

Canadian Association of General Surgeons Evidence Based Reviews in Surgery. 10.

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

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CAGS Evidence Based Reviews in Surgery

In September 2000, the Canadian Association of General Surgeons (CAGS) initiated a program titled CAGS Evidence Based Reviews in Surgery (CAGS-EBRS) to help practising clinicians improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. Both methodologic and clinical reviews of the article are made by experts in the relevant areas. The *Canadian Journal of Surgery* publishes 4 of these reviews each year. Each review includes an abstract of the selected article and summarizes the methodologic and clinical reviews. We hope that readers will find these useful and learn skills that can be used to evaluate other articles. For more information about CAGS-EBRS or about participating in the program, email mckenzie@mtsina.on.ca

Selected article

Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, et al. **Laparoscopy-assisted colectomy versus open colectomy for treatment of nonmetastatic colon cancer: a randomised trial.** *Lancet* 2002;359:2224-9.

Abstract

Question: Is there a difference in cancer-related survival between laparoscopic assisted colectomy (LAC) and open colectomy (OC)? **Design:** Randomized controlled trial. **Setting:** Single-centre trial, Barcelona, Spain. **Patients:** Two hundred and nineteen of 442 eligible patients with adenocarcinoma of the colon were included. Patients were excluded if the tumour was below 15 cm from the anal verge or was in the transverse colon; if there were distant metastases, adjacent organ involvement or obstruction; or the patient had previous colonic surgery. One

hundred and eleven were randomized to the LAC group and 108 to the OC. **Interventions:** Randomization was done the day before surgery. Patients were stratified into 2 groups according to tumour location (right or left side with respect to the splenic flexure) and assigned to the LAC or OC group by means of sealed opaque envelopes containing computer-generated random numbers. Patients in both groups had surgery by a single gastrointestinal surgical team. Pre- and postoperative care was standardized for bowel prep and perioperative antibiotics. Patients received either LAC or OC using a no-touch technique and initial vascular ligation. **Main outcome measure:** Overall survival. **Results:** 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

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due to differences in patients with stage III tumours (freedom from recurrence $p = 0.04$, overall survival $p = 0.02$, and cancer-related survival $p = 0.006$). **Conclusion:** LAC is more effective than OC for treatment in terms of morbidity, hospital stay, tumour recurrence and cancer-related survival.

Commentary

This month's article by Lacy and colleagues reports the results of a randomized controlled trial comparing laparoscopic assisted to open colectomy for nonmetastatic colon cancer. With the introduction and dissemination of laparoscopic cholecystectomy in the late 1980s and early 1990s, surgeons sought to apply minimally invasive surgery to a wide variety of other abdominal procedures, hoping to realize its proposed benefits: less postoperative pain, reduced hospital stays and quicker postoperative recovery. Although laparoscopic approaches for many procedures have become commonplace, concern over the possibility of adverse cancer outcomes from the potential dissemination of cancer cells through port sites has slowed the adoption of laparoscopic colectomy for colon cancer.

This is the first published study comparing the 2 techniques in patients with colon cancer. In this trial, 219 of a possible 442 eligible patients with stage I–III colon cancer from 1 European centre were randomized to LAC or OC. The authors stated that the study was designed to determine whether survival after LAC was equivalent to that following an open approach.

Interestingly, they calculated the sample size needed based on a difference in survival of 15%, even though most surgeons and patients would probably find the 2 procedures inequivalent if the difference in cancer survival were indeed 15%! Those of us who are statistics aficionados will also note that the values used in the calcu-

lation are probably reversed: α of 0.20 and β of 0.05, when they probably meant an α of 0.05 and β of 0.20.

The investigators found that outcomes were superior in the laparoscopic group. The Cox model showed that the risk of tumour relapse (hazard ratio 0.39, 95% confidence interval 0.19–0.82), death from any cause (HR 0.48, CI 0.23–1.01) and death from a cancer-related cause (HR 0.38, CI 0.16–0.91) were decreased after LAC compared with OC.

How can this unexpected finding be explained? Methodologically the trial was done rigorously (notwithstanding the sample size calculation). Patients were randomized, although the scheme involved concealment in opaque envelopes, a method with potential for bias. However, the 2 groups appear to have been similar at the start of the trial, as revealed by their baseline characteristics.

Relatively few patients were excluded from the analysis, and these because metastatic disease was found at the time of surgery. The excluded patients were equally divided between the groups. Only 2 other patients were lost to follow-up.

One potential confounder might be the uneven administration of adjuvant therapy, but the authors report that 61% in the LAC and 55% in the OC group received adjuvant chemotherapy, so this was unlikely to have caused a spurious outcome improvement in the LAC group.

Finally, patients and surgeons were not blinded to treatment allocation. As in many surgical trials, it would have been impossible to do so. Lack of blinding may significantly bias patient assessment in trials where outcomes are subjective, but that is not the case here, where survival and mortality related to all causes and to cancer were the primary outcomes.

One potential explanation for the apparent improved outcome for the LAC group is that the locoregional recurrence rate was unusually high in the OC group, possibly making the outcome in the LAC group appear

to be superior (14% v. 7%). Furthermore, it is worrisome that the numbers of lymph nodes identified in each group were small (LAC mean 7.9, OC mean 7.4, range 1–11). Although the mean number of nodes was similar in both groups, the relatively small number suggests that the overall quality of the surgery or pathology in both groups from an oncological standpoint may have been suboptimal. This clinical weakness may be relevant if the unexpected apparent cancer-related survival benefit in the LAC group was almost entirely due to an improvement in the stage III (node-positive) group only. Although this is interesting, its significance is conjectural, since there is no apparent biological rationale for stage III carcinomas having a more favourable result with LAC.

This trial is important and interesting for several reasons. First, new technology and surgical procedures are being introduced with unprecedented magnitude and rapidity. How to assess and implement new technology are issues that should be of concern not only to health care administrators but to practising surgeons as well. The implications are great, ranging from the cost of new technology, the need for acquiring new skills and issues of credentialing.

The results of this study themselves are also of importance to all general surgeons. People in Canada develop some 15 000 new colorectal cancers each year, and most are treated surgically by general surgeons. Although it may be debatable whether LAC leads to better outcomes, results from this study and other reported case series¹ suggest that it is highly unlikely that LAC worsens cancer-related survival. Thus, both OC and LAC currently seem appropriate as options for individuals requiring surgery for colon cancer. Whether LAC is offered to patients may depend on the hospital resources and the individual training of the surgeons available. As the authors point out, laparoscopic colectomy skills are certainly greater than those

necessary to do laparoscopic cholecystectomy. Thus, surgeons wishing to start performing LACs probably should not start with cancer patients but those requiring colectomy for benign disease.

What are the implications of this trial? The unexpectedly high rate of cancer recurrences in the conventional OC group should inspire cautious interpretation of the results of this trial and emphasize the need for confirmatory trials. The North American Clinical Outcomes of Surgical Therapy (COST) group has enrolled about double the number of patients into a study of similar design. To date, quality-of-life outcomes have been reported,² but not survival.

The results of this trial do raise an interesting possibility: What if the COST and other large, well designed trials show that LAC is not only as good as but better than open surgery? The finding of a large benefit from laparoscopic-assisted surgery

would necessitate adoption of the technique to provide optimal care to patients. The sudden adoption of LAC by surgeons who have been trained in and have primarily used open surgery for the treatment of colon cancer could easily result in a host of unintended consequences, such as the technical surgical errors associated with the learning curve for the new surgical procedure.

Regionalization of surgical procedures, the most popular health-policy proposal cited in response to evidence of outcome variation in surgical procedures, is likely not a practical option for the treatment of colon cancer, which is too prevalent to be regionalized at specific centres. On the other hand, there is little evidence that the new technical skills involved in such a complex procedure could be effectively and quickly disseminated to a large number of surgeons. Thus, surgical educators, policy makers and surgical associations

as well as practising surgeons would have to grapple quickly with the problems of education and credentialing of surgeons, a task that might be enormous.

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References

1. Schlacta CM, Mammazza J, Gregoire R, Burpee SE, Poulin EC. Could laparoscopic colon and rectal surgery become the standard of care? A review and experience with 750 procedures. *Can J Surg* 2003;466:432-40.
2. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G, the Clinical Outcomes of Surgical Therapy (COST) Study Group. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs. open colectomy for colon cancer: a randomized trial. *JAMA* 2002;287:321-8.

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