ORIGINAL ARTICLE

COLOR II

A randomized clinical trial comparing laparoscopic and open surgery for rectal cancer

The COLOR II study group

Principal investigators: H.J. Bonjer, A.M. Lacy.

Protocol committee: A.M. Lacy, H.J. Bonjer, E. Haglind, J.F. Lange, A. D'Hoore, G. Kurlberg, W.C.J. Hop, E. Kuhry.

Statistician: W.C.J. Hop.

Writing committee: M. Buunen, H.J. Bonjer, W.C.J. Hop, E. Haglind, G. Kurlberg, J. Rosenberg, A.M. Lacy, M.A. Cuesta, A. D'Hoore, A. Fürst, J.F. Lange, P. Jess, O. Bulut, P. Poornoroozy, K. Juul Jensen, M. Mark Christensen, E. Lundhus, H. Ovesen, D. Birch, I. Iesalnieks, C. Jäger, M. Kreis, Y. van riet, E. van der Harst, M.F. Gerhards, W.A. Bemelman, B.M.E. Hansson, P.A. Neijenhuis, H.A. Prins, C. Balague, E. Targarona, J.A. Luján Mompeán, J.D. Franco Osorio, F.J. Garcia Molina, S. Skullman, Z. Läckberg, U. Kressner, P. Matthiessen, S.H. Kim, A. Alfredo Poza.

Collaborators: Belgium: A. D'Hoore (Universitair Ziekenhuis Leuven). Canada: H.J. Bonjer, K. Inglis (Dalhousie University, Halifax). Denmark: P. Jess, O. Bulut (Hilleröd Hospital); J. Rosenberg (Gentofte Amtssygehus); P. Poornoroozy (Esbjerg Hospital); M. Mark Christensen (Aalborg Hospital). Germany: A. Fürst (Caritas Krankenhaus St Josef Regensburg); I. Iesalnieks (University Hospital Regensburg); C. Jäger (Marien Hospital Stuttgart); M. Kreis (Ludwigs Maximilians University Hospital Großhadern). the Netherlands: J.F. Lange, M. Buunen, J. Jeekel (Erasmus MC Rotterdam); E. van der Harst, P.P.L.O. Coenen (MCRZ Rotterdam); M.A. Cuesta (VU Medical Center Amsterdam); M.F. Gerhards (OLVG Amsterdam); W.A. Bemelman (AMC Amsterdam); J.J. Jakimowicz, Y.E.A. van Riet (Catharina Ziekenhuis Eindhoven); B.M.E. Hansson, C. Rosman (Canisius Wilhelmina Ziekenhuis Nijmegen); P.A. Neijenhuis, A.J. den Outer (Rijnland Ziekenhuis Leiderdorp); H.A. Prins (Jeroen Bosch Ziekenhuis's Hetogenbosch). Spain: E.M. Targarona, C. Balague (Hospital de Sant Pau Barcelona); A.M; Lacy, S. Delgado (Hospital Clinic i Provincial Barcelona); J. Luján Mompeán (Arrixaca Hospital Universitario Murcia); F.J. Garcia Molina (Hospital SAS de Jerez). Sweden: S. Skullman (Skövde Hospital), E. Haglind, G. Kurlberg (Sahlgrenska University Hospital Göteborg), Z. Läckberg (Uddevalla Hospital), L. Påhlman (Uppsala Hospital); U. Kressner (Danderyds Hospital); P. Matthiessen (Orebro Hospital). Korea: S.H. Kim (Korea University Anam Hospital).

Correspondence: M. Buunen, Department of Surgery, Dalhousie University, QE II Health Sciences Center, Victoria Building Room 8-838, 1278 Tower Road, Halifax, NS B3H 2Y9, Canada.

E-mail: mbuunen@color2.org

Dan Med Bull 2009;56:89-91

ABSTRACT

Introduction: Laparoscopic resection of rectal cancer has been proven efficacious but morbidity and oncological outcome need to be investigated in a randomized clinical trial. Trial design: Non-inferiority randomized clinical trial.

Methods: The COLOR II trial is an ongoing international randomized clinical trial. Currently 27 hospitals from Europe, South Korea and Canada are including patients. The primary endpoint is loco-regional recurrence rate three years post-operatively. Secondary endpoints cover quality of life, overall and disease free survival, post-operative morbidity and health economy analysis.

Results: By July 2008, 27 hospitals from the Netherlands, Belgium, Germany, Sweden, Spain, Denmark, South Korea and Canada had included 739 patients. The intra-operative conversion rate in the laparoscopic group was 17%. Distribution of age, location of the tumor and radiotherapy were equal in both treatment groups. Most tumors are located in the mid-rectum (41%).

Conclusion: Laparoscopic surgery in the treatment of rectal cancer is feasible. The results and safety of laparoscopic surgery in the treatment of rectal cancer remain unknown, but are subject of interim analysis within the COLOR II trial. Completion of inclusion is expected by the end of 2009. Trial registration: Clinicaltrials.gov, identifier: NCT00297791 (www.clinicaltrials.gov).

Laparoscopic colectomy for cancer is associated with less postoperative pain, earlier restoration of bowel function and shorter hospital stay [1, 2]. Various randomized clinical trials have provided evidence that cancer free survival after laparoscopic resection of colonic cancer does not differ from survival after open colectomy [3-5].

The current standard in surgery for rectal cancer is complete atraumatic removal of the mesorectum, total mesorectal excision (TME) [6]. Several groups have demonstrated that laparoscopic total mesorectal excision can be done safely [7-9]. These single centre studies reported favorable morbidity rates and low recurrence rates. However, randomized clinical trials are required to evaluate the role of laparoscopic rectal cancer surgery and to assess oncological outcomes.

The COLOR (COlorectal cancer Laparoscopic or Open Resection) II trial has been designed to investigate short- and long-term outcomes of laparoscopic and open surgery for rectal cancer.

PATIENTS AND METHODS

ELIGIBILITY

A total of 1275 consecutive patients scheduled for rectal cancer surgery will be included in the COLOR II trial. Patients suitable for elective surgical resection, with a solitary rectal cancer observed at colonoscopy or at barium enema X-ray are eligible. The distal border of the tumor must be within 15 cm of the anal verge at rigid rectoscopy or distally to the conjugate line at CT or MRI. Imaging of liver and chest must be available to exclude distant metastases. Staging of the tumor must be performed before pre-operative radiotherapy is administered. Informed consent is mandatory and must comply with the requirements of the local ethics board.

Exclusion criteria are T1 tumors which can be treated by local excision, T3 tumors with a margin smaller than 2 mm from the endopelvic fascia and tumors staged as T4, malignancies other than adenocarcinoma at cytological or histological examination, patients under the age of 18 years or presenting with signs of acute intestinal obstruction as well as the presence of a secondary colorectal tumor. Other causes of exclusion are medical history of Familial Adenomatosis Polyposis Coli, Hereditary Non-Polyposis Colorectal Cancer, active Crohn's disease, active colitis ulcerosa or malignancies other than rectal carcinoma, absolute contra-indications to general anesthesia or prolonged pneumoperitoneum (ASA > III), synchronous abdominal or colon surgery and pregnancy. No adenocarcinoma found or local invasion of the uterus and/or vagina at operation is a pre-fixed exclusion criterium.

Hospitals participating in the COLOR II trial keep track of all patients presenting with rectal cancer. Data on patients who are not included in the COLOR II trial are registered.

RANDOMIZATION

Once eligibility is established and patient details have been logged, the patient will be allocated to either laparoscopic or open surgery. The trial design involves allocation of all suitable consecutive patients with rectal carcinoma to either of the two procedures at a randomization ratio of 2:1 in favor of the laparoscopic procedure, on the basis of a computer generated list (www.color2.org). This randomization list is stratified for participating centre, pre-operative radiotherapy (yes or no) and the location of the tumor. The location of the tumor is defined as within 0-5 (low), 5-10 (mid) or 10-15 (high) cm from the anal verge, assessed at rigid rectoscopy, CT or MRI. When patients are not subjected to the allocated treatment modality, analysis will be performed on an intention-to-treat basis. Data will be collected centrally at the coordinating centre at Dalhousie University in Halifax, Canada.

SURGICAL PROCEDURE

To ensure quality control, a feasibility study is performed at each participating centre. The unedited images of five consecutive laparo-

scopic TME's are captured. These images are accompanied by anonymous pathology reports, operation reports and letters of discharge, the videos will be sent to the coordinating centre for review by a monitoring committee.

Laparoscopic dissection of the mesorectum is mandatory to qualify the procedure as a "laparoscopic TME". The level of transection of the inferior mesenteric artery is up to the surgeon's preference. Both right and left hypogastric nerves should be preserved. The splenic flexure should be mobilized when undue tension at the anastomosis is likely. Other aspects of the surgical procedure such as type of anastomosis, use of diverting ileostomy and drainage of surgical field are up to the discretion of the surgeon.

FOLLOW-UP

Every year, up to seven years after surgery, medical history and physical examination are recorded. Three years after index surgery, imaging of the chest, liver, colorectum and pelvis is performed to assess distant and local recurrences. Imaging at other times during follow-up is up to the discretion of the surgeon. Recurrences should be reported to the coordinating centre within two weeks. Follow-up of patients with recurrent disease should be until three years after diagnosis of the recurrence. Interim analyses will be performed by a monitoring committee each time that 20 recurrences have been reported in the combined groups.

ENDPOINTS

The primary endpoint of this study is the loco-regional recurrence rate three years after index surgery. Secondary endpoints are survival free of cancer recurrence, overall survival, distance of the tumor to the endopelvic fascia and the distal resection margin, portsite and wound-site recurrences, distant metastases rate, 28-days or in-hospital operative mortality and morbidity and macroscopic evaluation of the resected specimen. Pathological staging is performed according to the TNM classification (AJCC Cancer Staging Manual, 2002). Quality of life endpoints are duration of in-hospital-stay, duration of absence of work, post-operative health related quality of life (assessed by usage of EORTC-QLQ-C30, -CR38, VAS and EuroQol-5D). Cost and cost-effectiveness analyses will be performed on a national basis.

STATISTICAL ANALYSIS

Loco-regional recurrence rates at three years post resection of rectal cancer staged as T1, T2 or T3 is estimated to be 10%. The primary objective of the study is to show that laparoscopic surgery is not associated with an increased loco-regional recurrence rate. Non-inferiority of laparoscopic surgery is considered to be shown if the resulting two-sided 95% confidence limits of the difference in 3-yrs loco-regional recurrence rates exclude a difference greater than 5% in favor of the open procedure. At a randomization ratio of 2:1, and assuming a recurrence rate of 10% in each group, 850 laparoscopic patients and 425 open patients are required to generate a power of 80% for this study. All analyses will be carried out on an "intention to treat" basis: patients, whose randomized laparoscopic operation was converted to an open resection, will be analyzed in the laparoscopic group. In hospital mortality, pathological resection margins and complication rates will be compared using the Chi-square test. Locoregional recurrence rate, disease free survival and overall survival will be compared between the two procedures using Cox-regression, with participating center as covariate. Exploratory analysis of the prognostic effects of various baseline data will be done using multivariate Cox-regression.

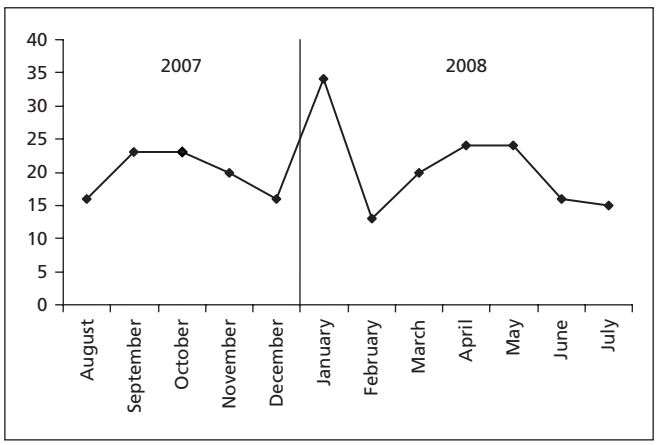

Figure 1. Monthly accrual rates in the Color II study.

Table 1. Baseline characteristics.

	Laparoscopic (n=487)	Open (n=252)
F/M ratio	0.64	0.56
Age, years*	67 (34-94)	67 (32-91)
ASA		
I	28%	21%
II	56%	63%
III	16%	15%
BMI (kg/m²)*	26	26
Location of the tumor		
High	35%	35%
Mid	40%	41%
Low	25%	24%
Radiotherapy	56%	56%
Conversion rate	17%	n.a.

*) Avarage and range

TRIAL REGISTRATION

The trial has been registered at www.clinicaltrials.gov, with identifier: NCT00297791.

RESULTS

By January 2008, 27 centers in six countries in Europe, one in Canada and one in South Korea have randomized 739 patients; 487 were randomized in the laparoscopic group and 252 patients in the open group. The current accrual rate is about 25 patients per month (see Figure 1).

The distribution of American Society of Anesthesiologists (ASA) classification was 26% in ASA I, 58% in ASA II and 16% in ASA III. The distribution of the location of the tumor was as follows: 257 patients (35%) had a high rectum tumor, 300 patients (41%) had a midrectum and 182 patients (25%) had a low rectum tumor; 415 patients (56%) received pre-operative radiotherapy (Table 1).

22% of patients with a high rectum tumor, 71% of patients with a mid-rectum tumor and 80% patients with a low rectum tumor received pre-operative radiotherapy. Intra-operative conversion rate was 17%.

DISCUSSION

Colorectal cancer is a common disease affecting over 20,000 men and women in Europe (or Denmark) [10]. Despite improvements in pre-operative staging and adjuvant chemotherapy and radiation therapy, surgery remains the cornerstone of the treatment of rectal cancer. The traditionally poor prognosis associated with rectal cancer was mainly caused by local recurrences and distant metastases. Several prognostic factors have been identified like histological grade, type of tumor, vascular and perineural invasion. However the completeness of the resection is key in the treatment of colorectal cancer to prevent local recurrence and prolong survival [11].

Local recurrences of rectal cancer originate from direct spread through veins and lymphatic vessels draining the rectum resulting in tumor deposits in lymph nodes discontinuous from the main growth [12]. In 1982, based on anatomical studies Heald et al introduced the Total Mesorectal Excision technique (TME) [6]. By re-

secting the rectum with all its surrounding fatty tissue and the perirectal lymph nodes enveloped by the thin parietal fascia, local recurrence rates dropped from 30-40% to 5-15%. With accumulating evidence of substantial reductions of recurrence rates and overall survival, TME has been widely adopted by surgeons as the surgical treatment of choice for rectal cancer.

After the introduction of laparoscopic surgery for colorectal cancer in 1991 several large randomized clinical trials comparing laparoscopic and open resection for colonic cancer show advantages of laparoscopic surgery [2-5]. Short-term benefits such as less post-operative pain, shorter hospital stay, an earlier return to daily activities and a comparable disease free survival have secured the role of laparoscopic surgery in treatment of malignant disease.

Pioneers have shown feasibility of laparoscopic resection of rectal cancer [7-9]. Feasibility and afore mentioned short-term benefits for colon cancer have been proven to be of value in rectal cancer. Other outcomes such as operating time, anastomotic dehiscence and post-operative infections did not differ between open and laparoscopic surgery. Reported conversion rates ranges widely between 3% and 27%. Endpoints such as sexual- and urinary dysfunction have been the subject of research in several trials. These frequently reported morbidities after TME are caused by unintentional injury to the autonomic plexus. The limited workspace in the pelvis makes it technically challenging to operate on the rectum. The advantages of the laparoscope such as up-close and magnified view may facilitate identification of autonomic nerves and a complete nerve sparing resection.

But most importantly these studies show an equal oncological clearance after laparoscopic and open surgery. Circumferential resection margins are comparable between groups as is the number of lymph nodes harvested during surgery. However all of these studies are single-center studies. The necessity to assess the long-term oncological outcome in a multi-center international clinical trial is clear.

Currently 27 centers participate in the COLOR II trial. The average monthly accrual rate exceeds 25 patients. Centers with expertise in laparoscopic surgery, which are interested to join the COLOR II trial, are encouraged to contact the coordinator of the COLOR II trial (www.color2.org).

ACKNOWLEDGEMENTS

Supported by grants from Ethicon Endo-Surgery (Europe) GmbH, Norderstedt, Germany.

References

1. Kuhry E, Bonjer HJ, Haglind E et al. Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer. Surg Endosc 2005;19:687-92.
2. Veldkamp R, Kuhry E, Hop WC et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
3. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-9.
4. Bonjer HJ, Hop WC, Nelson H et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg 2007;142:298-303.
5. Lacy AM, Garcia-Valdecasas JC, Delgado S et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-9.
6. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? Br J Surg 1982;69:613-6.
7. Morino M, Parini U, Giraudo G et al. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. Ann Surg 2003;237:335-42.
8. Poulin EC, Schlachta CM, Gregoire R et al. Local recurrence and survival after laparoscopic mesorectal resection forrectal adenocarcinoma. Surg Endosc 2002;16:989-95.
9. Anthuber M, Fuerst A, Elser F et al. Outcome of laparoscopic surgery for rectal cancer in 101 patients. Dis Colon Rectum 2003;46:1047-53.
10. Marrett L DD, Logan H, Mery L et al. Canadian Cancer Statistics 2007. Canadian Cancer Society/National Cancer Institute of Canada, 2007.
11. Gosens MJ, Klaassen RA, Tan-Go I et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. Clin Cancer Res 2007;13:6617-23.
12. Wang C, Zhou ZG, Wang Z et al. Mesorectal spread and micrometastasis of rectal cancer studied with large slice technique and tissue microarray. J Surg Oncol 2005;91:167-72.