test. 95% CIs of the differences were also reported. Additionally, a multi-level model was fitted to account for any surgeon effect and for stratification factors. Sensitivity analyses were done to assess the effect on results of missing data and of conversions to open surgery. Because sensitivity analyses or adjustment for surgeon and stratification factors made little difference to conclusions, the analyses presented were therefore unadjusted.

See [Lancet Online](#) for webappendix

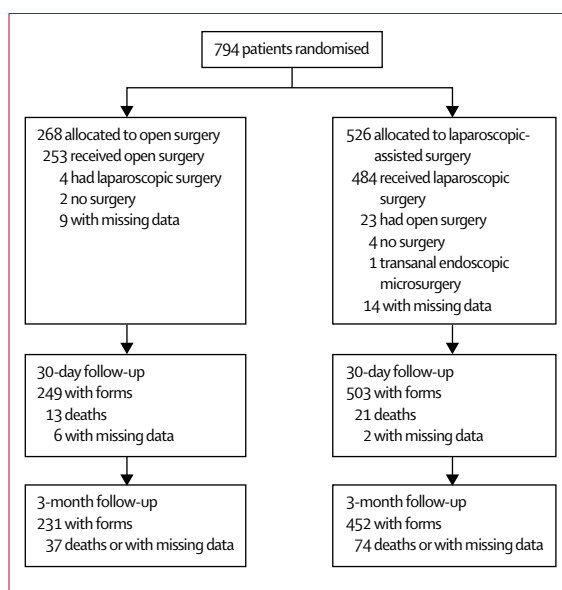


Figure 1: Trial profile

	Intention-to-treat population		Actual treatment group		
	Open	Laparoscopic	Open	Laparoscopic	Conversion*
Number of patients	268	526	276	345	143
Age (years, mean [SD])	69 (12)	69 (11)	69 (11)	69 (11)	68 (10)
Body-mass index (kg/m <sup>2</sup> , mean [SD])	26 (4)	25 (4)	26 (4)	25 (5)	26 (4)
Sex (female)	123 (46%)	230 (44%)	121 (44%)	167 (48%)	49 (34%)
WHO performance status					
0	145 (54%)	323 (61%)	148 (54%)	221 (64%)	90 (63%)
1	86 (32%)	139 (26%)	93 (34%)	83 (24%)	37 (26%)
2	30 (11%)	54 (10%)	29 (11%)	36 (10%)	13 (9%)
3	6 (2%)	7 (1%)	5 (2%)	4 (1%)	2 (1%)
4	..	2	..	1	1 (1%)
Missing	1	1	1	..	..
Tumour site					
Colon	140 (52%)	273 (52%)	144 (52%)	185 (54%)	61 (43%)
Rectum	128 (48%)	253 (48%)	132 (48%)	160 (46%)	82 (57%)
ASA grade					
I	99 (37%)	193 (37%)	102 (37%)	141 (41%)	49 (34%)
II	121 (45%)	248 (47%)	132 (48%)	169 (49%)	68 (48%)
III	36 (13%)	62 (12%)	39 (14%)	33 (10%)	26 (18%)
Missing	12 (4%)	23 (4%)	3 (1%)	2 (1%)	..
Number of patients with pathology forms	241	462	219	276	119
pT stage					
T0	1	4 (1%)	..	..	..
T1	12 (5%)	26 (6%)	9 (4%)	17 (6%)	4 (3%)
T2	35 (15%)	68 (15%)	36 (16%)	48 (17%)	16 (13%)
T3	136 (56%)	261 (56%)	141 (64%)	175 (63%)	71 (60%)
T4	33 (14%)	70 (15%)	33 (15%)	36 (13%)	28 (24%)
Missing	24 (10%)	33 (7%)	..	..	..
pN stage					
N0	129 (54%)	244 (53%)	130 (59%)	159 (58%)	63 (53%)
N1	52 (22%)	107 (23%)	51 (23%)	70 (25%)	33 (28%)
N2	38 (16%)	72 (16%)	38 (17%)	46 (17%)	21 (18%)
Not investigated	..	4 (1%)	..	1	2 (2%)
Missing	22 (9%)	35 (8%)	..	..	..
pM stage					
M0	91 (38%)	167 (36%)	96 (44%)	98 (36%)	57 (48%)
M1	7 (3%)	12 (3%)	8 (4%)	4 (1%)	7 (6%)
Not investigated	112 (46%)	229 (50%)	107 (49%)	159 (58%)	52 (44%)
Missing	31 (13%)	54 (12%)	8 (4%)	15 (5%)	3 (3%)
R stage					
R0	185 (77%)	356 (77%)	184 (84%)	241 (87%)	88 (74%)
R1	19 (8%)	45 (10%)	20 (9%)	24 (9%)	18 (15%)
R2	6 (2%)	13 (3%)	7 (3%)	3 (1%)	8 (7%)
Missing	31 (13%)	48 (10%)	8 (4%)	8 (3%)	5 (4%)

All data are number (%) unless otherwise indicated. \*Laparoscopic-assisted surgery converted to open surgery.

**Table 1: Patient baseline characteristics and pathological tumour node metastasis (pTNM) staging**

	Intention-to-treat population		Actual treatment group		
	Open	Laparoscopic	Open	Laparoscopic	Conversion
Length of incision (mm)	220 (180–290)	100 (60–170)	228 (180–300)	70 (55–100)	200 (150–285)
Total anaesthetic time (min)	135 (100–180)	180 (135–220)	135 (100–175)	180 (140–220)	180 (135–223)
Time to first bowel movement (days)	6 (4–7)	5 (4–7)	6 (4–7)	5 (4–7)	5.5 (4–7)
Colon	6 (4–7)	5 (4–7)	6 (4–5–7)	5 (4–6–5)	5 (4–6–5)
Rectum	6 (4–7)	5 (4–7)	6 (4–7)	5 (3–7)	6 (4–8)
Time to patients resuming normal diet (days)	6 (5–8)	6 (5–7)	6 (5–8)	5 (4–7)	7 (5–9)
Colon	6 (5–7)	6 (4–7)	6 (5–8)	5 (4–7)	6 (5–8)
Rectum	6 (5–8)	6 (5–8)	7 (5–8)	6 (5–7)	7 (5–9)
Time to discharge (days)	11 (8–15)	9 (7–14)	11 (8–15)	9 (7–13)	12 (9–16)
Colon	9 (8–13)	9 (7–12)	10 (8–13)	8 (6–11)	9 (7–13)
Rectum	13 (9–18)	11 (9–15)	13 (9–17)	10 (8–14)	13 (11–21)

All data are median (IQR).

**Table 2: Operative details and postoperative recovery**

The QLQ-C30 was scored according to EORTC guidelines,<sup>21</sup> and QLQ-CR38 was analysed as single items. We calculated mean quality-of-life scores and 95% CIs (adjusted for baseline) at 2 weeks and 3 months after surgery. Differences between treatment arms for the QLQ-C30 were assessed by a multi-level, repeated-measures model that allowed for time, treatment, treatment-by-time interaction, and adjusted for quality-of-life at baseline (all fixed effects); and for patient and patient-by-time interaction (random effects). Descriptive statistics only were summarised for the QLQ-CR38.

All hypothesis tests were at the 5% and 1% significance levels (two-sided) for primary and secondary short-term endpoints, respectively. Analysis was by intention-to-treat and by actual treatment group (ie, analysed according to treatment actually received; open, laparoscopic, or laparoscopic converted to open surgery). All statistical analyses were done by use of SAS version 8.2 (SAS Institute, Cary, NC, USA). This trial has been assigned the International Standard Randomised Controlled Trial Number ISRCTN74883561.

### Role of the funding source

An MRC trial development group participated in the study design, but had no further role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

During the trial, 794 patients (268 randomly allocated to open surgery, 526 to laparoscopic surgery) from 32 surgeons were recruited (figure 1). 657 (83%) patients were recruited by surgeons who randomised more than 20 patients. The two groups were balanced with respect to baseline characteristics and pathological staging (table 1). Most procedures were undertaken with curative intent (ie, R0 or R1 classifications). As expected, length of incision was shorter for the laparoscopic group than for the open-surgery group (table 2). Duration of operation was shorter in open surgery than in laparoscopic-assisted surgery. Time to first bowel movement and the resuming of normal diet were similar between treatments and between patients with colon, rectal, and conversion procedures (table 2). Median hospital stay was 2 days longer for patients allocated open surgery than for those allocated laparoscopic surgery (table 2). Conversion from laparoscopic to open surgery extended hospital stay to almost 2 weeks. Hospital stay for colon resections was the same in both treatments. For rectal resections, hospital stay was 2 days shorter for laparoscopic than for open surgery, but for successful laparoscopic-assisted excisions, hospital stay was 3 days shorter than for converted patients.

Type of procedure	Intention-to-treat population		Actual treatment group		
	Open	Laparoscopic	Open	Laparoscopic	Conversion
<b>Anterior resection</b>	96 (36%)	196 (37%)	102 (37%)	129 (37%)	61 (43%)
Colon	17 (12%)	29 (11%)	19 (13%)	17 (9%)	10 (16%)
Rectum	79 (62%)	167 (66%)	83 (63%)	112 (70%)	51 (62%)
<b>Right hemicolectomy</b>	63 (24%)	125 (24%)	66 (24%)	94 (27%)	28 (20%)
Colon	62 (44%)	125 (46%)	65 (45%)	94 (51%)	28 (46%)
Rectum	1 (1%)	..	1 (1%)	..	..
<b>Sigmoid colectomy</b>	33 (12%)	66 (13%)	34 (12%)	53 (15%)	12 (8%)
Colon	26 (19%)	59 (22%)	27 (19%)	49 (26%)	9 (15%)
Rectum	7 (5%)	7 (3%)	7 (5%)	4 (3%)	3 (4%)
<b>Abdominoperineal resection</b>	34 (13%)	63 (12%)	36 (13%)	41 (12%)	20 (14%)
Colon	..	..	..	..	..
Rectum	34 (27%)	63 (25%)	36 (27%)	41 (26%)	20 (24%)
<b>Left hemicolectomy</b>	23 (9%)	36 (7%)	25 (9%)	24 (7%)	10 (7%)
Colon	23 (16%)	31 (11%)	25 (17%)	22 (12%)	7 (11%)
Rectum	..	5 (2%)	..	2 (1%)	3 (4%)
<b>Other</b>	8 (3%)	21 (4%)	12 (4%)	4 (1%)	12 (8%)
Colon	4 (3%)	13 (5%)	7 (5%)	3 (2%)	7 (11%)
Rectum	4 (3%)	8 (3%)	5 (4%)	1 (1%)	5 (6%)
<b>Missing</b>	11 (4%)	19 (4%)	1 (0%)	..	..
Colon	8 (6%)	16 (6%)	1 (1%)	..	..
Rectum	3 (2%)	3 (1%)	..	..	..
<b>Total mesorectal excision (TME)*</b>					
TME undertaken	84 (66%)	196 (77%)	88 (67%)	127 (79%)	65 (79%)
Anterior resection†	49 (62%)	131 (78%)	51 (61%)	85 (76%)	44 (86%)
Abdominoperineal resection	34 (100%)	62 (98%)	36 (100%)	40 (98%)	20 (100%)
TME not undertaken	31 (24%)	33 (13%)	32 (24%)	21 (13%)	10 (12%)
Anterior resection	26 (33%)	28 (17%)	27 (33%)	21 (19%)	6 (12%)
Abdominoperineal resection	..	..	..	..	..
<b>Missing</b>	13 (10%)	24 (9%)	12 (9%)	12 (8%)	7 (9%)
Anterior resection	4 (5%)	8 (5%)	5 (6%)	6 (5%)	1 (2%)
Abdominoperineal resection	..	1 (2%)	..	1 (2%)	..
<b>Opinion of surgery</b>					
<b>Curative</b>	211 (79%)	432 (82%)	224 (81%)	312 (90%)	107 (75%)
Colon	112 (80%)	199 (73%)	118 (82%)	156 (84%)	37 (61%)
Rectum	99 (77%)	233 (92%)	106 (80%)	156 (98%)	70 (85%)
<b>Palliative</b>	40 (15%)	64 (12%)	43 (16%)	30 (9%)	31 (22%)
Colon	18 (13%)	53 (19%)	22 (15%)	26 (14%)	23 (38%)
Rectum	22 (17%)	11 (4%)	21 (16%)	4 (3%)	8 (10%)
<b>Unresectable</b>	6 (2%)	7 (1%)	7 (3%)	2 (1%)	4 (3%)
Colon	2 (1%)	4 (1%)	3 (2%)	2 (1%)	1 (2%)
Rectum	4 (3%)	3 (1%)	4 (3%)	..	3 (4%)
<b>Missing</b>	11 (4%)	23 (4%)	2 (1%)	1	1 (1%)
Colon	8 (6%)	17 (6%)	1 (1%)	1 (1%)	..
Rectum	3 (2%)	6 (2%)	1 (1%)	..	1 (1%)

Data are number (%). \*TME for patients with cancer of the rectum only. †38 (15 open and 23 laparoscopic) patients with cancer of the rectum in the intention-to-treat population underwent procedures other than anterior resection or abdominoperineal resection; 31 (13 open, seven laparoscopic, and 11 conversion) patients with cancer of the rectum in the actual treatment group underwent procedures other than anterior resection or abdominoperineal resection.

**Table 3: Operative procedure undertaken**

The same operative procedures were undertaken in both treatment groups (table 3). About 10% more patients underwent total mesorectal excision in the laparoscopic than in the open surgery group. Rate of abdominoperineal resection for cancers of the rectum was 27% (34 patients) in the open-surgery group and 25% (63) in the laparoscopic group; these resections were undertaken because the tumour locations were too low, which arose in more than 90% of both treatment groups (33 and 57, respectively).

143 (29%) of 488 patients underwent intraoperative conversion from laparoscopic to open surgery, varying

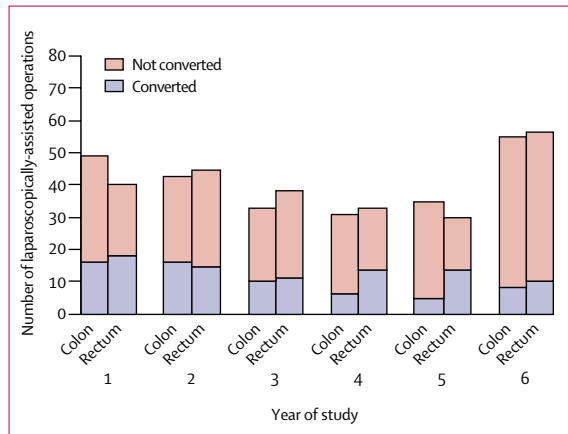


Figure 2: Intraoperative conversions by year of study

between 61 (25%) of 246 patients with cancer of the colon and 82 (34%) of 242 with cancer of the rectum. The most common causes for conversion in cancer of the colon were excessive tumour fixity—ie, how difficult the tumour is to remove (37, 61%), uncertainty of tumour clearance (13, 21%), and obesity (five, 8%). For cancer of the rectum, the most common reasons were excessive tumour fixity or uncertainty of tumour clearance (34, 41%), obesity (21, 26%), anatomical uncertainty (17, 21%), and inaccessibility of tumours (16, 20%). The rate of intraoperative conversions fell by year of study, from 34 of 89 (38%) laparoscopic operations attempted in year 1 to 18 of 111 (16%) in year 6 (figure 2). Sensitivity analyses confirmed that the conversion rate had no effect on the interpretation of results.

742 (93%) resection specimens were centrally reviewed. Lymph-node yield was high; median 13.5 (IQR 8–19) in open surgery and 12 (8–17) in laparoscopic surgery. Proportion of Dukes' C2 tumours was similar between the treatments (18 [7%] patients, open vs 34 [6%], laparoscopic; difference -0.3%, 95% CI -3.9 to 3.4%,  $\chi^2$  test,  $p=0.89$ ). We recorded a higher proportion of Dukes' C2 tumours in converted patients and those randomised in open surgery (16 [12%] of 131) than in non-converted individuals; however, this difference was not significant after adjustment for stratification factors ( $p=0.12$ ).

In cancers of the colon confirmed by central pathology review, positive CRMs were identified in six (5%) of 131 patients allocated open surgery and 16 (7%) of 246 allocated laparoscopic surgery, but the difference was not significant (1.9%, 95% CI -2.8 to 6.6%,  $\chi^2$  test,  $p=0.45$ ). Positivity rates did not differ when analysed according to actual treatment received. No positive longitudinal resection margins were detected in the open-surgery group and only one was detected in the laparoscopic-surgery group for a patient who underwent conversion. Distance of tumour from mesenteric resection margin (surgical high-tie) was similar in both open and laparoscopic surgery groups (median 9 cm [IQR 7–11] vs 8 cm [6.5–10], respectively).

In cancers of the rectum, positive CRMs were identified in 14 (14%) of 97 patients with open surgery and 30 (16%) of 193 with laparoscopic excisions (difference 1.1%, 95% CI -7.6% to 9.8%,  $\chi^2$  test,  $p=0.8$ ). CRM positivity also did not differ when analysed according to treatment actually received. Of patients undergoing anterior resection, CRM positivity was greater in the laparoscopic than in the open-surgery group (16 [12%] of 129 individuals vs four [6%] of 64, respectively) but this difference was not significant (95% CI -2.1 to 14.4%,  $p=0.19$ ). For abdominoperineal resections, no difference was seen in CRM positivity between the laparoscopic (ten [20%] of 49) and open (seven [26%] of 27) groups. Longitudinal resection margins did not differ significantly between treatments (Fisher's exact test,  $p=1.00$ ). The distance to high tie was slightly higher in the open surgery group (median 14 cm [IQR 10–17]) than in the laparoscopic surgery group (12 cm [9–15]).

34 patients died in hospital (13 [5%] after open surgery vs 21 [4%] after laparoscopic surgery; difference -0.9%, 95% CI -3.9 to 2.2%,  $\chi^2$  test,  $p=0.57$ ). Patients who underwent conversion had a higher death rate than open or laparoscopic patients (13 [9%] vs 15 [5%] and 16 [1%], respectively). However, this difference was not significant after adjustment for stratification factors ( $p=0.34$ ). The main cause of death was cardiorespiratory failure (16, 47%).

81 (10%) patients had intraoperative complications (table 4), with no difference between treatments (difference 0.2%, 95% CI -4.2% to 4.6%,  $\chi^2$  test,  $p=0.93$ ). Clinically significant intraoperative haemorrhage and cardiac insufficiency/dysrhythmia were the most common complications. Complication rates were

	Intention-to-treat population	
	Open	Laparoscopic
Patients with complications	27 (10%)	54 (10%)
Colon	11 (8%)	19 (7%)
Rectum	16 (13%)	35 (14%)
Total complications	29 (11%)	67 (13%)
Colon	11 (8%)	22 (8%)
Rectum	18 (14%)	45 (18%)
Complications (colon)		
Clinically significant haemorrhage	5 (4%)	2 (1%)
Cardiac/pulmonary insufficiency	4 (3%)	10 (4%)
Bowel injury	..	6 (2%)
Ureteric injury	..	2 (1%)
Vessel/bladder injury	..	..
Other	2 (1%)	2 (1%)
Complications (rectum)		
Clinically significant haemorrhage	7 (5%)	17 (7%)
Cardiac/pulmonary insufficiency	4 (3%)	11 (4%)
Bowel injury	1 (1%)	3 (1%)
Ureteric injury	4 (3%)	..
Vessel/bladder injury	..	5 (2%)
Other	2 (2%)	9 (4%)

Data are number (%).

Table 4: Intraoperative complications

	Intention-to-treat population		Actual treatment group		
	Open	Laparoscopic	Open	Laparoscopic	Conversion
Patients with complications	85 (32%)	172 (33%)	86 (31%)	99 (29%)	64 (45%)
Colon	38 (27%)	71 (26%)	37 (26%)	48 (26%)	16 (26%)
Rectum	47 (37%)	101 (40%)	49 (37%)	51 (32%)	48 (59%)
Total complications	113 (42%)	246 (47%)	115 (42%)	133 (39%)	99 (69%)
Colon	49 (35%)	96 (35%)	48 (33%)	62 (34%)	23 (38%)
Rectum	64 (50%)	150 (59%)	67 (51%)	71 (44%)	76 (93%)
Complications (colon)					
Wound infection	7 (5%)	14 (5%)	7 (5%)	8 (4%)	5 (8%)
Chest infection	5 (4%)	18 (7%)	5 (3%)	10 (5%)	6 (10%)
Anastomotic dehiscence	4 (3%)	9 (3%)	5 (3%)	7 (4%)	1 (2%)
Deep-vein thrombosis	..	5 (2%)	..	5 (3%)	..
Other	33 (24%)	50 (18%)	31 (22%)	32 (17%)	11 (18%)
Complications (rectum)					
Wound infection	15 (12%)	33 (13%)	16 (12%)	16 (10%)	16 (20%)
Chest infection	5 (4%)	25 (10%)	6 (5%)	12 (8%)	12 (15%)
Anastomotic dehiscence	9 (7%)	26 (10%)	10 (7%)	13 (8%)	12 (15%)
Deep-vein thrombosis	2 (2%)	1	2 (2%)	..	1 (1%)
Other	33 (26%)	65 (26%)	33 (25%)	30 (19%)	35 (43%)

Data are number (%).

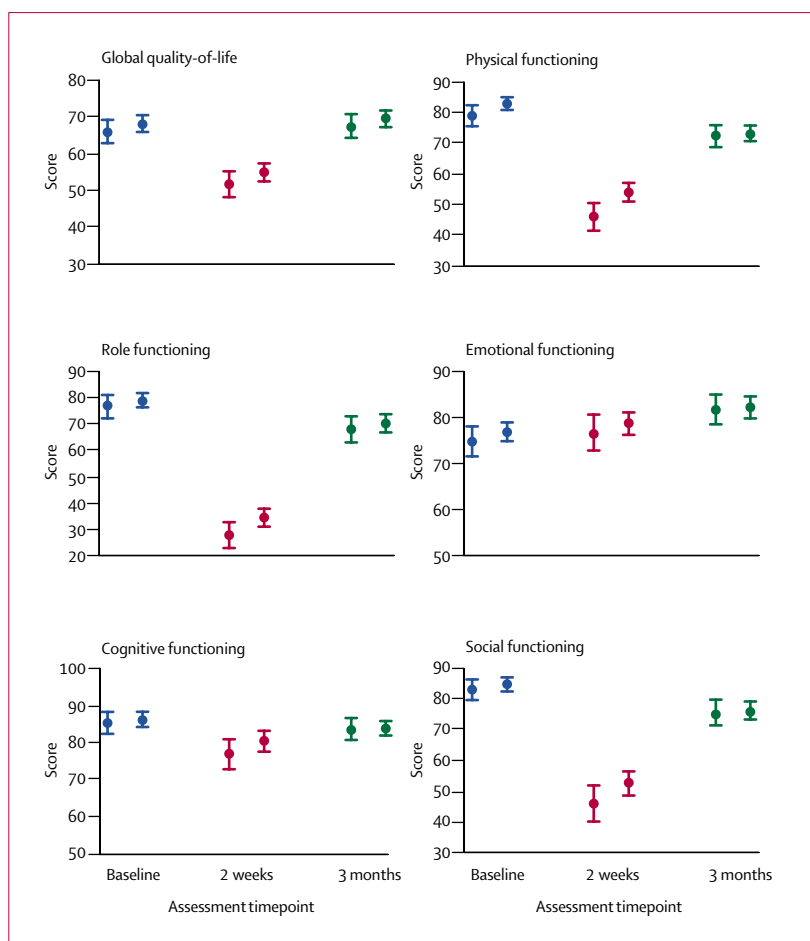
**Table 5: 30-day postoperative complications**

higher for rectal than colon procedures, (51 [13%] of 381 vs 30 [7%] of 413, respectively). The rate was also higher in converted than in non-converted patients and in those who underwent open surgery, even after adjustment for stratification factors ( $p=0.002$ ).

257 (32%) patients had 30-day postoperative complications (table 5). No difference was recorded between treatments (difference 1%, 95% CI  $-5.9\%$  to  $7.8\%$ ,  $\chi^2$  test,  $p=0.78$ ). Chest infection was more common in laparoscopic surgery than in open surgery (43 [8%] vs 10 [4%]), of which most were pneumonias. 18 (42%) of 43 respiratory infections in the laparoscopic arm were in converted patients. Complication rates between actual treatment groups did not differ after adjustment for stratification factors ( $p=0.04$ ). Again, rates were higher for rectal than for colonic procedures (148 [39%] vs 109 [26%]).

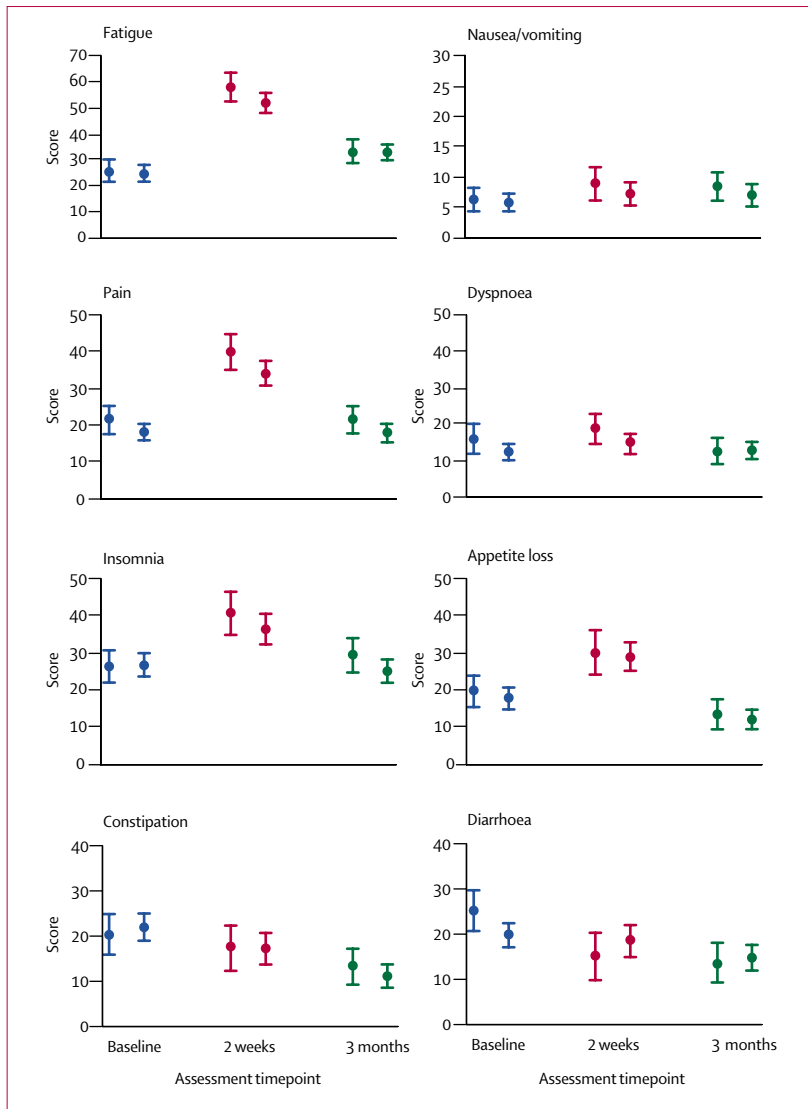
56 (7%) patients had 3-month postoperative complications, which also did not differ between treatments (difference  $-0.1\%$ , 95% CI  $-3.8\%$  to  $3.7\%$ ,  $\chi^2$  test,  $p=0.98$ ). Intestinal obstruction and persistent wound infection were the most frequent complications. Similar rates of major or minor complications were recorded for both treatment groups (41 [5%] major, 27 [3%] minor). Complication rates at 3-month follow-up did not differ for converted patients ( $p=0.35$ ).

During the first 7 days post-surgery, no difference was seen in the transfusion requirements between open and laparoscopic groups (41 [15%] vs 105 [20%], respectively; difference  $4.7\%$ , 95% CI  $-0.8\%$  to  $10.2\%$ ,  $\chi^2$  test,  $p=0.11$ ). All patients had allogeneic transfusions. The transfusion requirement rate increased in converted patients ( $p=0.01$ ) after adjustment for stratification factors.



**Figure 3: EORTC QLQ-C30 scores for global quality-of-life and functional scales**

Pairs of dots show scores for open surgery (left) and laparoscopic-assisted surgery (right). High scores indicate good functioning.



**Figure 4:** EORTC QLQ-C30 scores for symptom scales

Pairs of dots show scores for open surgery (left) and laparoscopic-assisted surgery (right). High scores indicate severe symptoms.

Compliance with questionnaires was high in both treatment groups (562 of 696 [81%] patients at baseline, 454 of 674 [67%] at 2 weeks, and 512 of 658 [78%] at 3 months after surgery). Analysis of dropout patterns did not suggest any clear association with failure to complete questionnaires. No differences in any of the scales or symptoms were recorded between the treatment groups ( $p > 0.01$ ).

QLQ-C30 scores showed similar patterns between surgery groups (figures 3 and 4). At 2 weeks, scores for global quality-of-life and cognitive functioning fell, and score for pain and appetite loss rose; these values returned to at least baseline values by 3 months. More problems than baseline were reported at 2 weeks and 3 months for role functioning and fatigue. Patients

reported fewer problems with diarrhoea after 2 weeks and increased problems with physical and social functioning at 2 weeks. Physical and social functioning scores returned to baseline values at 3 months in the open surgery group but not in the laparoscopic surgery group.

In QLQ-CR38, many symptoms were reported to be worse at 2 weeks but had either returned to baseline values (for frequency and pain on micturition, buttock pain, dry mouth, taste changes, and body dissatisfaction) or were better than baseline (bloating abdomen and weight loss) by 3 months. Patients reported that they felt less attractive and less feminine or masculine at both follow-up assessments. Bowel movement (without production of stool samples) was improved by 3 months. Patients reported less blood in stool samples at 2 weeks, with substantial improvement by 3 months. Painful bowel movement was worse at 2 weeks but improved by 3 months. 252 of 794 (32%) patients in both treatments had a stoma. The scores for stoma problems were similar at both follow-up assessments.

## Discussion

In our study, no differences were recorded between open surgery and laparoscopic-assisted surgery for colorectal cancer with respect to tumour and nodal status, short-term endpoints, and quality of life. Apart from patients undergoing laparoscopic anterior resection for rectal cancer, the positivity rates of surgical resection margins were also similar between the two treatment groups. In patients with cancer of the rectum, total mesorectal excision was undertaken more frequently in the group undergoing laparoscopic-assisted surgery than in the open surgery group. Conversions from laparoscopic to open surgery were more common in patients with cancer of the rectum. Converted individuals had the most complications from surgery.

To our knowledge, this trial has features not compared in detail previously, such as patients with cancer of the rectum, and so far only non-randomised studies have suggested that laparoscopic-assisted surgery is safe for these patients.<sup>24,25</sup> Second, a detailed pathological examination of resected tumours is likely to provide a surrogate endpoint for local recurrence.<sup>26,27</sup>

Because patients had similar characteristics between treatments, especially with regard to tumour and nodal status, no bias in favour of early-stage disease was indicated. This non-selective approach could partly explain the high conversion rate, because patients with advanced cancer and high body-mass index were included.<sup>28</sup> In the study design, which was based on the best available data, duration of surgeons' learning curves was set at 20 laparoscopic resections.<sup>22</sup> This number was clearly underestimated.<sup>13</sup> The learning curve was operative in this trial as shown by conversion rates falling for every year of recruitment. Inclusion of

cancer of the rectum, in which conversion rates as high as 33% have been reported,<sup>29</sup> also contributed to our high conversion rate. The most common causes for conversion in this trial indicated the need for accurate preoperative imaging of tumours. However sensitivity analyses confirmed that conversions had no effect on the interpretation of the results. Our conversion rate for colon cancer parallels results from the COST and Hong Kong trials (21% and 23%, respectively).<sup>11,13</sup> However, emphasis should still be placed on the importance of laparoscopic colorectal-cancer surgery being undertaken by appropriately trained surgeons.

Pathological analyses indicated high-quality surgery in both treatment groups, with high lymph-node yield equalling or exceeding that in several other trials.<sup>11,30,31</sup> Rates of abdominoperineal resection for cancer of the rectum were not excessive and were similar between surgery groups, which indicated no selection bias. The similar results of tumour and nodal statuses and positive surgical resection margins for cancer of the colon between surgery groups confirmed that from a surgical standpoint, the laparoscopic approach provides as good a resection as the open approach.

For cancers of the rectum, overall CRM positivity rates did not differ significantly between treatments. However, in patients undergoing anterior resection, a non-significant difference in CRM positivity was recorded, suggesting that the laparoscopic procedure could be associated with a slightly raised risk of local recurrence. Therefore, caution is currently advisable in the application of laparoscopic approaches to anterior resection. Patients with cancer of the rectum were more likely to undergo total mesorectal excision if the operation was laparoscopically assisted, and this finding shows the increased ease of this part of the procedure with a laparoscope, although long-term clinical outcomes need to be carefully examined. As reported in non-randomised studies,<sup>25</sup> no difference in CRM positivity have been shown in patients undergoing abdominoperineal resection, and therefore no differences in local recurrence are expected.

Intraoperative complication rates did not differ significantly between treatments in our study, although there was an increased proportion in converted patients similar to that recorded elsewhere.<sup>6</sup> In-hospital mortality also was not different, which confirms the short-term clinical safety of the laparoscopic-assisted approach.<sup>11</sup> This finding is bolstered by no significant differences in the 30-day and 3-month complication rates. The unexpected raised rate of respiratory complications in laparoscopic surgery could be due to the required protracted anaesthetic times. The quality-of-life results confirm those of the COST study—ie, that short-term quality-of-life advantages from laparoscopic-assisted surgery are very small.<sup>32</sup>

Although the data support the clinical and oncological safety of laparoscopic-assisted surgery, they raise

questions about outcomes in patients whose laparoscopic procedure was converted. These patients had high complication rates, in-hospital mortality, transfusion requirements, and proportions of Dukes' C2 tumours. Is this finding due to the procedural conversion itself,<sup>6</sup> or the type of patient who needs such a conversion? Further analysis can identify those at high risk of conversion before surgery. Since some published reports have suggested that transfusions are related to a raised rate of recurrence, this theory will need careful analysis for long-term data.

Our short-term results lend support to those of previous studies,<sup>11–13</sup> which show that for colon cancer, the laparoscopic procedure is oncologically safe, that local recurrence rates will be no higher than for open surgery, and that cancer-related survival will be at least no lower than after conventional resection. Nothing yet suggests laparoscopic surgery improves survival for patients with node-positive cancer of the colon.<sup>12</sup>

For cancer of the rectum, the increased frequency of total mesorectal excisions in the laparoscopically-assisted group could be because this procedure is technically easier in laparoscopic surgery than in open surgery. However, this approach should be set against the slightly raised risk of a positive CRM in patients undergoing sphincter-sparing surgery. We cannot comment on functional outcome in these patients, but this factor is a parameter that should be addressed in any future trials of laparoscopic-assisted rectal excision. Conversion rates are raised for patients undergoing laparoscopic rectal excision. Because operative mortality and complication rates were higher in the converted group, they were consequently higher in the laparoscopic rectal group than the laparoscopic colon group.

For cancer of the colon, little difference seems to exist between laparoscopic-assisted and open resection and on the basis of pathological data, there is no reason to expect long-term oncological outcomes to be different. Laparoscopic-assisted rectal excision might have encouraged surgeons to do total mesorectal excisions more frequently but the slightly raised positive CRMs after laparoscopic-assisted anterior resection could result in increased local recurrence rates. Impaired short-term outcomes and pathological features after laparoscopic anterior resection do not yet justify routine use of the approach in cancers of the rectum.

#### Contributors

P J Guillou and P Quirke participated in the design of the trial, data monitoring, interpretation of results, and drafting of the manuscript. H Thorpe participated in the data monitoring, analysis of data, interpretation of results, and drafting of the manuscript. J Walker participated in the data monitoring, data co-ordination, interpretation of results, and drafting of the manuscript. D G Jayne, A M H Smith, and R M Heath participated in the data collection and data monitoring. J M Brown participated in the design of the trial, data monitoring, analysis of data, interpretation of results, and drafting of the manuscript. All authors saw and approved the final version of the report.

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**Conflict of interest statement**

We declare that we have no conflict of interest.

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