Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial

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Summary

Background Although early reports on laparoscopy-assisted colectomy (LAC) in patients with colon cancer suggested that it reduces perioperative morbidity, its influence on long-term results is unknown. Our study aimed to compare efficacy of LAC and open colectomy (OC) for treatment of non-metastatic colon cancer in terms of tumour recurrence and survival.

Methods From November, 1993, to July, 1998, all patients with adenocarcinoma of the colon were assessed for entry in this randomised trial. Adjuvant therapy and postoperative follow-up were the same in both groups. The main endpoint was cancer-related survival. Data were analysed according to the intention-to-treat principle.

Findings 219 patients took part in the study (111 LAC group, 108 OC group). Patients in the LAC group recovered faster than those in the OC group, with shorter peristalsis-detection (p=0·001) and oral-intake times (p=0·001), and shorter hospital stays (p=0·005). Morbidity was lower in the LAC group (p=0·001), although LAC did not influence perioperative mortality. Probability of cancer-related survival was higher in the LAC group (p=0·02). The Cox model showed that LAC was independently associated with reduced risk of tumour relapse (hazard ratio 0·39, 95% CI 0·19–0·82), death from any cause (0·48, 0·23–1·01), and death from a cancer-related cause (0·38, 0·16–0·91) compared with OC. This superiority of LAC was due to differences in patients with stage III tumours (p=0·04, p=0·02, and p=0·006, respectively).

Interpretation LAC is more effective than OC for treatment of colon cancer in terms of morbidity, hospital stay, tumour recurrence, and cancer-related survival.

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Introduction

Colorectal cancer is the second leading cause of cancer-related death in Western countries. Prognosis associated with this disease has improved due to early diagnosis and changes in medical therapy. Adjuvant chemotherapy in colon cancer, radiotherapy, and introduction of the total mesorectal excision technique in rectal cancer have increased survival, especially in patients with stage III tumours. Moreover, oxaliplatin and irinotecan have improved the prognosis associated with metastatic colorectal cancer.[1]

Laparoscopic surgery has led to great progress in the treatment of many gastrointestinal diseases.[2] Early reports on laparoscopy-assisted colectomy (LAC) in patients with colon cancer suggest that it lowers surgical trauma, decreases perioperative complications, and leads to more rapid recovery.[3–6] However, development of port-site metastases in some cases showed that this approach was questionable.[7,8]

Few preliminary data that compare LAC with open colectomy (OC) in colon cancer have been reported. They suggest that LAC is associated with reduced perioperative morbidity and very low risk of wound metastasis.[4,6,9,10] However, there are no studies that compare LAC and OC in terms of tumour recurrence and survival.

In this article we report the results of a randomised trial in patients with non-metastatic colon cancer. The aim of the trial was to assess whether there are differences in cancer-related survival between LAC and OC.

Methods

Patients

From November, 1993, to July, 1998, all patients admitted to our unit with adenocarcinoma of the colon, 15 cm above the anal verge, were assessed. Exclusion criteria were: cancer located at the transverse colon, distant metastasis, adjacent organ invasion, intestinal obstruction, past colonic surgery, and no consent to participate in the study.

Randomisation was done the day before surgery. Patients were stratified in two groups according to tumour location (right or left side, with respect to the splenic flexure), and subsequently assigned to LAC or OC by means of sealed opaque envelopes containing computer-generated random numbers. To prevent selection bias, random numbers were generated by an investigator (AC) who was not involved in enrolment of participants.

Due to the limited evidence about LAC at the beginning of the study, interim analyses that assessed early morbidity, tumour recurrence, and port-site metastasis were planned during the first period.[9,10] The study was approved by the institutional ethics of research committee and oral consent was obtained from each patient.

Operative procedures

Patients were preoperatively prepared with anterograde intestinal cleansing (polyethylene glycol, Solución Evacuante Bohm, Madrid, Spain) and oral antibiotics (neomycin and vancomycin). Surgery was done under general anaesthesia by staff members with previously described techniques.[9] Both LAC and OC were done by a single gastrointestinal surgical team with wide experience in laparoscopic procedures. Metronidazole was given intravenously at the time of anaesthesia induction and 3 h later. For LAC, a pneumoperitoneum with intra-abdominal pressure between 10 mm Hg and 14 mm Hg was maintained throughout the operation. The average length of the incision for colonic extraction was 45 mm for left-sided tumours and 65 mm for right-sided lesions. Manoeuvres to prevent port-site metastasis—ie, non-touch technique with initial vascular ligation, use of a wound edge protector, reduction of intra-abdominal pressure before tumour extraction, and extensive cleansing with 5% iodopovidone solution—were used routinely. Non-touch technique was also used for OC. Both LAC and OC were done with initial vascular ligation.

Processing of specimens

Surgical specimens were opened, spread on a flat surface, and fixed in formalin overnight. Sections were taken from the margin and entire thickness of the tumour, from mucosa that appeared normal away from the neoplasm, and from proximal and distal resection margins. We took care to note any lymph nodes in the resected specimen, all of which were registered and processed by the pathologist. Blocks were dehydrated and embedded in paraffin wax. 5 μm sections were cut and stained with haematoxylin-eosin for microscopic study. Tumours were classified according to the tumour node metastases (TNM) system (International Union Against Cancer).[11]

Postoperative management

The nasogastric tube was removed immediately after surgery and the urinary catheter the next day. Oral intake was started on the morning (0700 h) of the next day after surgery that peristalsis was detected (peristalsis was assessed twice a day, at 0700 and 1700 h). Initially, clear liquid (100 mL hourly) was given; later full liquids were given. Patients who tolerated liquid intake (no severe nausea, vomiting, or abdominal distension) for 4–6 h were given a liquid diet during the first 24 h, and a soft diet subsequently. For patients who did not tolerate liquid intake, the process was interrupted and started 24–48 h later. Oral-intake time was counted from the first liquid intake of the tolerant cycle. Patients were discharged when oral diet was well accepted and no complications were detected. Duration of hospital stay was defined as the time from intervention to hospital discharge.

Unless contraindicated, postoperative adjuvant chemotherapy with fluorouracil and either levamisole (patients entered from November, 1993, to August, 1995) or calcium folinate (patients entered from September, 1995, to July, 1998) was routinely given to all patients with stage II and III tumours. Standard schedules and doses were used.[1]

Postoperative surveillance consisted of medical history, physical examination, and laboratory studies, including serum carcinoembryonic antigen (CEA) concentrations 1 month after surgery and every 3 months thereafter. At each visit, patients' symptoms were recorded, and wound scars examined for subcutaneous metastasis. Abdominal ultrasonography or computed tomography, and chest radiographs were done every 6 months, and total colonoscopy was done every year. When colonoscopy was incomplete, a combination of sigmoidoscopy and barium enema was used.

Recurrences were histologically confirmed and classified as distant metastasis, locoregional relapse (tumour growth restricted to the anastomosis or the region of primary operation), peritoneal seeding, or port-site metastasis. Diagnosis of port-site metastasis required the absence of peritoneal carcinomatosis.

Statistical analysis

The main endpoint of the study was cancer-related survival. The working hypothesis was that there would be no significant differences in this variable between LAC and OC, but that differences in variables related to the short-term outcome (ie, morbidity and duration of hospital stay) would favour LAC. We assumed that a difference in cancer-related survival of less than 15% between treatments indicates an equivalent efficacy. Assuming a 70% 5-year cancer-related survival in the OC group, a minimum of 100 patients per group was required to show that both surgical techniques were equivalent with an α level of 0·20 and a β error of 0·05. We also assessed other important long-term variables: probability of overall survival and probability of being free of recurrence.

Data were assessed according to the intention-to-treat principle. Because the scope of the study was non-metastatic colon cancer, patients in whom metastasis was detected intraoperatively were not included in the analyses of long-term outcome. Survival was calculated from surgical resection of primary tumour to the last visit or death. For cancer-related survival, patients who died from other causes were censored from the study at time of death. We constructed probability curves with the Kaplan-Meier method and compared them with the log-rank test. Statistical analysis was done in February, 2001.

We used proportional-hazards modelling with forward selection to determine the influence of patients' baseline characteristics on cancer-related survival and other variables.[12] The surgical procedure and any variable reaching a p value of less than 0·10 in the univariate analysis were introduced in the multivariate analysis to identify independent predictors. Predefined baseline variables for the univariate analysis were: sex, age, intervention period (1993–1995 or 1996–1998), preoperative serum CEA concentrations, size, extent and degree of differentiation of primary tumour, and lymph-node metastasis. For continuous variables, the cut-off level chosen was their median value. Tumour stage was not included as a single covariable but was divided into the corresponding original counterparts (extent of primary tumour and lymph-node metastasis). Nevertheless, we also constructed probability curves after classifying the patients according to the TNM system.

Categorical variables were compared by χ^2 test, with the Yates correction when necessary. Continuous variables were compared by the Student's t test or the Mann-Whitney U test, depending on their distribution.

All p values were two-sided. A p value of less than 0·05 indicated a significant difference. All calculations were done with SPSS (version 10.0).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

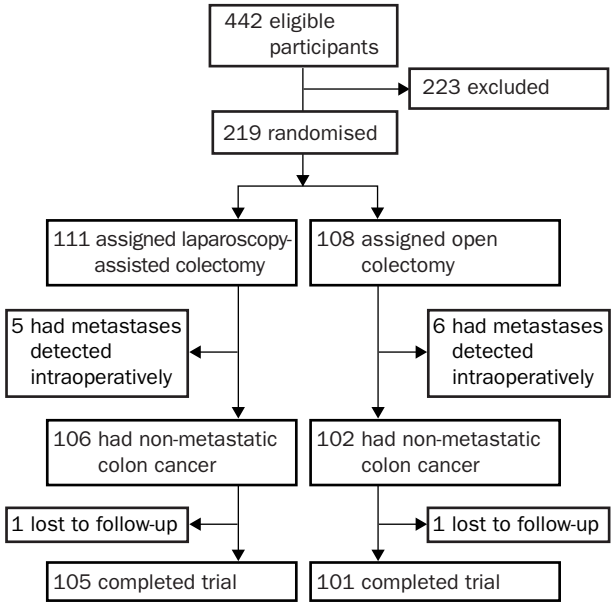

Figure 1: **Trial profile**

Results

442 patients were eligible for the study. 223 were excluded owing to: distant metastasis in 64 patients, tumour located at the transverse colon in 40, previous colon surgery in 27, intestinal obstruction in 13, and refusal to participate in 79. Therefore, 219 patients with colon cancer took part in the study, 111 in the LAC group and 108 in the OC group (figure 1). Baseline characteristics did not differ greatly between groups (table 1).

12 patients (11%) assigned to the LAC group underwent OC instead, because we suspected tumour invasion of adjacent organs. Seven of these patients had a stage II tumour, and five had a stage III tumour.

After surgery, 68 (61%) of the LAC group and 59 (55%) of the OC group received adjuvant chemotherapy according to the established protocol.

Operative time was significantly longer and intraoperative blood losses significantly lower with LAC than with OC. Patients from the LAC group recovered significantly faster than those from the OC group, with shorter peristalsis-detection and oral-intake times, and shorter stays in hospital (table 2). Overall morbidity was significantly lower in patients who had LAC (relative risk

	Laparoscopy-assisted colectomy (n=111)	Open colectomy (n=108)
Age (years)	68 (12)	71 (11)
Sex (male/female)	56/55	50/58
Previous abdominal surgery	40	47
Preoperative serum CEA (ng/mL)	17 (41)	6 (12)
Intervention before 1996	42	42
Tumour location		
Caecum	32	21
Ascending colon	7	17
Hepatic flexure	10	11
Descending colon	8	11
Sigmoid colon	54	48
Intervention		
Right colectomy	49	49
Left colectomy	4	1
Sigmoidectomy	52	46
High anterior resection	3	9
Subtotal colectomy	1	2
Hartmann procedure	2	1
Lymph nodes in resected specimen (number)	11·1 (7·9)	11·1 (7·4)
Extent of primary tumour*		
1	16	10
2	14	13
3	76	75
4	5	10
Lymph-node metastasis		
No	70	67
Yes	41	41
Tumour stage*		
I	27	18
II	42	48
III	37	36
IV	5	6
Histological characteristics†		
Well differentiated	10	10
Moderately differentiated	79	80
Undifferentiated	9	14

Data are number of patients or mean (SD). CEA=carcinoembryonic antigen. *According to TNM classification. †Differentiation degree data for the 202 patients for whom this information was available.

Table 1: **Baseline characteristics**

	Laparoscopy-assisted colectomy (n=111)	Open colectomy (n=108)	p
Duration of intervention (min)	142 (52)	118 (45)	0·001
Blood loss (mL)	105 (99)	193 (212)	0·001
Initiation of peristalsis (h)	36 (31)	55 (40)	0·001
Reinsertion of nasogastric tube	3	9	0·08
Initiation of oral intake (h)	54 (42)	85 (67)	0·001
Duration of hospital stay (days)	5·2 (2·1)	7·9 (9·3)	0·005
Morbidity	12	31	0·001
Postoperative complications			
Wound infection	8	18	..
Persistent ileus	3	9	..
Evisceration	..	2	..
Intraperitoneal haemorrhage	..	1	..
Intraluminal haemorrhage	..	1	..
Anastomotic leak	..	2	..
Intra-abdominal collection	..	1	..
Pneumonia	..	..	..
Acute renal failure	2	1	..
Hepatic cirrhosis decompensation	..	2	..
Infection of the urinary tract	1	..	..

Data are mean (SD) or number of patients.

Table 2: **Data related to surgical intervention and morbidity**

	Laparoscopy-assisted colectomy (n=106)	Open colectomy (n=102)	Hazard ratio (95% CI)	p
Tumour recurrence	18 (17%)	28 (27%)	0·72 (0·49–1·06)	0·07
Type of recurrence				
Distant metastasis	7	9	..	0·57
Locoregional relapse	7	14	..	..
Peritoneal seeding	3	5	..	..
Port-site metastasis	1	0	..	..
Time to recurrence (months)	15 (14)	17 (12)	..	0·66
Surgical treatment of recurrence with curative intention	6 (33%)	9 (32%)	..	1·00
Overall mortality	19 (18%)	27 (26%)	0·77 (0·53–1·12)	0·14
Cancer-related mortality	10 (9%)	21 (21%)	0·68 (0·50–0·90)	0·03
Causes of death	..	..	..	0·19
Perioperative mortality*	1	3	..	..
Tumour progression	9	18	..	..
Others†	9	6	..	..

Data are number of patients or mean (SD) unless otherwise stated. *Laparoscopy-assisted colectomy group: myocardial infarction (n=1); open colectomy group: multiorganic failure (n=3). †Laparoscopy-assisted colectomy group: stroke (n=4), other neoplasms (n=3), Alzheimer's disease (n=1), and car accident (n=1); open colectomy group: stroke (n=2), Alzheimer's disease (n=1), myocardial infarction (n=1), chronic respiratory failure (n=1), and hepatic failure (n=1).

Table 3: **Tumour recurrence and mortality in patients with non-metastatic colon cancer**

	Hazard ratio (95% CI)	p
Probability of being free of recurrence		
Lymph-node metastasis (presence *vs* absence)	0·31 (0·16–0·60)	0·0006
Surgical procedure (OC *vs* LAC)	0·39 (0·19–0·82)	0·012
Preoperative serum CEA concentrations (⩾4 ng/mL *vs* <4 ng/mL)	0·43 (0·22–0·87)	0·018
Overall survival		
Surgical procedure (OC *vs* LAC)	0·48 (0·23–1·01)	0·052
Lymph-node metastasis (presence *vs* absence)	0·49 (0·25–0·98)	0·044
Cancer-related survival		
Lymph-node metastasis (presence *vs* absence)	0·29 (0·12–0·67)	0·004
Surgical procedure (OC *vs* LAC)	0·38 (0·16–0·91)	0·029

OC=open colectomy; LAC=laparoscopy-assisted colectomy; CEA=carcinoembryonic antigen.

Table 4: **Results of Cox's regression analysis in patients with non-metastatic colon cancer**

0·49; 95% CI 0·30–0·82). Postoperative complications are shown in table 2. One patient from the LAC group and three from the OC group died within 30 days of surgery (relative risk of perioperative mortality 0·49; 0·09–2·68). Causes of death are shown in table 3.

One patient from each group was lost to follow-up 12 months after surgery. All other patients complied with the proposed postoperative surveillance protocol. Metastases were detected intraoperatively in 11 patients (five in the LAC group and six in the OC group) and, consequently, they were not included in the assessment of long-term outcome (figure 1). The median length of follow-up was 43 months (range 27–85) in the whole series, 44 months (range 27–85) in the LAC group, and 43 months (range 27–85) in the OC group.

The rate of tumour recurrence was not significantly different between groups (table 3). Data on probability of staying free of recurrence are not shown. The type of recurrence, time to recurrence, and number of patients who had curative reoperation were similar in both groups (table 3).

Lymph-node metastasis (p<0·0001), extent of primary tumour (p<0·0001), and preoperative serum CEA concentrations (p<0·005) were significantly associated with tumour recurrence in the univariate analysis. These

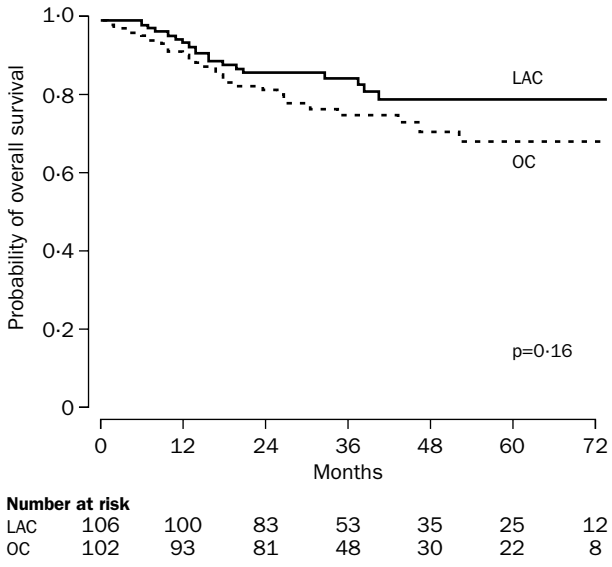

Figure 2: **Kaplan-Meier estimates of overall survival**
LAC=laparoscopy-assisted colectomy; OC=open colectomy.

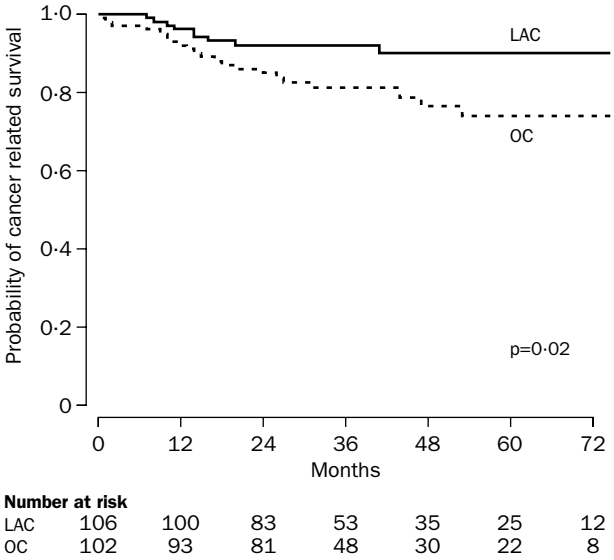

Figure 3: **Kaplan-Meier estimates of cancer-related survival**
LAC=laparoscopy-assisted colectomy; OC=open colectomy.

variables, the degree of differentiation of the tumour (p=0·06 in the univariate analysis), and surgical procedure were included in a Cox's regression model. Lymph-node metastasis, surgical procedure, and preoperative serum CEA were independent predictors of tumour recurrence (table 4).

Overall survival was not significantly different between groups (table 3). By contrast, cancer-related survival was significantly higher in the LAC group than in the OC group (table 3). Probability of overall survival was not significantly different between groups (figure 2). Probability of cancer-related survival was significantly higher (p=0·02) in the LAC group than in the OC group (figure 3).

Extent of primary tumour (p<0·0001), lymph-node metastasis (0·005), degree of differentiation (0·001), and preoperative serum CEA concentrations (0·01) were associated with overall survival in the univariate analysis. These variables, age (p=0·07), and surgical procedure were included in Cox's regression analysis. Lymph-node metastasis was the only independent predictor of overall survival (table 4).

Other variables that were associated with cancer-related survival were extent of primary tumour (p<0·0001), lymph-node metastasis (p=0·003), degree of differentiation (p=0·04), age (p=0·03), and preoperative serum CEA concentrations (p=0·02). These variables were included in Cox's regression analysis. Lymph-node metastasis was and surgical procedure were independent predictors of cancer-related survival (table 4).

Figure 4 shows the probabilities of being free of recurrence, overall survival, and cancer-related survival after the patients were stratified according to tumour stage. The superiority of LAC over OC in terms of these variables was due to differences in patients with stage III tumours (freedom from recurrence, p=0·04; overall survival, p=0·02; cancer-related survival, p=0·006). Probability curves in patients with stage I and II tumours were almost identical with both therapeutic approaches.

When the results were analysed based on actual treatment, probabilities of freedom from tumour recurrence (p=0·002), overall survival (0·02), and cancer-related survival (0·0006) were significantly higher in patients treated by LAC than in those treated by OC.

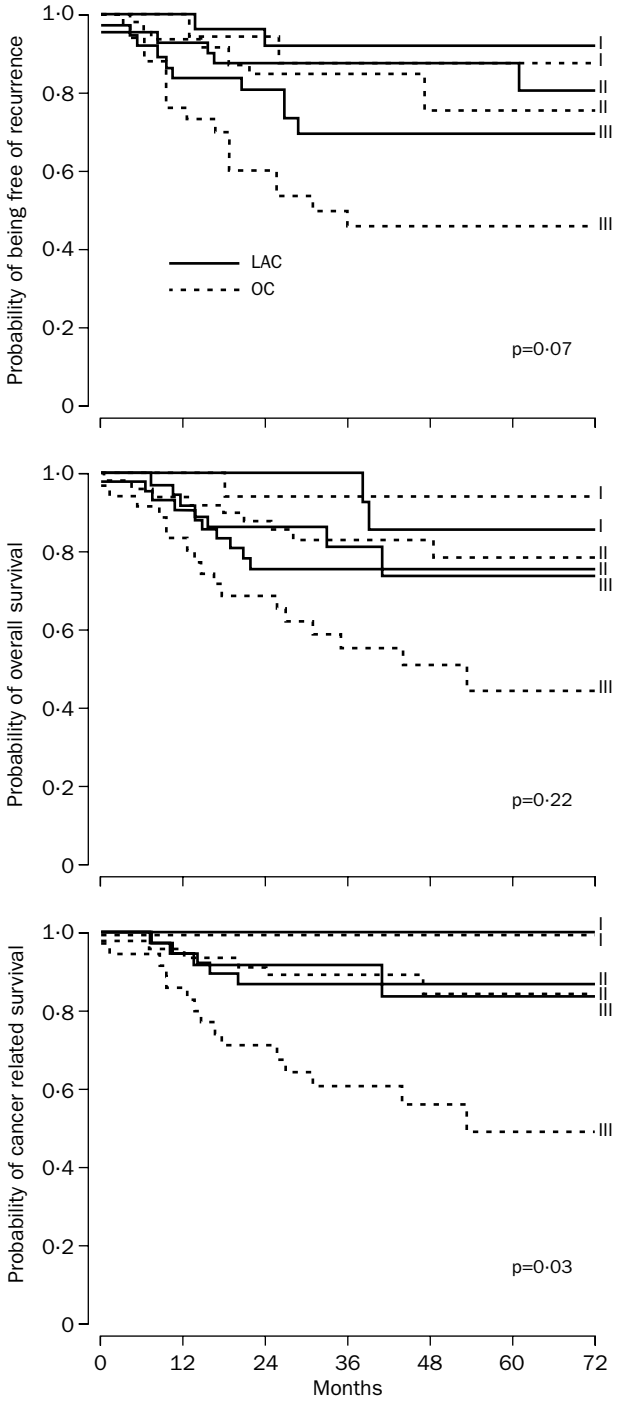

Figure 4: **Kaplan-Meier estimates of probability of being free of recurrence, overall survival, and cancer-related survival after stratifying patients according to TNM tumour stage**
LAC=laparoscopy-assisted colectomy; OC=open colectomy.

Discussion

The first report on LAC in colon cancer was published in 1991,[13] but this procedure is used by very few groups,[4–5,14–18] although it is the treatment of choice for cholecystectomy.[2] There are several possible explanations for this disparity. First, LAC is a technically difficult procedure that requires intensive training. Second, there is no randomised clinical trial that compares LAC with conventional open surgery in colon cancer; therefore, there are no data to counteract the non-substantiated traditional view that appropriate oncological surgery requires an open approach. Finally, early reports suggested that LAC in colon cancer may favour tumour dissemination.[7,8]

Our study was started in November, 1993. It was a single centre trial because at that time a multicentre study was difficult to organise, since most surgeons were not experienced in LAC. The duration of the trial and follow-up were consequently very long (almost 6 and 4 years). At the start of the trial, the surgeons who participated had much experience in laparoscopic surgery, so data obtained during the first 3 years about morbidity, tumour recurrence, and survival in patients treated by LAC were similar to those obtained in the next 3 years. We expected to show that patients treated with LAC would have lower morbidity and shorter hospital stays than those treated with OC, but that tumour recurrence and survival would be unaffected by the choice of treatment.

Our results clearly indicate that postoperative recovery is faster and complications are fewer in patients treated by LAC than in patients treated by OC. However, the most interesting result of the trial is that LAC seems to improve the long-term outcome in patients with colon cancer.

These unexpected positive findings are in agreement with those of a recently reported uncontrolled series, which showed that long-term survival of patients submitted to laparoscopic colon cancer resection was slightly higher than that described in historical series of conventional open surgery. In that respect, published 4-year or 5-year survival in large historical series varies around 60% for patients on stages I–III,[19] whereas a recent study reported a 4-year survival of 73% in patients with laparoscopic resection.[5] On the other hand, port-site metastases occurred in only one patient from the LAC group. The low rate of such an event is again in keeping with the results of more recent laparoscopic series in which figures regarding port-site metastases range from 0% to 1·3%.[4,7,18,20] That incisional tumour recurrences after open surgery do occur, albeit infrequently, should be kept in mind. Two retrospective reviews, each involving over 1000 patients, reported a 0·6% to 0·68% incidence of incisional tumours and an overall abdominal wall tumour incidence of 1%.[21,22] Therefore, on the basis of available data, the incidence of wound tumours after both open and closed colorectal cancer resection seems to be similar.

The second important finding was that the superiority of LAC over OC was due only to the results obtained in patients with advanced non-metastatic cancer (stage III). In these patients, LAC was associated with significantly lower probability of tumour recurrence and higher probability of overall and cancer-related survival. By contrast, in patients with stage I and II tumours, these variables were almost identical in both therapeutic groups. The improvement in tumour recurrence and survival in patients with stage III tumours operated on by LAC was of such magnitude that they were similar to those observed in patients with stage II tumours.

We do not know the mechanism by which LAC is associated with lower tumour recurrence and, therefore, longer survival. There is evidence that surgical stress impairs immunity[23,24] and that this feature is more intense in open surgery than in laparoscopic surgery.[25,26] Immunity has a critical role in tumour progression and metastatic spread.[27–29] This association could explain our findings, particularly the observation that LAC is associated with better outcome only in stage III tumours. In stage I and II tumours, the probability of dissemination is very low and probably not affected by changes in immunological status.

However, this situation could not be the case in patients with stage III tumours, in whom a normal immunity may be essential to prevent tumour dissemination. Another possible explanation for the favourable long-term outcome with LAC is reduced surgical stress. Manipulation of the tumour has been claimed to promote spread of cancer. In fact, there is some evidence that mobilisation of tumours during surgery is associated with exfoliation of malignant cells into the peritoneal cavity and portal vein upstream, which might be prevented by non-touch isolation techniques or eventually by minimising tumour manipulation. Preliminary reports have shown that cell spillage is not made worse by the laparoscopic technique,[30] but so far we have no evidence that dissemination of malignant cells is reduced by comparison with conventional open surgery. However, if we accept that surgical manoeuvres could have an effect on long-term survival, we could hypothesise that careful LAC by a group of surgeons highly motivated in doing a trial might prevent cancer spread in some patients.

In summary, our results show that LAC should be preferred to OC in patients with colon cancer because it reduces perioperative morbidity, shortens hospital stay, and prolongs cancer-related survival. This latter benefit was mainly due to differences in the subset of patients with stage III tumours, in whom LAC was also associated with lower tumour recurrence and longer overall survival. If these results are confirmed by ongoing multicentre randomised trials, LAC could become the standard surgical approach in patients with colon cancer.

Contributors

A M Lacy, J C García-Valdecasas, J M Piqué, and J Visa designed the protocol; A M Lacy was the study coordinator; J C García-Valdecasas, S Delgado, and P Taurá collected data; A Castells and J M Piqué did independent outcome assessment; A Castells did statistical analysis; A M Lacy, A Castells, and J M Piqué wrote and edited the report.

Conflict of interest statement

None declared.

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References

1 Boland CR, Sinicrope FA, Brenner DE, Carethers JM. Colorectal cancer prevention and treatment. *Gastroenterology* 2000; **118:** S115–28.
2 Johnson A. Laparoscopic surgery. *Lancet* 1997; **349:** 631–35.
3 Lacy AM, García-Valdecasas JC, Delgado S, et al. Postoperative complications of laparoscopic-assisted colectomy. *Surg Endosc* 1997; **11:** 119–22.
4 Milsom JW, Bohm B, Hammerhofer KA, Fazio V, Steiger E, Elson P. A prospective, randomised trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. *J Am Coll Surg* 1998; **187:** 46–54.
5 Poulin EC, Mamazza J, Schlachta CM, Gregoire R, Roy N. Laparoscopic resection does not adversely affect early survival curves in patients undergoing surgery for colorectal adenocarcinoma. *Ann Surg* 1999; **229:** 487–92.
6 Franklin ME, Kazantsev B, Abrego D, Diaz EJ, Balli J, Glass L. Laparoscopic surgery for stage III colon cancer: long term follow up. *Surg Endosc* 2000; **14:** 612–16.
7 Berends FJ, Kazemier G, Bonjer HJ, Lange JF. Subcutaneous metastases after laparoscopic colectomy. *Lancet* 1994; **344:** 58.
8 Vukasin P, Ortega AE, Greene FL, et al. Wound recurrence following laparoscopic colon cancer resection: results of the American Society of Colon and Rectal Surgeons Laparoscopic Registry. *Dis Colon Rectum* 1996; **39:** S20–S23.
9 Lacy AM, García-Valdecasas JC, Piqué JM, et al. Short-term outcome analysis of a randomised study comparing laparoscopic vs open colectomy for colon cancer. *Surg Endosc* 1995; **9:** 1101–05.
10 Lacy AM, Delgado S, García-Valdecasas JC, et al. Port site metastases and recurrence after laparoscopic colectomy: a randomised trial. *Surg Endosc* 1998; **12:** 1039–42.
11 Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ. Manual for staging of cancer, 4th edn. Philadelphia: J B Lippincott Co, 1993.
12 Cox DR. Regression models and life tables. *J R Stat Soc (B)* 1972; **34:** 187–220.
13 Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991; **1:** 144–50.
14 Stocchi L, Nelson H, Young-Fadok TM, Larson DR, Ilstrup DM. Safety and advantages of laparoscopic vs open colectomy in the elderly: matched-control study. *Dis Colon Rectum* 2000; **43:** 326–32.
15 Schiedeck TH, Schwandner O, Baca I, et al. Laparoscopic surgery for the cure of colorectal cancer: results of a German five-centre study. *Dis Colon Rectum* 2000; **43:** 1–8.
16 Fleshman JW, Nelson H, Peters WR, et al. Early results of laparoscopic surgery for colorectal cancer: retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) Study Group. *Dis Colon Rectum* 1996; **39:** S53–S58.
17 Leung KL, Yiu RY, Lai PB, Lee JF, Thung KH, Lau WY. Laparoscopic-assisted resection of colorectal carcinoma: five year audit. *Dis Colon Rectum* 1999; **42:** 327–32.
18 Pearlstone DB, Mansfield PF, Curley SA, Kumparatana M, Cook P, Feig BW. Laparoscopy in 533 patients with abdominal malignancy. *Surgery* 1999; **125:** 67–72.
19 Newland RC, Chapuis PH, Pheils MT, Macpherson JG. The relationship of survival to staging and grading of colorectal carcinoma: a prospective study of 503 cases. *Cancer* 1981; **47:** 1424–29.
20 Hartley JE, Mehigan BJ, MacDonald AW, Lee PW, Monson JR. Patterns of recurrence and survival after laparoscopic and conventional resections for colorectal carcinoma. *Ann Surg* 2000; **232:** 181–86.
21 Reilly WT, Nelson H, Schroeder G, Wieand HS, Bolton J, O'Connell MJ. Wound recurrence following conventional treatment of colorectal cancer. *Dis Colon Rectum* 1996; **39:** 200–07.
22 Hughes ESR, McDermott FT, Polglase AL, Johnson WR. Tumor recurrence in the abdominal wall scar after large-bowel cancer surgery. *Dis Colon Rectum* 1983; **26:** 571–72.
23 Hansbrough JF, Bender EM, Zapata-Sirvent R, Anderson J. Altered helper and suppressor lymphocyte populations in surgical populations in surgical patients: a measure of postoperative immunosuppression. *Am J Surg* 1984; **148:** 303–07.
24 Decker D, Schondorf M, Bidlingmaier F, Hirner A, von Ruecker AA. Surgical stress induces a shift in the type-1/type-2 T-helper cell balance, suggesting down regulation of cell mediated and up-regulation of antibody-mediated immunity commensurate to the trauma. *Surgery* 1996; **119:** 316–25.
25 Vittimberga FJ Jr, Foley DP, Meyers WC, Callery MP. Laparoscopic surgery and the systemic immune response. *Ann Surg* 1998; **227:** 326–34.
26 Delgado S, Lacy AM, Filella X, et al. Acute phase response in laparoscopic and conventional colectomy in colon cancer: a randomised study. *Dis Colon Rectum* 2001; **44:** 638–46.
27 Cole WH. The increase in immunosuppression and its role in the development of malignant lesions. *J Surg Oncol* 1985; **30:** 139–44.
28 DaCosta ML, Redmond HP, Finnegan N, Flynn M, Bouchier-Hayes D. Laparotomy and laparoscopy differentially accelerate experimental flank tumour growth. *Br J Surg* 1998; **85:** 1439–42.
29 Bouvy ND, Marquet RL, Jeekel J, Bonjer HJ. Laparoscopic surgery is associated with less tumour growth stimulation than conventional surgery: an experimental study. *Br J Surg* 1996; **84:** 358–61.
30 Bessa X, Castells A, Lacy AM, et al. Laparoscopic-assisted versus open colectomy for colorectal cancer: influence on neoplastic cell mobilization. *J Gastrointest Surg* 2001; **5:** 66–73.