

COLOR: A Randomized Clinical Trial Comparing Laparoscopic and Open Resection for Colon Cancer

The COLOR Study Group

Key Words

Laparoscopy · Colorectal cancer · Multicenter · Randomized trial

Abstract

Background: Laparoscopic surgery has proven to be safe and effective. However, the value of laparoscopic resection for malignancy in terms of cancer outcome can only be assessed by large prospective randomized clinical trials with sufficient follow-up. **Methods:** COLOR (COlon carcinoma Laparoscopic or Open Resection) is a European multicenter randomized trial which has started in September 1997. In 24 hospitals in Sweden, The Netherlands, Germany, France, Italy and Spain, 1,200 patients will be included. The primary end point of the study is cancer-free survival after 3 years. **Results:** Within <2 years, more than 540 patients have been randomized for right hemicolectomy (45%), left hemicolectomy (10%) and sigmoidectomy (45%). 33 patients (6%) were excluded after randomization. The accrual rate is approximately 25 patients/month. Current survival rates for the whole study group are: stage I: 95%, stage II: 98%, stage III: 93%, stage IV: 64%. For all patients with stage I disease, the mortality was not cancer related. **Conclusions:** Although laparoscopic surgery appears of value in colo-

rectal malignancy, results of randomized trials have to be awaited to determine the definitive place of laparoscopy in colorectal cancer. Considering the current accrual rate, the COLOR study will be completed in 2002.

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Introduction

Laparoscopy has improved surgical treatment of various diseases due to its limited surgical trauma. After its implementation for laparoscopic cholecystectomy, minimally invasive techniques have been established for other surgical procedures such as: fundoplication, appendectomy, splenectomy and (donor) nephrectomy. However, one of the controversial topics in laparoscopic surgery remains laparoscopic resection of colorectal malignancy. Although early experiences with laparoscopic colorectal resection showed that laparoscopy was technically feasible and improved patient comfort, the application of laparoscopic surgery for malignancy has been restricted to few centers. Reports of tumor recurrence at port sites after laparoscopic resection of colorectal cancers have caused major concern among surgeons [1, 2]. As a consequence, many abandoned or did not adopt the laparoscopic approach in patients with colorectal malignancy. Until now,

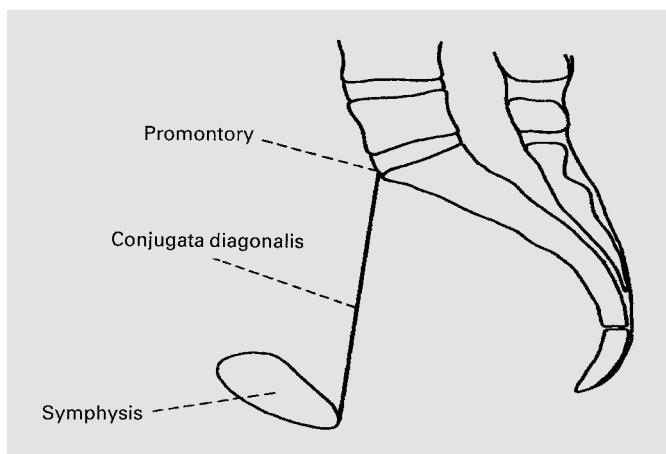


Fig. 1. Location of rectosigmoid tumor. Patients can be included when the tumor is situated cranially to the line from the promontory to the lower margin of the symphysis (conjugata diagonalis) on a lateral image of a barium enema study. Tumors at or caudally to this line are not eligible.

the pathogenesis of port site recurrences has not yet been clarified, and with growing data on reduced morbidity after laparoscopic resection of colorectal cancer, controversy persists. Unfortunately, the available trials assessing the value of laparoscopy in colorectal cancer lacked sufficient statistical power due to small numbers of patients or had a short follow-up period which did not allow proper evaluation [3, 4]. The debate whether laparoscopy should be employed in oncologic colorectal surgery can only be addressed by large-scale prospective randomized trials. In this article, we present the design and current status of the COLOR (Colon carcinoma Laparoscopic or Open Resection) trial, a European multicenter randomized trial which started in September 1997.

Patients and Methods

Eligibility

In the COLOR trial, 1,200 patients will be randomized for either laparoscopic or open colorectal resection. Patients who are eligible for a curative cancer resection by means of right hemicolectomy, left hemicolectomy or sigmoidectomy can be included. Strong suspicion of colon carcinoma at colonoscopy or on barium enema suffices for inclusion in the COLOR trial. In case of a polyp, a colonoscopic biopsy must have proven invasive carcinoma to allow entry into the trial. For rectosigmoid tumors, patients can be included, if the tumor is cranial to the line from the promontory to the symphysis (conjugata diagonalis) on a lateral image of a barium enema study (fig. 1). Exclusion criteria are metastases, synchronous or previous malignancies (except for adequately treated basocellular carcinoma of the skin or

in situ carcinoma of the cervix uteri), obesity (body mass index $>30 \text{ kg/m}^2$) and pregnancy. More extensive surgery or signs of acute intestinal obstruction are other factors prohibiting participation. Also, if preoperatively invasion of adjacent structures is apparent, patients are not considered eligible. Patients with lesions of the transverse colon and lesions which require resection of the splenic flexure are not included in this study. Patients requiring (low) anterior resection or abdominoperineal resection of the rectum are not eligible. Finally, in all patients informed consent must be obtained according to local standards. Patients which are eligible, but refuse participation, will receive a conventional resection.

Randomization

Once eligibility has been confirmed, the patient will be allocated to either laparoscopic or conventional resection. Randomization will be performed by computerized random numbers at time of randomization. Randomizations will be balanced and stratified for participating center and proposed type of resection. Operative treatment should be within 14 days following randomization. Randomization is performed by sending a fax with patient details to the coordinating center in Rotterdam.

Surgical Procedure

To ensure quality control, a colorectal procedure can only be performed if one member of the operating team has experience with at least 20 procedures. Standardization of laparoscopic technique is pursued by organizing live demonstrations and computerized demonstrations of laparoscopic colorectal resections by participating surgeons.

Alternative techniques, such as gasless laparoscopy or hand-assisted laparoscopy, are allowed within the COLOR trial. The use of a pneumatic sleeve for operating with an intra-abdominal hand is allowed, but should be documented in the case record forms.

Follow-Up

For the COLOR trial, follow-up will continue for 5 years. Minimal requirements are follow-up visits at 1, 2, 4 and 5 years after surgery. At 3 years after surgery, either colonoscopy or barium enema should be performed to exclude cancer recurrence at the anastomosis or de novo malignancies. In addition, imaging studies of lungs and liver are necessary to exclude metastases. Follow-up of patients with recurrent disease will continue at least 3 years after diagnosis of recurrence.

End Points

The primary end point of the study is cancer-free survival after 3 years. Secondary end points include early and late postoperative morbidity, cancer recurrences at port sites, differences in quality of life and costs. Resection margins and number of harvested lymph nodes are compared through documented pathology reports. Pathological staging will be performed according to the TNM classification.

Quality of Life Studies and Costs

Quality of life and cost studies are being performed on a national basis. Quality of life is being studied in participating centers in The Netherlands. Visual analogue scores and questionnaires are used as instruments for quality of life measurement. In all participating centers analgetic medication used during the first 3 postoperative days is registered.

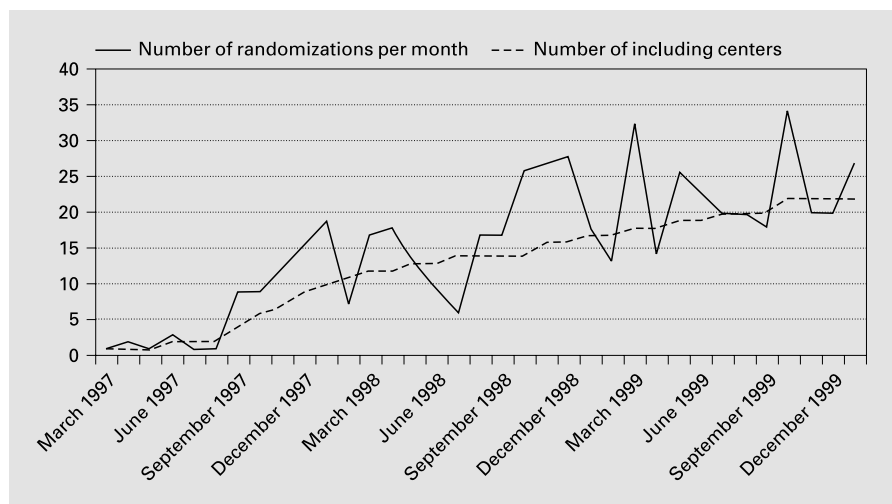


Fig. 2. Number of participating centers and randomizations per month.

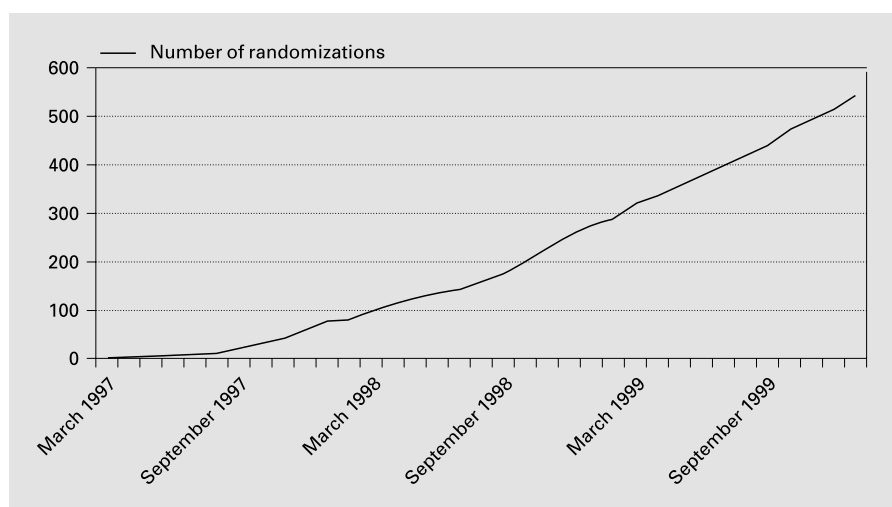


Fig. 3. Current accrual for the COLOR trial.

Statistical Analysis

For statistical analysis an equal distribution between stage of disease and early recurrences is anticipated for both treatment arms. The disease-free survival after 3 years for a selected group of stage I–III patients is currently about 70–75%. To detect a difference of 7% in disease-free survival rate after 3 years between open and laparoscopic colorectal cancer resection, 1,200 patients will be included. All analyses will be carried out on an ‘intention-to-treat’ basis: patients in whom the laparoscopic operation was converted to an open resection will be analyzed in the laparoscopic group. Cancer-free survival, overall survival and local recurrence rates will be compared between the two treatment arms using log-rank statistics and will be stratified by participating centers. Analysis of the primary end point will be performed after inclusion of all patients. Interim analyses will be performed after the first 50, 100 and 200 recurrences. If an obvious difference in recurrence rate between the two treatment arms appears during the inclusion phase of the trial, accrual of patients will be stopped.

Results

At present, 24 centers in six European countries are participating in the COLOR trial (table 1). Until March 2000, 546 patients have been enrolled by these centers. The current accrual rate of the study is 25 patients per month (fig. 2, 3). Thirty-three patients were excluded after randomization because they refused participation (n = 2), required urgent surgery (n = 4), were inoperable (n = 4), or no malignancy was found after pathological examination (peridiverticulitis: n = 4, adenoma: n = 15, no tumor: n = 4).

The distribution of randomized procedures was as follows (table 2): right hemicolectomy: 45%, left hemicolectomy: 10%, sigmoidectomy: 45%. The mean age of the enrolled population was 70 years. The ASA classification

Table 1. Participating Centers in the COLOR trial

Sweden
Kärnsjukhuset, Skövde
Sahlgrenska University Hospital, Göteborg
University Hospital Uppsala
Huddinge University Hospital
Centrallassarettet Västerås
Norrlands University Hospital, Umeå
University Hospital Linköping
S:t Görans Hospital, Stockholm
Mälarsjukhuset, Eskilstuna
Malmö University Hospital
Östersund Sjukhus
Uddevalla Hospital
The Netherlands
University Hospital-Dijkzigt, Rotterdam
St.Clara Hospital, Rotterdam
Rijnstate Hospital, Arnhem
Catharina Hospital, Eindhoven
Free University Hospital, Amsterdam
Italy
University Hospital Turin
Spain
University Hospital Barcelona
Hospital Jerez de la Frontera, Cádiz
Germany
University Hospital Lübeck
Zentralkrankenhaus, Bremen Ost
University Hospital Hamburg-Eppendorf
France
Louis-Mourier Hospital, Colombes

is: ASA I: 29%, ASA II: 55% and ASA III: 16%. Pathological examination reports showed the following distribution of stages of disease: stage I: 25%, stage II: 39%, stage III: 33% and stage IV: 3%. 34 months after start of the trial, the overall recurrence rate is 4%. Current survival rates for the whole study group are: stage I: 95%, stage II: 98%, stage III: 93 %, stage IV: 64%. For all patients with stage I disease, the mortality was not cancer related.

Discussion

Several studies have reported the occurrence of wound metastases after laparoscopic resection of colorectal cancers. As a consequence, many surgeons have been reluctant to adopt the laparoscopic approach for malignant disease, because it could have an adverse effect on cancer outcomes. Experimental studies were undertaken to un-

Table 2. Current accrual in the COLOR trial

Randomized patients	546	
Exclusions	33	
Inclusions	513	
Mean age, years	70	
Gender, % females	46	
ASA, %		
I	29	
II	55	
III	16	
Randomized procedures, %		
Right hemicolectomy	45	
Left hemicolectomy	10	
Sigmoidectomy	45	
Procedures performed	Laparoscopic	Open
Right hemicolectomy	96	92
Left hemicolectomy	23	24
Sigmoidectomy	79	80
Other	12	20
Stage distribution, %		
I	25	
II	39	
III	33	
IV	3	

ravel the pathogenesis of port site recurrences [5, 6]. Tumor cell seeding by gas turbulence (e.g., the 'chimney effect', referring to leakage of CO₂ alongside trocars causing a high local gas flow at trocar sites) and aerosolization of tumor cells have been proposed as causative factors [7–9]. Also, manipulation of the resected bowel segment through the wound and contamination of instruments appear to be of significance. Initially, the first reports of port site metastases mentioned extremely high incidences, sometimes as high as 21% [1]. However, recent series of laparoscopic resections of colon cancers report incidences of 1% and lower [10, 11]. Apparently the incidence of port site metastases after laparoscopy for colorectal malignancy depends greatly on experience and skill of the surgical team. For the COLOR trial, participating surgeons must have experience with more than 20 laparoscopic colorectal resections. In addition, selection of patients is of paramount importance. Tumors which show invasion of adjacent structures or severe obesity prompt an open approach.

The controversy in treatment of colon cancer by means of laparoscopy has not withheld surgeons from applying this technique. However, the general opinion of surgeons is that colorectal cancer procedures should only be performed within the context of clinical trials [12].

Table 3. Randomized clinical trials investigating laparoscopic versus open resection for colon carcinoma

Country	Name of study	Principal investigator	Start date	Target accrual	Status (March 2000)
USA	NIH trial	H. Nelson	1994	1,200	715
Great Britain	CLASSIC	P.J. Guillou	1996	1,000	± 400
Australia	–	P.J. Hewett	1998	1,200	?
Germany	LAPKON	B. Böhm	1998	1,200	± 100
Spain	–	A.M. Lacy	1993	250	completed

In recent years, several randomized clinical trials on laparoscopic colorectal cancer resection have started (table 3). Many of these studies share the same aim: defining cancer outcome, technical feasibility, quality of life and cost aspects. Results from these studies will possibly allow a powerful meta-analysis to be performed in due time. Nevertheless, all of these trials encounter the importance of statistical power necessitating large patient numbers.

The interest of European surgeons in the COLOR trial is still growing, and with the current accrual rate in mind, it is expected that a first analysis will be performed within 3 years. Results from this study and similar studies around the world will determine the definitive place of laparoscopy for colorectal cancer resection.

Acknowledgement

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Appendix

Collaborators

The following centers are participating in the COLOR trial:

Sweden: S. Skullman (Skövde), E. Haglind, S. Nordgren (Göteborg), L. Pahlman (Uppsala), B. Anderberg, M. Janson (Huddinge), K. Smedh (Västerås), Å. Öberg, O. Lundberg (Umeå), P.-O. Nyström, A. Kald (Linköping), J. Dalén, I. Svedberg (Stockholm), R. Hellberg (Eskilstuna), P. Magnell (Malmö), G. Edlund (Östersund), U. Kressner (Uddevalla).

The Netherlands: H.J. Bonjer, E.J. Hazebroek, Ph. Wittich, G. Kazemier, J. Jeekel (coordinating center, Rotterdam), J.F. Lange (Rotterdam), E.J. Spillenaar Bilgen, I.M.C. Janssen (Arnhem), J.J. Jakimowicz (Eindhoven), M.A. Cuesta, F.J. Berends (Amsterdam).

Italy: M. Morino, G. Giraudo (Turin).

Spain: A.M. Lacy, S. Delgado, J.C. García Valdecasas (Barcelona), J. Medina Diez (Jerez).

Germany: O. Schwandner, T.H.K. Schiedeck (Lübeck), I. Baca, J. Weiss (Bremen Ost), Ch. Bloechle (Hamburg).

France: S. Msika (Colombes).

Invited Commentary

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The preceding is not really a scientific manuscript per se, but a current 'state-of-the-trial' progress report on the 'laparoscopic surgery for colon cancer trial' that has been ongoing for some time. To date, more than 500 patients have been entered. It is, however, still early in terms of patient accrual and follow-up, especially considering that the trial was only begun in 1997 and that the median time to recurrence for most patients with recurrent colon cancer is 18 months postoperatively. It is commendable that the authors are recruiting approximately 25 patients per month from 24 hospitals. The goal is to accrue 1,200 patients.

There are several laparoscopic surgery trials that are slowly nearing completion. The next 2 years should be particularly interesting for the practicing surgeon, as results from these trials become available. It is likely that, if carefully performed, laparoscopic surgery for colon cancer will be an adequate cancer operation as compared

with open procedures. The proviso, however, is that these procedures are performed *carefully*, with attention to proper oncologic approach and surgical technique.

Today, in the era of instant information, it is particularly difficult for clinicians to create valid and well-designed clinical trials. I applaud the authors for constructing such a trial and for maintaining steady patient accrual from multiple centers. Such trials may be *far* more meaningful for the practicing surgeon than trials in which the majority of patients are accrued by two or three 'experts'. Trials such as this one will more accurately reflect 'real world' rather than tertiary referral center results. It is only by such trials and investigators that believable, reproducible information will be obtained. Carefully controlled clinical trials are necessary not only for laparoscopic surgery, but also in the field of reflux surgery, surgery for morbid obesity, recurrent colon cancer surgery, and in many other areas of digestive surgery.