REVIEW ARTICLE

Laparoscopically Assisted vs Open Colectomy for Colon Cancer

A Meta-analysis

*Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group**

Objective: To perform a meta-analysis of trials randomizing patients with colon cancer to laparoscopically assisted or open colectomy to enhance the power in determining whether laparoscopic colectomy for cancer is oncologically safe.

Data Sources: The databases of the Barcelona, Clinical Outcomes of Surgical Therapy (COST), Colon Cancer Laparoscopic or Open Resection (COLOR), and Conventional vs Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (CLASICC) trials were the data sources for the study.

Study Selection: Patients who had at least 3 years of complete follow-up data were selected.

Data Extraction: Patients who had undergone curative surgery before March 1, 2000, were studied. Three-year disease-free survival and overall survival were the primary outcomes of this analysis.

Data Synthesis: Of 1765 patients, 229 were excluded, leaving 796 patients in the laparoscopically assisted arm and 740 patients in the open arm for analysis. Three-year disease-free survival rates in the laparoscopically assisted and open arms were 75.8% and 75.3%, respectively (95% confidence interval [CI] of the difference, –5% to 4%). The associated common hazard ratio (laparoscopically assisted vs open surgery with adjustment for sex, age, and stage) was 0.99 (95% CI, 0.80-1.22; *P* = .92). The 3-year overall survival rate after laparoscopic surgery was 82.2% and after open surgery was 83.5% (95% CI of the difference, –3% to 5%). The associated hazard ratio was 1.07 (95% CI, 0.83-1.37; *P* = .61). Disease-free and overall survival rates for stages I, II, and III evaluated separately did not differ between the 2 treatments.

Conclusion: Laparoscopically assisted colectomy for cancer is oncologically safe.

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***Authors/Writing Committee:** The following individuals constitute the Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group and take authorship responsibility for the study: H. Jacob Bonjer, MD; Wim C. J. Hop, PhD; Heidi Nelson, MD; Daniel J. Sargent, PhD; Antonio M. Lacy, MD; Antoni Castells, MD; Pierre J. Guillou, MD; Helen Thorpe, MSc; Julia Brown, MSc; Salvadora Delgado, MD; Esther Kuhrij, MD; Eva Haglind, MD; Lars Påhlman, MD.

Group Information: Author affiliations are listed at the end of this article.

A SUCCESSFUL LAPAROscopic sigmoidectomy for cancer was reported in 1991 by Jacobs et al.[1] Reports of port-site metastases observed after laparoscopic removal of colon cancer and other malignant neoplasms caused serious concern among surgeons and halted the rapid adoption of minimally invasive surgery for colon cancer.[2,3] Trials randomizing patients with colon cancer to laparoscopically assisted surgery or open resection were initiated simultaneously in Europe and in North America to evaluate the oncological safety of laparoscopic colectomy. The survival data from the Barcelona trial[4] and from the Clinical Outcomes of Surgical Therapy (COST) study[5] were published in 2002 and 2004, respectively. Because of low numbers of patients, the confidence intervals (CIs) of these trials were too wide to rule out clinically relevant survival differences between laparoscopic and open colectomy for cancer.[6] The long-term survival data of the Colon Cancer Laparoscopic or Open Resection (COLOR)[7] and Conventional vs Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (CLASICC)[8] trials are not yet available.

We aimed to enhance the power in determining whether laparoscopic colectomy for cancer is oncologically safe. Therefore, a meta-analysis was conducted of the Barcelona, COST, COLOR, and CLASICC trials.

METHODS

IDENTIFICATION OF TRIALS

Randomized clinical trials comparing laparoscopic and open surgery for colon cancer were identified by systematic PubMed search and by random search of abstracts presented at international meetings. Only trials with a primary end point of survival that accrued more than 150 patients with colon cancer overall were included. The Barcelona (evaluated by A.M.L, A.C., and S.D.), COST (H.N. and

Table 1. Details of Trials According to Consolidated Standards for Reporting of Trials (CONSORT) Criteria

Detail	Barcelona Trial[4]	COST Trial[5]	COLOR Trial[7]	CLASICC Trial[8]
Intervention allocation	Randomization 1 d before surgery, 1:1 ratio	Randomization before surgery, 1:1 ratio	Randomization before surgery, 1:1 ratio	Randomization before surgery, 2:1 laparoscopic-open ratio
Eligibility	Colon cancer ≥15 cm from anal verge, written informed consent	Colon adenocarcinoma, age >17 y, absence of prohibitive abdominal adhesions, written informed consent	Cancer of left or right colon, age >17 y, written informed consent	Cancer of colon or rectum, written informed consent
Objective	Show difference in cancer-related survival <15%	Noninferiority trial	To exclude a difference of 7.4% or more in 3-y disease-free survival	Comparison of short-term end points to predict long-term outcome
Primary outcomes	Cancer-related survival	Time to tumor recurrence	Cancer-free survival 3 y after surgery	Positivity rates of circumferential and longitudinal resection margins, in-hospital mortality
Sample size	n = 208, α = .05, β = .20	n = 1735, 1-sided $P<.09$ in favor of open colectomy, would declare open colectomy superior	n = 1248, 95% Confidence intervals, 80% power	n = 794, Confidence intervals of 10% around differences
Randomization sequence generation	Site of primary tumor	Site of primary tumor, American Society of Anesthesiologists score, surgeon	Site of primary tumor	Site of primary tumor, presence of liver metastases, surgeon, preoperative radiotherapy
Randomization allocation concealment	Sealed opaque envelopes, computer generated	Central telephone	Central telephone	Central telephone
Randomization implementation	Single center (Spain)	48 Centers (United States and Canada)	29 Centers (Sweden, the Netherlands, Spain, Italy, France, United Kingdom, Germany)	27 Centers (United Kingdom)
Blinding	Not blinded	Not blinded	Not blinded	Not blinded
Statistical methods	Log-rank test	1-Sided log-rank test	2-Sided log-rank test	Pearson product moment correlation, χ^2 test, Fisher exact test
Recruitment	November 1993 to July 1998	August 1994 to August 2001	March 1997 to March 2003	July 1998 to July 2002
No. analyzed	n = 219, Intention to treat	n = 872, Intention to treat	n = 1248, Intention to treat	n = 794, Intention to treat and actual treatment
Outcomes	Laparoscopic resection superior in stage III	Similar rate of recurrent cancer	Not published	Not published

Abbreviations: CLASICC, Conventional vs Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer; COLOR, Colon Cancer Laparoscopic or Open Resection; COST, Clinical Outcomes of Surgical Therapy.

D.J.S.), COLOR (H.J.B., W.C.J.H., E.K., E.H., and L.P.), and CLASICC (P.J.G., H.T., and J.B.) trials fit these criteria.

TRIAL DESIGNS

All trials had been approved by ethics committees. The trial designs are summarized in **Table 1**.

The Barcelona trial (November 1993 to July 1998) enrolled patients with colon cancer at least 15 cm above the anal verge.[4] Exclusion criteria were past colon surgery, distant metastasis, intestinal obstruction, adjacent organ invasion, and cancers located at the transverse colon. Procedures were performed by a single surgical team. In the Barcelona trial, 219 patients were randomized, and 208 patients were included in survival analyses (exclusions included 11 patients with distant metastases).

In the COST trial (August 1994 to August 2001), patients who were pregnant or patients with familial polyposis, inflammatory bowel disease, rectal or transverse colon cancer, advanced local or metastatic disease, concurrent or previous malignant tumors, and acute bowel obstruction or perforation from cancer were excluded.[5] Forty-eight centers participated in the COST trial. Patients were randomly assigned to undergo laparoscopically assisted or open colectomy. In total, 872 patients were randomized and 863 patients were analyzed in the COST trial (exclusions included 1 patient with prostate cancer, 1 patient with distant metastasis, and 1 patient without institutional review board approval).

The COLOR trial (March 1997 to March 2003) excluded patients who were pregnant or patients with distant metastases, synchronous colon cancer, other malignant neoplasms, previous ipsilateral colon surgery, acute intestinal obstruction, invasion of adjacent organs, carcinomas located in the transverse colon or splenic flexure, and body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 30.[7] Twenty-nine centers from Western Europe participated in the trial. At the time of closure of entry of patients into the study, 1248 patients had been randomized to undergo laparoscopic or open colectomy for cancer.

In the CLASICC trial (July 1998 to July 2002), patients with synchronous adenocarcinomas, acute intestinal obstruction, cancer of the transverse colon, malignant neoplasm within the previous 5 years, or absolute contraindications to pneumoperitoneum were excluded from participation.[8] Patients were allocated using a 2:1 ratio to the laparoscopically assisted arm; 794 patients in total were recruited, 413 of whom had colon cancer.

META-ANALYSIS

An analysis of individual pooled data of 4 trials was performed. This meta-analysis was based on individual patient data focusing on overall and disease-free survival 3 years after randomization. The trial statisticians of the Barcelona, COST, COLOR, and CLASICC trials (W.C.J.H., D.J.S., A.C., H.T., and J.B.) operated under strict confidentiality conditions ruling that data of individual trials were only to be shared among the statisticians of the involved trials. The principal investigators of the 4 trials (H.J.B., H.N., A.M.L., and P.J.G.) only had access to the pooled summary data.

Patients with colon cancer who were randomized before March 1, 2000, within the context of the 4 trials and who had undergone curative surgery were included. The exclusion criteria in this meta-analysis were no surgery, absence of data, other carcinoma, irresectable tumor, presence of benign disease, withdrawn informed consent, and presence of distant metastases. All efforts were made to obtain complete data to at least 3 years after randomization. Disease-free survival and overall survival during the first 3 years following randomization were evaluated and compared between the 2 types of surgery. Follow-up after 3 years of randomization was censored. The following data were collected: age, sex, death, metastatic stage, tumor stage, date of surgery, date of last follow-up, date of randomization, unique patient identification number, 30-day postoperative or in-hospital mortality, involvement of margins of the resected specimens, treatment allocation (laparoscopically assisted or open), number of resected lymph nodes and lymph node stage, date and type (local, distant, or combined) of first tumor recurrence, and type of performed surgical procedure (laparoscopically assisted, conversion from laparoscopy to open, or open surgery). Tumor staging was based on the TNM staging criteria of the American Joint Committee on Cancer and International Union Against Cancer.[9]

Because some patients had open surgery after they had been randomized to laparoscopic surgery and vice versa, an analysis based on the randomized treatment and another analysis based on the received treatment were performed. Patients who underwent conversion to an open procedure remained in their allocated group for analyses. The numbers of patients excluded from the meta-analysis with the corresponding reasons for exclusion were provided for each trial to confirm that the study populations were similar among the 4 trials.

Disease-free survival was defined as time from randomization to death or recurrent disease. Disease-free survival and overall survival after randomization were assessed using the Kaplan-Meier method. Univariate comparisons between the 2 randomized procedures were performed using the log rank test. Multivariate analysis of these outcomes, including an assessment of heterogeneity of treatment effects among the 4 studies, was performed using a stratified Cox proportional hazards regression model that stratified by study and adjusted for sex, age, and stage. A comparison of the number of lymph nodes harvested during surgery was performed using analysis of variance. In this analysis, the number of lymph nodes was transformed logarithmically to obtain approximate normal distributions. The proportions of positive resection margins and postoperative mortality were compared between procedures using exact conditional logistic regression analysis with stratification by trial and included an assessment of heterogeneity of treatment effects. All P values were 2-sided, and $P<.05$ was considered the limit to denote statistical significance.

RESULTS

The total number of patients randomized before March 1, 2000, was 1765. Of these, 229 (13.0%) were excluded from this analysis, most for presence of distant metastases (46.3%) or benign colon disease (41.5%), with similar patterns in the laparoscopically assisted and open arms (**Figure 1**). Data for the remaining 1536 patients (208, 640, 520, and 168 patients in the Barcelona, COST, COLOR, and CLASICC trials, respectively) were analyzed. The laparoscopically assisted arm included 796 patients, and the open arm included 740 patients.

CHARACTERISTICS

Baseline characteristics were similar in the 2 treatment groups (Figure 1). The mean age was 69 years in both arms, and men were as frequently present as women in each treatment group. The stage distribution was similar in both arms. Stage I disease was present in 27.7%, stage II in 39.8%, and stage III in 31.3% of patients, while data were missing to determine the stage in 1.2% of patients.

The mean±SD number of lymph nodes found in the laparoscopically resected specimens was 11.8±7.4, while 12.2±7.8 lymph nodes were found in the specimens obtained in open colectomy. Analysis of variance showed that this was not significantly different ($P=.40$) and that the difference did not significantly vary among the 4 studies.

Data on resection margins were missing in 43 patients (who underwent 20 open and 23 laparoscopic colectomies). Positive resection margins were found in 2.1% of the specimens in the open arm and in 1.3% of the specimens in the laparoscopically assisted arm. This was not significantly different between the 2 groups (common odds ratio for open vs laparoscopically assisted surgery for positivity, 1.8; 95% CI, 0.7-4.5; $P=.23$).

Conversion of laparoscopic to open surgery occurred in 19.0% of patients. Postoperative mortality was 1.6% in the open arm and 1.4% in the laparoscopically assisted arm (common odds ratio for open vs laparoscopically assisted surgery, 1.3; 95% CI, 0.5-3.4; $P=.63$).

SURVIVAL

Analysis according to randomized treatment showed that disease-free survival ($P=.83$) and overall survival ($P=.56$) for all stages combined after laparoscopically assisted or open resection did not differ (**Figure 2**). Three-year disease-free survival in the open and laparoscopically assisted arms was 75.3% and 75.8%, respectively. The 95% CI of the difference (open minus laparoscopically assisted surgery) ranged from –5% to 4%. The corresponding figures for overall survival were 83.5% and 82.2%, respectively, with the 95% CI of the difference ranging from –3% to 5%.

For various reasons, 6 patients had laparoscopic surgery despite randomization to the open arm and 5 patients had open surgery instead of laparoscopic surgery. The results of the analysis of disease-free survival and overall survival based on the received treatment did not differ from the results of the analysis based on the randomized procedure.

Cox proportional hazards regression model analyses for disease-free survival and overall survival stratified by trial, adjusting for sex, age, and tumor stage, revealed no differences between the treatments (**Table 2** and **Table 3**). The

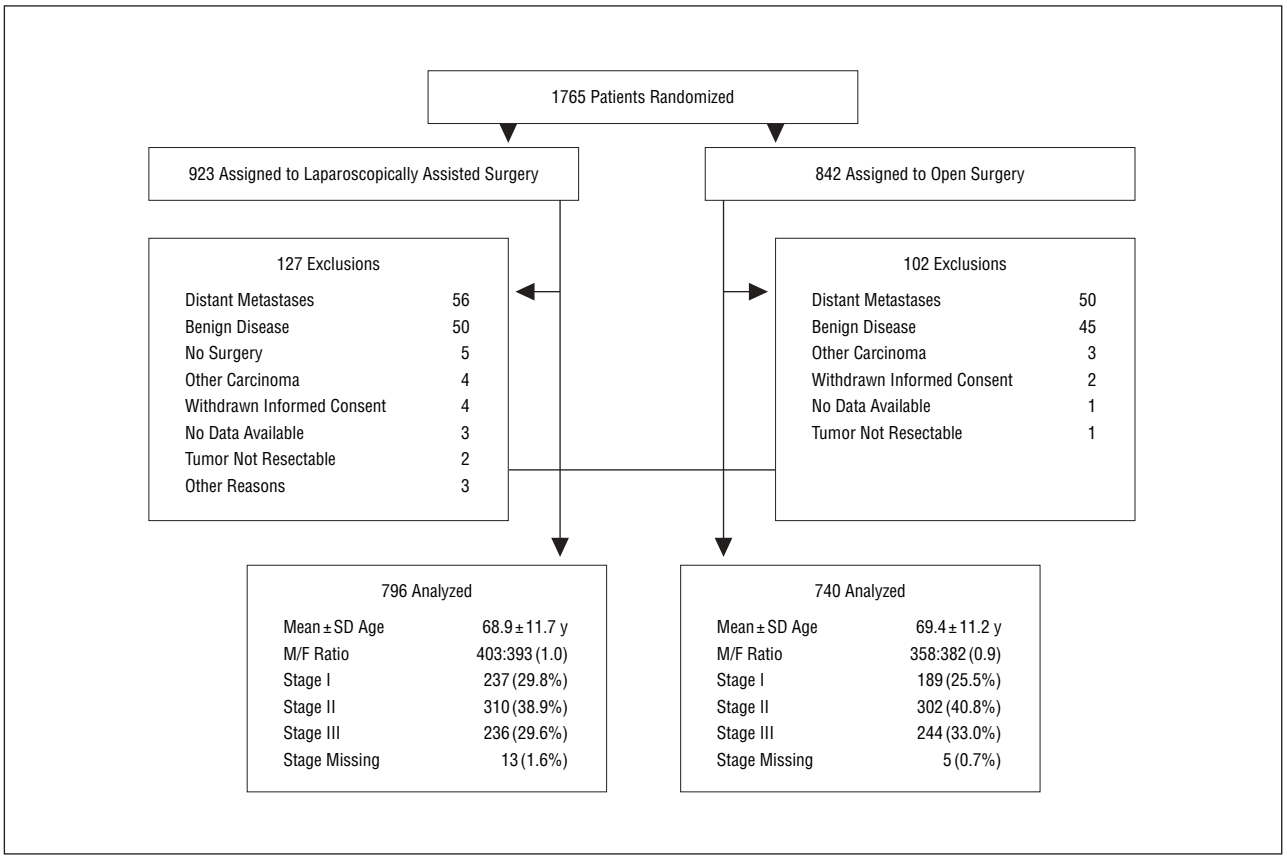

Figure 1. Patient characteristics.

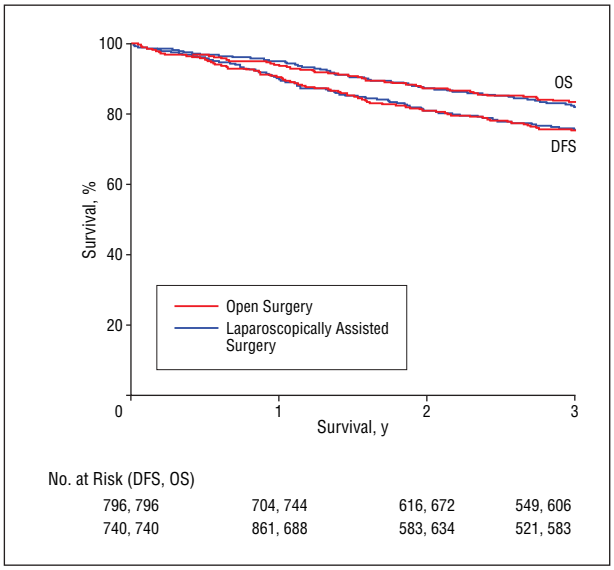

Figure 2. Disease-free survival (DFS) and overall survival (OS) according to randomized open surgery or laparoscopically assisted surgery. The numbers of patients at risk are shown at the bottom: the top row gives the numbers who underwent laparoscopically assisted surgery; the bottom row, open surgery.

treatment effects did not significantly differ among the trials for disease-free survival ($P=.38$) or for overall survival ($P=.35$). The hazard ratios for the 4 trials separately and the pooled common hazard ratios are shown in **Figure 3** for disease-free survival and for overall survival.

Table 2. Multivariate Analysis of Disease-Free Survival According to Various Factors*

Factor	Hazard Ratio (95% Confidence Interval)	*P* Value
Procedure†	0.99 (0.80-1.22)	.92
Stage II vs stage I	2.10 (1.50-2.94)	<.001
Stage III vs stage I	3.81 (2.75-5.28)	<.001
Female vs male	0.81 (0.66-0.99)	.04
Age >70 vs ≤70 y	1.27 (1.03-1.57)	.03

*Cox proportional hazards regression model with stratification by trial.
†Laparoscopically assisted vs open surgery.

Tumor recurrence was recorded in 234 patients (who underwent 121 open and 113 laparoscopic procedures). Of 121 recurrences in the open arm, 40 (33.1%) were local, 73 (60.3%) were distant metastases, and 8 (6.6%) were combined local and distant metastases; the corresponding figures in the laparoscopically assisted arm were 29 (25.7%), 74 (65.5%), and 10 (8.8%), respectively. These patterns did not significantly differ between the 2 treatment groups ($P=.43$, χ^2 test).

Disease-free survival and overall survival according to randomized treatment group by stage are shown in **Figure 4**. Significant differences between the 2 treatments were not found in any stages for disease-free survival ($P=.92$, $P=.44$, and $P=.53$ for stages I, II, and III, respectively); the associated hazard ratios (laparoscopically assisted vs open surgery) were 1.03 (95% CI, 0.58-

Table 3. Multivariate Analysis of Overall Survival According to Various Factors*

Factor	Hazard Ratio (95% Confidence Interval)	*P* Value
Procedure†	1.07 (0.83-1.37)	.61
Stage II vs stage I	1.89 (1.29-2.77)	<.001
Stage III vs stage I	2.88 (1.98-4.20)	<.001
Female vs male	0.72 (0.56-0.92)	.009
Age >70 vs ≤70 y	1.81 (1.40-2.34)	<.001

*Cox proportional hazards regression model with stratification by trial.
†Laparoscopically assisted vs open surgery.

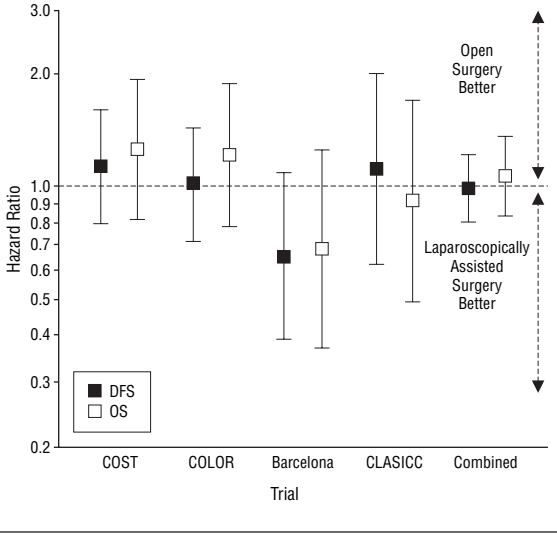

Figure 3. Hazard ratios (laparoscopically assisted surgery vs open surgery) with 95% confidence intervals regarding disease-free survival (DFS) and overall survival (OS) during the first 3 years after randomization according to study and for the 4 studies combined (adjusted for sex, age, and stage). Barcelona indicates Barcelona trial[4]; CLASICC, Conventional vs Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer trial[8]; COLOR, Colon Cancer Laparoscopic or Open Resection trial[7]; and COST, Clinical Outcomes of Surgical Therapy trial.[5]

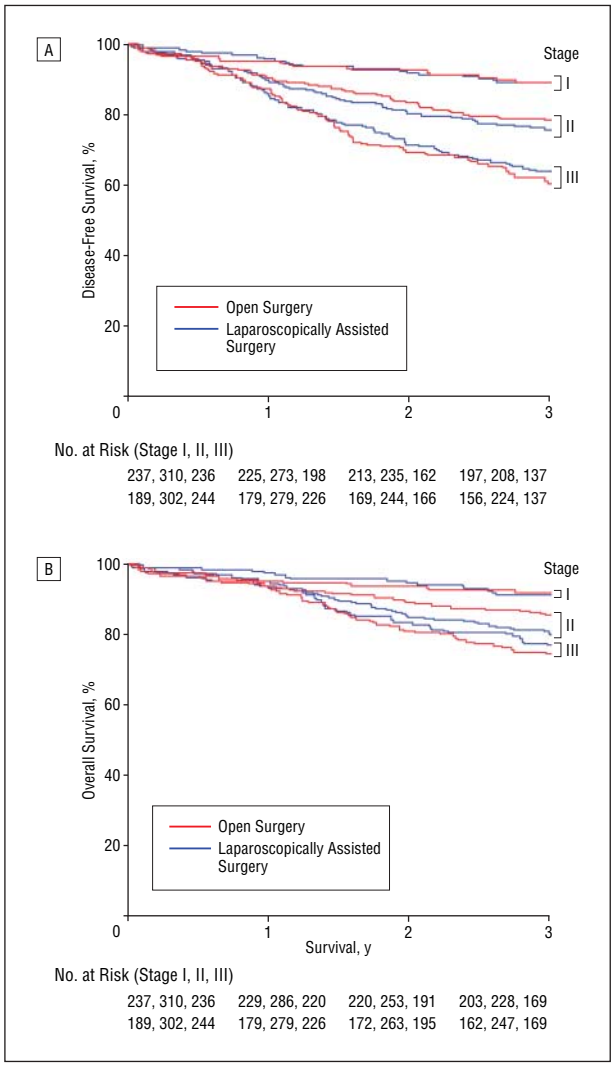

Figure 4. Disease-free survival (A) and overall survival (B) according to randomized procedure and stage. The numbers of patients at risk for each stage are shown at the bottom: the top row gives the numbers who underwent laparoscopically assisted surgery; the bottom row, open surgery.

1.85), 1.14 (95% CI, 0.82-1.60), and 0.91 (95% CI, 0.68-1.22), respectively. Overall survival was similar between the randomized procedures for all stages as well (*P*=.78, *P*=.09, and *P*=.52 for stages I, II, and III, respectively); the associated hazard ratios were 1.10 (95% CI, 0.57-2.14), 1.40 (95% CI, 0.95-2.07), and 0.89 (95% CI, 0.61-1.28), respectively.

COMMENT

Colorectal cancer annually affects more than 150 000 Europeans, while 100 000 colon resections are performed each year in the United States.[10] Aging of the Western population will increase the number of patients with colon cancer. Although adjuvant chemotherapy can improve survival of these patients, resection of the malignant colon tumor remains the only curative therapy. The surgical technique to resect colon cancer has undergone significant changes in the past decades. In the late 1960s, Turnbull et al[11] advocated no-touch techniques using early ligation of the mesocolic vessels and bowel and atraumatic manipulation of the tumor to avoid spreading tumor cells. The value of reducing surgical trauma in cancer was shown by Eggermont et al[12] in an experimental study. Tumor recurrence rates were found to be proportional to the extent of laparotomy wounds. The greatest advantage of laparoscopic surgery in comparison with open surgery is reduction of tissue trauma. Access to the peritoneal cavity is established through small incisions, manual retraction of viscera is avoided, and blood loss is minimal because of meticulous dissection facilitated by videoscopic magnification. Bouvy et al[13] showed in an experimental study that laparoscopic surgery was associated with less tumor recurrence than open surgery. After initial enthusiasm about laparoscopic colectomy for cancer in the early 1990s, reports of port-site metastases after laparoscopic resection of colon cancer withheld many surgeons from adopting this novel technique.[4] As a consequence, clinical trials randomizing patients with colon cancer to open or laparoscopic

resection were initiated in the mid 1990s simultaneously in North America and in Europe to evaluate the oncological safety of laparoscopic colectomy. In 2001, the principal investigators of the Barcelona, COST, COLOR, and CLASICC trials convened to explore pooling of data. Because long-term results from individual trials were not yet available, the incentive was to provide an early robust answer based on all available evidence to the question of whether laparoscopic resection of colon cancer is oncologically safe.

In 2002, Lacy et al[4] reported improved survival after laparoscopic colectomy in patients with stage III colon cancer after a median follow-up of 43 months. However, the outcome of this study was criticized because the total number of patients was low and the study involved a single high-quality laparoscopic center.[14] In 2004, the COST study group[5] reported similar disease-free survival after laparoscopically assisted or open colectomy for cancer at a median follow-up of 4.4 years. The COST study was a multicenter trial; therefore, the outcome was a better reflection of general surgical practice in North America. The CIs of the survival difference in the COST study were considered too wide, allowing for a 16% increased risk of death and an 11% increased risk of recurrence after laparoscopic colectomy.[6]

A possible limitation of this meta-analysis is that follow-up was censored at 3 years after surgery instead of at 5 years. However, 80% of recurrences of colon cancer occur in the first 3 years.[15] Sargent et al[15] noted in their review of data from almost 21 000 patients with colon cancer that the correlation between 3-year disease-free survival and 5-year overall survival was 0.89.

To our knowledge, this meta-analysis provides data on the largest population available to date across North America and Europe comparing long-term outcomes after laparoscopically assisted and open surgery for colon cancer. The present data originate from 48 institutions in North America and from 44 institutions in Europe. The CIs of the difference between open and laparoscopic colectomy for disease-free survival and overall survival were narrow in this meta-analysis, which allows a statement that laparoscopic colectomy for cancer is safe.

The results of these trials were produced by centers with expertise in laparoscopic colon surgery. Structured training in laparoscopic colon surgery is mandatory to reproduce these results in practices that have not yet adopted this novel technique.

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Author Affiliations: Departments of Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands (Drs Bonjer, Hop, and Kuhrij), Mayo Clinic, Rochester, Minn (Drs Nelson and Sargent), Hospital Clinic, University of Barcelona, Barcelona, Spain (Drs Lacy, Castells, and Delgado), University of Leeds, Leeds, England (Dr Guillou and Mss Thorpe and Brown), Goteborg University, Goteborg, Sweden (Dr Haglind), and University of Uppsala, Uppsala, Sweden (Dr Påhlman). Dr Bonjer is now with the Department of Surgery, Dalhousie University, and Capital Health, Halifax, Nova Scotia.
Correspondence: H. Jacob Bonjer, MD, Department of Surgery, Dalhousie University, and Capital Health, 1278 Tower Rd, Halifax, Nova Scotia, Canada B3H 2Y9 (jaap.bonjer@dal.ca).
Author Contributions: The trial statisticians of the Barcelona, COST, COLOR, and CLASICC trials (W.C.J.H., D.J.S., A.C., H.T., and J.B.) performed the meta-analysis in collaboration and had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Bonjer, Hop, Nelson, Castells, Guillou, Thorpe, Brown, Kuhrij, Haglind, and Påhlman. *Acquisition of data:* Bonjer, Hop, Castells, Guillou, Thorpe, Brown, and Kuhrij. *Analysis and interpretation of data:* Bonjer, Hop, Sargent, Lacy, Castells, Guillou, Thorpe, Brown, and Delgado. *Drafting of the manuscript:* Bonjer, Hop, Guillou, Brown, and Kuhrij. *Critical revision of the manuscript for important intellectual content*: Bonjer, Nelson, Sargent, Lacy, Castells, Guillou, Thorpe, Brown, Delgado, Haglind, and Påhlman. *Statistical analysis:* Hop, Sargent, Lacy, Castells, Thorpe, Delgado, and Haglind. *Obtained funding:* Bonjer and Guillou. *Administrative, technical, and material support:* Bonjer, Sargent, Guillou, and Kuhrij. *Study supervision:* Bonjer, Nelson, Sargent, Lacy, Guillou, Brown, Delgado, and Påhlman.
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