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*Surg Innov* 2006; 13; 5

DOI: 10.1177/155335060601300102

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# Minimally Invasive Management of Colon Cancer

Marc Zerey, MD, Justin M. Burns, MD, Kent W. Kercher, MD, Timothy S. Kuwada, MD, and B. Todd Heniford, MD

One of the most controversial issues in minimally invasive surgery has been the implementation of laparoscopic techniques for the curative resection of colorectal malignancies. Initial concerns included the potential violation of oncologic principles, the effects of carbon dioxide, and the phenomenon of port site tumor recurrence. Basic science research and large randomized controlled trials are now demonstrating that these fears were unjustified. Long-term outcomes of laparoscopic colon resection compared with open colon resection for malignancy are comparable, and there may even be a survival benefit for a subset of patients who undergo laparoscopic resection.

**Key words:** colorectal malignancy, laparoscopic resection, port site tumor.

Laparoscopy has been reported to potentially offer several advantages over conventional, open procedures, including less postoperative pain, shorter hospital stay, decreased incidence of ileus, improved cosmesis, less intraoperative blood loss, and fewer postoperative wound complications.<sup>1-3</sup> Despite the prospective benefits, surgeons previously described as controversial the application of minimally invasive techniques in the curative resection of colon cancer. Historically, concern has been raised regarding the potential violation of oncologic principles established for open surgery, including technical aspects of the procedure and the ability to perform adequate staging of the malignancy. Additional concerns have included the systemic and local effects of carbon dioxide gas used for insufflation of the abdomen, the phenomenon of port site tumor recurrence, and the relative lack of long-term data from prospective randomized trials comparing laparoscopy with open resection for colon cancer.

Subsequent research has demonstrated that these early fears may have been unfounded. Laparoscopic colon resection is an advanced procedure that can be executed without violating oncologic standards once an appropriate skill level is achieved.<sup>4,5</sup> The incidence of port site tumor recurrence has also been reported to be similar to wound recurrence in open colon resection for malignancy.<sup>6-13</sup> Finally, reports of long-term follow-up after laparoscopic colectomy for colon cancer have observed that survival rates are comparable with open procedures,<sup>14</sup> including results from recent prospective, randomized, controlled trials.<sup>3,15-17</sup>

## Technique

The use of laparoscopy for large-bowel resection is technically challenging. The learning curve has been estimated to be 35 to 50 procedures,<sup>18,19</sup> but it certainly depends on the surgeon's ability, knowledge of the anatomy, and experience with laparoscopy.<sup>20</sup> Recent randomized, controlled trials required credentialing of surgeons by submission of a least 20 surgical reports of laparoscopic colectomy (with videotape evidence) that met proper oncologic technique.<sup>15-17</sup> Interestingly, a review of 2434 general surgeons who were taking the recertification examination for the American Board of Surgery showed that most surgeons perform fewer than 20 colon resections a year,<sup>21</sup> and the actual number may be much less than that. The ability to acquire and maintain the skills necessary to perform a safe and oncologically sound bowel resection therefore remains a debated issue.

In general, three minimally invasive techniques are used to resect the colon: laparoscopic colectomy, laparoscopic-assisted colectomy, and hand-assisted laparoscopic colectomy.

- In laparoscopic colectomy, the mesentery and bowel are mobilized and transected laparoscopically. The anastomosis of the colon is done intracorporeally or extracorporeally. The specimen is removed from the abdomen via a small extraction incision, often the same incision through which the anastomosis may be performed.

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- Laparoscopic-assisted colectomy is executed with full laparoscopic mobilization of the colon followed by externalization of the bowel through a small incision. The resection and anastomosis are done extracorporeally.
- In hand-assisted laparoscopic colectomy, a hybrid that shares techniques of laparoscopic and open surgery, a hand port is used to aid in the retraction, mobilization, and dissection of the bowel. The actual resection and anastomosis of the colon can be performed as in a laparoscopic colectomy or laparoscopic-assisted colectomy.

Laparoscopic colectomy has been associated with a longer operative time, and it is questioned whether it offers additional postoperative benefit compared with laparoscopic-assisted colectomy and hand-assisted laparoscopic colectomy.<sup>22</sup> The hand-assisted procedure has some advantages over laparoscopic colectomy and laparoscopic-assisted colectomy in that the surgeon maintains tactile sensation, which aids in the dissection and mobilization of the bowel. Hand-assisted laparoscopic colectomy has been reported to be easier to learn and requires shorter operative times than traditional laparoscopic surgery.<sup>23</sup> Furthermore, it has a lower rate of conversion to open surgery and facilitates the completion of complex procedures.

Conversion rates vary in the recent literature from 11% to 35%.<sup>1,3,15-17</sup> Common reasons for converting include advanced disease, inadequate margins of resection, lack of visualization of critical structures, difficulty with colon mobilization, adhesions, intraoperative complications, and equipment failure. Accurate preoperative staging, tumor localization, experienced operating room staff, patient selection, and surgeon experience all contribute to minimize conversion to an open resection.<sup>24,25</sup>

## Oncologic Principles

Oncologic principles established for open colon resection should be maintained during a laparoscopic resection for malignancy. These standards include minimal handling of the bowel, avoiding manipulation of the lesion, proximal vascular ligation, obtaining adequate margins and length of resection, and accurately evaluating tumor stage.

Minimal handling of the bowel can be achieved by blunt retraction or grasping the epiploica. Guidelines established by the 2000 Colon and Rectal Cancer Surgery National Cancer Institute

(NCI)-sponsored consensus panel state that the ideal proximal margin for resection of a colonic lesion is 5 cm or more, and the ideal distal margin is 2 cm or more.<sup>19</sup> The ideal extent of resection is defined by removal of the blood supply and lymphatics at the level of the origin of the primary feeding arterial vessel. Furthermore, the lesion should be excised en bloc with tumor-free radial margins (R0) to be considered curative.<sup>4,19</sup>

The NCI-sponsored Clinical Outcomes of Surgical Therapy (COST) Study Group published results on 872 patients consisting of 437 open colectomies and 435 laparoscopic-assisted colectomies.<sup>4,15</sup> The resection data, which were comparable for the laparoscopic-assisted colectomies and open procedures, were proximal margins, 13 cm vs 12 cm; distal margins, 10 cm vs 11 cm; and mesenteric length, 9 cm vs 8 cm, respectively.<sup>4</sup> Results of prospectively collected data from our institution between 1997 and 2001 were similar. The mean proximal margin for laparoscopic-assisted colectomies vs open was 10.9 vs 11.6 ( $P = .88$ ), and the distal margin was 7.38 vs 7.18 ( $P = .98$ ).<sup>5</sup>

## Assessing Metastatic Disease

Concern regarding the aptitude of laparoscopy to stage colon cancer involves the ability to accurately assess for metastatic intra-abdominal disease, particularly hepatic lesions, before resection of the primary tumor and to obtain an adequate number of lymph nodes. The 2000 Colon and Rectal Cancer Surgery NCI-sponsored panel also addressed the topic of lymphadenectomy. The consensus statement was that a minimum of 12 lymph nodes negative for disease should be removed en bloc to assure with 90% accuracy that the tumor does not involve the nodes.<sup>19</sup> The 2004 NCI-sponsored COST trial evaluated the number of nodes obtained for laparoscopic colectomy and found the number to be essentially the same (mean, 12 lymph nodes) as that for open surgery (mean, 13 nodes).<sup>4</sup>

Short-term results from the Colon Cancer Laparoscopic or Open Resection (COLOR) Study Group and the UK Medical Research Council-sponsored trial of conventional versus laparoscopic-assisted surgery in colorectal cancer (MRC-CLASICC) have not demonstrated a significant difference in the total or number of positive nodes between specimens retrieved laparoscopically or via the open technique.<sup>16,17</sup> Similarly, prospective data from our institution found a comparable number of nodes obtained from open resection (12.5) compared with laparoscopic resection (12.7).<sup>5</sup>

Traditionally, the evaluation of potential intra-abdominal metastasis of a large-bowel tumor has involved a preoperative computed tomography (CT) scan followed by intraoperative inspection and palpation of the peritoneum and liver. The laparoscope provides comparable or often improved visualization of the entire abdomen, but concern has been raised regarding the potential to miss hepatic lesions because of loss of tactile sensation. Several clinical studies have recently reported on their use of intraoperative laparoscopic ultrasonography to effectively evaluate the liver for lesions. Milsom et al<sup>26</sup> randomized 60 patients to laparoscopic-assisted or open colectomy in which intraoperative laparoscopic ultrasonography was compared with preoperative CT scans and open intraoperative ultrasonography with bimanual palpation of the liver. They reported that the staging modalities were comparable and that intraoperative laparoscopic ultrasonography was superior in the detection of benign hepatic lesions.<sup>26</sup>

These studies demonstrate that minimally invasive techniques can be comparable with open surgery in maintaining oncologic principles. It is important, however, to reiterate that a learning curve is involved in developing proficiency in laparoscopic colectomy or laparoscopic-assisted colectomy. Initial steps include acquisition of the ability to perform standard, uncomplicated laparoscopy, knowledge of instrumentation, dissection techniques, and the aptitude to control hemorrhage. Colonic resection should be restricted to benign disease until proficiency is reached. At first, a surgeon might consider avoiding patients with multiple previous surgeries or extensive abdominal inflammation, although starting such operations laparoscopically usually adds little morbidity if they are converted in a timely fashion.

### Systemic and Local Effects of Minimally Invasive Surgery

The systemic immune system's physiologic response to surgical trauma affects several metabolic pathways, producing a state of immunosuppression that varies according to the extent of operative trauma.<sup>27</sup> Several recent studies have compared the systemic impact of surgical stress caused by open and laparoscopic surgery<sup>28-34</sup> and have shown smaller elevations in serum interleukin (IL)-6 and C-reactive protein (CRP) after laparoscopic surgery than after

the open approach, suggesting a close relationship between these acute inflammatory mediators and the degree of surgical trauma. Schwenk et al<sup>29</sup> randomized 30 patients each to laparoscopic or open resection for colorectal malignancy. Postoperative peak concentrations of IL-6 ( $P = .05$ ) and CRP ( $P < .001$ ) and the overall postoperative plasma concentrations of IL-6 ( $P = .03$ ) and CRP ( $P = .002$ ) were lower in the laparoscopic than in the open group. The investigators concluded that the less intense inflammatory response may be an indicator of the milder surgical trauma inflicted by laparoscopic compared with conventional, open colorectal resection.<sup>29</sup>

IL-6 has a key role in modulating the immune system by stimulating IL-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) production. Ordemann et al<sup>28</sup> randomized 20 patients each to laparoscopic or open colorectal tumor resection and evaluated postoperative systemic immune function. They found that plasma peak levels of IL-6 and TNF- $\alpha$  were lower after laparoscopic compared with open resection. Moreover, ex-vivo monocytes from the laparoscopic group maintained a greater ability to produce IL-6 and TNF- $\alpha$  when stimulated with endotoxin.<sup>28</sup>

TNF- $\alpha$  is the principal proinflammatory cytokine released by several types of cells, but especially by macrophages. Low levels of the cytokine may help maintain homeostasis and promote the remodeling of injured tissue by stimulating fibroblast growth. Additional beneficial functions of TNF- $\alpha$  include its role in the immune response to bacterial and certain fungal, viral, and parasitic invasions and its role in the necrosis of specific tumors. Excess production of this proinflammatory mediator, however, may result in a detrimental, vicious cycle of repeated activation that may render monocytes less able to respond to pathogens in the postoperative period and have deleterious physiologic effects for the host.<sup>35</sup> Enhanced expression of IL-6 seen after open surgery may also promote depletion of circulating cell growth regulatory serum proteins such as insulin-like growth factor-binding protein-3 via proteolytic degradation.<sup>36-38</sup> Insulin-like growth factor-binding protein-3 has been shown to act as a tumor growth suppressor by inducing tumor cell apoptosis and inhibition of DNA synthesis.

The immunosuppressive effects of surgical trauma on cytokines and other inflammatory mediators impair cell-mediated immunity by decreasing delayed-type hypersensitivity responses,<sup>39-41</sup> down-regulation of T-helper type 1 cytokine response (favoring humoral rather than cellular immunity),<sup>42,43</sup>

decreased lymphocyte proliferation, natural killer cell function, neutrophil and lymphocyte chemotaxis, cytokine elaboration, and monocyte human leukocyte antigen (HLA)-DR expression.<sup>31,40</sup>

Most studies have determined that the greater the degree of surgical trauma, the greater the change from baseline on cellular immunity. These alterations are relatively short-term (hours to days)—and the long-term implications on tumor recurrence and patient survival are currently unknown—but some effects that result from open surgery may be more deleterious than when the same operation is performed laparoscopically. Wu et al<sup>40</sup> found that in patients with colonic carcinoma, postoperative leukocyte counts and leukocyte subpopulations normalized earlier after laparoscopic colectomy than after open surgery. Monocyte HLA-DR expression was more suppressed in the open colectomy group than in the laparoscopic group on postoperative day 4.<sup>40</sup>

The ability to process foreign antigen and to present peptide segments to T-helper lymphocytes is one of the most important functions of monocytes and tissue macrophages.<sup>31</sup> T-helper lymphocytes can only recognize foreign antigen peptide segments when they are presented in conjunction with major histocompatibility complex class II surface protein on the surface of monocytes, macrophages, or other antigen-presenting cells.

A third contemporary study evaluated the influence of minimally invasive surgery on postoperative polymorphonuclear leukocyte (PMN) function. Seventeen patients scheduled for Nissen fundoplication were randomized to undergo a laparoscopic or conventional procedure. The phagocytic capacity of PMN decreased significantly within 2 hours after open surgery but was preserved after laparoscopic surgery. Furthermore, there was less production of oxygen radicals and a preservation of the opsonic capacity of the PMN in the laparoscopic group compared with the conventional group.<sup>30</sup>

In contrast to the apparent preservation of systemic immunity, laparoscopic surgery has been shown in several animal models to have a potential adverse effect on the local intraperitoneal environment. The etiology of this observation is thought to be related to the use of carbon dioxide as an insufflation gas and the potential effects of super physiologic abdominal pressures caused by insufflation. A research group from Australia has reported studies evaluating the effects of carbon dioxide on intraperitoneal immunity.<sup>32,33</sup> One study demonstrated that peritoneal macrophages from control and tumor-bearing rats that underwent laparoscopy

with carbon dioxide produced significantly less TNF- $\alpha$  in vitro compared with gasless laparoscopy or laparotomy groups.<sup>33</sup> A follow-up study investigated the effects of carbon dioxide on peritoneal macrophages in vivo and showed that carbon dioxide insufflation caused depressed peritoneal macrophage activity that may have been mediated by pH changes resulting in an acidic environment.<sup>32</sup> These observations were further corroborated by Hajri et al,<sup>34</sup> who demonstrated a failure in peritoneal cell-mediated immunity after carbon dioxide pneumoperitoneum.

These observations have serious implications in the management of oncologic disease because of the potential influence of a weakened intraperitoneal immune system on tumor behavior, including growth and spread of the disease. Intuitively, there could be a benefit for laparoscopic resection of malignancy owing to the preservation of the systemic immune function. However, the local effect of carbon dioxide on peritoneal macrophage function is thought to potentially increase the risk of port site tumor recurrence, which would outweigh systemic advantages. These issues have been a topic of substantial debate and research and are outlined in subsequent sections of this review.

## Port Site Tumor Recurrence

Early in the debate concerning implementation of laparoscopic techniques for the treatment of colorectal cancer, the greatest trepidation arose from the phenomenon of port site tumor recurrence. Several studies have documented the occurrence of port site metastases after laparoscopic and thoracoscopic procedures.<sup>44-49</sup> Incisional tumor cell implantation after malignant resection is not unique to laparoscopic surgery, however. Several studies have also demonstrated tumor recurrences in open surgery wounds at a rate of 0.64% to 2.5%,<sup>6-8</sup> and the incidence is believed to be under-recognized.<sup>8</sup> This range is comparable with port site tumor recurrence following laparoscopic colorectal surgery, which is reported to be 0% to 2.5%.<sup>9-13,50</sup> In fact, each randomized prospective trial has demonstrated no difference in wound recurrence between laparoscopic and open colorectal operations.<sup>1,3,15-17</sup> The high incidence of port site metastasis in early reports on laparoscopic surgery appear to reflect inexperience with the technique, such that an oncologically appropriate operation was not performed.<sup>50</sup>

Several theories have been proposed for the possible increased incidence of wound metastases associated with laparoscopic surgery, including mechanical, metabolic, immunologic, and hematogenous routes of tumor implantation.<sup>51</sup> Direct, mechanical contamination from contact between the excised tumor mass and the wound site was initially believed to be a logical etiology, although wound metastases have occurred at port sites other than those where the tumor was extracted,<sup>48</sup> suggesting the role of alternative mechanisms.

The relative importance of the carbon dioxide pneumoperitoneum and local wound factors in precipitating port site metastases has been examined. Despite the apparent benefit in the reduction of systemic cell-mediated immune suppression<sup>28,29</sup> associated with laparoscopy, the use of carbon dioxide insufflation has been shown to result in an acidotic intraperitoneal environment and impaired peritoneal macrophage function that may contribute to local tumor implantation.<sup>31,52,53</sup> Further studies have demonstrated that alternative means of insufflation, such as helium gas, may result in less tumor growth on peritoneal surfaces.<sup>54</sup>

The effects of local immune enhancement were investigated in an animal model through the intraperitoneal injection of endotoxin. Endotoxin is an immune stimulator that enhances peritoneal macrophage function and subsequent production of TNF- $\alpha$  and interleukins. Local immune enhancement significantly reduced the incidence of port site metastases.<sup>55</sup>

These reports highlight the potential influence of carbon dioxide insufflation on tumor growth and local wound immune suppression resulting in tumor implantation at incision sites. Nevertheless, in a small-animal model of peritoneal micrometastasis, the presence of the trocar itself was the most significant factor contributing to port site recurrence, and the carbon dioxide pneumoperitoneum did not have an important role.<sup>56</sup>

Wu et al<sup>57</sup> showed that implantation of cancer cells into the port site is not limited to the intraoperative time frame. Complete excision of the trocar sites after 10 minutes of pneumoperitoneum in a controlled animal model decreased—but did not eliminate—the occurrence of tumor implantation at the former trocar sites.<sup>57</sup> Therefore, tumor implantation within the port sites may occur during the pneumoperitoneum and after it is released. The effects of a carbon dioxide pneumoperitoneum on intraperitoneal tumor growth was recently investigated in a rat model<sup>58</sup>. Tumor growth after carbon dioxide laparoscopy, gasless laparoscopy, midline

celiotomy, and general anesthesia were reported to be similar in all groups. The conclusions from these studies seem to minimize the direct effect of carbon dioxide insufflation on port site tumor implantation.

Multiple prevention strategies have been used in the clinical setting in an effort to prevent port site tumor recurrence. These include relatively simple tactics that prevent direct contamination of incision sites, such as the use of a wound protector or removing the specimen in an extraction bag. Other more elaborate strategies have been investigated in various animal models. One method used anticoagulation agents to prevent tumor adhesion. Neuhaus et al<sup>59</sup> investigated the effects of intraperitoneal heparin administration in a rat laparoscopy model. Results indicated that animals with heparin administration had a lower incidence of port site tumor implantation. The mechanism was suggested to be a result of competitive inhibition in blocking tumor cell adherence to areas of peritoneal injury or, alternatively, restoring the negative surface charge to the peritoneum, which is altered by injury.

The use of tumoricidal agents with direct cellular toxicity has also been advocated as a means to prevent tumor implantation onto the raw peritoneal surface associated with port sites. Schiavon et al<sup>60</sup> investigated the effects of intraperitoneal administration with saline, heparin, and doxorubicin in a rat model. The results demonstrated a significant reduction in tumor implantation with saline and heparin irrigation compared with controls, but no cases of tumor implantation occurred after the intraperitoneal administration of doxorubicin.

Neuhaus et al reported two studies investigating the effects of cytotoxic chemotherapeutic agents on tumor implantation at port sites.<sup>61,62</sup> The initial study showed that the intraperitoneal administration of diluted povidone-iodine eliminated the incidence of tumor implantation, but other cytotoxic agents (methotrexate) failed to demonstrate a benefit.<sup>61</sup> A follow-up study included a second administration of methotrexate 24 hours after the primary procedure.<sup>62</sup> The authors observed a significant reduction in tumor implantation in all treatment groups, including diluted povidone-iodine and both intraperitoneal and intramuscular administration of methotrexate.

Recently, Wittich et al<sup>63</sup> compared the effectiveness of povidone-iodine, a mixture of tauridine and heparin, and sodium chloride at preventing port site recurrence in a rat model. Tumor cells were introduced in the rat's abdomen after a carbon dioxide pneumoperitoneum was established. Port sites were irrigated after completion of the

pneumoperitoneum with one of the three solutions. Tumor growth was evaluated 4 weeks after the procedure, and no difference in tumor growth at the trocar wounds was found.<sup>63</sup>

The benefit of tumoricidal agents in the reduction of tumor implantation may be the result of a direct reduction in the number of viable free tumor cells in the abdomen, but results from experimental data remain mixed. The use of a general cytotoxic substance such as povidone-iodine may be the best choice as a prevention strategy for port site or extraction site incisional tumor implantation after laparoscopy, although concerns regarding the potential adverse effects on wound healing and macrophage function must be considered.

Perhaps the most important factor influencing the adherence of tumor cells to port sites is the wound-healing environment. A great deal of attention has recently been drawn to the possible role of peritoneal injury and repair in the process of port site tumor implantation. Several studies have shown that the number of cells needed to induce tumor growth was significantly reduced when the cells were injected into a surgical wound compared with nonwounded tissue.<sup>64,65</sup> Furthermore, growth factors isolated from surgical wound fluid significantly facilitated tumor progression when injected into nontraumatized tissue in conjunction with a concentration of tumor cells, which did not normally result in tumor growth.<sup>65</sup>

It has been suggested that the intact peritoneum or its mesothelial monolayer serves as an unfavorable substrate or physical barrier against cancer cell implantation into the abdominal wall.<sup>66</sup> Ovarian tumor cells have been shown to adhere only to the exposed extracellular matrix in the injured mesothelium.<sup>67</sup> Repair of the injured peritoneum at the trocar sites by wound closure has been recommended to reduce the frequency of wound recurrence after laparoscopic surgery.<sup>66,68</sup>

Port site tumor implantation following laparoscopic tumor resection likely has a multifactorial etiology. The carbon dioxide pneumoperitoneum, direct wound contamination, sudden loss of the pneumoperitoneum, suppression of local intraperitoneal immune function, and changes in the local wound environment have been suggested to contribute to this phenomenon. As previously discussed, however, the true incidence is probably comparable with wound recurrence following open resection for colonic malignancy. A benefit of the early hesitation for implementing minimally invasive techniques for resection of colon cancer has been the massive amount of basic science research this controversy

spawned followed by the initiation of large, randomized, controlled trials comparing laparoscopic and open resection. Our understanding of tumor recurrence in laparoscopic and open surgery continues to advance, and many of the resulting prevention strategies may further reduce the incidence of tumor recurrence in the future.

### Prospective Randomized Controlled Trials: Long-Term Outcomes

Basic science studies and reports of clinical experiences are essential in establishing the optimal management of colon malignancy; however, outcomes from prospective, randomized controlled trials comparing laparoscopic with open resection are the ultimate standard. Several recently published studies have completed short-to-medium range follow-up. Curet et al<sup>1</sup> conducted a small, prospective randomized trial from January 1993 to November 1995 comparing laparoscopic-assisted colectomy and open colectomy for resection of colon cancer. This study enrolled 43 patients over 2 years and had a mean follow-up of 4.9 years (range, 3.5 to 6.3 years). From a technical standpoint, the length of specimen and number of lymph nodes per specimen were similar. The conversion rate was 28% for laparoscopic resection and, predictably, was due to large, bulky lesions that could have potentially caused technical compromise of the procedure. There was no attempt in this study to first perform hand-assisted laparoscopic colectomy as a bridge for difficult cases before conversion to open colectomy. This study demonstrated that laparoscopic-assisted colectomy for malignant disease can be performed safely, with morbidity and mortality rates comparable with open colectomy. Long-term follow-up revealed similar outcomes in both groups of patients, and importantly, there was no port site or abdominal wall tumor recurrence.<sup>1</sup>

Lacy et al<sup>3</sup> compared laparoscopic-assisted colectomy with open resection for malignant disease of the colon in 219 patients. Patients were enrolled from November 1993 to July 1998, and the mean length of follow-up was 43 months (range, 27 to 85 months). Primary end points of the study were tumor recurrence and cancer-related survival. The study demonstrated that the probability of cancer-related survival was significantly longer in the laparoscopic-assisted colectomy group. Furthermore, laparoscopic-assisted colectomy was found to be independently associated with a lower risk of

tumor relapse, death from any cause, and death from a cancer-related cause compared with open colectomy. These observations reflected significant differences in patients with stage III tumors, whereas probability curves for stage I and stage II tumors were similar between the two groups.<sup>3</sup>

This was the first randomized prospective trial to demonstrate a potential benefit of laparoscopic-assisted colectomy over open colectomy in a subset of patients undergoing curative resection for colon cancer. The etiology of this observation is unknown but likely reflects the preservation of the systemic immune function in minimally invasive surgery. The probability of tumor spread is less in stage I and stage II cancer, so it is reasonable that a survival benefit was only observed for stage III lesions.<sup>3</sup>

In addition to the Lacy et al and Curet et al studies, several large randomized studies have been published with short-term and long-term outcomes (Table 1). In 2004, the Clinical Outcomes of Surgical Therapy Study Group published a landmark study<sup>15</sup> effectively lifting the moratorium on laparoscopic colectomy for colon carcinoma outside of a clinical trial. This study was initiated in 1994 to ensure that laparoscopic-assisted colectomy for

colon cancer was properly tested before its widespread use, and addressed serious concerns such as adequacy of resection, possible staging inaccuracies, and the role of the pneumoperitoneum as a facilitator of tumor dissemination.

The trial involved 48 institutions and randomly assigned 872 patients with adenocarcinoma of the colon to undergo open colectomy (OC) or laparoscopic-assisted colectomy (LAC) performed by credentialed surgeons. The median follow-up was 4.4 years. The primary end point was the time to tumor recurrence. At 3 years, the rate of recurrence in the LAC group (16%) was similar to that in the OC group (18%). Recurrence rates in surgical wounds were less than 1% in both groups ( $P = \text{NS}$ ). The overall survival rate at 3 years was also very similar in the two groups (LAC, 86%; OC, 85%), with no significant difference between groups in the time to recurrence or overall survival for patients with any stage of cancer ( $P = .51$ , hazard ratio for death in the LAC group, 0.91; 95% confidence interval, 0.68 to 1.21).

Not surprisingly, postoperative recovery was faster in the LAC group, as reflected by a shorter median hospital stay of 5 days vs 6 days ( $P < .001$ )

**Table 1.** Comparison of prospective randomized controlled trials comparing laparoscopic assisted colectomy and open colectomy.

Ref #	Study groups	FU	OR time (min)	EBL (mL)	CONV (%)	LN	PSM (%)	LOS (d)	Morbidity (%)	DR (%)	EM (%)	LM (%)
1	OC=18	4.9 y	138	407	28	10.0	0	7.3	27.8	5.60	0	33.3
	LAC=18		210*	284*		11.0	0	5.2*	5.6	0.00	0	22.2
	COS=7		194	683		12.0	0	8.0	33.3	14.3	14.3	14.3
3	OC=108	5 y	118	193	11	11.1	0	7.9	26.3	27.0	3	17.6
	LAC=111		142*	105*		11.1	1.0	5.2*	10.8*	17.0	1	8.50
15	OC=428	4.4 y	95	N/A	21	13.0	0.2	6.0	21.0	19.6	1	23.0
	LAC=435		150*	N/A		12.0	0.5	5.0*	20.0	17.4	<1	23.0
16	OC=276	3 m	135	N/A	25	13.5	N/A	11.0	33.0	N/A	5	N/A
	LAC=345		180*	N/A		12.0	N/A	9.0*	34.0	N/A	1	N/A
	COS=143		180	N/A		N/A	12.0	38.0	N/A	9	N/A	
17	OC=621	1 m	115	175	17	10.0	N/A	9.3	20.0	N/A	2	N/A
	LAC=627		145*	100*		10.0	N/A	8.2*	21.0	N/A	1	N/A

Studies are listed according to reference number. Short-term outcomes that were compared among the study groups of open colectomy (OC), laparoscopic assisted colectomy (LAC), and converted to open surgery (COS). included follow-up (FU) in years (y) and months (m), operative time (OR time) in minutes (min), estimated blood loss (EBL) in milliliters (mL), conversion rate (CONV), average number of lymph nodes resected (LN), incidence of port site metastases (PSM) as a percentage, length of stay (LOS) in days (d), morbidity, distant recurrence (DR), early mortality (EM), and late mortality (LM). \*Significant differences ( $P < .05$ ) between open and laparoscopic groups.

and briefer use of parenteral narcotics (3 days vs 4 days) ( $P < .001$ ) and oral analgesics (1 day vs 2 days) ( $P = .02$ ). The rates of intraoperative complications, 30-day postoperative mortality, complications at discharge and at 60 days, hospital readmission, and reoperation were similar between groups. The authors concluded that LAC provided no additional risk of cancer and is an acceptable alternative to open surgery for colon cancer.

### Future trials: MRC-CLASICC and COLOR

The short-term outcomes from other large, multicenter prospective randomized controlled trials have recently been published. The UK Medical Research Council trial of conventional versus laparoscopic-assisted surgery in colorectal cancer (MRC-CLASICC) involved 27 centers and was designed to incorporate the standard clinical end points of survival and disease-free intervals and to provide a detailed pathologic analysis of all resected specimens.<sup>16</sup> A total of 794 patients were randomized to either open colectomy or laparoscopic-assisted colectomy. An important difference with the COST trial was that patients with rectal cancer were included in this trial.

In their study, no differences were recorded between open colectomy and laparoscopic-assisted colectomy with respect to tumor and nodal status, short-term end points, and quality of life. The positivity rates of surgical resection margins were also similar between the two treatment groups. Conversion rates were relatively high—61 (25%) of 246 patients with colon cancer and 82 (34%) of 242 with cancer of the rectum (overall, 29%)—but similar to the rate published in the COST study (21%).

Interestingly, converted individuals had a higher mortality rate (9%) than the laparoscopic-assisted (5%) and open surgery groups (1%), although this was not significant after adjustment for stratification factors. Furthermore, respiratory infections were more common in laparoscopic surgery than in open surgery, possibly resulting from protracted anesthetic times. In the laparoscopic arm, 42% of the 43 respiratory infections were in converted patients.

The European, multicenter prospective randomized controlled Colon cancer Laparoscopic or Open Resection (COLOR) trial aimed to assess laparoscopic surgery as curative treatment for colon cancer by analysis of short-term outcome and of

cancer-free survival 3 years after laparoscopic surgery ( $n = 627$ ) or open surgery ( $n = 621$ ) for colon cancer. The authors recently reported short-term results of clinical characteristics, operative findings, and postoperative outcome.<sup>17</sup> Tumors resected by laparoscopy or by open surgery did not differ in stage, distribution, size, histology, number of positive resection margins, and number of total and positive lymph nodes. Furthermore, hospital stay after laparoscopic colectomy was 1 day shorter in the laparoscopic group than in the open group, consistent with findings from Lacy et al and the COST study group. Conversion of laparoscopic procedures to open surgery was needed in 19% of patients, mainly because of the presence of a large and invasive cancer.

CLASICC and COST both evaluated quality of life and found no significant advantages with a laparoscopic approach. Possibly, patients with cancer are more concerned with cure from their malignancy and survival than with daily quality of life. All studies found similar pathologic endpoints in the laparoscopic and open groups when the number of lymph nodes harvested and resection margins were evaluated. The most important finding from the COST and Lacy et al studies is that there were no differences in survival between open and laparoscopic resection except for patients with stage III disease, who, in the Lacy et al study, had prolonged survival for unknown reasons. These long-term results have not been reported in the CLASICC and COLOR studies, but it will be important to assess whether results from these trials support those of the COST and Lacy et al trials.

### Conclusion

The advent of laparoscopic surgery has revolutionized general surgery over the last 15 years. The proven advantages of minimally invasive surgery include less pain, quicker return of gastrointestinal function, shorter hospital stay, fewer wound complications, quicker postoperative recovery, and less systemic immunosuppression.

The use of minimally invasive techniques for resection of the large bowel was first reported in 1991.<sup>69</sup> Initially, there was substantial enthusiasm for utilization of this technique for a variety of colorectal pathologies, including malignancy. This initial euphoria was quickly tempered as potential disadvantages associated with laparoscopic resection for colon cancer were identified. These included a

steep learning curve for the procedure that requires the surgeon and the ancillary operating room staff to have advanced skills in laparoscopy, the potential violation of oncologic principles that are standard in open surgical cancer resection, and the concern for port site tumor recurrence.

This controversy has led to a vast outpouring of basic science and clinical research during the past decade. Mounting evidence indicates that wound recurrence following LAC and open colectomy are comparable. Short-term and long-term results from prospective, randomized trials show that patients with colorectal cancer can be offered laparoscopic-assisted resection. These studies provide data that demonstrate that in experienced hands, laparoscopic-assisted colon resection is a safe and oncologically sound modality. The preoperative work-up should focus on identifying patients who are at high risk for conversion. It is expected that future long-term outcomes to be published by the MRC-CLASSIC and the COLOR trials will support the long-term safety and efficacy of laparoscopic colorectal resection.

As we potentially come full circle in this process, it will be of paramount importance for surgeons to police their individual skills and outcomes with this procedure. The learning curve may be shortened with the use of the hand-assisted techniques; however, initial endeavors in laparoscopic colectomy should be undertaken for benign colorectal pathology until adequate proficiency is obtained. Ultimately, standardization of the techniques should be considered to ensure quality control in the event that this procedure is widely used after the current and upcoming reports of the randomized trials. Future studies will also need to weigh the absence of oncologic risk and the short-term benefits with the cost-effectiveness of laparoscopically assisted colectomy.

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