Laparoscopic Colectomy for Cancer Is Not Inferior to Open Surgery Based on 5-Year Data From the COST Study Group Trial

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Purpose: Oncologic concerns from high wound recurrence rates prompted a multi-institutional randomized trial to test the hypothesis that disease-free and overall survival are equivalent, regardless of whether patients receive laparoscopic-assisted or open colectomy.

Methods: Eight hundred seventy-two patients with curable colon cancer were randomly assigned to undergo laparoscopic-assisted or open colectomy at 1 of 48 institutions by 1 of 66 credentialed surgeons. Patients were followed for 8 years, with 5-year data on 90% of patients. The primary end point was time to recurrence, tested using a noninferiority trial design. Secondary endpoints included overall survival and disease-free survival. (Kaplan–Meier)

Results: As of March 1, 2007, 170 patients have recurred and 252 have died. Patients have been followed a median of 7 years (range 5–10 years). Disease-free 5-year survival (Open 68.4%, Laparoscopic 69.2%, $P = 0.94$) and overall 5-year survival (Open 74.6%, Laparoscopic 76.4%, $P = 0.93$) are similar for the 2 groups. Overall recurrence rates were similar for the 2 groups (Open 21.8%, Laparoscopic 19.4%, $P = 0.25$). These recurrences were distributed similarly between the 2 treatment groups. Sites of first recurrence were distributed similarly between the treatment arms (Open: wound 0.5%, liver 5.8%, lung 4.6%, other 8.4%; Laparoscopic: wound 0.9%, liver 5.5%, lung 4.6%, other 6.1%).

Conclusion: Laparoscopic colectomy for curable colon cancer is not inferior to open surgery based on long-term oncologic endpoints from a prospective randomized trial.

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Fourteen years ago the Clinical Outcomes of Surgical Therapy (COST) Study Group began the first multicenter, randomized, controlled trial to evaluate the use of laparoscopic colectomy for colon cancer.[1] The trial was initiated in response to oncologic concerns over the appropriateness of the technique for potentially curable disease; stimulated by a number of reports in the literature of abdominal wall recurrences in trocar and specimen extraction sites.[2–5] A group of diverse surgeons interested in and experienced in laparoscopic colectomy formed the COST Study Group to evaluate the technique and measure the outcomes of laparoscopic colon cancer surgery.[1] Quality of life and recovery data published in 2002 by the COST Study Group confirmed the benefits of laparoscopic colectomy in the early post operative period.[6] International trials, including the Conventional versus Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer and Colon Cancer Laparoscopic or Open trials have also published early results of short-term recovery and confirmed similar patient benefits.[7,8] There is now substantial evidence to support early recovery benefits and modest quality of life benefits for patients treated with laparoscopic colectomy.[9,10] In contrast to recovery benefits, only limited information has been reported on cancer outcomes and none on 5-year survival.

The initial analysis of the COST trial including 872 patients revealed no difference in recurrence or survival rates at 3 years for patients undergoing open versus laparoscopic colectomy for cancers of the right, left, and sigmoid colon.[11] Recent pooled analyses of several international multicenter

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Members all participating members of the Clinical Outcomes of Surgical Therapy Study Group are listed in the Appendix.

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trials confirmed this equivalence for early oncologic outcomes in a larger comparison, including over 1500 patients.[12,13] A smaller randomized trial, conducted at a single institution, found a significant improvement in 3-year survival in the laparoscopic group.[14] This difference was explained by an improved survival in patients with stage III cancer in the laparoscopic group. This has not been confirmed by other reports of 3-year follow-up. Our present report contains the first 5-year outcomes data and furthermore, examines patient, tumor-specific, and surgical technique factors, which may assist in predicting successful surgical treatment and good oncologic outcomes after laparoscopic treatment of colon cancer.

METHODS

The details of the design and methods for this noninferiority trial have been previously reported.[1,6,11] Only patients with adenocarcinoma in the right, left, or sigmoid colon were eligible for randomization to either treatment with elective laparoscopic-assisted colectomy or open colectomy. Patients with advanced local (T4) or systemic (stage IV) cancer, inflammatory bowel disease, polyposis, diffuse abdominal adhesions, severe medical illness, pregnancy, circumstances requiring emergency operation, or age <18 years were excluded. Patients signed a written consent for the institutional review board approved study at each participating institution.

The 66 participating surgeons were credentialed after submitting 20 operative reports describing oncologically appropriate laparoscopic procedures and a video of a laparoscopic colectomy, which included all of the features of an oncologically appropriate resection (proximal mesenteric vascular ligation, adequate proximal and distal margins and lymph node harvest, mobilization of the intestine and identification of critical structures without handling the tumor, containment of the bowel contents during tissue extraction and anastomosis, and a thorough exploration of the abdomen). Hand access techniques were not included in this trial. Specimen extraction sites were protected and used for the anastomotic portion of the procedure in most cases.

The open and laparoscopic colectomy procedures were intended to provide similar cancer resection specimens for each segment of the colon requiring resection, as previously described. Conversion to an open procedure was defined as the creation of an abdominal wall incision to accomplish a critical portion of the procedure before the laparoscopic portion of the procedure was completed and was mandated for patients with previously undetected invasion of local structures or inability to identify or handle structures "critical" to the achievement of an oncologically sound procedure. Enlarging the extraction site incision to remove a bulky tumor was not considered a conversion to an open procedure. Postoperative care and adjuvant chemotherapy standards were dictated by the individual surgeon's practice and the same standards applied to patients in both treatment arms.

Randomization

Randomization to either laparoscopic-assisted colectomy or open colectomy was performed centrally at the time of scheduling the procedure through the North Central Cancer Treatment Group. A minimization algorithm was used to balance the groups based on 3 stratification variables; Primary tumor site along the length of the colon, American Society of Anesthesiology class, and surgeon.

Follow-Up

Patients were evaluated for tumor recurrence as follows: physical examination (including checking for recurrence at wound sites) and carcinoembryonic antigen testing every 3 months the first year and then every 6 months until year 5 completed; chest radiography every 6 months for 2 years and then annually; and total colon evaluation every 3 years. Confirmation of recurrence required imaging or pathologic evaluation.

Statistical Analysis

The plan for statistical analysis has been detailed previously.[1] This trial was designed as a noninferiority study to demonstrate that laparoscopic colectomy was not worse than open colectomy on the primary end point of time to tumor recurrence. Time to tumor recurrence was defined as the time from randomization to the first confirmed recurrence. Documented recurrence-free death within 5 years of randomization resulted in the patient's data being censored for recurrence at the time of death; otherwise patients were assumed to have a recurrence at death for the primary analysis. The protocol specified primary analysis was a one-sided log-rank test comparing time to recurrence in the laparoscopic and open colectomy groups and included converted cases with the laparoscopy group consistent with the intention-to-treat approach. If the one-sided P value was less than 0.09 in favor of open colectomy, the open-colectomy group's time to recurrence was to be declared superior; otherwise, the laparoscopic procedure would be declared noninferior to the open procedure. The planned accrual of 1200 patients provided 81% power to declare the laparoscopic procedure inferior if the hazard ratio for recurrence with the laparoscopic procedure, as compared with the open procedure, was 1.23. If the hazard ratio was 1.0 (the 2 procedures were equivalent), there was a 9% chance of declaring the laparoscopic procedure inferior. This calculation assumed a 21% conversion rate from laparoscopic to open surgery, that patients who were converted would have the same recurrence rate as those undergoing open colectomy, and a 3 year recurrence-free rate of 80% among patients treated with open colectomy.

The protocol specified a plan for a modified analysis for less than complete accrual. In such a case, the significance value for the log-rank test was to be modified based on the actual number of recurrences in the open-colectomy group such that the test retained an 81% chance of declaring the laparoscopic procedure inferior if associated with 23% increase in the risk of recurrence. The external data-monitoring committee for the protocol approved the final analysis plan before release of efficacy results to the study investigators. Based on the observed number of recurrences, if the one-sided P value in favor of the open procedure was less than 0.41, the open procedure would be declared superior; otherwise, the laparoscopic procedure would be declared noninfe-

rior. The readjustment of the total numbers of patients downward to 872 preserved adequate statistical power primarily due to the fact that enough events occurred in the longer than originally anticipated period of enrollment and follow-up (14 years). The power of 81% still applies to the conclusion that laparoscopy is not inferior to open surgery.

Secondary endpoints included disease-free survival (DFS), overall survival (OS), complications, recovery parameters, and quality of life. All eligible patients for whom operative treatment was attempted were included in the analysis, except those with benign disease, who were excluded from analyses of time to recurrence, DFS and OS. Five patients were analyzed in the laparoscopic group after being randomized to the open group but treated with laparoscopic colectomy. Univariate comparison of surgical and postoperative data was conducted with the use of a 2-sample *t* test for continuous variables and χ^2 test for categorical data.

Cumulative incidence methods were used to estimate the rate of tumor recurrence,[15] the hazard ratio for cumulative incidence used the method of Fine and Gray.[16] Kaplan-Meier curves were used to estimate the distribution of DFS and OS.[17] The log-rank test was used to compare time-to-event distributions[18]; the Cox proportional hazards regression model was used for multivariate models.[19] All reported *P* values were two-sided with the exception of a one-sided test for the primary analysis of the time to recurrence; *P* values of less than 0.05 were considered to indicate statistical significance.

Patients and Follow-Up

A total of 872 patients with curable colon cancer were randomly assigned to undergo laparoscopic colectomy or open colectomy from August 1994 to 2001 at 1 of 48 institutions and operated on by 1 of 66 credentialed participating surgeons.[11] Two patients refused surgery and 7 were considered screening failures and ineligible for the study, leaving 863 patients for the final analysis. Seventy-nine patients were excluded from long term follow-up due to benign disease (53) or stage IV disease (26). Five year follow-up has been completed in 852 patients as of March 2007 and data points are calculated at this time point. Only 20 patients were lost to follow-up. These 20 patients were included in the analysis but censored at the point of last follow-up.

Surgery

As previously reported, 428 patients underwent open colectomy and 435 were treated with laparoscopic colectomy; 21% of the laparoscopic cases required conversion.[11] Enrolled patients were distributed among the 66 surgeons as follows: >50 cases: 3 surgeons; <50, >10 cases: 23 surgeons, <10 cases: 40 surgeons. The open colectomy group had a higher rate of concomitant resection of adjacent involved structures (8% laparoscopic, 15% open, $P = 0.001$), whereas the laparoscopic group had more adhesions to the abdominal wall (35% laparoscopic, 25% open, $P = 0.002$) and to the bowel (22% laparoscopic, 14% open, $P = 0.002$). Resection parameters were similar between the groups with no difference in margins or lymph node harvest (median 12). Operative times were longer for the laparoscopic colectomy group (median 166 minutes laparoscopic, 108 minutes open, $P < 0.001$) but hospital stay (median 5.5 days laparoscopic, 6.7 days open, $P > 0.001$) and narcotic use were shorter for the laparoscopic group (median 3 days laparoscopic, 4 days open, $P < 0.001$). Complications were also similar between the groups. Chemotherapy usage paralleled the number of patients with stage III disease in both groups.

Survival and Recurrence

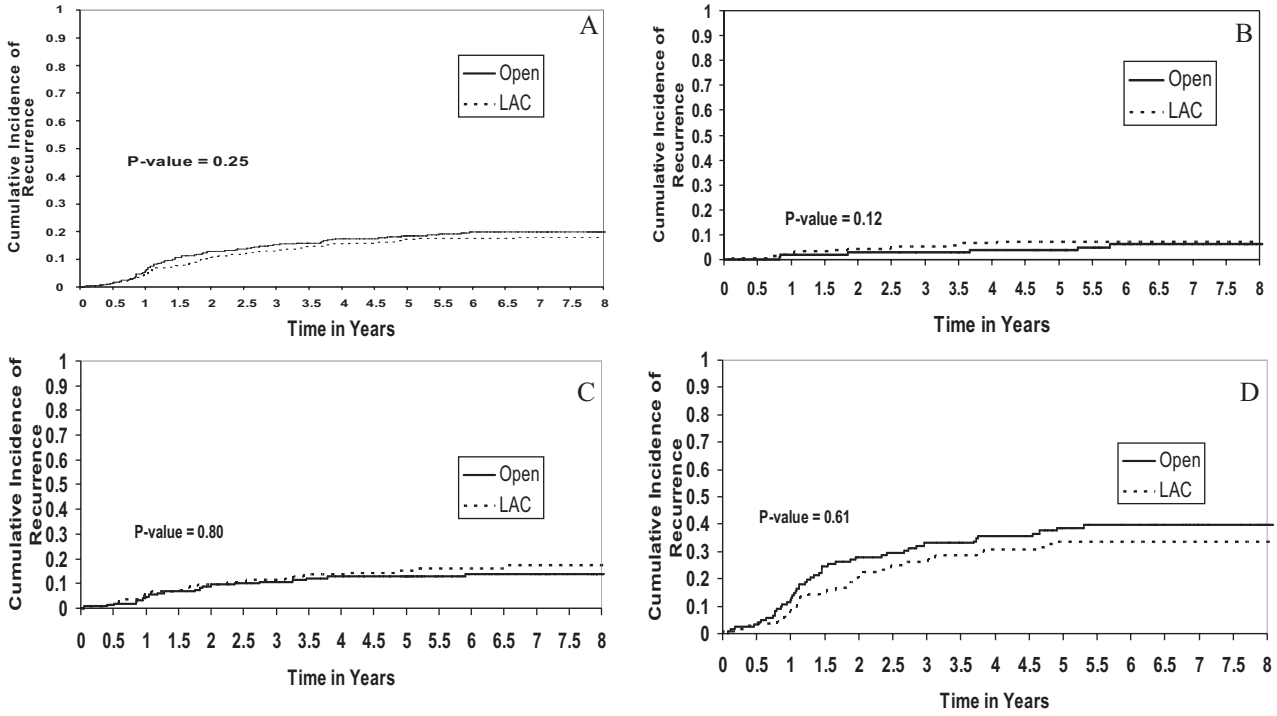
As of March 1, 2007, 170 patients have recurred and 252 have died. Disease-free 5-year survival, overall 5-year survival, overall recurrence rates and sites of first recurrence (including wound recurrences) were similar for the 2 groups (Table 1). The one-sided *P* value for time to recurrence in favor of the open procedure was 0.75, again satisfying the criteria to declare the laparoscopic procedure non inferior to the open procedure. As shown in Figure 1, the cumulative incidence of recurrence among patients treated with the laparoscopic procedure did not differ significantly from that for the open group (two-sided 0.25 hazard ratio for recurrence = 0.84; 95% confidence interval, 0.62–1.13). Adjusting analyses for the stratification factors of site of the primary tumor and American Society of Anesthesiology class[20] did not affect the recurrence or survival rates.

Recurrence rates (Fig. 1) and disease free survival (Fig. 2) did not differ between the groups by stage of disease. In this subset analysis, the OS in patients with stage I disease was significantly higher in the open group (Fig. 3) (Open 93%, Laparoscopic 85%, $P = 0.04$). There was, however, no difference between the 5-year DFS or cumulative incidence of recurrence for stage I patients treated with either operation. Among stage I patients, the number of cancer-related deaths was identical between the 2 arms (4 in each group).

An exploratory subset analysis, not powered to make a statement of significance, was undertaken to identify potential factors affecting cancer treatment outcome and the ability to successfully complete the operation through a laparoscopic approach (ie, conversion). Tumor depth (T classification), tumor differentiation, surgeon experience (expressed as number of study cases contributed), and bowel margins were not different between converted and completed cases (Table 2). Five year DFS and cumulative incidence of recurrence were not affected by conversion to open surgery (DFS: converted

TABLE 1. Five-year Cancer Outcomes for Laparoscopic and Open Colectomy Patients

Outcome	Open (n = 428)	LAC (n = 435)	*P*
Overall survival	74.6%	76.4%	0.93
Disease-free survival	68.4%	69.2%	0.94
Local recurrence rates	2.6%	2.3%	0.79
Overall rates of recurrence	21.8%	19.4%	0.25
Sites of first recurrence			
Wound	0.5%	0.9%	0.43
Liver	5.8%	5.5%	0.85
Lung	4.6%	4.6%	0.95
Other	8.4%	6.1%	0.21



Cumulative Rates of Recurrence: A: All Stages; B: Stage I; C: Stage II; D: Stage III

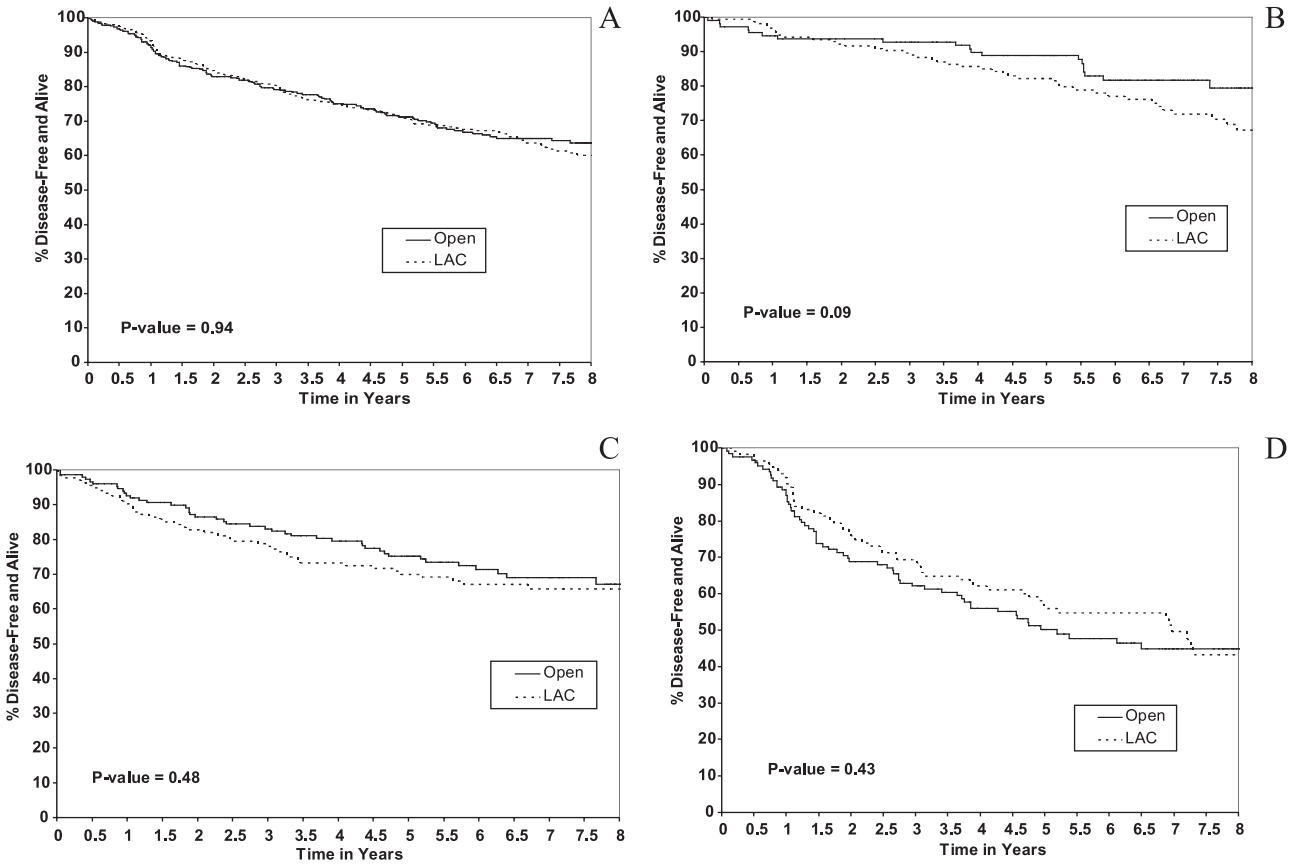
FIGURE 1. Cumulative incidence of recurrence.

73%, completed 63%, $P = 0.06$, CIR: converted 20%, completed 17%, $P = 0.56$). Five-year OS was better in those whose surgery was completed laparoscopically (80%) compared with those converted to open (69%) ($P = 0.04$). Reasons for conversion are diverse and included conversions encouraged or protocol mandated for safety or oncologic purposes including presence of advanced disease, complicating diseases, or inadequate margins (Table 3). Conversion to an open operation was significantly associated with the presence of adhesions (positive = 30% conversion, negative = 12% conversion, $P = 0.001$) as were postoperative intra-abdominal infection complications (positive = 41% conversion, negative = 20% conversion, $P = 0.04$).

DISCUSSION

The 5-year follow-up data of the COST Study Trial confirms that we are doing no harm by offering patients with curable colon cancer a minimally invasive approach to removing the disease. The COST Study Group Trial comparing laparoscopic and open colectomy for curable cancer was conceived of in response to the concern that laparoscopic techniques applied to curable colon cancer may change the incidence or patterns of recurrent cancer.[21] The low cure rate for surgical and medical treatment of recurrent colon cancer dictates that there is very little room for error when surgically removing a potentially curable tumor. As the COST group established a protocol that would answer this question, we realized that it would be impossible to prove true equivalence of laparoscopy and open operation in a study that would be finished in any practical time span. The estimated number of patients required would have been close to 3000. Thus the noninferiority trial was devised.[1] Dr. Wieand, the statistician, developed the noninferiority trial design to use a one-sided statistic to test whether or not there would be an inferior outcome for laparoscopic colectomy. The literature in 1993 did not suggest that laparoscopy might be superior so a noninferiority trial was developed based on oncologic outcomes. This one-sided trial design allowed for a smaller number of patients while preserving the greater than 80% power for the accuracy of the conclusion (a reasonable level of confidence in a clinical trial) that laparoscopic colectomy does not adversely affect the oncologic outcome of the patient. The ability to now demonstrate that the laparoscopic approach is not inferior is a benefit for patients because of the tangible benefits, including the lack of harm to patients and the potential for more novel approaches based on the laparoscopic approach in the future.

The problem of trocar site implants which stimulated a great deal of research, controversy and emotion has now been relegated to experience.[2–5,22] The success of this trial should demonstrate to the surgical community that new techniques which have the potential to negatively impact patient outcomes must first be scrutinized under the magnifying glass of controlled clinical trials, and the individual surgeon should now realize that surgical technique does matter. The learning curve is not a time to be practicing a new technique on patients with malignant disease. The learning curve for lapa-



5-yr Disease-Free Survival for:
A: All Stages; B: Stage I; C: Stage II; D: Stage III

FIGURE 2. Five-year disease-free survival.

roscopic colorectal surgery is likely greater than the 20 cases required to participate in this trial.[23–26] However, the quality control and standardization of technique applied to the surgical aspects of the study may demonstrate that learning curve issues may be diminished by the collaboration of interested colleagues to establish safe and reproducible operations even in the setting of new technology.

The conversion rate in this trial (21%) was not necessarily a result of the trial taking place in the early part of the laparoscopic colectomy experience, and in fact, the rate of conversion remained remarkably constant over the entire course of the study. The COST Group defined the standardized surgical technique up front and held the participating surgeons to those criteria for appropriate operative technique using random video audit and education. The criteria included adequate bowel and mesenteric margins, ligation of the first feeding vessel at its origin and limited handling of the bowel and tumor. The criteria for converting to an open operation required conversion to an open operation in patients with advanced disease and when critical structure could not be identified. These high standards are a probable reason that there is no difference in cancer outcomes between patients converted to an open procedure and those completed laparoscopically. These high standards may also be responsible for the improved local outcomes-no increase in wound implants of cancer and no increase in intra-abdominal recurrence of T_4 lesions. Our decision to start the trial early in the learning curve, combined with the patient advocacy stance of the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal Endoscopic Surgeons to recommend restriction of laparoscopic colectomy for curable cancer, served to stop the uncontrolled use of the technique and the possible disastrous consequences of patient injury and the condemnation of a potentially beneficial technique before those benefits could be demonstrated. Based on the experience and outcomes of this trial, consideration should be given to the practice of standardization of surgical technique to insure consistent outcomes throughout the surgical community.

The major criticism of this study has been that it did not reach the original accrual goal of 1200 patients and relied on a (prespecified) statistical back up plan to achieve the statistical goals. There were several reasons for the slower than expected accrual. Early trial participation by surgeons skilled in the novel techniques of laparoscopy were hampered by the very limited involvement of such surgeons in the National

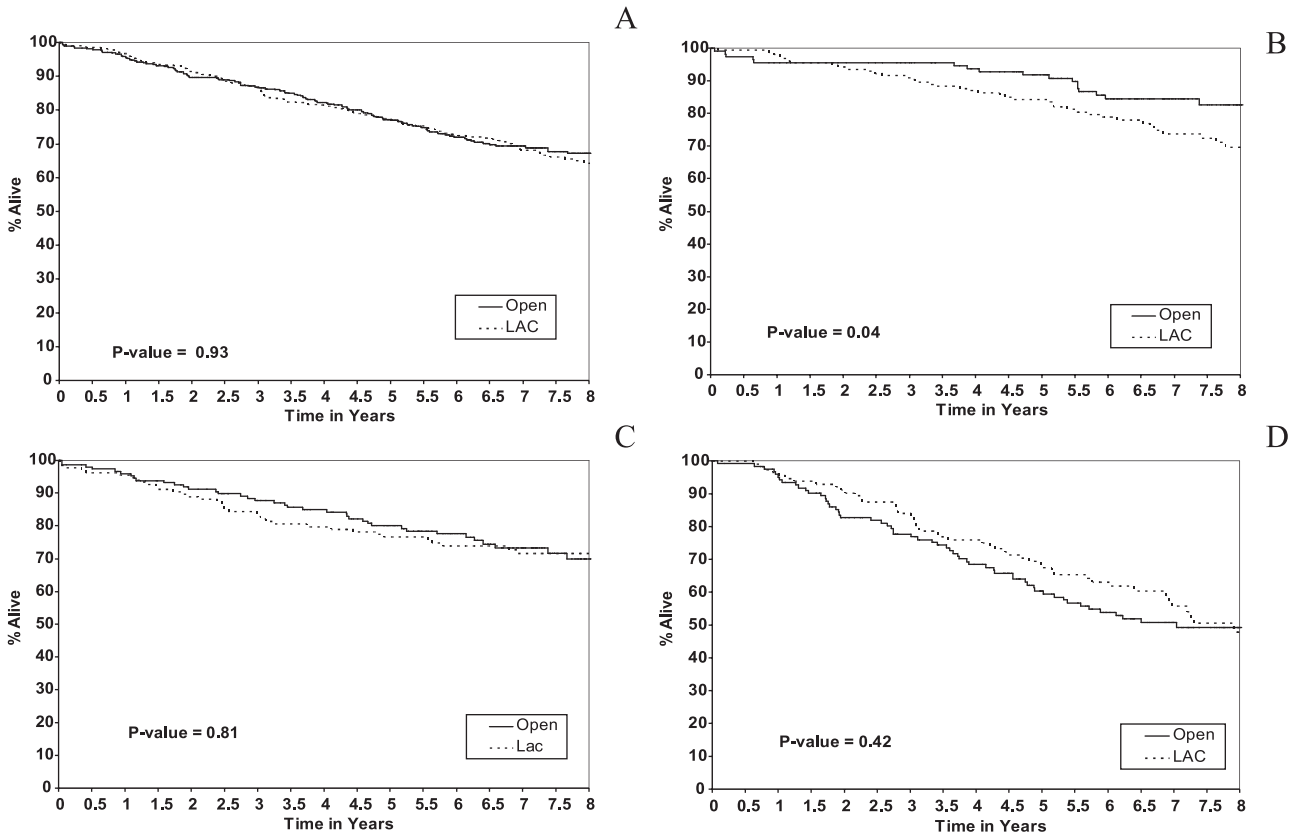


FIGURE 3. Five-year overall survival.

Cancer Institute funded Cooperative Groups. The initial barriers for early and broad trial involvement by laparoscopic surgeons included the need for such surgeons to join a cooperative group, establish a NIH-investigator number, and obtain protocol approval through their Cooperative Group and through their local institutional review board. Furthermore, each surgeon had to complete a novel and intensive credentialing process. It was time-consuming for both surgeons to provide the documents and videos, and for the review team to complete the credentialing process and approve each surgeon. The original target of 10 to 20 institutions had to be readjusted during the trial to ensure adequate enrollment for a meaningful result. Another reason for poor accrual evolved as the study progressed. Patients began self directing themselves to surgeons willing to perform laparoscopic colectomy for cancer off protocol; this influenced some participating surgeons and diminished their ability to recruit patients. These challenges demonstrate the essential commitment to offering a new technique only within the setting of a randomized trial to allow rigorous evaluation process, through randomization, to succeed. Those who persisted and finished the trial should be congratulated and be held as an example of what can be accomplished given the commitment to the science of clinical research and the benefits of practicing evidence-based medicine.

The overall 5-year survival rates for both groups (all stages of cancer) were almost identical ($P = 0.93$). However, the overall 5-year survival for patients with stage I tumors was significantly better for the open colectomy group. This difference was not present in disease free survival or cumulative incidence of recurrence for patients with stage I cancer, and the statistical interaction between type of procedure, and stage, was not significant for OS. Thus, the patients with stage I disease in the laparoscopic colectomy group who died either did so of noncancer causes, or the event rate was so low that a chance difference was found in the subset analysis of relatively small groups. It is possible that this underpowered subset analysis can explain the finding in the Barcelona trial that laparoscopic colectomy is superior for patients with stage III cancer of the colon. Thus, our data do not support the idea that outcomes may be improved with the laparoscopic procedure due to a significantly lower stress induced by the laparoscopic approach.

The reassurance that laparoscopic approaches to colon cancer cause no harm to patients allows us to look to future uses of minimally invasive techniques. The next logical step is to evaluate the laparoscopic treatment of rectal cancer. Because the rectum presents different technical challenges for the laparoscopic approach, the next study should focus on outcomes which reflect adequacy of technique such as ade-

TABLE 2. Analysis of Select Variables for Laparoscopic Cases Comparing Completed and Converted Procedures

Variables	Completed (n = 345)	Converted (n = 90)	*P*
Tumor depth (T classification), n (%)			0.79
T1–2	139 (40.2)	36 (40)	
T3–4	188 (54.5)	52 (57.8)	
Unknown	18 (5.2)	2 (2.2)	
Tumor differentiation, n (%)			0.99
Poor/undifferentiated	44 (12.8)	12 (13.3)	
Well/moderate	280 (81.1)	76 (84.5)	
Unknown	21 (6.1)	2 (2.2)	
Surgeon study cases, n (%)			0.23
<10	31 (9.0)	11 (12.2)	
>10	314 (91.0)	79 (87.8)	
Unknown	0 (0)	0 (0)	
Bowel margins, n (%)			0.07
<5 cm	14 (4.0)	8 (8.9)	
>5 cm	330 (95.7)	82 (91.1)	
Unknown	1 (0.3)	0 (0)	
Intraoperative adhesions, n (%)			<0.001
No	196 (56.8)	25 (27.8)	
Yes	148 (42.9)	65 (72.2)	
Unknown	1 (0.3)	0 (0)	
Surgical complications*, n (%)			0.4
No	335 (97.1)	83 (92.2)	
Yes	10 (2.9)	7 (7.8)	
Unknown	0 (0)	0 (0)	

*Includes complications identified during surgery; clearly related to surgery (abdominal sepsis or hemorrhage); or requiring additional surgery.

TABLE 3. Reasons for Converting from Laparoscopic to Open Colectomy

Reasons for Conversion	Freq. (n = 92)	Percent	Cum. Freq	Cum. %
Advanced disease	23	25%	798	92.04
Complicating disease	3	3%	801	92.39
Inadequate margins of resection	4	4%	802	92.85
No visualization of critical structure	12	13%	817	94.23
Unable to mobilize colon	10	11%	827	95.39
Due to adhesions	14	15%	841	97.00
Intraoperative complications	4	4%	845	97.46
Other	22	24%	867	100.00

quate circumferential margins and en bloc resection. The biologic considerations for a laparoscopic approach to colon cancer should translate to rectal cancer and one would expect local recurrence to be a more indicative surrogate for excellent technique than disease free survival. As we move to more technically challenging uses of the laparoscopic approach, credentialing of surgeons, standardization of technique and monitoring of outcomes becomes more important. It remains our most difficult task to balance the potential for improvement in the quality of life for patients with the risk of poor cancer outcomes as a result of a new technique. Only a controlled trial can provide these answers.

CONCLUSIONS

The evaluation of the 5-year follow-up of oncologic endpoints from the COST Study Group Trial comparing laparoscopic colectomy with open colectomy confirms the previous findings at 3 years. Laparoscopic colectomy for curable colon cancer is not inferior to open surgery.

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APPENDIX

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Discussions

DR. DAVID A. ROTHENBERGER (MINNEAPOLIS, MINNESOTA): I think members of the American Surgical Association probably recall that this study, when it was first proposed in 1994, was quite controversial. The idea of doing a protocol prospectively looking to compare laparoscopic or open colectomy for curable colon cancer in a randomized fashion was not something that many people embraced. And I will confess that I was certainly one of those bothered by the fact that at best it was hoped that this study would show the laparoscopic colectomy was not inferior to open colectomy. I remember that our group had several heated discussions about whether we wanted to participate in this trial or not and ultimately voted against doing so because of our concerns for the oncologic outcomes and our worries that we were just not at a point of being good enough to do laparoscopic colectomy for cancer. I am certainly happy that our fears were un-

founded and that you had the courage, tenacity, and confidence to fight for and then complete this trial. I have 4 questions for you.

Number 1, your manuscript describes the reasons that you chose to use a non-inferior trial methodology rather than trying to prove equivalence of laparoscopy and open colectomy. For us mere surgeons who are not advanced biostatisticians, could you explain the real world differences between these 2 designs and the reasons that you chose the non-inferiority method?

Number 2, despite the fact that you had 66 surgeons from 48 institutions who were so committed to this protocol that they submitted to special credentialing and monitoring of technique, you fell significantly short of your accrual goal of 1,200 patients. How confident are you that the conclusions you have reached are valid since they are based on 872 patients and your prior analysis was based on 1,200? Why was the accrual so difficult? What have you learned that might help the accrual in future similar trials?

Number 3, would you comment on the possible impact that your study may have on future credentialing of surgeons requesting privileges to perform colon cancer resections? Will video audits become commonplace?

Number 4, you report quite excellent results in both the laparoscopic and open groups. Is it possible that this is the result of selectivity, selectivity of surgeons who are intensely interested in the problem of colon cancer and of patients who were willing to be randomized in such a trial? And do the biases in such a selective study make it impossible to apply your results equally to all surgeons? Should everyone now abandon open colectomy and only perform laparoscopic resection for curable colon cancer?

Dr. Heidi Nelson (Rochester, Minnesota): You are correct; the COST trial was a non-inferiority trial, not an equivalence trial. When Dr. Wieand and I sat down and tried to imagine doing an equivalence trial, a 2-sided evaluation testing for both superiority and inferiority, we calculated that it would have required 3,000 patients. Being pragmatic, we realized that was an impossible goal. Dr. Wieand was creative enough to develop this non-inferiority statistical design method—a method that was not described in the statistical literature until 1997. With only the 1-sided statistic, this trial was powered to test whether there would be an inferior outcome for laparoscopic colectomy. There was nothing in the literature in 1994 to suggest there was a likelihood that laparoscopic colectomy would produce a superior result, hence the design, and the practicality of actually completing the study.

The accrual problems you mentioned are accurate. We planned 1,200 patients, we only enrolled 872, and it took us 7 years instead of 3. I think the most important lesson was that you want to have as many centers involved early. We tried to keep it a small group in the beginning so that we could better control the standardized surgery. We quickly learned this was not a viable approach, and we then opened the study to 48 institutions. The original target was 10 to 20 centers. Adding institutions helped the accrual. Surgeons were not experienced with conducting these kinds of trials. We indeed learned many lessons about performing surgical trials.

In regard to the power of the study, the Monitoring Committee of North Central Cancer Treatment Group closed the trial at 872 patients because the number of events occurring over 7 years of accrual had accumulated enough to achieve the same estimates of disease-free survival expected for 1,200 patients at 3 years of accrual. It maintained an 81% power. The conclusions still stand firm that laparoscopic colectomy is not inferior.

The impact of credentialing is an excellent point. Looking back, it impresses me that surgeons voluntarily underwent credentialing for this trial. This speaks highly of surgeon integrity. I look to the leaders in this audience to say, how does this go forward? We have a great opportunity because we can now video record surgical cases. In the future, one can imagine that a trainee enters their boards and they hand somebody a videotaped procedure that can be viewed and they can defend it. This study speaks to that as a possibility.

As far as the excellent results, I think your point is we cannot compare this study to other population-based data such as the National Cancer Database or to other trials because we do not know the impact of patient selection. So I would argue we should not compare. In regards to selection of the surgeons, I also think the trial might have achieved a higher standard due to credentialing and standardization. We needed the higher standard to truly test laparoscopy. The challenge now is to get this high level of standard into the laparoscopic practice safely as an alternative to open surgery.

Dr. Michael E. Zenilman (Brooklyn, New York): I would like to also congratulate you on setting the standard for how to bring new procedures into our armamentarium. I would like to ask about credentialing. How many procedures do you think somebody needs to do to perform laparoscopic surgery at a level to be considered competent?

As a second question, how should we handle the emergence of new procedures, for example resective surgery through natural orifices? You have set the standard to credential and monitor these new procedures.

Dr. Heidi Nelson (Rochester, Minnesota): In regards to the credentialing standards, we have never identified an absolute minimum number of cases. In fact, there are too many variables to consider only 1 number as appropriate for all training circumstances. The best we came up with was 20 cases. It seemed to work for this Study Group. Whether that is truly appropriate is difficult to ascertain.

In regards to newer procedures, I am optimistic that just as we conducted a clinical trial of this type, we will continue to do similar clinical trials as we usher in new and novel therapies. We have new opportunities; we have a new National Cancer Institute Cooperative Group with a surgical focus; the American College of Surgeons Oncology Group (ACOSOG). Dr. Fleshman will be doing a laparoscopic rectal trial through ACOSOG, and I am sure after the rectal trial is done, there will follow natural orifice surgery, and as it evolves, it will be put to the test in the same manner, first tested in a pilot fashion and then in a Phase III trial.

Dr. Stanley P. Leong (San Francisco, California): Although your trial name does not actually refer to the cost, what is the total cost of the study?

My second question is, how difficult is it to monitor and audit the study in terms of number of nurse and study coordinators, research nurses, and the overall non-surgical personnel for the study? Furthermore, you have indicated that we surgeons are just about to step into this major clinical trial arena. Therefore, it is important to understand the regulatory issues and standards of clinical trials to make sure that every protocol is streamlined and followed. How do you educate the surgeons and how do you monitor compliance?

Dr. Heidi Nelson (Rochester, Minnesota): Dr. Leong, you are correct in assuming that this trial was expensive and highly regulated. The exact cost of the study is hard to estimate. The grant was about $2 million from the National Institutes of Health. It did not cover anywhere near the total cost of the study, which was borne by the cooperative groups. These Cooperative Groups have infrastructures that are funded by the National Cancer Institute. And I would say the actual cost was probably at least 4 times that amount.

You raise excellent points regarding all the complex regulatory issues, which are far in excess now than they were in 1993. You increasingly need an established infrastructure at an institution to do this type of trial. You also need infrastructure within the clinical trials group to do these trials. We were fortunate that all participants could use their own cooperative groups to contribute patients.

Dr. Anton J. Bilchik (Santa Monica, California): Dr. Nelson, I applaud you for what has become the most important and widely quoted study in the field of laparoscopic colectomy.

Although the overall survival for both groups is similar and superior to the SEER database, can you comment on the disease-free survival of 69%, which is significantly less than the 78% reported in the MOSAIC trial, particularly since the COST trial required a minimum of 12 nodes and one-third of the patients from the MOSAIC trial had less than 10? Do you think this is a consequence of more effective adjuvant chemotherapy (oxaliplatin)?

Secondly, can you comment on the advantages of laparoscopy if patients undergoing an open colectomy are placed on an enteral feeding "fast track" and discharged from the hospital early after surgery?

Finally, given that the operative time was an additional 60 minutes in the laparoscopic group and laparoscopic equipment is expensive, do you have any data yet on the cost analysis and perhaps whether there is a role for selective laparoscopic colectomy?

Dr. Heidi Nelson (Rochester, Minnesota): We cannot properly compare this data to the SEER data, which is population-based, because we selected some patients and excluded others using protocol-specified criteria. Nor can we compare it to the MOSAIC chemotherapy trial, as you suggest, since oxaliplatin specifically has changed rates of disease-free survival.

The benefits of the fast track are related to this novel and important advance in the postoperative management of patients. The benefits of laparoscopic colectomy include both a faster recovery for the patient and a new manner of conducting surgery for the surgeon. Laparoscopy is but a stepping stone for future technical advances in the minimally invasive approach.

The cost effectiveness of laparoscopic surgery will be analyzed by Dr. Jane Weeks as part of the quality-adjusted life years (QALYs) approach to looking at the overall impact of the patient benefits, risks, and cost effectiveness.