Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial.

Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial

Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ.

The Colon Cancer Laparoscopic or Open Resection Study Group

Summary

Background

Laparoscopic surgery for colon cancer has been proven safe, but debate continues over whether the available long-term survival data justify implementation of laparoscopic techniques in surgery for colon cancer. The aim of the COlon cancer Laparoscopic or Open Resection (COLOR) trial was to compare 3-year disease-free survival and overall survival after laparoscopic and open resection of solitary colon cancer.

Methods

Between March 7, 1997, and March 6, 2003, patients recruited from 29 European hospitals with a solitary cancer of the right or left colon and a body-mass index up to 30 kg/m^2 were randomly assigned to either laparoscopic or open surgery as curative treatment in this non-inferiority randomised trial. Disease-free survival at 3 years after surgery was the primary outcome, with a prespecified non-inferiority boundary at 7% difference between groups. Secondary outcomes were short-term morbidity and mortality, number of positive resection margins, local recurrence, port-site or wound-site recurrence, and blood loss during surgery. Neither patients nor health-care providers were blinded to patient groupings. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00387842.

Findings

During the recruitment period, 1248 patients were randomly assigned to either open surgery (n=621) or laparoscopic surgery (n=627). 172 were excluded after randomisation, mainly because of the presence of distant metastases or benign disease, leaving 1076 patients eligible for analysis (542 assigned open surgery and 534 assigned laparoscopic

surgery). Median follow-up was 53 months (range 0·03–60). Positive resection margins, number of lymph nodes removed, and morbidity and mortality were similar in both groups. The combined 3-year disease-free survival for all stages was 74·2% (95% CI 70·4–78·0) in the laparoscopic group and 76·2% (72·6–79·8) in the open-surgery group (p=0·70 by log-rank test); the difference in disease-free survival after 3 years was 2·0% (95% CI −3·2 to 7·2). The hazard ratio (HR) for disease-free survival (open *vs* laparoscopic surgery) was 0·92 (95% CI 0·74–1·15). The combined 3-year overall survival for all stages was 81·8% (78·4–85·1) in the laparoscopic group and 84·2% (81·1–87·3) in the open-surgery group (p=0·45 by log-rank test); the difference in overall survival after 3 years was 2·4% (95% CI −2·1 to 7·0; HR 0·95 [0·74–1·22]).

Interpretation

Our trial could not rule out a difference in disease-free survival at 3 years in favour of open colectomy because the upper limit of the 95% CI for the difference just exceeded the predetermined non-inferiority boundary of 7%. However, the difference in disease-free survival between groups was small and, we believe, clinically acceptable, justifying the implementation of laparoscopic surgery into daily practice. Further studies should address whether laparoscopic surgery is superior to open surgery in this setting.

Funding

Ethicon Endo-Surgery (Hamburg, Germany) and the Swedish Cancer Foundation (grant number 4287-B01-03XCC).

Introduction

Cancer of the colon is the third most common cancer in men and women in the developed world,[1] and resection is the only curative treatment. Traditionally, cancers of the colon were removed through large abdominal incisions. More than a decade ago, the first report on laparoscopic resection of colon cancer was published.[2] Laparoscopic colectomy is associated with improved convalescence and decreased morbidity compared with open resection.3,4,5 and 6 However, reports of tumour recurrence at the port sites after laparoscopic resection of colon cancer have questioned the oncological safety of laparoscopic surgery in patients with bowel cancer.[7] Thus, disease-free survival after

laparoscopic colectomy for cancer needs to be proven non-inferior to that after open resection of bowel cancer.

The European multicentre COlon cancer Laparoscopic or Open Resection (COLOR) trial aimed to assess disease-free survival and overall survival 3 years after laparoscopic surgery or open surgery for colon cancer. The short-term outcomes of the COLOR trial have been published previously.[6] Here, we present the data for long-term outcome.

Methods

Patients and procedures

Patients with colon cancer presenting at 29 participating hospitals in Europe were considered for inclusion in the trial. Patients with a solitary adenocarcinoma, localised in the caecum, ascending colon, descending colon, or sigmoid colon above the peritoneal deflection, who were aged 18 years or more, and who provided written informed consent, were eligible for random assignment to either laparoscopic or open surgery. Exclusion criteria included: a body-mass index (BMI) greater than 30 kg/m^2; distant metastases; acute intestinal obstruction; multiple primary tumours of the colon; a scheduled need for synchronous intra-abdominal surgery; preoperative evidence of invasion of adjacent structures, as assessed by CT, MRI, or ultrasonography; previous ipsilateral colon surgery; previous malignancies (except adequately treated basocellular carcinoma of the skin or in-situ carcinoma of the cervix); absolute contraindications to general anaesthesia; and a long-term pneumoperitoneum. Because adenocarcinomas of the transverse colon or the splenic flexure are rare, and laparoscopic removal is technically demanding, patients with such tumours were excluded from this study. Randomisation was done centrally at the coordinating centre by fax or telephone using a computer-generated list. This list was stratified by participating centre and proposed type of resection (ie, right hemicolectomy, left hemicolectomy, or sigmoidectomy). Stratification was done by centre because all surgeons who participated in the COLOR trial work in colorectal surgery teams, instead of working as individual surgeons. After randomisation, patients could only be excluded if metastasised disease was detected during surgery, microscopic examination of the resected specimen showed no signs of malignancy, other primary malignancies were discovered before or during surgery, emergency surgery was required, or if patients withdrew their consent. The ethics committee of each participating centre approved the trial.

Diagnosis of colon cancer was confirmed either by barium-enema radiography or colonoscopy. Biopsies were required for polyps, but not for macroscopically evident carcinomas. To exclude distant metastases, radiographic imaging of liver and chest was mandatory. In patients with rectosigmoid carcinoma, a lateral barium-enema radiograph was needed to determine the exact location of the tumour. Bowel preparation, antibiotic prophylaxis, and thrombosis prophylaxis were done according to local standards without consideration of group designation.

Conventional and laparoscopic surgery was done according to standardised protocols as described previously.[6] The planned extent of resection was similar for laparoscopic and conventional open surgery. In laparoscopic procedures, either the specimen or the extraction site was protected during removal of the affected bowel. The decision to convert to conventional surgery was made by the surgical team. Conversion was defined as an inability to complete all intended laparoscopic steps laparoscopically. All surgical teams had done at least 20 laparoscopically assisted colectomies before entering the trial. An unedited videotape of a laparoscopic colectomy was submitted to HJB, EH, MM, or AL before a centre participated in the trial to assess safe and oncologically sound techniques.

Interim analyses were done by an external monitoring committee after 50, 100, and 150 recurrences in the entire study population. The trial was to be stopped if open surgery was associated with a lower recurrence ($p<0·01$) than laparoscopic surgery, or if laparoscopic surgery was followed by a lower recurrence ($p<0·001$).

Postoperative care, including use of narcotics, was according to the surgeon's standard practice. Preoperative and postoperative adjuvant therapy was allowed at the physician's discretion, according to local standards, as long as patients in each treatment group were treated according to the same protocol. Neither patients nor health-care providers were blinded to patient groupings.

Last follow-up was completed in April, 2006. In view of the variations of practice between countries, minimum requirements for follow-up were determined. These stipulated that annual follow-up at the outpatient clinic was needed for a minimum period of 5 years. At 3 years' follow-up, the entire colon was inspected by barium enema or colonoscopy, the chest was imaged by plain radiography, CT, or MRI, and the liver was assessed by ultrasonography, CT, or MRI. Determining carcinoembryonic antigen levels at follow-up was not mandatory.

The primary outcome of this non-inferiority trial was disease-free survival at 3 years after surgery. Secondary outcomes were short-term morbidity and mortality; number of positive

resection margins; recurrence at the site of the primary tumour, at port sites, and at wound sites; distant metastases; overall survival; blood-transfusion requirements; quality of life; and cost. Recurrences at the site of the primary tumour, at port sites, and at wound sites were considered as local recurrences. Distant metastases were considered as distant recurrences. Patient record forms were regularly collected by the coordinating centre in Rotterdam, Netherlands. Short-term morbidity and mortality were defined as 28-day postoperative or in-hospital morbidity and mortality. Morbidity and mortality were separately recorded on patient record forms. The coordinating centre was informed of all postoperative complications within 2 weeks after occurrence. Detailed macroscopic and microscopic examination of the resected specimens was done by local pathologists according to standardised techniques.[8] Pathologists were not informed of the type of resection. This trial is registered with ClinicalTrials.gov, number NCT00387842.

Statistical analysis

The power calculation of the COLOR trial was based on disease-free survival 3 years after surgery. Disease-free survival of patients with colon cancer without distant metastases at surgery was estimated as 75% at 3 years for both groups at the time of the start of the trial.[9] To show non-inferiority, the two-sided 95% CI for the difference (open minus laparoscopic surgery) should not exceed the prespecified non-inferiority margin.[10] The determination of the non-inferiority boundary was based on clinical and statistical considerations. We arbitrarily chose 7% as the non-inferiority margin, which required accrual of 1200 patients (600 in each group) at a power of 80%. The level of significance for this non-inferiority test was set at 0·025 (one-sided test for non-inferiority).

Analyses were done according to the intention-to-treat principle, in such a way that patients who did not receive their allocated surgical procedure were analysed in the treatment group to which they had been randomised. An additional as-treated analysis was also done, taking into account preoperative conversions to the open-surgery group. Overall survival was defined as time from surgery to death from any cause as the event of interest. Disease-free survival was defined as time from surgery to a recurrence or death from any cause as the event of interest.

Percentage differences between groups were compared with the χ^2 test or Fisher's exact test. Comparison of continuous data was done by use of the Mann-Whitney test. Disease-free survival and overall survival after surgery were assessed by use of Kaplan Meier

curves. The log-rank test was used to do univariate comparisons. Multivariable analysis of survival outcomes was done by use of Cox regression analysis, taking into account randomised procedure, age, sex, and stage of the tumour. The Cox regression models were tested and met the assumption of proportionality. According to protocol, patients had to be followed for a period of 5 years after their primary surgery. All analyses were restricted to these 5-year intervals. All p values were two-sided and $p<0·05$ was considered to be of statistical significance. Data were entered into Microsoft Access 2000 and transported into SPSS version 11.0 for statistical analysis. All survival analyses were done with the Stata package (version 8.2).

Role of the funding source

This trial was supported by Ethicon Endo-Surgery (Hamburg, Germany) and the Swedish Cancer Foundation (grant number 4287-B01-03XCC). Both sponsors had no role in the initiation and design of the study, data collection, analysis and interpretation, writing of the report, or the decision to submit for publication, nor did they have access to the raw data. The corresponding author had full access to all data and the final responsibility to submit for publication.

Results

Between March 7, 1997, and March 6, 2003, 1248 patients were randomly assigned to either laparoscopic or open surgery. 153 patients were excluded after randomisation for various reasons (figure 1) and 19 patients were lost to follow-up. Of the 1076 patients who were available for analysis, 542 had an open colectomy and 534 had a laparoscopic colectomy. The average number of patients included per centre was 37, with a median follow-up in the laparoscopic group of 52 months (SD 17·0; range 0·03–60) and in the open-surgery group of 55 months (SD 17·0; 0·03–60), with a p value for the difference of 0·64.

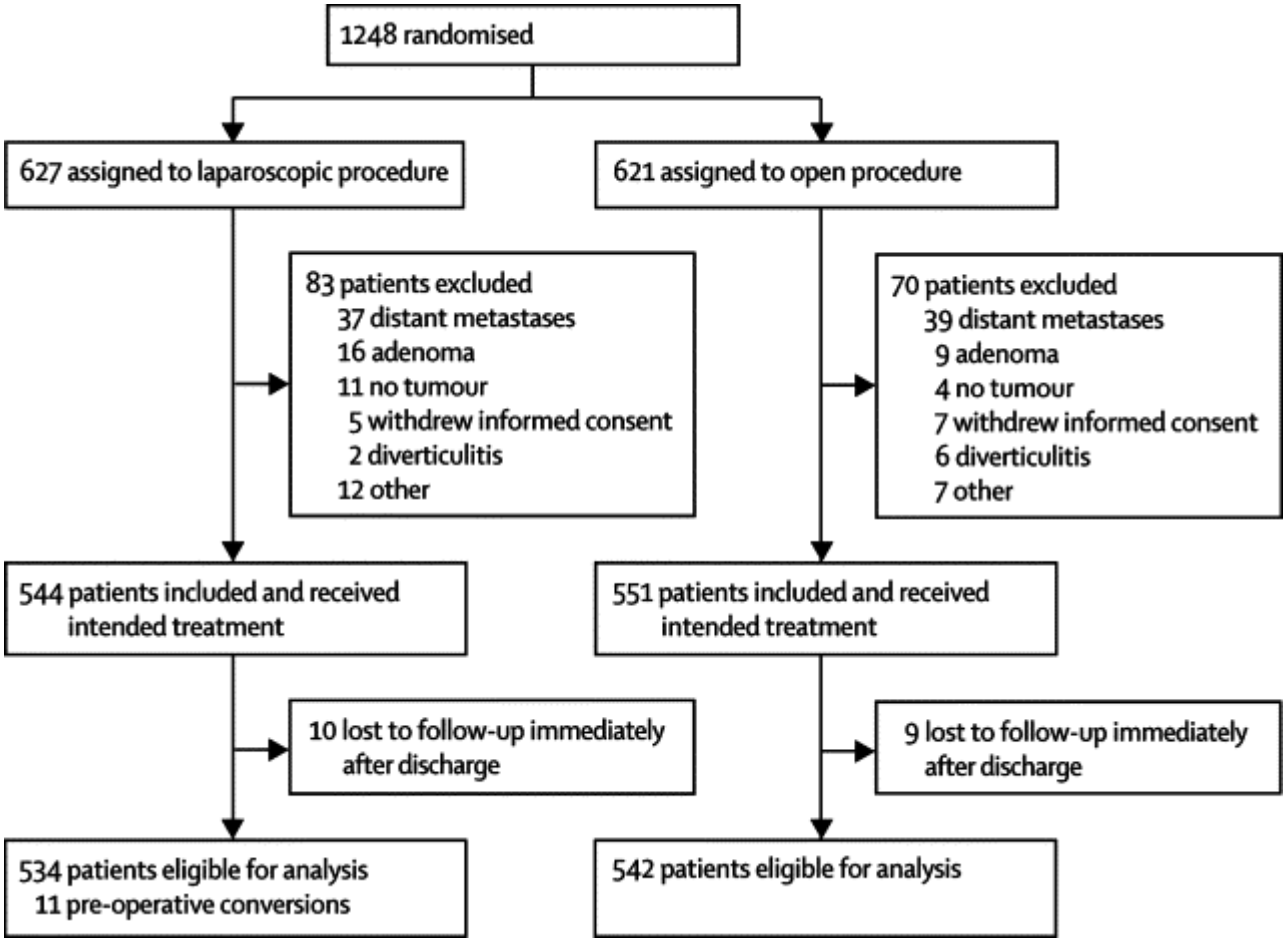

Figure 1.

Flow chart of patients in the COLOR trial

No relevant differences were noted between the two groups in terms of age, sex, BMI, American Society of Anesthesiologists classification, number of previous abdominal operations, localisation of the tumour, and operative procedure (table 1).

Table 1.

Patient baseline clinical characteristics

	Laparoscopic colectomy (n=534)	**Open colectomy (n=542)**	**Total (N=1076)**
Age (years), median (range)	71 (54–84)	71 (55–83)	71 (54–83)
Sex, n (%)			
Men	277 (52)	289 (53)	566 (53)
Women	257 (48)	253 (47)	510 (47)
ASA group, n (%)			
I	138 (26)	149 (28)	287 (27)
II	301 (56)	276 (51)	577 (54)
III	84 (16)	99 (18)	183 (17)
IV	3 (1)	4 (1)	7 (1)
Data missing	8 (2)	14 (3)	22 (2)
Body-mass index (kg/m^2), median (range)	24·5 (20·0–29·1)	24·9 (20·5–29·7)	24·7 (20·3–29·4)
Previous abdominal surgeries			
0	332 (62)	335 (62)	667 (62)
1	141 (26)	143 (26)	284 (26)
2	36 (7)	42 (8)	78 (7)
3	13 (2)	9 (2)	22 (2)
Missing data	12 (2)	13 (2)	25 (2)

Range=10th to 90th percentile. ASA=American Society of Anesthesiologists.

A comparable number of sigmoid resections and left and right hemicolectomies was done in both groups. Operative time was significantly longer and blood loss was significantly lower in the laparoscopic group compared with the open-surgery group. Macroscopic invasion of the tumour in surrounding tissues was noted in 96 of 1076 patients (9%) during surgery: 49 of 534 (9%) in the laparoscopic group and 47 of 542 (9%) in the open-surgery group, with no significance difference between groups (table 2).

Table 2.

Operative data

	Laparoscopic colectomy (n=534)	Open colectomy (n=542)	p value
Intervention, n (%)			
Right hemicolectomy	258 (48)	252 (47)	0·66
Left hemicolectomy	56 (11)	57 (11)	..
Sigmoid resection	200 (38)	210 (39)	..
Other	20 (4)	23 (4)	..
Duration of intervention (min), median (range)			
In theatre	202 (140–315)	170 (113–255)	<0·001
Skin to skin	145 (102–230)	115 (70–180)	<0·001
Blood loss (mL)	100 (19–410)	175 (40–500)	0·003
Macroscopic metastases, n (%)	15 (3)	28 (5)	0·062
Macroscopic invasion, n (%)	49 (9)	47 (9)	0·095
Conversions, n (%)			
Preoperatively	11 (2)	..	..
Intraoperatively	91 (17)	..	..
Morbidity (<28 days after surgery), n (%)			
Overall	111 (21)	110 (20)	0·90
Wound infection	20 (4)	16 (3)	0·58
Wound dehiscence	2 (0·4)	7 (1)	0·18
Pulmonary	8 (1)	13 (2)	0·40
Cardiac	4 (1)	9 (2)	0·28
Bleeding	13 (2)	8 (1)	0·36
Urinary tract infection	12 (2)	13 (2)	1·00
Anastomotic failure	15 (3)	10 (2)	0·40
Bowel obstruction >3 days	10 (2)	15 (3)	0·44
Other	45 (8)	40 (7)	0·60
Mortality (within 28 days after surgery), n (%)	6 (1)	10 (2)	0·47
Chemotherapy (within 28 days after surgery), n (%)	55 (10)	57 (11)	0·99

Range=10th to 90th percentile.

The procedure was converted to open surgery in 102 of 534 patients assigned to undergo laparoscopic surgery (19% [95% CI 16–20]). 11 of 534 patients (2%) randomly assigned laparoscopic surgery underwent open surgery because of malfunctioning laparoscopic equipment or the absence of a skilled surgeon, whereas the remaining 91 patients (17%) had laparoscopic procedures converted to open surgery intraoperatively. 31 of these 91 conversions were because of fixation to, or invasion of, adjacent structures. Reasons for the other conversions have been published elsewhere.[6] 15 of 30 (50%) patients with T4 colon cancers were converted to open surgery, and six of 41 patients (15%) with T1 cancers, 11 of 107 patients (10%) with T2 cancers, and 59 of 348 patients (17%) with T3 cancers had their laparoscopies converted. The frequency of resorting to conversion in patients with T4 cancers was significantly higher than in the other groups (p=0·02). According to the intention-to-treat principle, all converted patients remained in the laparoscopic group for analysis.

Operative and postoperative data are shown in table 2. Adjuvant therapy within 28 days after surgery was recorded. Administration of adjuvant chemotherapy was similar after laparoscopic and open surgery (55 of 534 patients [10·3%] and 57 of 542 patients [10·5%], respectively).

Microscopic assessment of the specimens showed no differences in positive resection margins after laparoscopic resection compared with open resection. There were nine circumferential positive margins and one positive aboral longitudinal margin in the laparoscopic group and eight positive circumferential margins, one positive longitudinal oral margin, and one positive longitudinal aboral margin in the open-surgery group. Stage distribution, size of tumour, and histological typing were similar in both groups. The median number of lymph nodes harvested during surgery was ten in both groups (10th to 90th percentile range 3–20 in laparoscopic group and 4–20 in open-surgery group; table 3).

Table 3.

Pathological characteristics of resected tumours

	Overall	Laparoscopic colectomy	Open colectomy	p value
Size of tumour (cm), median (range; n=1065)[*]	4·5(2·0–8·0)	4·0(2·0–7·5)	4·5(2·1–8·0)	0·07
Resection margins, n (%)[†]				
Positive	20/1059 (2)	10/524 (2)	10/535 (2)	0·96
Negative	1039/1059 (98)	514/524 (98)	525/535 (98)	..
T[†]				
1	80/1059 (8)	41/526 (8)	39/533 (7)	0·94
2	211/1059 (20)	107/526 (20)	104/533 (20)	..
3	704/1059 (66)	348/526 (66)	356/533 (67)	..
4	64/1059 (6)	30/526 (6)	34/533 (6)	..
N[‡]				
0	707/1061 (67)	345/526 (66)	362/535 (68)	0·44
1	246/1061 (23)	125/526 (24)	121/535 (23)	..
2	92/1061 (9)	45/526 (9)	47/535 (9)	..
3	16/1061 (2)	11/526 (2)	5/535 (1)	..
Tumour stage, n (%)[‡]				
I	254/1061 (24)	129/526 (25)	125/535 (23)	0·57
II	453/1061 (43)	216/526 (41)	237/535 (44)	..
III	354/1061 (33)	181/526 (34)	173/535 (32)	..
Histology differentiation, n (%)[§]				
Well differentiated	175/1060 (17)	90/526 (17)	85/534 (16)	0·87
Well–moderately differentiated	60/1060 (6)	28/526 (5)	32/534 (6)	..
Moderately differentiated	636/1060 (60)	321/526 (61)	315/534 (59)	..

	Overall	Laparoscopic colectomy	Open colectomy	p value
Moderately–poor	28/1060 (3)	13/526 (2)	15/534 (3)	..
Poor/undifferentiated	100/1060 (9)	45/526 (9)	55/534 (10)	..
Not specified	61/1060 (6)	29/526 (6)	32/534 (6)	..
Lymph nodes in resected specimen, median (range; n=1040)[¶]	10 (3–20)	10 (3–20)	10 (3–20)	0·32

Range=10th to 90th percentile. Data missing for:

*

11 patients

†

17 patients

‡

15 patients

§

16 patients

¶

36 patients.

The number of combined events (ie, recurrence or death without recurrence) in the laparoscopic group and open-colectomy group was 166 and 158, respectively. 197 patients had recurrence (92 in the open-colectomy group and 105 in the laparoscopic-colectomy group; log-rank, p=0·24; hazard ratio (HR; open *vs* laparoscopic surgery) for recurrence of disease was 0·84 (95% CI 0·64–1·12).

In the laparoscopic group, the number of local recurrences, distant recurrences, and combined recurrences (defined as a local and distant recurrence at time of diagnosis) were 26, 56, and 23, respectively. In the open-colectomy group, these numbers were 26, 54, and 12, respectively. These distributions of recurrence did not differ between groups (p=0·24).

Tumour recurrence in the abdominal wall was noted in 1·3% of patients (seven of 534) who had been assigned to laparoscopic colectomy and in 0·4% of patients (two of 542) who had been assigned to open colectomy (p=0·09 by log-rank test). In the laparoscopic group, five of the seven tumours were at trocar sites whereas two tumours were at the extraction site. Isolated abdominal-wall recurrences, in the absence of recurrent disease elsewhere, were identified in three patients in the laparoscopic group and in one patient in the open-surgery group.

253 patients had died at the time of analysis: 125 in the open-surgery group and 128 in the laparoscopic group. 127 patients (69 and 58 in each group, respectively) died from colon cancer and 11 patients (four and seven in each group, respectively) died as a result of another cancer. Total follow-up, truncated at 5 years, for the laparoscopic and open-surgery groups was 2046 and 2096 person-years, respectively (mean values 3·8 and 3·9 years).

Overall survival and disease-free survival in patients who had laparoscopic surgery did not differ from patients who underwent open colectomy (Figure 2 and Figure 3). The 3-year disease-free survival for all stages combined was 74·2% (95% CI 70·4–78·0) in the laparoscopic group and 76·2% (72·6–79·8) in the open-surgery group (p=0·70 by log-rank test). The overall 3-year survival for all stages was 81·8% (78·4–85·1) in the laparoscopic group and 84·2% (81·1–87·3) in the open-surgery group (p=0·45 by log-rank test). When patients were analysed by stage, no differences in disease-free survival (figure 2) or overall survival (figure 3) were present between the treatment groups. It is important to note that the stage-specific comparisons are underpowered.

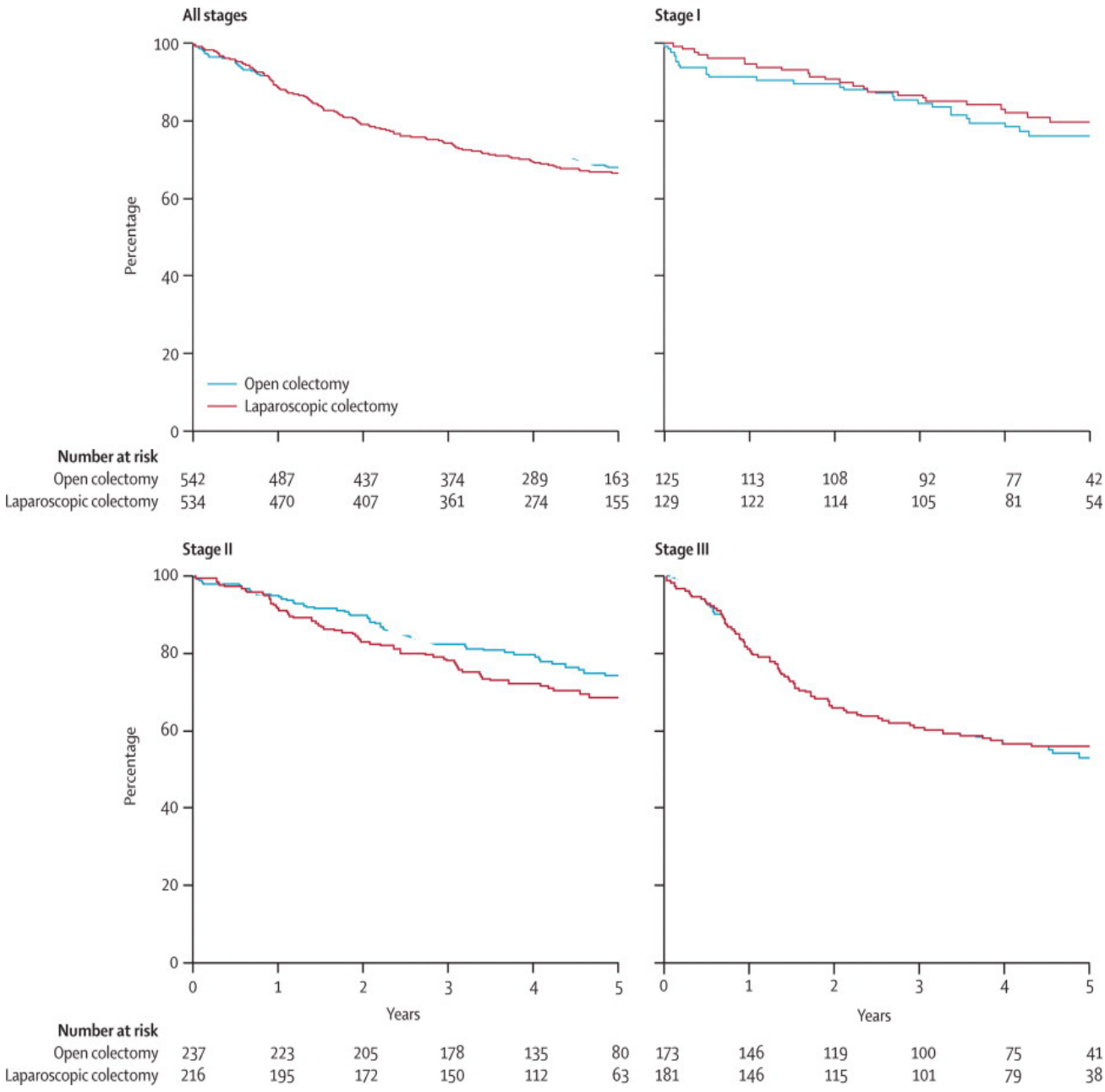

Figure 2.

Kaplan-Meier curves for comparison of disease-free survival between patients with different tumour stages

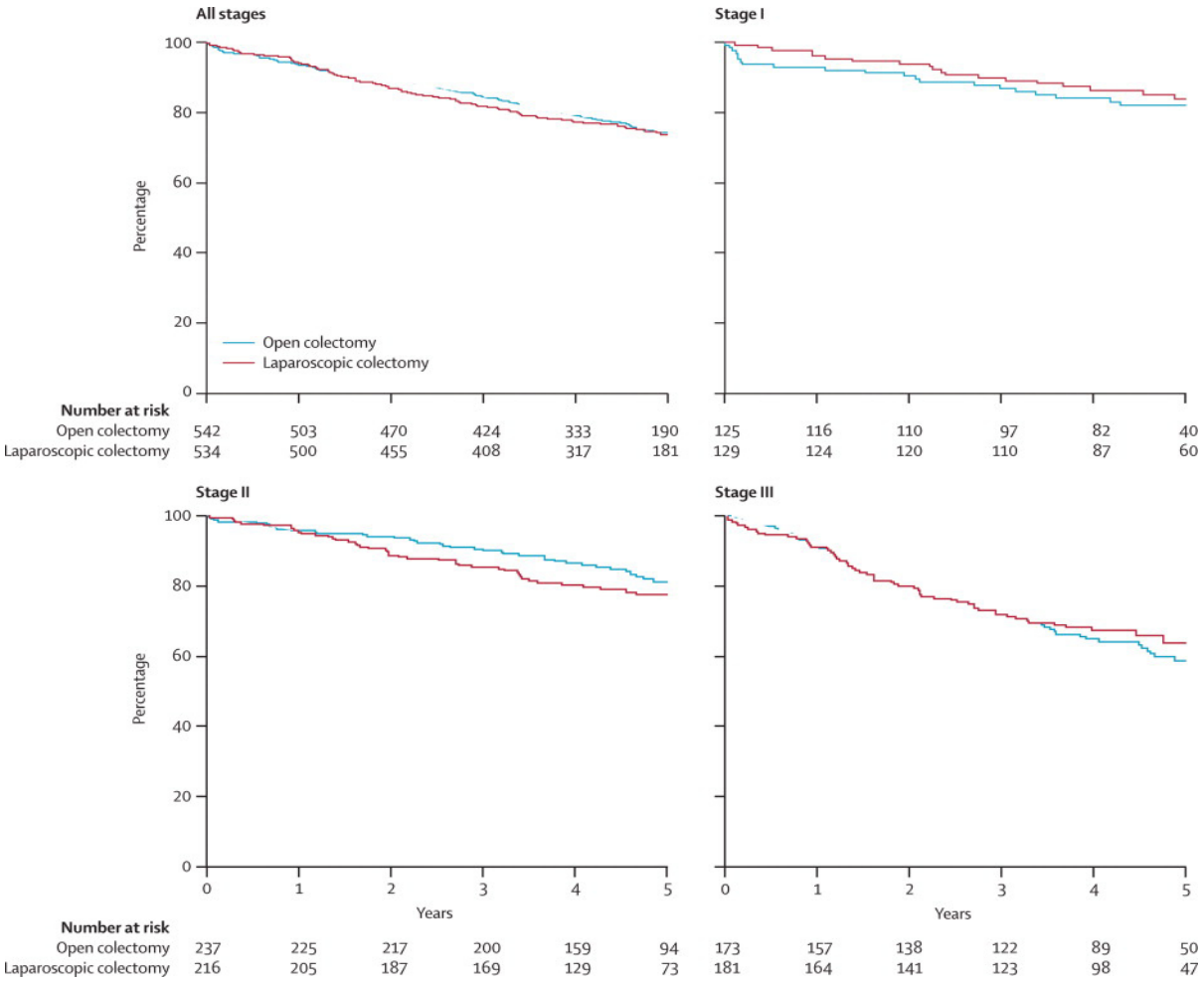

Figure 3.

Kaplan-Meier curves for comparison of overall survival between patients with different tumour stages

The difference in disease-free survival at 3 and 5 years (ie, open colectomy minus laparoscopic colectomy) was 2·0% (95% CI −3·2 to 7·2) and 1·4% (−4·6 to 7·5), respectively (HR 0·92 [95% CI 0·74–1·15]). The corresponding differences in overall survival were 2·4% (95% CI −2·1 to 7·0) and 0·4% (−5·3% to 6·1), respectively (HR 0·95 [0·74–1·22]; table 4). The p value for non-inferiority regarding the primary endpoint of 3 years' disease-free survival was 0·030, which does not meet our predetermined significance level of 0·025.

Table 4.

Survival at 3 and 5 years according to procedure

	Open colectomy	laparoscopic colectomy	Difference
Disease-free survival			
3 years	76·2 (72·6–79·8)	74·2 (70·4–78·0)	2·0 (–3·2 to 7·2)
5 years	67·9 (63·6–72·2)	66·5 (62·2–70·7)	1·4 (–4·6 to 7·5)
Overall survival			
3 years	84·2 (81·1–87·3)	81·8 (78·4–85·1)	2·4 (–2·1 to 7·0)
5 years	74·2 (70·1–78·2)	73·8 (69·7–77·9)	0·4 (–5·3 to 6·1)

Data given are percentages (95% CI).

Multivariable analysis of disease-free survival and overall survival did not show differences between laparoscopic and open surgery (table 5). Overall survival was significantly better in women (table 5). Disease-free survival and overall survival were significantly worse in older patients. Both endpoints were significantly affected by stage (table 5).

Table 5.

Multivariable analysis (Cox-regression) of disease-free survival (DFS) and overall survival (OS) according to various factors

	Cancer recurrence or death from any cause (DFS)		Overall mortality (OS)	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Procedure				
Open *vs* laparoscopic colectomy	0·93 (0·74–1·15)	0·49	0·95 (0·74–1·22)	0·70
Stage				
II *vs* I	1·29 (0·93–1·79)	0·13	1·13 (0·77–1·65)	0·53
III *vs* I	2·64 (1·92–3·63)	<0·001	2·60 (1·82–3·71)	<0·001
Sex				
Women *vs* men	0·81 (0·65–1·01)	0·06	0·67 (0·52–0·86)	0·002
Age				
Per 10-year increase	1·42 (1·27–1·59)	<0·001	1·80 (1·57–2·06)	<0·001

Reference categories for the categorical variables are laparoscopy procedures, stage I disease, and male sex.

Further analysis by investigating appropriate interaction terms in the Cox models showed that the treatment effect did not significantly differ between the three stage groups (effect modification: p=0·36 and p=0·45 for disease-free survival and overall survival, respectively). Additionally, the treatment effect did not differ between centres (p=0·19 for disease-free survival and p=0·21 for overall survival). Repeating these analyses with

recurrence of colon cancer as the endpoint showed that only stage of disease was significantly related to recurrence, indicating that the worse outcomes for men and for older patients are not due to a higher incidence of recurrence (data not shown). The adjusted HR (open *vs* laparoscopic surgery) for recurrence in this analysis was 0·86 (95% CI 0·65–1·14; p=0·30).

An as-treated analysis, counting the preoperative conversions as open surgery, did not affect the conclusions: 3-year disease-free survival for the open-surgery group and laparoscopic group was 76·0% (95% CI 72·5–9·5) and 74·3% (70·5–78·0), respectively (difference=1·7% [−3·5 to 6·9; p=0·51]).

Discussion

Data from the COLOR trial could not rule out a difference in disease-free survival at 3 years in favour of open colectomy, because the upper limit of the 95% CI for the difference just passed the predetermined non-inferiority boundary of 7%. However, in a per-protocol analysis, done as per CONSORT guidelines to prevent a false conclusion of non-inferiority,[11] in which those patients who were randomly assigned to laparoscopic surgery but were switched pre-operatively to receive open surgery were analysed as treated, laparoscopic surgery was non-inferior to open surgery. Furthermore, the actual difference in disease-free survival between groups was small and, we believe, clinically acceptable; taken together, we feel that these results justify the implementation of laparoscopic surgery into daily practice.

The Clinical Outcomes of Surgical Therapy (COST) and Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trials have provided disease-free survival data for 770 and 413 patients with colon cancer, respectively, who had either laparoscopic or open resection. Although actual numerical differences in disease-free survival were not reported by these trials, there were no significant differences reported (HR 0·86 in COST; p=0·51 in CLASICC).[3,4,12 and 13]

Survival data for the first 520 patients recruited in the COLOR trial were included in a meta-analysis of four trials that randomly assigned patients with colon cancer to laparoscopically assisted surgery or open colectomy.[14] This meta-analysis had a censored follow-up at 3 years after primary surgery. Disease-free survival and overall survival for stages I, II, and III, and all three stages combined did not differ between the two treatment groups. The 95% CI of the difference in 3-year disease-free survival was −5% to 4%. One

of the four trials of this meta-analysis was done in a single centre with a high volume of laparoscopic surgery. The COST and CLASICC trials had an average case load per centre of 16 and 15 patients, respectively, whereas the COLOR centres accrued 37 patients on average. We reported previously that operating time and the frequency of resorting to conversion is lower in centres with larger patient volumes.[15] The actual frequency with which surgeons resorted to intraoperative conversion in the COLOR trial was 17%, whereas the frequency in the COST and CLASICC trials was 21% and 25%, respectively. The centres that participated in the COLOR trial seem to reflect a realistic cross-section of current practice of open and laparoscopic surgery in Europe. Furthermore, surgeons could only participate in this trial after an expert surgeon had reviewed and approved an unedited recording of a laparoscopic colectomy. We consider that this secured safety and standardisation of the laparoscopic technique.

Bilimoria and colleagues[16] did a retrospective cohort study of 11 038 laparoscopic and 231 381 open colectomies in patients with non-metastatic colon cancer. 5-year overall survival of patients with stage I disease was significantly better after laparoscopic surgery. The design of this study does not justify firm conclusions, but indicates the ongoing close monitoring of outcomes of laparoscopic surgery is crucial.

The findings of Bilimoria and colleagues[16] are also of interest in light of a single-centre trial done by Lacy and colleagues,[5] which reported improved survival after laparoscopic colectomy for lymph-node positive disease. Although some have suggested that the improved survival shown by Lacy and colleagues was the consequence of less use of adjuvant chemotherapy and of high locoregional recurrence in the conventional group, further studies remain necessary to establish whether laparoscopic surgery for cancer is associated with improved survival.[17, 18 and 19]

Overall survival differed between men and women and both disease-free survival and overall survival differed between older and younger patients in the current trial (table 5). Such differences are expected in view of general population data. However, no differences were noted regarding colon-cancer recurrence in our study.

In this trial, about half the patients with T4 colon cancers undergoing laparoscopic surgery needed conversion. Preoperative imaging of colon cancer in the COLOR trial was mainly based on barium enema and colonoscopy. CT and MRI can provide more information about size and invasiveness of colon cancers than barium enema and colonoscopy. Less than 5% of all patients in the COLOR trial had preoperative abdominal CT or MRI scans, and this might have resulted in the high need for conversion in our study. Hence, we

recommend use of abdominal CT or MRI to identify patients with large or invasive colon cancers who woulds be better served by open surgery. Indeed, the use of barium enema to diagnose cancer of the colon in the COLOR trial decreased steadily during the course of the trial. The rate of barium-enema use in 1998 was 31% and steadily decreased to 7% in 2002 as a result of the advantages of colonoscopy.

On average, we removed ten lymph nodes per patient. A suggestion has been made that at least 12 lymph nodes should be removed to ensure radical resection, However, the number of removed lymph nodes recorded by the pathologist is a function of the scrutiny of the detection method. The common yield of laparoscopic and open colectomy is ten lymph nodes.[6]

Although not statistically significant, more recurrences were noted in the abdominal wall after laparoscopic surgery than after open surgery (seven *vs* two; p=0·09). Other studies have not reported different rates of abdominal-wall recurrence between the two treatment groups. [3, 4 and 5]

The role of chemotherapy in the treatment of colon cancer has increased over the past decade. All patients in the COLOR trial received postoperative therapy according to the protocols of the centres, regardless of the type of surgery. In Europe, standard practice is to discuss all patients with cancer in multidisciplinary groups that oversee compliance with standard protocols. There was no difference in administration of adjuvant chemotherapy between the laparoscopic and open-surgery group in this study (table 2).

A limitation of this study is the exclusion of patients with a BMI greater than 30 kg/m^2, due to the fact that obesity is increasing in the developed world. The COLOR trial was started in 1997 at a time when experience with laparoscopic colectomy in obese patients was limited. For the purpose of patient safety, patients with a BMI exceeding 30 kg/m^2 were excluded. Experience with complex laparoscopic procedures in obese patients has increased during the past decade to a point where laparoscopic surgery has become the preferred surgical technique for weight-loss surgery.

Another limitation of this study is an incomplete registry of all eligible patients who could potentially have been enrolled. However, because the characteristics of the patients in our study correspond closely to those of patients in three similar trials that have been published,[3, 4 and 5] we do not think the external validity of our study was compromised by this omission.

Despite current knowledge, further studies are necessary, and should address whether laparoscopic surgery is superior to open surgery. Prospective registries of laparoscopic

and open surgeries for cancer are also needed to comprehensively collect accurate data on large numbers of patients. Together, these data should provide direction for the further improvement of treatment for colon cancer.

Writing committee

Mark Buunen, Ruben Veldkamp, Wim C J Hop, Esther Kuhry, Johannes Jeekel (Erasmus University Medical Centre, Rotterdam, Netherlands); Eva Haglind (Sahlgrenska University Hospital, Göteborg, Sweden); Lars Påhlman (Uppsala University Hospital, Uppsala, Sweden); Miguel A Cuesta (VU Medical Centre, Amsterdam, Netherlands); Simon Msika (Louis Mourier Hospital, Colombes, France); Mario Morino (University Hospital Turin, Turin, Italy); Antonio Lacy (Hospital Clinic, University of Barcelona, Barcelona, Spain); Hendrik J Bonjer (Dalhousie University, Halifax, Canada).

Protocol committee

Hendrik Jaap Bonjer, Eva Haglind, Johannes Jeekel, Geert Kazemier, Lars Påhlman

Data manager

Anneke van Duuren (Erasmus University Medical Centre, Rotterdam, Netherlands)

Participating investigators and centres

Sweden—R Hellberg (Mälarsjukhuset, Eskilstuna); E Haglind, G Kurlberg, P G Lindgren, E Lindholm (Sahlgrenska University Hospital, Göteborg); L Påhlman, M Dahlberg, Y Raab (Uppsala University Hospital, Uppsala); B Anderberg, S Ewerth, M Janson, J E Åkerlund (Huddinge Hospital, Huddinge); K Smedh (Centrallasarettet, Västerås); A Montgomery (University Hospital Malmö, Malmö); S Skullman (Kärnsjukhuset, Skövde); P O Nyström, A Kald, A Wänström (University Hospital Linköping, Linköping); J Dàlen, I Svedberg (St Görans Hospital, Stockholm); G Edlund (Östersund Sjukhus, Östersund); U Kressner (University Hospital Uddevalla, Uddevalla); A N Öberg, O Lundberg, G E Lindmark (Norrlands University Hospital, Umeå); *Finland*—T Heikkinen (Oulu Hospital, Oulu); *Italy*—M Morino, G Giraudo (University Hospital Turin, Turin); *Spain*—A M Lacy, S Delgado (Hospital Clinic i Provincial de Barcelona, Barcelona); E Macarulla Sanz (Fundacio Sanitaria d'Igualada, Igualada); J Medina Díez (Hospital Jerez de la Frontera, Cadiz); *Germany*—O Schwandner, T H Schiedeck, H Shekarriz (University Hospital Lübeck, Lübeck); C Bloechle (University Hospital Hamburg, Hamburg); I Baca, O Weiss (Zentrall krankenhaus Bremen Ost, Bremen); *France*—S Msika (Louis Mourier Hospital, Colombes); G Desvignes (Centre Hospital de Montargis, Amilly); *UK*—K L Campbell, A Cuschieri (Ninewells Hospitals, Dundee); *Netherlands*—H J Bonjer, W R Schouten, G Kazemier (Erasmus University Medical Centre, Rotterdam); J F Lange, E van der Harst, P

Plaisier, M J O E Bertleff (St Clara Hospital, Rotterdam); M A Cuesta, W van der Broek (University Hospital VU, Amsterdam); J W H J Meijerink (Leeuwarden Medical Centre, Leeuwarden); J J Jakimowicz, G Nieuwenhuijzen, J Maring, J Kivit (Catharina Hospital, Eindhoven); I M C Janssen, E J Spillenaar-Bilgen, F Berends (Rijnstate Hospital, Arnhem).

Contributors

The members of the protocol committee (HJB, EH, JJ, GK, and LP) contributed to the design of the study. MAC, SM, MM, and AL assisted with data interpretation. RV, EK, MB, and HJB coordinated the study and supervised the enrolment and follow-up of patients. RV, EK, and MB participated in data entry and collection of data. Statistical analyses were done by WCJH. All authors participated in the preparation of the report and approved the final version.

Conflicts of interest

All authors declared no conflicts of interest.

Correspondence to: Prof Hendrik J Bonjer, Department of Surgery, QE II Health Science Center, Capital District Health Authority and Dalhousie University, 1278 Tower Road, Halifax, B3H 2Y9, Canada Jaap.Bonjer@Dal.Ca

References

1.

LAG HD Ries, M Krapcho, A Mariotto (Eds.) *et al.*, SEER cancer statistics review, National Cancer Institute, Bethesda, MD (1975–2003)

2.

M Jacobs, JC Verdeja, HS Goldstein. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc, 1 (1991), pp. 144–150

3.

The Clinical Outcomes of Surgical Therapy (COST) Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med, 350 (2004), pp. 2050–2059

4.

PJ Guillou, P Quirke, H Thorpe *et al.*Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet, 365 (2005), pp. 1718–1726

5.

AM Lacy, JC Garcia-Valdecasas, S Delgado *et al.* Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet, 359 (2002), pp. 2224–2229

6.

R Veldkamp, E Kuhry, WC Hop *et al.* Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol, 6 (2005), pp. 477–484

7.

FJ Berends, G Kazemier, HJ Bonjer, JF Lange. Subcutaneous metastases after laparoscopic colectomy. Lancet, 344 (1994), p. 58

8.

CC Compton, LP Fielding, LJ Burgart *et al.* Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med, 124 (2000), pp. 979–994

9.

JM Jessup, LS McGinnis, GD Steele Jr, HR Menck, DP Winchester. The National Cancer Data Base. Report on colon cancer. Cancer, 78 (1996), pp. 918–926

10.

European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on the choice of the non-inferiority margin. http://www.sctweb.org/presentations/2008/GuidelineontheChoiceoftheNon-inferiorityMargin.pdf (accessed Nov 25, 2008).

11.

G Piaggio, DR Elbourne, DG Altman, SJ Pocock, SJ Evans. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA, 295 (2006), pp. 1152–1160

12.

J Tinmouth, G Tomlinson. Laparoscopically assisted versus open colectomy for colon cancer. N Engl J Med, 351 (2004), pp. 933–934

13.

DG Jayne, PJ Guillou, H Thorpe *et al.* Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol, 25 (2007), pp. 3061–3068

14.

HJ Bonjer, WC Hop, H Nelson *et al.* Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg, 142 (2007), pp. 298–303

15.

E Kuhry, HJ Bonjer, E Haglind *et al.* Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer. Surg Endosc, 19 (2005), pp. 687–692 |

16.

KY Bilimoria, DJ Bentrem, H Nelson *et al.* Use and outcomes of laparoscopic-assisted colectomy for cancer in the United States. Arch Surg, 143 (2008), pp. 832–839

17.

R Ceulemans, M Henri, E Dutson, J Leroy, J Marescaux. Open versus laparoscopy-assisted colectomy .Lancet, 361 (2003), pp. 73–74

18.

S Evrard, S Mathoulin-Pelissier, A Kramar. Open versus laparoscopy-assisted colectomy. Lancet, 361 (2003), p. 73

19.

T Lehnert, U Abel, P Kienle, U Hinz . Open versus laparoscopy-assisted colectomy. Lancet, 361 (2003), p. 74