Surgical Management of Colorectal Cancer in the Laparoscopic Era: A Review of Prospective Randomized Trials

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Key Words
Colorectal carcinoma, colon cancer, laparoscopy, prospective randomized trial

Abstract
The benefits of laparoscopy in benign diseases are quite clear. Patients generally can expect smaller incisions, less narcotic usage, quicker return of bowel function, and shorter hospitalizations. The benefits of laparoscopy in oncologic surgery are less clear, and laparoscopic oncology surgery has many critics. Early reports of long surgical times, high operating room costs, and alarming rates of port-site recurrences after laparoscopic colectomy for colorectal cancer all but stopped this less-invasive approach outside the confines of clinical protocols. As the results of larger retrospective studies began to refute these earlier detrimental claims, prospective randomized trials began to take a foothold. In this article, we review these randomized trials with particular attention to the perioperative effects of laparoscopic colectomy and the short-term oncologic outcomes. (JNCCN 2005;3:xxx–xxx)

The concept of minimally invasive techniques for benign diseases was embraced rapidly by the surgical community in the early 1990s. Since inception, advanced laparoscopic techniques have been used in gastrointestinal reflux, achalasia, diseases of the biliary tree, hernia surgery, benign diseases of the gastrointestinal tract, and obesity surgery. As skills continue to develop, laparoscopic techniques have begun to infiltrate the traditionally maximally invasive world of surgical oncology, but not without critics. Colorectal cancer has become the focal point in the discussion of safety, efficacy, and applicability of laparoscopic surgery in oncology. This article reviews the current status of laparoscopic surgery in the management of primary colorectal cancer with particular focus on the results of recent prospective randomized trials.

Multi-Institutional Trials
Three large multi-institutional prospective randomized trials began in the mid 1990s and are in various stages of follow-up. These include: the Clinical Outcomes of Surgical Therapy (COST) Study Group trial in the United States and Canada, sponsored by the National Institutes of Health; the Colon Carcinoma Laparoscopic or Open Resection (COLOR) trial in Europe; and the Medical Research Council Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (MRC CLASICC) trial in the United Kingdom.

The COST trial began enrolling patients in 1994, with a planned accrual of 1,200 patients with histologically confirmed adenocarcinoma of the colon. The hypothesis was that laparoscopic colectomy is safe and equal in efficacy to standard open colectomy for colon cancer with regards to disease-free and overall survival.1-4 Excluded from the study were patients with locally advanced or metastatic disease, rectal or transverse colon cancer, acute bowel obstruction or perforation from cancer, severe medical illness, inflammatory bowel disease, familial polyposis, pregnancy, or concurrent or previous cancer. Sixty-six surgeons from 48 institutions participated after undergoing a video screening process to ensure competency in advanced laparoscopic skills and oncologic principals. Each participating surgeon must...
have completed 20 laparoscopic cases for benign disease. In 2004, the authors reported on 872 randomized patients. Conversion to open colectomy occurred in 21% and was not influenced by surgeon experience or volume. Laparoscopic-assisted colectomy resulted in significantly longer operative times but shorter duration of parenteral narcotic usage (4 days vs. 3) and length of hospital stay (Table 1). There were no significant differences in proximal margin, distal margin, lymph node harvest, 30-day mortality (1%), or postoperative complications (20%). At median follow-up of 4.4 years, there were no significant differences in recurrence rates, time to recurrence, or overall survival (Table 2). Surveillance continues with planned follow-up of eight years.

The COLOR trial, sponsored by Ethicon EndoSurgery, started in 1997 with an accrual goal of 1200 patients with the primary endpoint of disease-free survival at three years. Secondary end points are postoperative morbidity, port site recurrence, five-year disease-free and overall survival, quality of life differences, and costs. Eligible patients consist of those with a histologically-proven solitary colon adenocarcinoma amenable to curative resection by right hemicolectomy, left hemicolectomy, or sigmoid colon resection. Patients were excluded if they had evidence of locally advanced or metastatic disease, synchronous or previous malignancies, obesity (BMI >30 kg/m²), pregnancy, tumors located in the transverse colon or rectum, or if resection of the splenic flexure was anticipated. Surgeons from the 27 participating centers must have completed at least 20 laparoscopic colectomies to participate and surgical technique was standardized. Interim analyses were planned after 50, 100, and 200 recurrences with the plan to terminate the trial if obvious differences in recurrence rates are seen. At the time of their 2002 report, 859 patients had been enrolled, 57 of whom were excluded after randomization. The conversion rate was 16.7%. At 46 months follow-up, the overall recurrence rate is 6.8% and is stage-dependent. While accrual is complete for this trial, final results are pending.

The MRC CLASICC trial began enrollment in 1996 in the United Kingdom. This trial was modeled after the COST trial in the United States with primary end-points of pathological resection margins, postoperative mortality and morbidity, local recurrence rates, disease-free survival, and overall survival. Secondary end-points include quality of life and cost-effectiveness. The trial aims to recruit 1000 patients with adenocarcinoma of the colon from 15 centers. Recruitment for this trial is nearing completion and follow-up data should be forthcoming.

**Single Institution Prospective Randomized Trials**

Kaiser and Kang et al. prospectively randomized 49 patients with adenocarcinoma of the colon to open

### Table 1 Perioperative Outcomes in Prospective Randomized Trials Comparing Laparoscopic-Assisted Colectomy (LAC) to Open Colectomy (OC) for Colon Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N (LAC, OC)</th>
<th>Conversion rate</th>
<th>OR time (min)</th>
<th>EBL (mL)</th>
<th>Time to first diet/BM (d)</th>
<th>LOS (d)</th>
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</thead>
<tbody>
<tr>
<td>Kaiser et al.</td>
<td>2004</td>
<td>49 (29, 20 OC)</td>
<td>45%</td>
<td>125 b</td>
<td>100 100</td>
<td>1 b</td>
<td>3 5 6</td>
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<tr>
<td>Milsom et al.</td>
<td>1998</td>
<td>109 (55, 54 OC)</td>
<td>NR</td>
<td>200 125 a</td>
<td>252 344</td>
<td>4.8 4.8</td>
<td>6 7</td>
</tr>
<tr>
<td>Lacy et al.</td>
<td>2002</td>
<td>219 (111, 108 OC)</td>
<td>NR</td>
<td>142 118 a</td>
<td>105 193</td>
<td>2.3 3.5</td>
<td>5.2 7.9</td>
</tr>
<tr>
<td>Hasegawa et al.</td>
<td>2003</td>
<td>59 (29, 30 OC)</td>
<td>17%</td>
<td>275 188 a</td>
<td>58 137</td>
<td>1.6 3.2</td>
<td>7.1 12.7</td>
</tr>
<tr>
<td>Delgado et al.</td>
<td>2000</td>
<td>255 (129, 126 OC)</td>
<td>14%</td>
<td>147 120 a</td>
<td>105 193</td>
<td>2.3 3.4</td>
<td>5.5 7</td>
</tr>
<tr>
<td>Schwenk et al.</td>
<td>1998</td>
<td>60 (30, 30 OC)</td>
<td>NR</td>
<td>225 150 a</td>
<td>NR</td>
<td>NR</td>
<td>10.1 11.6</td>
</tr>
<tr>
<td>Stage et al.</td>
<td>1997</td>
<td>29 (15, 14 OC)</td>
<td>17%</td>
<td>150 95 a</td>
<td>275 300</td>
<td>NR</td>
<td>5 8</td>
</tr>
<tr>
<td>Curet et al.</td>
<td>2000</td>
<td>43 (25, 18 OC)</td>
<td>28%</td>
<td>210 138 a</td>
<td>284 407</td>
<td>2.7 4.4</td>
<td>5.2 7.3</td>
</tr>
<tr>
<td>COST trial.</td>
<td>2004</td>
<td>863 (435, 428 OC)</td>
<td>21%</td>
<td>150 95 a</td>
<td>NR</td>
<td>NR</td>
<td>5 6</td>
</tr>
</tbody>
</table>

Abbreviations are: OR, operating room; EBL, estimated blood loss; LOS, hospital length of stay; NR, not reported; BM, bowel movement.

*P < 0.05 compared to LAC

*P < 0.05 compared to OC
(n = 20) or laparoscopic-assisted colectomy (n = 29) between 1995 and 2001. One patient was lost to follow-up. End points of the study were perioperative events, quality of life, tumor recurrence rates, and survival. Randomization was further stratified by tumor site and surgeon. Thirteen (45%) of patients randomized to laparoscopic colectomy were converted to open colectomy and treated as a third group of patients for comparison. Patients undergoing open colectomy or who were converted to open colectomy tended to have more advanced tumors than those undergoing laparoscopic colectomy, though this was not statistically significant. Laparoscopic colectomy and conversions to open colectomy took significantly longer to complete but did have similar blood loss (Table 1). Resection specimens were similar in all three groups with regards to tumor size and stage, margins (all negative), and lymph node harvest, though specimen length was significantly longer following open colectomy (Table 2). Mean time to first diet, time to first bowel movement, and hospital length of stay were significantly shorter following laparoscopic colectomy (Table 1). At a mean follow-up of 35 months, recurrence rates and survival were similar between groups (Table 2).

In 1998, Milsom et al. reported on 109 patients with adenocarcinoma of the right or sigmoid colon randomized to laparoscopic (n = 55) or open colectomy (n = 54) between 1993 and 1997. End-points included perioperative morbidity, analgesia usage, changes in pulmonary function testing, return of bowel function, and recurrence rates. Four patients randomized to laparoscopic colectomy were converted to open and, subsequently, excluded from the study. Median follow-up was 1.5 years for patients undergoing laparoscopic colectomy and 1.7 years for those randomized to open colectomy. Complications occurred in 15% of patients and were similar between groups. Overall surgical mortality was 1.8% (one from each group). Laparoscopic cases took significantly longer to complete with similar blood loss (Table 1). Margin status and lymph node harvest was similar between groups as well (Table 2). Laparoscopic colectomy resulted in more rapid return to normal pulmonary functions (3.0 days vs. 6.0), less early parenteral narcotic usage, and shorter time to passage of flatus (3 days vs. 4). Wound recurrences occurred in two patients following open colectomy as a manifestation of widespread disease; no port site recurrences occurred (Table 2). Overall survival was not significantly different between groups. Lacy et al. randomized 219 patients with adenocarcinoma of left or right colon to laparoscopic (n = 111) or open (n = 108) colectomy. The primary aim of this study between 1993 and 1998 was to assess cancer-related survival. Operative time was significantly longer and blood loss was significantly less following laparoscopic colectomy (Table 1). Complications were

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<th>Wound Recurrences</th>
<th>Actual Survival</th>
<th>Median Follow-Up (months)</th>
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<td>0%</td>
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<td>25</td>
<td>NR</td>
<td></td>
<td>0%</td>
</tr>
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<td>11.1</td>
<td>11.1</td>
<td>17%</td>
<td>27%</td>
<td>1%</td>
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<tr>
<td>Hasegawa et al.¹¹</td>
<td>23</td>
<td>26</td>
<td>NR</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Delgado et al.¹²</td>
<td>10.8</td>
<td>10.5</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Stage et al.¹³</td>
<td>7</td>
<td>8</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Curet et al.¹⁶</td>
<td>11</td>
<td>10</td>
<td>0%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>COST trial²</td>
<td>12</td>
<td>12</td>
<td>20%</td>
<td>17%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Overall means</td>
<td>13.1</td>
<td>14.6</td>
<td>7.4%</td>
<td>11%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

NR, not reported.

¹P < 0.05 compared to LAC
²P < 0.05 compared to OC
³Survival reported for entire cohort (i.e., no comparison between LAC and OC was made)
Laparoscopic colectomy resulted in significantly longer operating times, less blood loss, shorter time to tolerance of oral intake, more rapid transit of radio-opaque markers, and shorter length of hospital stay (Table 1). Time to successful initiation of oral intake and hospital length of stay was significantly shorter following laparoscopic colectomy (Table 1). Extent of resection and lymph node harvest were similar between groups (Table 2). Median follow-up was 43 months overall and was similar between the two groups. The type of recurrence, time to recurrence, and number of patients who had curative reoperation were similar in both groups (Table 2). There was a trend toward significant improvement in recurrence rate \((P = .07)\) following laparoscopic colectomy. Overall survival was similar between groups, though cancer-related survival favored laparoscopic colectomy, particularly in patients with node-positive disease, though the sample size in this subgroup was small (37 patients with laparoscopic colectomy vs. 36 with open) and slightly more patients undergoing laparoscopic colectomy with stage III disease received adjuvant chemotherapy (61% vs. 55%). Still, surgical approach was an independent predictor of tumor recurrence and cancer-related survival by multivariate regression analysis favoring laparoscopic colectomy.

Between June 1998 and October 2000, Hasegawa et al. randomized 59 patients with T2 or T3 colorectal cancers to laparoscopic \((n = 29)\) or open \((n = 30)\) colectomy. The primary end-point of the study was overall and disease-free survival. \(^{11}\) Secondary endpoints included time to oral intake, hospital length of stay, postoperative complications, and immunologic parameters. Since laparoscopic colectomy was already considered the preferred approach to early-stage colon cancer, in situ and T1 tumors were not included in the study. Rectal and transverse colon cancers were also excluded. Mean follow-up was similar between the two groups (19–20 months) as was tumor site, tumor stage, and lymph node harvest (Table 2). Laparoscopic colectomy resulted in significantly longer operating times, less blood loss, shorter time to tolerance of oral intake, and shorter hospital stay (Table 1). Complications were similarly uncommon in each group and there were no deaths. Serum C-reactive protein levels rose in both groups after colectomy but to a lesser degree following laparoscopic colectomy. Other measures of immune functions (e.g., interleukin-6 [IL-6], leukocyte count, and natural killer cell activity) were not different between groups. No port site recurrences were noted during follow-up. Long-term oncologic comparison is still pending.

Delgado et al. randomized 255 patients with colon cancer to laparoscopic or open colectomy between 1993 and 1998. \(^{12}\) They further stratified patients by age greater than or less than 70, thus comparing four groups (laparoscopic colectomy <70 years old, 70 patients; laparoscopic colectomy >70 years old, 59 patients; open colectomy <70 years old, 59 patients; open colectomy >70 years old, 67 patients). The primary end point was 30-day outcomes including postoperative complications, time to oral intake, and length of hospital stay. Excluded from the study were patients with transverse colon cancers, rectal cancers, suspected T4 tumors, and previous colon resection. The four groups were similar in terms of gender, tumor stage, and lymph node harvest. While the older group tended to have more comorbidities and more right-sided cancers, these factors were equally distributed between laparoscopic and open colectomy. Conversion to open colectomy occurred in 11% of patients under 70 years of age compared to 17% in those over 70 \((P = NS)\). Operations were longer with less blood loss when done laparoscopically regardless of patient age (Table 1). Time to tolerance of oral intake and hospital length of stay was significantly shorter following laparoscopic colectomy in both age groups. Complications occurred with similar frequency following laparoscopic and open colectomy in patients under 70 while complications were significantly reduced following laparoscopic colectomy in patients over 70 (10% vs. 31%). This was a result of the decreased incidence of wound infections in this group (5% vs. 12%).

Between April 1995 and October 1996, Schwenk et al. equally randomized 60 patients with colorectal tumors considered candidates for resection by right colectomy, left colectomy, proctosigmoidectomy, or abdominoperineal resection. \(^{13,14}\) All patients were kept in the hospital for at least seven days to complete all data collection. Laparoscopic colectomy resulted in longer operating times, lower pain scores, lower fatigue scores, shorter time to first flatus (50 vs. 79 h), shorter time to tolerance of oral intake, more rapid transit of radio-opaque markers, and shorter length of hospital stay (Table 1).

Stage et al. reported on 34 patients randomized to laparoscopic \((n = 18)\) or open \((n = 16)\) colectomy in 1997. \(^{15}\) Twenty-nine patients were included in the
Surgical Management of Colorectal Cancer

Immune Effects of Laparoscopic Colectomy

One theoretic benefit of laparoscopic colectomy relates to potential blunting of changes in the immune system compared to open colectomy, which may, in turn, impart an oncologic benefit. Several prospective randomized studies specifically address this issue by measuring various components of immunity.

Tang et al. conducted a study in the United Kingdom in parallel with the MRC CLASICCC trial comparing changes in immune response in 236 patients with left-sided colorectal cancers randomized to laparoscopic or open colectomy (n = 118 each). Parameters measured before and three days following surgery were C3, C4, immunoglobulin (Ig) G, IgM, IgA, B cells, T cells, CD4:CD8 ratio, natural killer cell activity, and leukocyte phagocytic activity. Complete data were available in only 161 of the 236 patients but there were no differences in cell-mediated or humoral responses between patients undergoing laparoscopic or open colectomy. In fact, very little change was noted between preoperative and postoperative values regardless of surgical technique in any parameters measured.

As part of their study in which 60 patients with colon cancer underwent laparoscopic or open colectomy (n = 30 each), Schwenk et al. also reported on inflammatory response by measuring plasma levels of interleukin-1 receptor antagonist (IL-1RA), IL-6, IL-10, and C-reactive protein (CRP) at baseline and throughout the postoperative course. They showed that overall and peak postoperative concentrations of IL-6 and CRP were lower following laparoscopic colectomy compared to open colectomy. No difference was seen in overall and peak postoperative levels of IL-1RA and IL-10 between groups, however. The authors concluded that there was a less intense inflammatory response following laparoscopic colectomy compared to open colectomy, thus indicative of less surgical trauma, essentially echoing the findings of Stage et al., who reported a more exaggerated increase in IL-6 and CRP levels following open colectomy. Similarly, Delgado et al. found significant attenuation in inflammatory response following laparoscopic colectomy compared to open colectomy in a randomized study of 97 patients measuring similar parameters.

In a smaller study, Hewit et al. measured serum levels of IL-6, relative proportions of lymphocytes, and monocyte human leukocyte antigen-DR expression in 16 patients randomized to laparoscopic or open colectomy. IL-6 levels peaked at four hours following surgery and returned to baseline by 48 hours in all patients, but to a lesser extent following laparoscopic colectomy (313 pg/mL vs. 173). While both open and laparoscopic colectomy affected the immune response within the first three weeks after operation, there were no significant differences between the two surgical approaches. The authors concluded that there was no clear immunologic advantage of laparoscopic colectomy over open colectomy in patients with colorectal cancer. These findings were later reiterated by Wu et al. in a similar study of 26 patients measuring serum and peritoneal cytokine and leukocyte reactions following laparoscopic and open colectomy.
Costs
There are very few data addressing specifically cost issues related to laparoscopic colectomy, though it is an important end-point in the COST,23 MRC CLASSIC,27 and COLOR24 trials. While most retrospective reports agree that operating room costs are greater for laparoscopic cases, consensus on overall hospitalization cost differences is lacking.25–28 The offset of operating room costs is directly linked to shorter hospitalizations with laparoscopic colectomy. What is not easily measurable is the overall societal economic impact if patients are able to return to the workforce earlier. To date, only one prospective randomized trial has specifically reported on costs.24 In this study, Janson et al. reviewed 234 patients from 12 Swedish centers contributing to the COLOR trial. These patients were randomized to laparoscopic (n = 111) or open colectomy (n = 123) as per study protocol as described earlier. Twenty-four of these patients were excluded from the COLOR trial after randomization for inclusion criteria violations and therefore removed from the initial cost analysis. A second analysis was then undertaken with these 24 patients included as an external validation. All relevant direct medical costs (hospital costs and costs of outpatient care) and indirect costs (e.g., loss of productivity due to time absent from work) were sought from the time of admission for surgery up to 12 weeks postoperatively. Resource costs from the various institutions were standardized to the largest contributing institution and disposable operating room instrument costs were based upon mean expenditure for the instrument of all participating centers. The initial cost analysis was completed on 210 patients and then confirmed utilizing all 234. Total cost of first admission was significantly higher following laparoscopic colectomy, mostly as a function of increased operating room costs. Since there was no difference in hospital length of stay (mean = 9 days for both groups), these costs were not offset. As well, 14 patients were converted to open operation and included in the cost analysis with the laparoscopic group. Surprisingly, costs associated with subsequent care after discharge was also higher following laparoscopic colectomy resulting in significantly higher total costs before adjusting for productivity loss. When this was factored into total costs, the statistical advantage of open colectomy was lost (P = 0.1), in part due to less productivity loss following laparoscopic colectomy, but also in part to increase in data variability. Likely, this study was under powered to detect true differences in costs.

Wound Recurrences
Early reports of port-site metastases greatly curtailed many surgeons’ enthusiasm for laparoscopy in malignancy.30–31 With the first case report of port-site metastasis in 1993 following curative laparoscopic right hemicolectomy,32 and an alarming 21% incidence reported in 14 patients in a letter to the editor in 1994,33 great concerns were raised about the safety of laparoscopic colectomy in malignancy. As experience grew, more reports with larger numbers of patients began to quell these initial worries as wound recurrences appeared to be more consistent with open colectomy and more of a harbinger of widespread disease.34–36

Only one prospective randomized trial specifically addressed port-site metastases as a primary end-point. In 1998, Lacy et al reported on 91 patients randomized to laparoscopic (n = 44) or open (n = 47) colectomy for malignancy.37 With relatively short term follow-up ranging from 13 to 41 months (mean 21.4), no wound recurrences were seen in either group. Several other randomized trials have reported similar results as secondary end-points (Table 2).

Discussion
Many early non-randomized studies documented shorter hospitalizations following laparoscopic-assisted colectomy, which were mainly related to earlier return of bowel function and less narcotic use.25,34,40–54 These findings persist in nearly all of the prospective randomized trials discussed above. Indeed, the reduction in hospital lengths of stay are only one to two days, which many would argue is not of much clinical relevance. However, considering there are nearly three million surgical procedures undertaken annually resulting in at least one day of postoperative ileus, decreasing hospital stay by one day has the potential savings of over $1 billion per year.55 But as the early results from the COLOR trial point out, these potential savings may be offset by the increases in operative expenditures.12 The more difficult question to answer is if there is an overall societal economic advantage to shorter hospitalization, less narcotic usage, and, ultimately, quicker return to the workforce following laparoscopic colectomy.

While early reports of port-site recurrences have been refuted by more recent retrospective and...
prospective studies, the oncologic effects of laparoscopic colectomy still remain the greatest concern to surgeons. It at least appears from the smaller single-institution trials and the early report from the COST trial that laparoscopic colectomy does not appear to have a negative impact on specimen size, margin status, lymph node harvest, perioperative mortality, recurrence rate, or survival. These studies, however, still lack the sample size or length of follow-up to definitely determine the efficacy of laparoscopic colectomy for colorectal cancer. Until the final results from the COST, COLOR, and MRC CLASICC trials mature, the final verdict on the general application of laparoscopic colectomy for malignancy should be considered carefully and offered only to patients by experienced surgeons within the guidelines set forth by the American Society of Colon and Rectal Surgeons (ASCRS), the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), and the National Comprehensive Cancer Network.

References

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