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SURGICAL ENDOSCOPY
and Other Interventional Techniques

COLOR

A randomized clinical trial comparing laparoscopic and open resection for colon cancer

The Color Study Group*

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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 that began in 1997. In 27 hospitals in Sweden, The Netherlands, Germany, France, Italy, Spain, and the United Kingdom, 1200 patients will be included. The primary endpoint of the study is cancer-free survival after 3 years.
Results: In <3.5 years, >850 patients have been randomized for right hemicolectomy (47%), left hemicolectomy (11%), and sigmoidectomy (42%). Fifty seven patients were excluded after randomization. Forty six months after the start of the trial, the overall recurrence rate is 6.8%. The distribution of stage of disease is as follows: stage I, 25%; stage II, 41%; stage III, 32%; stage IV, 2%.
Conclusion: Although laparoscopic surgery appears to be of value in the treatment of colorectal cancer, the final, results of randomized trials need to be considered to determine its definitive role. Given the current accrual rate, the COLOR study will be completed in 2002.

Key words: Laparoscopy — Colorectal cancer — Multicenter randomized trial — Cancer

Laparoscopic surgery is now considered to be an integral part of the surgeon's armamentarium. After the widespread acceptance of laparoscopic cholecystectomy, minimally invasive techniques were established for other surgical procedures such as fundoplication, appendectomy, splenectomy, and nephrectomy. However, one of the most controversial areas in laparoscopic surgery is the resection of colorectal cancer. Although early experiences with laparoscopic colorectal resection showed that laparoscopy was a technically feasible procedure that reduced morbidity, the application of laparoscopic surgery to cancer has been restricted to few centers. Reports of tumor recurrence at port sites after the laparoscopic resection of colorectal cancers have raised major concerns [1, 10]. As a consequence, many surgeons abandoned or rejected the laparoscopic approach in patients with colorectal cancer. Although the incidence of port site metastases now appears to be far lower than initially suggested, controversy persists. The available randomized studies on laparoscopy in colorectal cancer involved small numbers of patients or had a short follow-up, rendering proper evaluation impossible [6, 7]. Ultimately, the equestion of whether laparoscopy should be employed in oncologic colorectal surgery can only be addressed by a large prospective randomized trial. In this article, the design and current status of the COLOR trial (COlon carcinoma Laparoscopic or Open resection), a European multicenter randomized trial that started in 1997, are presented.

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*A list of participants is presented at the end of this article

Methods

Eligibility

In the COLOR trial, 1200 patients will be randomized to undergo 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. Solitary colon carcinoma observed at colonoscopy or on a barium enema study 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 located cranial to a line drawn between the sacral promontory

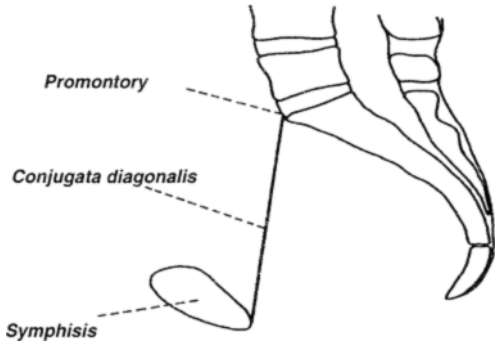

Fig. 1. Location of rectosigmoid tumor. For rectosigmoid tumors, patients can be included if the tumor is located cranial to a line drawn between the sacral promontory and the symphysis pubis (=conjugata diagonalis) on a lateral image of a barium enema study. Tumors at or caudally to this line are not eligible.

and the symphysis pubis 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 kg/m^2), and pregnancy. More extensive surgery or signs of acute intestinal obstruction are other factors prohibiting participation. Chest radiograph and abdominal ultrasound are considered routine measures to investigate pulmonary or liver metastases, respectively. Although a preoperative computed tomography (CT) scan of the abdomen may be preferred, this is not required by the study protocol. The employed preoperative evaluation of metastases is documented in the case record forms. Also, if invasion of adjacent structures is apparent preoperatively, patients are not considered eligible. Lesions of the transverse colon and lesions that 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 who are eligible but refuse participation will receive a conventional resection.

Randomization

Once eligibility has been confirmed, the patient will be allocated to undergo either laparoscopic or conventional resection. Randomization will be performed by computerized random numbers at the 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. Participating surgeons are required to specify by ICD-10 classification which of their patients with colon carcinoma were not eligible for randomization in the COLOR trial.

Surgical procedure

To ensure quality control, a colorectal procedure can only be performed if one member of the operating team has experience with more than 20 procedures. Standardization of laparoscopic technique is pursued by organizing live demonstrations and computerized demonstrations of laparoscopic colorectal resections by participating surgeons. Surgeons are required to specify which of the following steps were performed laparoscopically: mobilization of the bowel, ligation of the artery, transsection of the bowel, resection of the bowel, and anastomosis.

Alternative techniques, such as gasless laparoscopy or hand-assisted laparoscopy, are allowed within the COLOR trial. The use of a pneumo-sleeve for operating with an intraabdominal hand is allowed, but should be documented in the case record forms. In addition, the location and size of incision must be mentioned.

Table 1. Participating Centers of COLOR trial

Country	Center
Sweden	Kärnsjukhuset, Skövde
	Sahlgrenska University Hospital, Göteborg
	University Hospital Uppsala
	Huddinge University Hospital
	Centrallassarettet Västerås
	Norrlands University Hospital, Umeå
	University Hospital Linköping
	St. Göran Hospital, Stockholm
	Mälarsjukhuset, Eskilstuna
	Malmö University Hospital
	Östersunds Sjukhus
	Uddevalla Hospital
The Netherlands	University Hospital–Dijkzigt, Rotterdam
	St. Clara Hospital, Rotterdam
	Rijnstate Hospital, Arnhem
	Catharina Hospital, Eindhoven
	Free University Hospital, Amsterdam
	Medical Center, Leeuwarden
Italy	University Hospital Turin
Spain	Hospital Clínic i Provincial de Barcelona
	Hospital Jerez de la Frontera, Cádiz
Germany	University Hospital Lübeck
	Zentrallkrankenhaus, Bremen Ost
	University Hospital Hamburg–Eppendorf
France	Louis Mourier Hospital, Colombes
	Hospital de Montargis, Amilly
United Kingdom	Ninewells Hospital and Medical School, Dundee

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. The frequency of follow-up is low because in Scandinavian countries people may live at great distance from their hospital.

During the first 2 years after surgery, CT scans or ultrasonography for evaluation of recurrent disease are performed according to the surgeon's preference. However, 3 years after surgery, either colonoscopy or barium enema should be performed to exclude cancer recurrence at the anastomosis or de novo malignancy. Furthermore, imaging studies of lungs and liver are necessary to exclude metastases. Recurrences should be reported by fax to the co-ordinating center within 2 weeks of detection. Follow-up of patients with recurrent disease will continue until death.

Endpoints

The primary endpoint of the study is cancer-free survival after 3 years. Secondary endpoints include early and late postoperative morbidity, cancer recurrences at port sites, disease-free and overall survival after 5 years, 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, analgesic medication used during the first 3 postoperative days is registered.

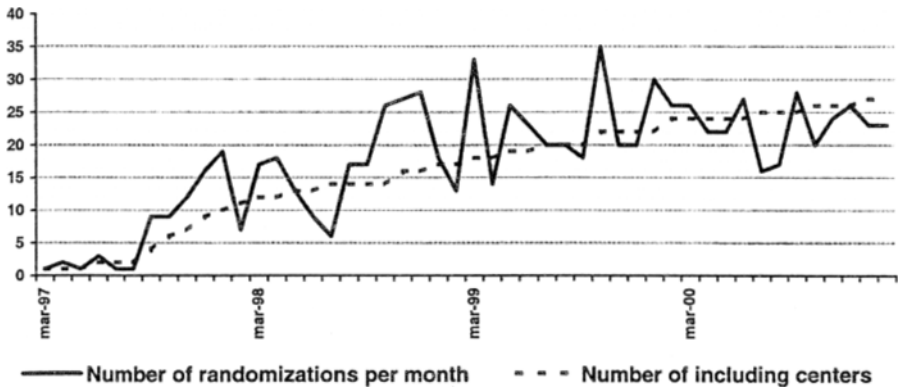

Fig. 2. Number of participating centers and randomizations per month.

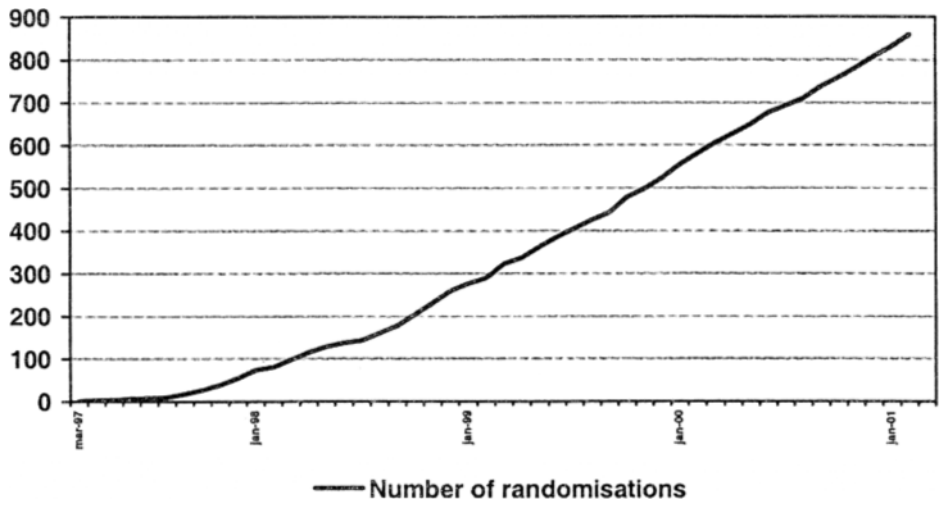

Fig. 3. Current accrual of COLOR trial.

Statistical analysis

For statistical analysis, an equal distribution between stage of disease and early recurrences is anticipated for both treatment arms. Disease-free survival after 3 years for a selected group of stage I–III patients is currently 70–75%. To detect a difference of 7% in disease-free survival rate after 3 years between open and laparoscopic colorectal cancer resection, 1200 patients will be included. All analyses will be earned 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 center. Analysis of the primary endpoint 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.

Table 2. Current accrual and patient data for COLOR trial

Randomized patients	859
Exclusions	57
Inclusions	802
Mean age (yr)	70
Gender (% females)	47
ASA I (%)	29
ASA II (%)	55
ASA III (%)	16
Randomized procedures	
Right hemicolectomy (%)	47
Left hemicolectomy (%)	11
Sigmoidectomy (%)	42
Conversion rate (%)	16.7
Stage distribution	
Stage I (%)	25
Stage II (%)	41
Stage III (%)	32
Stage IV (%)	2

Results

At present, 27 centers in seven European countries are participating in the COLOR trial (Table 1). By March 2001, 859 patients had been enrolled by these centers. The current accrual rate of the study is ~25 patients per month. (Figs. 2, and 3). Fifty seven patients were excluded after randomization because they refused participation (n = 5), required urgent surgery (n = 4), were inoperable (n = 10), had inadequate preoperative work up (n = 6), or no malignancy was found after pathological examination (peridiverticulitis: n = 3, adenoma: n = 22, no tumor: n = 7).

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

Country	Name of study	Principal investigator	Start date	Target accrual	Status (March 2001)
USA	NIH trial	H. Nelson	1994	1200	850
Great Britain	CLASSIC	P. J. Guillou	1996	1000	± 550
Australia	—	P. J. Hewett	1998	1200	± 100
Germany	LAPKON	B. Böhm	1998	1200	± 200
Spain	—	A. M. Lacy	1993	250	Completed

The distribution of randomized procedures was as follows (Table 2): right hemicolectomy, 47%; left hemicolectomy, 11%; sigmoidectomy, 42%. The mean age of the enrolled population was 70 years. The American Society of Anesthesiologists (ASA) classification is as follows: ASA I, 29%; ASA II, 55%; and ASA III, 16%. In 68 cases, (16.7%) laparoscopic resection of a colon carcinoma was converted to a laparotomy. Pathological examination reports showed the following distribution of stage of disease: stage I, 25%; stage II, 41%; stage III, 32%; stage IV, 2%. At 46 months after the start of the trial, the overall recurrence rate is 6.8%. Stage distribution for recurrent disease was 7% for stage I, 30% for stage II, and 63% for stage III.

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 they feared a worse cancer survival. Experimental studies were undertaken to unravel the pathogenesis of port site recurrences [2, 11]. Tumor cell seeding by gas turbulence (e.g., the chimney-effect, by which the leakage of carbon dioxide alongside trocars causes a high local gas flow at trocar sites) and aerosolization of tumor cells have been proposed as causative factors [5, 9, 11]. In addition, manipulation of the resected bowel segment through the wound and the contamination of instruments appear to be significant factor. Early reports of port site metastases cited extremely high incidences, sometimes as high as 21% [1]. However, in recent series of laparoscopic resections of colon cancers, the incidence has been 1% and lower [3, 4]. Apparently, the incidence of port site metastases after laparoscopy for colorectal cancer depends greatly on the 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, the selection of patients is of paramount importance. Patients with tumors that show invasion of adjacent structures or severe obesity require an open approach.

Hand-assisted laparoscopy has been allowed in this study since several surgeons employ this technique for a variety of disorders, particularly large pathology such as large spleens or colonic cancer. Furthermore, the incision required for hand-assisted laparoscopic colon resection may be used to facilitate extraction of the bowel segment.

Three-year disease-free survival was chosen as a primary endpoint because it has been shown that most recurrences in patients with colon carcinoma occur during the first 3 years after resection [8]. In addition, secondary endpoints include disease-free and overall survival after 5 years.

The controversy over the treatment of colon cancer by means of laparoscopy has not stopped surgeons from applying this technique. However, the general opinion of surgeons is that laparoscopic colorectal cancer procedures should be performed only within the context of clinical trials [12]. In recent years, several randomized clinical trials on laparoscopic colorectal cancer resection have started (Table 3). Many of these studies share the same aims: defining cancer outcome, technical feasibility, quality of life, and cost aspects. Results from these studies should allow a powerful meta-analysis to be performed in due time.

Considering the current accrual rate of the COLOR trial, this study will be completed by the end of 2002. Results of the COLOR study and similar studies will determine the definitive place of laparoscopic techniques in curative resections of cancer of the colon.

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Collaborators

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