Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial

*Martijn H G M van der Pas, Eva Haglind, Miguel A Cuesta, Alois Fürst, Antonio M Lacy, Wim C J Hop, Hendrik Jaap Bonjer, for the COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group**

Lancet Oncol 2013; 14: 210–18

Published Online February 6, 2013 http://dx.doi.org/10.1016/S1470-2045(13)70016-0

See Comment page 179

*Members are listed in the appendix

VU University Medical Center, Amsterdam, Netherlands (M H G M van der Pas MD, Prof M A Cuesta MD, Prof H J Bonjer MD); **Sahlgrenska Universitetssjukhuset, Göteborg, Sweden** (Prof E Haglind MD); **Caritas Krankenhaus St Josef, Regensburg, Germany** (Prof A Fürst MD); **Hospital Clinic I Provincial de Barcelona, Barcelona, Spain** (Prof A M Lacy MD); **and Erasmus University Medical Centre, Rotterdam, Netherlands** (W C J Hop PhD)

Correspondence to: Prof Hendrik Jaap Bonjer, VU University Medical Center, Surgery, 1117 De Boelelaan, Amsterdam, 1007 MB, Netherlands
j.bonjer@vumc.nl

See Online for appendix

Summary

Background Laparoscopic surgery as an alternative to open surgery in patients with rectal cancer has not yet been shown to be oncologically safe. The aim in the COlorectal cancer Laparoscopic or Open Resection (COLOR II) trial was to compare laparoscopic and open surgery in patients with rectal cancer.

Methods A non-inferiority phase 3 trial was undertaken at 30 centres and hospitals in eight countries. Patients (aged ≥18 years) with rectal cancer within 15 cm from the anal verge without evidence of distant metastases were randomly assigned to either laparoscopic or open surgery in a 2:1 ratio, stratified by centre, location of tumour, and preoperative radiotherapy. The study was not masked. Secondary (short-term) outcomes—including operative findings, complications, mortality, and results at pathological examination—are reported here. Analysis was by modified intention to treat, excluding those patients with post-randomisation exclusion criteria and for whom data were not available. This study is registered with ClinicalTrials.gov, number NCT00297791.

Findings The study was undertaken between Jan 20, 2004, and May 4, 2010. 1103 patients were randomly assigned to the laparoscopic (n=739) and open surgery groups (n=364), and 1044 were eligible for analyses (699 and 345, respectively). Patients in the laparoscopic surgery group lost less blood than did those in the open surgery group (median 200 mL [IQR 100–400] *vs* 400 mL [200–700], p<0·0001); however, laparoscopic procedures took longer (240 min [184–300] *vs* 188 min [150–240]; p<0·0001). In the laparoscopic surgery group, bowel function returned sooner (2·0 days [1·0–3·0] *vs* 3·0 days [2·0–4·0]; p<0·0001) and hospital stay was shorter (8·0 days [6·0–13·0] *vs* 9·0 days [7·0–14·0]; p=0·036). Macroscopically, completeness of the resection was not different between groups (589 [88%] of 666 *vs* 303 [92%] of 331; p=0·250). Positive circumferential resection margin (<2 mm) was noted in 56 (10%) of 588 patients in the laparoscopic surgery group and 30 (10%) of 300 in the open surgery group (p=0·850). Median tumour distance to distal resection margin did not differ significantly between the groups (3·0 cm [IQR 2·0–4·8] *vs* 3·0 cm [1·8–5·0], respectively; p=0·676). In the laparoscopic and open surgery groups, morbidity (278 [40%] of 697 *vs* 128 [37%] of 345, respectively; p=0·424) and mortality (eight [1%] of 699 *vs* six [2%] of 345, respectively; p=0·409) within 28 days after surgery were similar.

Interpretation In selected patients with rectal cancer treated by skilled surgeons, laparoscopic surgery resulted in similar safety, resection margins, and completeness of resection to that of open surgery, and recovery was improved after laparoscopic surgery. Results for the primary endpoint—locoregional recurrence—are expected by the end of 2013.

Funding Ethicon Endo-Surgery Europe, Swedish Cancer Foundation, West Gothia Region, Sahlgrenska University Hospital.

Introduction

Rectal cancer afflicts more than 50 women and men per 100 000 individuals per year in Europe and accounts for more than 80 000 deaths per year.[1,2] The outcome of surgery for this cancer has improved substantially during the past two decades because of the introduction of total mesorectal excision (TME),[3] which entails complete removal of the mesorectum—adipose lymphatic tissue surrounding the rectum—with preservation of the pelvic autonomic nerves. Local recurrence rates of rectal cancer have fallen sharply because radially spread cancer cells in the mesorectum are removed by complete resection of this tissue. Radiotherapy and chemotherapy are important components of multimodal treatment in patients with more advanced rectal cancer.[4]

The introduction of TME in the early 1990s coincided with the progressive use of laparoscopic surgery in patients with colorectal disease. Laparoscopic resection of colonic cancer has proven to be safe, causing less postoperative pain, allowing earlier recovery, and is associated with cancer survival similar to that obtained with traditional open colectomy.[5,6]

Although the findings of various reports have shown that laparoscopic TME is safe, studies with sufficient numbers of patients allowing clinical acceptance of laparoscopic surgery in rectal cancer are lacking.[7,8] We compared laparoscopic and open surgery in patients with rectal cancer in the COlorectal cancer Laparoscopic or Open Resection (COLOR II) trial and report the short-term (secondary) outcomes.

Methods

Patients

COLOR II, a non-inferiority, open-label, randomised trial, was undertaken in 30 centres and hospitals in eight countries (Belgium, Canada, Denmark, Germany, the Netherlands, Spain, South Korea, and Sweden). Patients with a single rectal cancer within 15 cm from the anal verge at colonoscopy, rigid rectoscopy, or barium enema without evidence of distant metastases who were candidates for elective surgery were eligible for participation in this study. The localisation of the tumour was categorised as upper (distal border of tumour 10–15 cm from the anal verge), middle (5–10 cm), and lower rectum (<5 cm). Rectal cancer invading adjacent tissues or organs, T4 tumours, or T3 rectal cancers within 2 mm of the endopelvic fascia, ascertained by use of CT or MRI, were excluded. Other exclusion criteria were T1 tumour treated with local transanal excision, rectal cancer other than adenocarcinoma, history of other malignancy except basocellular carcinoma of the skin or in-situ carcinoma of the cervix uteri, signs of acute intestinal obstruction, need for synchronous colorectal surgery, familial adenomatous polyposis coli, hereditary non-polyposis colorectal cancer, active Crohn's disease or active ulcerative colitis, absolute contraindications to general anaesthesia or prolonged pneumoperitoneum, American Society of Anesthesiologists category greater than III, and pregnancy.

Each participating centre or hospital obtained institutional review board approval. Patients provided written informed consent.

Randomisation and masking

After eligibility had been established and patients provided written informed consent, the local investigator registered patients on the trial's website to ensure allocation concealment. Patients were then randomly assigned in a 2:1 ratio to laparoscopic surgery or open surgery in accordance with a list of randomisation numbers and treatment allocation. This list was computer generated by the trial statistician with stratification for centre, tumour location, and preoperative radiotherapy. It was implemented by use of an internet application to allow central randomisation. Patients and individuals assessing outcomes were not masked to treatment assignment. All case record forms were gathered and stored at Dalhousie University, Halifax, NS, Canada.

Procedures

The protocol stipulated that perioperative care—eg, antibiotic prophylaxis, bowel preparation, thrombosis prophylaxis, analgesic care, and postoperative resumption of diet, should be used in accordance with the local standards without differences between the laparoscopic surgery and open surgery groups. Data for these variables were not gathered. In terms of radiotherapy and chemotherapy regimens (also administered as per local standards), use of preoperative radiotherapy and chemotherapy was recorded in the short-term outcomes and use of postoperative radiotherapy and chemotherapy was recorded at 1 year follow-up.

For the **trial protocol** see http://www.color2.org/

Assignment of patients to individual surgeons was according to local practice; in some centres and hospitals, the surgeon who assessed the patient in clinic would consistently be the on-record surgeon for the entire surgical treatment whereas in other centres and hospitals patients were assigned to surgeons by operating room coordinators irrespective of earlier clinic visits.

All procedures had to comply with the principles of TME[9] or partial mesorectal excision (PME). TME requires removal of the entire mesorectum down to the pelvic floor. It was done with either preservation of the anal sphincter or with excision of the anal sphincter (abdominoperineal resection [APR]). Rectal cancers located in the upper part of the rectum can be resected with sufficient margin by transecting the mesorectum at about 5 cm distally from the lower margin of the tumour, resulting in PME.

Preservation of the right and left hypogastric nerves was mandatory and the level of transection of the inferior mesenteric artery and creation of a diverting (loop) ileostomy was at the discretion of the surgeon. Completion of laparoscopic dissection of the mesorectum was judged necessary to qualify a procedure as laparoscopic. All other laparoscopic procedures were judged conversions to open surgery.

Surgical teams that wished to participate in the COLOR II trial were requested to submit unedited recordings of five consecutive laparoscopic TMEs for assessment or were observed by one of the five governors (HJB, EH, MAC, AF, and AML) of the COLOR II trial to verify that the procedure was done properly. The pathology reports of these five consecutive cases were reviewed to confirm completeness of the specimen. Quality approval within the COLOR II trial was only done at entry into the trial.

Processing and assessment of the pathology specimens are described in detail in the study protocol. Surgeons who participated in the COLOR II trial reviewed this description with their respective pathologists. Central pathology review was not done. The macroscopic and microscopic assessments of the pathology specimens were done by the pathologists at the participating centres.

All specimens were processed and analysed as described by Quirke.[10] The following definitions to macroscopically assess the quality of the specimen were used: complete, the mesorectal surface showed only minimum irregularities with a depth of less than 5 mm, no coning toward the distal margin, and smooth circumferential margin; partially incomplete, most of the mesorectum had been removed, moderate coning of the specimen toward the distal margin, and moderate irregularity of the circumferential margin; and

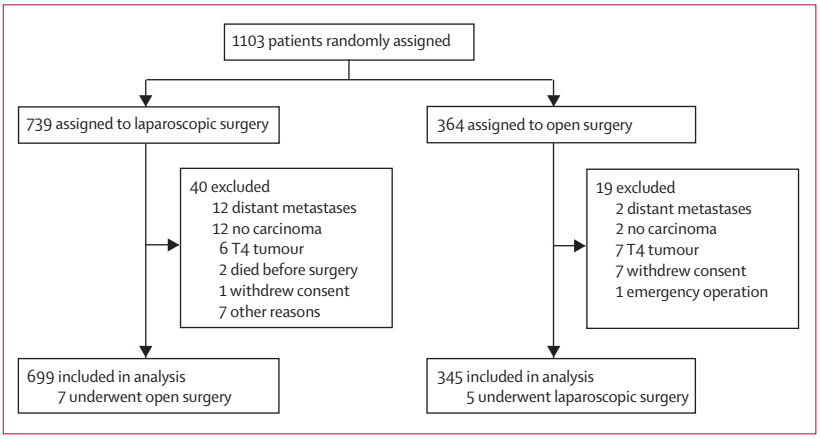

Figure: **Trial profile**

	Laparoscopic surgery (n=699)	Open surgery (n=345)
Sex		
Male	448/699 (64%)	211/345 (61%)
Female	251/699 (36%)	134/345 (39%)
Age (years)	66·8 (10·5)	65·8 (10·9)
American Society of Anesthesiologists category		
I	156/678 (23%)	65/338 (19%)
II	386/678 (57%)	211/338 (62%)
III	131/678 (19%)	61/338 (18%)
IV	5/678 (<1%)	1/338 (<1%)
Missing data	21/699 (3%)	7/345 (2%)
Body-mass index (kg/m²)	26·1 (4·5)	26·5 (4·7)
Location of tumour (distance from anal verge)		
Lower rectum (<5 cm)	203/699 (29%)	93/345 (27%)
Middle rectum (5–10 cm)	273/699 (39%)	136/345 (39%)
Upper rectum (10–15 cm)	223/699 (32%)	116/345 (34%)
Clinical stage		
I	201/667 (30%)	96/329 (29%)
II	209/667 (31%)	107/329 (33%)
III	257/677 (38%)	126/329 (38%)
Missing data	32/699 (5%)	16/345 (5%)
Preoperative radiotherapy	412/699 (59%)	199/345 (58%)
Preoperative chemotherapy	196/609 (32%)	99/295 (34%)
Missing data	90/699 (13%)	50/345 (14%)

Data are n/N (%) or mean (SD).

Table 1: **Clinical characteristics of patients**

incomplete, the mesorectum showed defects as far as the muscularis propria, coning, or very irregular circumferential margin.

Circumferential resection margins (CRMs) were defined as positive if malignant cells were found at microscopy at a distance of less than 2 mm between the outermost part of the tumour[11] and the CRM or between lymph nodes bearing tumour cells and the CRM. Proximal and distal resection margins and number of resected lymph nodes were recorded.

The primary outcome in the COLOR II trial is the proportion of patients with local recurrence at 3 years after index surgery; these data are not yet mature and will be reported at a later date. Short-term secondary endpoints were operating time, conversion rate, blood loss, postoperative recovery of gastrointestinal function, postoperative pain medication, length of hospital stay, morbidity and mortality within 28 days after surgery, and histopathological outcomes (including completeness of the resection, circumferential, proximal, and distal resection margins, and number of resected lymph nodes). Another secondary outcome was anastomotic leakage, which was defined as clinical evidence of a defect of the integrity of the intestinal wall at the anastomotic site or presence of a pelvic abscess adjacent to the anastomosis.[12]

Statistical analysis

To show non-inferiority, the proportion of patients with local recurrence at 3 years after the index surgery was assumed to be 10% in the open surgery group and the power was set at 80% with a non-inferiority margin of 5 percentage points. The calculations showed that 1000 patients were required for the trial. We aimed to enrol 1100 patients to allow for post-randomisation exclusions. Between-group comparisons of categorical outcome data were done with the χ^2 test or Fisher's exact test; comparison of continuous data was by use of the Mann-Whitney *U* test. For this test, we calculated exact p values because of the heavily tied data for time until first bowel movement, time until intake of more than 1 L of fluid, and length of hospital stay. Analysis was on a modified intention-to-treat basis, based on all individuals with data for each particular outcome and excluding patients who had been randomised but met post-randomisation exclusion criteria. We used two-sided p values. The p values of 0·05 or lower were judged to be significant. Statistical analyses were done with SPSS (version 17.0).

This trial is registered with ClinicalTrials.gov, number NCT00297791.

Role of the funding source

The sponsor of the study had no role in study design, data gathering, analysis, and interpretation, or writing of the report. MHGMvdP, MAC, WCJH, and HJB had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 20, 2004, and May 4, 2010, 1103 patients with rectal cancer were randomly assigned to either laparoscopic or open surgery. 260 patients were from Dutch hospitals, 475 from Scandinavian hospitals, 138 from Spanish hospitals, and 230 from other European, Canadian, and Asian centres. The median number of patients per centre was 32 (range 1–113). 59 patients were excluded after randomisation; reasons for exclusion included distant

metastases, no malignant tumour, or a T4 tumour (figure). Of 1044 patients who were available for analysis, 699 (67%) were assigned to laparoscopic surgery and 345 (33%) to open surgery (figure). 12 patients underwent the surgery they were not assigned to (figure). These patients remained in their allocated group for analyses.

Table 1 shows the clinical characteristics of the patients. The proportions of patients given preoperative radiotherapy and preoperative chemotherapy were similar in the laparoscopic and open surgery groups (table 1). In the laparoscopy group, 212 patients had short-course radiotherapy and 166 had long-course radiotherapy; data were missing for 34 patients. In the open surgery group, 95 patients had short-course radiotherapy and 87 had long-course radiotherapy; data were missing for 17 patients.

Table 2 shows the operative findings. The distributions of the different procedures were similar in the two groups. In 36 patients in the laparoscopic surgery group and 25 in the open surgery group, an end colostomy was created after sphincter preserving (Hartmann) procedures. A diverting ileostomy was created in about a third of all patients (table 2).

Of 338 patients with a tumour located in the upper rectum (data were missing for one patient in the laparoscopic surgery group), 241 (71%) had a TME (156 in the laparoscopic surgery group *vs* 85 in the open surgery group); 90 (27%) had a PME (60 *vs* 30, respectively); seven (2%) underwent an APR (six *vs* one, respectively). Of 403 patients with cancer of the middle rectum (data were missing for six patients in the laparoscopic surgery group), 340 (84%) had a sphincter-saving TME (218 in the laparoscopic surgery group *vs* 122 in the open surgery group); 48 (12%) underwent an APR (38 *vs* ten, respectively); and 15 (4%) had a PME (11 *vs* four, respectively). Of 294 patients with a tumour located within 5 cm from the anal verge (data were missing for two patients in the laparoscopic surgery group), 225 (77%) had an APR (156 in the laparoscopic surgery group *vs* 69 in the open surgery group) and 67 (23%) had sphincter-saving TME (44 *vs* 23, respectively), and two (<1%) underwent a PME (one *vs* one, respectively).

Of 339 patients with cancer of the upper rectum, 306 (90%) had a stapled anastomosis (198 in the laparoscopic surgery group *vs* 108 in the open surgery group), three (<1%) had a hand-sewn anastomosis (one *vs* two, respectively), and 25 (7%) had a colostomy (17 *vs* eight); data were missing for five (1%) patients in the laparoscopic surgery group. Of 409 patients with cancer of the middle rectum, 311 (76%) had a stapled anastomosis (203 in the laparoscopic surgery group *vs* 108 in the open surgery group), 17 (4%) had a hand-sewn anastomosis (ten *vs* seven, respectively), 77 (19%) had a colostomy (54 *vs* 23, respectively); data were missing for four (1%) patients in the laparoscopic surgery group. Of 296 patients with cancer of the lower rectum, 39 (13%) had a stapled anastomosis (25 in the laparoscopic group *vs* 14 in the open group), 16 (5%) had a hand-sewn anastomosis (11 *vs* five, respectively), and 239 (81%) had a colostomy (165 *vs* 74, respectively); data were missing for two (1%) patients in the laparoscopic surgery group.

Of 574 non-converted laparoscopic patients, 198 (34%) had an APR or a Hartmann procedure, and therefore these patients did not have an anastomosis. Of 376 (66%) patients in the non-converted laparoscopic surgery group who had an anastomosis of the bowel (ie, did not have an APR or a Hartmann procedure), 269 (72%) underwent laparoscopy for their anastomoses and the anastomoses in the remaining 107 (28%) patients were treated with open surgery.

The median duration of laparoscopic surgery was 240 min (IQR 184–300) compared with 188 min (150–240; p<0·0001) for open surgery. Median blood loss was 200 mL (100–400) during laparoscopic surgery and 400 mL (200–700; p<0·0001) during open surgery.

Laparoscopic procedures were converted to open surgery in 121 (17%) of 695 patients; data regarding conversions were missing for four patients; seven (1%)

	Laparoscopic surgery	Open surgery	p value
Intervention			0·120
Resection with partial mesorectal excision	72/699 (10%)	35/345 (10%)	..
Resection with total mesorectal excision	418/699 (60%)	230/345 (67%)	..
Abdominoperineal resection	200/699 (29%)	80/345 (23%)	..
Missing data	9/699 (1%)	0	..
Hartmann procedure	36/699 (5%)	25/345 (7%)	0·243
Diverting ileostomy			
Total group*	243/690 (35%)	131/345 (38%)	0·343
Upper rectum†	74/222 (33%)	44/116 (38%)	0·453
Middle rectum†	135/276 (49%)	73/136 (54%)	0·484
Lower rectum†	34/201 (17%)	14/93 (15%)	0·844
Duration of intervention (min)‡	240 (184–300)	188 (150–240)	<0·0001
Blood loss (mL)			
Total group	200 (100–400)	400 (200–700)	<0·0001
Conversion	121/695 (17%)	..	..
Preoperative	7/695 (1%)	..	..
Intraoperative	114/695 (16%)	..	..
Missing data	4/699 (<1%)	..	..
Intraoperative complications§	81/694 (12%)	49/344 (14%)	0·281
Haemorrhage	22/694 (3%)	11/344 (3%)	1·000
Gastrointestinal perforation	6/694 (<1%)	8/344 (2%)	0·102
Hypercapnia	2/694 (<1%)	0/344	0·807
Anastomosis related	9/694 (1%)	8/344 (2%)	0·332
Ureter injury	9/694 (1%)	2/344 (<1%)	0·461
Nerve injury	0/694	3/344 (<1%)	0·036
Perforation of tumour	3/694 (<1%)	4/344 (1%)	0·342
Other	40/694 (6%)	20/344 (6%)	1·000
Missing data	5/699 (<1%)	1/345 (<1%)	..

Data are n/N (%) or median (IQR). *Denominator was number of patients who had an anastomosis. †Denominator was the number of patients who had ileostomies. ‡Time between first incision and closure of the surgical incision. §Each patient could have had more than one complication.

Table 2: **Operative findings**

patients were converted because of unavailability of laparoscopic expertise or equipment; and 114 (16%) were intraoperatively converted to open surgery for various reasons. These reasons were narrow pelvis (25 [22%]), extensive adhesions (14 [12%]), obesity (11 [10%]), fixation of the tumour (ten [9%]), technical (seven [6%]), anatomical difficulties (seven [6%]), poor vision (six [5%]), bleeding (six [5%]), large tumour (five [4%]), fibrosis (four [4%]), ureter injury (two [2%]), and other reason (17 [15%]).

	Laparoscopic surgery	Open surgery	p value
Days until first bowel movement			
Total group	2·0 (1·0–3·0)*	3·0 (2·0–4·0)*	<0·0001
Missing data	33/699 (5%)	8/345 (2%)	..
Days until intake of more than 1 L of fluid			
Total group	2·0 (1·0–3·0)†	2·0 (1·0–3·0)†	0·005
Missing data	39/699 (6%)	12/345 (3%)	..
Use of analgesic drugs			
Day 1			
Opiates	242/676 (36%)	129/338 (38%)	0·504
Non-opiates	616/674 (91%)	310/336 (92%)	0·727
Epidural	394/676 (58%)	237/338 (70%)	0·0003
Day 2			
Opiates	238/676 (35%)	126/337 (37%)	0·540
Non-opiates	619/675 (92%)	314/336 (93%)	0·392
Epidural	345/675 (51%)	215/338 (64%)	0·0001
Day 3			
Opiates	288/676 (43%)	164/338 (49%)	0·085
Non-opiates	605/675 (90%)	309/338 (91%)	0·428
Epidural	200/677 (30%)	129/339 (38%)	0·007
Morbidity (patients with at least one postoperative complication)‡	278/697 (40%)	128/345 (37%)	0·424
Cardiac	17/697 (2%)	11/345 (3%)	0·617
Anastomotic leak§	58/461 (13%)	25/240 (10%)	0·462
Upper rectum	22/205 (11%)	7/108 (6%)	0·288
Middle rectum	32/218 (15%)	17/113 (15%)	0·869
Lower rectum	4/38 (11%)	1/19 (5%)	1·000
Missing data	2/699 (<1%)	0/345	..
Respiratory	20/697 (3%)	10/345 (3%)	1·000
Abscess	51/697 (7%)	22/345 (6%)	0·667
Wound infection	28/697 (4%)	17/345 (5%)	0·604
Ileus	33/697 (5%)	12/345 (3%)	0·437
Other	194/697 (28%)	103/345 (30%)	0·544
Reintervention	113/697 (16%)	52/345 (15%)	0·701
Hospital stay (days)			
Total group	8·0 (6·0–13·0)¶	9·0 (7·0–14·0)¶	0·036
Missing data (including in-hospital deaths)	15/699 (2%)	8/345 (2%)	..
Mortality within 28 days‖	8/699 (1%)	6/345 (2%)	0·409

Data are n/N (%) or median (IQR). *Time until first bowel movement: mean 2·9 days (SD 3·8) in the laparoscopic surgery group versus 3·7 days (3·6) in the open surgery group. †Mean time until intake of more than 1 L of fluid: 2·6 days (4·3) in the laparoscopic surgery group versus 2·8 days (3·6) in the open surgery group. ‡More than one complication could have occurred per patient. §The numerator was number of leaks and the denominator was the total number of patients after excluding those without an anastomosis—ie, abdominoperineal resection or Hartmann's procedure. ¶Hospital stay: 11·9 days (11·8) in the laparoscopic surgery group versus 12·1 days (10·6) in the open surgery group. ‖Two additional patients in the open surgery group and one in the laparoscopic group died in hospital later than 28 days after surgery.

***Table 3*: Postoperative recovery, morbidity, and mortality within 28 days**

Intraoperative complications occurred in 130 patients (table 2).

890 (86%) of 1034 laparoscopic and open procedures were done by surgeons who performed both laparoscopic and open rectal operations in this trial; data for identification of the surgeons were missing for ten (1%) patients.

The postoperative use of opiates or non-opiates did not differ significantly between groups. Epidural analgesics on the first, second, and third days after surgery were used by a greater proportion of patients in the open surgery group than in the laparoscopic surgery group (table 3). First bowel movement occurred on the second day after laparoscopic surgery, 1 day earlier than after open surgery (table 3). Oral intake of more than 1 L of fluid was tolerated a mean 0·2 days earlier after laparoscopic surgery (table 3). Median hospital stay after laparoscopic surgery was 8 days, 1 day shorter than after open surgery (table 3).

Morbidity (at least one postoperative complication) was reported in 278 (40%) of 697 patients in the laparoscopic surgery group (with data missing for two patients [<1%]), and 128 (37%) of 345 patients in the open surgery group (table 3). Anastomotic leaks were noted in 58 (13%) of 461 patients after laparoscopic surgery and 25 (10%) of 240 patients in the open surgery group (table 3).

The proportion of patients who needed reintervention within 28 days after surgery was similar in the two groups (table 3). The procedures undertaken were relaparotomies or relaparoscopies (42 [6%] of 697 in the laparoscopic surgery group *vs* 20 [6%] of 345 patients in the open surgery group), percutaneous or transrectal drainages of abscesses (21 [3%] *vs* four [1%]), revisions of ileostomies or colostomies (13 [2%] *vs* four [1%]), debridements of wounds (12 [2%] *vs* 9 [3%]), and other procedures (25 [4%] *vs* 15 [4%]).

Eight (1%) patients in the laparoscopic surgery group and six (2%) in the open surgery group died within 28 days (difference 0·6% [95% CI –1·0 to 2·2]; p=0·409; table 3). Causes of death in the laparoscopic surgery group were pulmonary aspiration (two [<1%] of 699), abdominal sepsis (two [<1%]), pulmonary embolism (one [<1%]), acute respiratory distress syndrome (one [<1%]), myocardial infarction (one [<1%]), and bleeding from anastomosis (one [<1%]). The causes of death in the open surgery group were pulmonary aspiration (one [<1%]), pneumonia (one [<1%]), multiorgan failure (one [<1%]), mesenteric ischaemia (one [<1%]), cerebral bleeding (one [<1%]), and abdominal sepsis (one [<1%]).

Macroscopically incomplete resected specimens were recorded in 19 (3%) of 666 patients after laparoscopic surgery and nine (3%) of 331 after open surgery (table 4). In a subgroup analysis, patients with upper rectal cancer who underwent laparoscopic surgery had significantly more incomplete resections than did patients in the open surgery group (table 4).

The median distal resection margin was 3·0 cm in both groups; the proximal resection margin was 16 cm

after laparoscopic surgery and 19 cm after open surgery (table 4). There was no difference in the proportion of patients with a positive CRM between groups (difference 0·6% [95% CI −3·5 to −4·7]; p=0·850; table 4). The proportion of patients with low rectal cancers with positive CRM was significantly lower in the laparoscopic surgery group than in the open surgery group (difference 12·4% [2·1 to 22·7]; p=0·014; table 4). Of 225 patients who had an APR for lower rectal cancer, excluding 12 patients with complete remission, 11 (8%) of 131 patients in the laparoscopic group had positive CRMs versus 15 (25%) of 59 patients after open surgery (p=0·003); data for CRM were missing for 23 patients. The median number of lymph nodes harvested after surgery was not significantly different in the two groups (table 4).

The proportion of patients in whom no evidence of tumour was found after preoperative (neoadjuvant) radiation or preoperative chemoradiatherapy did not differ significantly between the two groups (table 4).

Discussion

The short-term outcomes of the COLOR II trial show that the radicality of laparoscopic resection (as assessed by pathology report) in patients with rectal cancer is no different to that of open surgery, and that laparoscopic surgery was associated with similar rates of intra-operative complications, morbidity, and mortality. Complete removal of the primary tumour and tumour deposits in the mesorectum is the goal of surgery in patients with rectal cancer. A resection is judged radical when the circumferential, distal, and proximal edges of the specimen are devoid of tumour cells. Clear circumferential margins are of great importance because the risk of local recurrence increases three to four times when these margins are invaded with tumour cells.[13]

More than 90% of patients had clear CRMs in the COLOR II trial. In our study, circumferential margins were judged positive when tumour cells were present within 2 mm from the lateral edge of the mesorectum. A limit of 2 mm was used because Nagtegaal and colleagues[11] concluded that tumour growth between 1 mm and 2 mm from the CRM was as relevant as within 1 mm from the CRM based on a 16·0% risk of a local recurrence at 2 years after surgery in patients with margins smaller than 2 mm whereas patients with margins greater than 2 mm had a 5·8% risk. However, other investigators[7] have used a distance of 1 mm instead of 2 mm from the edge of the specimen in judging CRMs as positive. Kang and colleagues[7] reported negative lateral margins in more than 95% of patients with cancer in the middle and lower portions of the rectum that had either open or laparoscopic surgery after preoperative chemo-radiotherapy. Use of a 1 mm margin in the COLOR II trial resulted in free margins in 545 (93%) of 588 patients after laparoscopic resection and in 274 (91%) of 300 after open surgery.

	Laparoscopic surgery	Open surgery	p value
Completeness of resection			0·250
Complete	589/666 (88%)	303/331 (92%)	..
Partially complete	58/666 (9%)	19/331 (6%)	..
Incomplete	19/666 (3%)	9/331 (3%)	..
Missing data	33/699 (5%)	14/345 (4%)	..
Incomplete resection specimen			
Upper rectum	7/699 (1%)	1/345 (<1%)	0·026
Middle rectum	3/699 (<1%)	4/345 (1%)	0·281
Lower rectum	9/699 (1%)	4/345 (1%)	0·994
Positive CRM*			
Total group	56/588 (10%)	30/300 (10%)	0·850
Upper rectum	18/196 (9%)	9/97 (9%)	1·000
Middle rectum	22/228 (10%)	4/115 (3%)	0·068
Lower rectum	15/164 (9%)	17/79 (22%)	0·014
Missing data	78/666 (12%)	26/326 (8%)	..
Median CRM (cm)			
Total group	1·0 (0·5–1·8)	1·0 (0·4–1·5)	0·158
Upper rectum	1·2 (0·5–2·0)	1·0 (0·5–2·0)	0·510
Middle rectum	1·0 (0·5–2·0)	1·0 (0·6–1·8)	0·545
Lower rectum	0·8 (0·4–1·4)	0·6 (0·2–1·0)	0·274
Missing data	78/666 (12%)	26/326 (8%)	..
Distance to proximal resection margin (cm)			
Total group	16·0 (11·0–21·0)	19·0 (14·0–24·0)	<0·0001
Upper rectum	12·4 (8·0–18·0)	16·0 (12·0–20·5)	0·001
Middle rectum	17·0 (12·0–21·0)	19·5 (14·5–24·0)	0·001
Lower rectum	20·0 (16·0–23·8)	22·0 (17·5–27·0)	0·032
Missing data	112/666 (17%)	64/326 (20%)	..
Distance to distal resection margin (cm)			
Total group	3·0 (2·0–4·8)	3·0 (1·8–5·0)	0·676
Upper rectum	3·5 (2·0–5·0)	3·5 (2·1–5·0)	0·644
Middle rectum	2·5 (1·5–4·0)	2·5 (1·5–4·0)	0·733
Lower rectum	3·8 (2·0–5·0)	3·5 (1·5–5·0)	0·617
Missing data	48/666 (7%)	16/326 (5%)	..
Number of harvested lymph nodes			
Total group	13·0 (10·0–18·0)	14·0 (10·0–19·0)	0·085
Upper rectum	15·0 (11·0–20·0)	15·0 (12·0–22·0)	0·359
Middle rectum	14·0 (10·0–18·0)	14·0 (11·0–19·0)	0·205
Lower rectum	12·0 (7·0–16·0)	13·0 (7·0–16·0)	0·724
Missing data	16/699 (2%)	4/345 (1%)	..
Pathology stage			0·367
I	231/681 (34%)	107/342 (31%)	..
II	180/681 (26%)	91/342 (27%)	..
III	233/681 (34%)	125/342 (37%)	..
IV	4/681 (<1%)	0	..
No residual tumour (complete remission)†	29/412 (7%)	17/199 (9%)	0·660
No residual tumour, positive lymph node†	4/412 (<1%)	2/199 (1%)	..
Missing data	18/699 (3%)	3/345 (<1%)	..

Data are n/N (%) or median (IQR). CRM=circumferential resection margin. *Denominator was the number of patients without complete remission. †Denominator was the number of patients who received preoperative radiation therapy.

Table 4: **Pathology**

Guillou and colleagues[14] noted positive CRMs in 12% of patients after laparoscopic anterior resection for cancer whereas only 6% of patients after open surgery had positive margins. However, at 3-year follow-up after surgery, local recurrence rates were similar: 7·8% in the laparoscopic surgery group versus 7·0% in the open surgery group.[15] In the COLOR II study, rates of positive CRMs after surgery for cancer located in the upper portion of the rectum were similar between groups, although at macroscopic assessment seven specimens after laparoscopic surgery were judged incomplete and only one was judged incomplete after open surgery (table 4). The higher rate of macroscopically incomplete specimens in the laparoscopic surgery group could be due to lacerations caused by grasping the mesorectum with forceps.

In this study, the rate of positive CRMs after laparoscopic resection of rectal cancer located within 5 cm from the anal verge was lower than that with open surgery (table 4). Three-quarters of patients with lower rectal cancer had an APR, in accordance with an earlier report about Scandinavian data.[16] In the CLASICC trial,[14] the occurrence of positive margins was 20% after laparoscopic and 27% after open APR. Nagtegaal and colleagues[17] reported positive CRMs (defined as tumour within 1 mm of the CRM) in 26·5% of patients with cancer of the distal 5 cm of the rectum after open surgery. In patients who had APRs in the COREAN trial,[7] positive margins were reported in 5·3% in the laparoscopic surgery group and 8·3% in the open surgery group. The lower rate of positive margins after laparoscopic resection of cancer of the lower rectum in the COLOR II trial could be attributed to improved visualisation of the lower pelvis by the laparoscope, which provides the entire surgical team with a magnified and well illuminated image of the surgical field, allowing a more radical resection.

The median distal resection margin was 3 cm in both groups, which is well above the minimally required margin of 2 cm in surgery for rectal cancer.[18] Proximal resection margins of 5 cm suffice and, hence, the difference that was noted between the proximal margin of 16 cm after laparoscopic resection and that of 19 cm after open surgery is of no clinical relevance.

Few data were missing, with the exception of those for tumour distance from CRM (10%) and proximal resection margin (18%; table 4), which did not significantly differ between treatment groups. The amount of missing data differed significantly between centres, but there was no significant association with the tumour stage (data not shown). Two patients with distal-third cancers had partial mesorectal excisions, but this was presumably a recording error.

Unplanned intraoperative conversions from laparoscopic to open surgery are a measure of the feasibility of the procedure. Conversion rates of 30% and higher were reported in earlier studies[8,14] in which the role for laparoscopic surgery in patients with rectal cancer was questioned. In the COLOR II trial, 114 (16%) of 695 laparoscopic surgeries were intraoperatively converted; this percentage is similar to the most recent data and therefore acceptable.[19]

In this first report of clinical outcomes of the COLOR II trial, laparoscopic surgery was associated with less blood loss, a longer operating time, less use of epidural analgesia, earlier restoration of bowel function, and reduction of the hospital stay. These findings are similar to those in other trials including the COLOR trial in which the outcomes of laparoscopic and open surgery were compared in patients with colonic cancer and seem to be associated with reduced surgical trauma.[5,13,20,21] Inclusion of pelvic abscesses in clinically evident anastomotic leakages resulted in a higher rate of leakages than those that did not include pelvic abscesses (13% in the laparoscopic group and 10% in the open surgery group; table 3). These percentages are in the same range as those in the CLASICC trial[14] (7% and 10%, respectively) whereas lower frequencies were reported by Kang[7] and Morino[21] and their colleagues.

Hospital stay in the COLOR II trial was similar to that in the COREAN trial and several days shorter than in the CLASICC trial.[7,14] Enhanced recovery protocols were not used routinely. The value of such protocols in patients after surgery for rectal cancer requires further study.

Urinary continence and sexual function, both dependent on preservation of the autonomic pelvic nerves, are important aspects of quality of life. These adverse events were recorded in the COLOR II trial 1 year after the index surgery and will be reported with the long-term outcomes. Other quality-of-life analyses will be undertaken and presented separately.

One of the limitations of the COLOR II trial was the lack of standardisation of perioperative protocols because it was not feasible in a study undertaken at 30 centres and hospitals in eight countries. Preoperative radiotherapy was administered to almost two-thirds of patients in both groups, and preoperative chemotherapy was administered to a third of patients in both groups. These findings indicate that perioperative protocols had been applied equally to both groups. However, other variables—eg, bowel preparation and postoperative dietary measures—were not documented, and therefore the value of enhanced recovery programmes cannot be assessed in this study. Another limitation of this study was that MRI, which is the imaging modality of choice in patients with rectal cancer, was not mandated at the time of design of the protocol in 2003. Quality-of-care debates focus on surgical expertise and necessary yearly volumes of specific procedures. In the COLOR II trial, surgical competency was assessed on the basis of review of recorded images or live observations of laparoscopic TME surgeries. The quality of open surgery was not confirmed. Accreditation was done by centre instead of by individual surgeon. Surgery requires a team approach generally and certainly in complex disease such as rectal cancer. In all participating centres and hospitals,

Panel: Research in context

Systematic review

In 2008, Kuhry and colleagues[22] published a Cochrane systematic review of randomised controlled trials about the long-term outcome of laparoscopic surgery in patients with colorectal cancer. We searched Cochrane Library, Medline, Embase, and CancerLit for published and unpublished randomised controlled trials of laparoscopic (or laparoscopically assisted) and open surgery in patients with non-metastasised colorectal cancer that were undertaken in 1991–2005. Results were reported for six trials in patients with rectal cancer; however, we concluded that the numbers of available studies and patients included were too small to draw any reliable conclusions.

Interpretation

Our study is, to the best of our knowledge, the first large randomised trial of the comparison of laparoscopic surgery and open surgery in patients with rectal cancer. Our results show that in selected patients treated by skilled surgeons, laparoscopic surgery resulted in similar safety, resection margins, and completeness of the resection to those of open surgery, and in-hospital recovery was improved after laparoscopic surgery. Long-term results are necessary to determine the definitive role of laparoscopic surgery in this group of patients.

management of patients with rectal cancer was discussed and decided by multidisciplinary teams. Most surgeries in this trial (86%) were done by surgeons who did both laparoscopic and open surgery for rectal cancer. Therefore, we think that the findings of this trial represent an assessment of laparoscopic versus open procedures rather than a comparison of surgeons for the two procedures. Numbers of patients included in the COLOR II trial varied substantially between centres because of differences in numbers of patients with rectal cancer per year per centre and varying times of entry into the trial. Hence, the findings of the COLOR II trial seem to represent a cross-section of hospitals with expertise in laparoscopic surgery for rectal cancer. The effects of the amount of surgery on operating time and conversion rate will be analysed, as will health economics, for later presentation.

COLOR II, to our knowledge, is the largest randomised trial in which laparoscopic and open surgeries were compared in patients with rectal cancer (panel). However, of note, the patients in this trial do not represent the entire population with rectal cancer presenting at the participating hospitals because of the exclusion of patients with T3 rectal cancer within 2 mm from the endopelvic fascia or T4 cancers. Therefore, the findings in this study are not applicable to all patients with rectal cancer.

In conclusion, in selected patients treated by skilled surgeons, laparoscopic resection of rectal cancer provided oncological radicality, using the pathology report as a proxy, similar to open surgery. In-hospital recovery after laparoscopic surgery was better than after open surgery. Long-term follow-up to assess local recurrence and survival is necessary to ascertain oncological safety of laparoscopic resection in patients with rectal cancer. Analysis of local recurrences will be started mid 2013.

Contributors

MHGMvdP wrote the report, and gathered and analysed the data. MAC wrote the report and participated in the trial design. AF wrote the report. EH and AML wrote the report and participated in the trial design. WJCH wrote the report and analysed the data. HJB wrote the report, designed and coordinated the study, and was the principal investigator.
Writing committee: Martijn H G M van der Pas, Miguel A Cuesta, Alois Fürst, Eva Haglind, Antonio M Lacy, Wim J C Hop, and Hendrik J Bonjer.
Protocol committee: Hendrik J Bonjer, Eva Haglind, Wim J C Hop, Miguel A Cuesta, Antonio M Lacy, Willem A Bemelman, Johan F Lange, and Lars Påhlman.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

Funding for the study was provided by Ethicon Endo-Surgery Europe (Hamburg, Germany), Swedish Cancer Foundation (2010/593), West Gothia Region, Sahlgrenska University Hospital (ALF grant 138751). We thank Karen Inglis, Kevin Druhan, Dalhousie University, Halifax, Canada, and Mark Buunen, Erasmus MC Rotterdam, Netherlands, for coordinating the trial and gathering and processing data.

References

1 International Agency for Research on Cancer. GLOBOCAN 2008. http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900#BOTH (accessed Dec 1, 2012).
2 Micheli A, Mugno E, Krogh V, et al. Cancer prevalence in European registry areas. *Ann Oncol* 2002; **13:** 840–65.
3 Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg* 1982; **69:** 613–16.
4 Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007; **246:** 693–701.
5 The COlon cancer Laparoscopic or Open Resection Study Group. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6:** 477–84.
6 The Colon Cancer Laparoscopic or Open Resection Study Group. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009; **10:** 44–52.
7 Kang SB, Park JW, Jeong SY, 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.
8 Ng SS, Leung KL, Lee JF, et al. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. *Ann Surg Oncol* 2008; **15:** 2418–25.
9 Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.
10 Quirke P. Limitations of existing systems of staging for rectal cancer. In: Soreide O, Norstein J, eds. Rectal cancer surgery: optimisation, standardisation, documentation. Berlin: Springer-Verslag, 1997: 63–81.
11 Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; **26:** 350–57.
12 Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010; **147:** 339–51.

13 Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002; **235:** 449–57.

14 Guillou PJ, Quirke P, Thorpe H, 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.

15 Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic–assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; **25:** 3061–68.

16 Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Soreide O. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. *Dis Colon Rectum* 2004; **47:** 48–58.

17 Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P. Low rectal cancer: a call for a change of approach in abdominoperineal resection. *J Clin Oncol* 2005; **23:** 9257–64.

18 Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Nat Cancer Inst* 2001; **93:** 583–96.

19 Ohtani H, Tamamori Y, Azuma T, et al. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and conventional open surgery for rectal cancer. *J Gastrointest Surg* 2011; **15:** 1375–85.

20 The Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; **350:** 2050–59.

21 Morino M, Parini U, Giraudo G, Salval M, Brachet CR, Garrone C. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. *Ann Surg* 2003; **237:** 335–42.

22 Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a Cochrane systematic review of randomised controlled trials. *Cancer Treat Rev* 2008; **34:** 498–504.