

LAPAROSCOPIC SURGERY FOR CANCER REDUCES ADVERSE IMMUNOLOGIC SEQUELAE AND MINIMIZES PLASMA PROTEIN ALTERATIONS

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Introduction

Are there meaningful immunologic differences between open and MIS methods in the setting of cancer? I am defending the viewpoint that there are measurable differences in the impact of open and closed methods on immune function in favor of laparoscopic methods. However, from the outset, it is important that we broaden the discussion so as to include surgery-related blood protein alterations. Although some of these plasma compositional changes are likely to impact immune function which may, in turn, indirectly influence tumor growth or recurrence, others are not immune system related at all. Instead these “other” alterations may impact angiogenesis, apoptosis, and tumor growth via other mechanisms. And though not immune system related, these other sequelae may be of great importance. Perhaps another way to phrase the initial question is, “How do open and MIS methods impact the hosts ability to fend off tumor recurrences and limit tumor growth after surgery? AND how does surgery influence tumor cells that remain in the host either the bloodstream or in tumor microfoci?”

As will be seen, there is a growing list of parameters which are affected in different ways by open and closed surgical techniques. Harder than finding such parameters, however, is demonstrating that the physiologic, immunologic, and other host differences in response to surgery are important clinically. The most challenging task has been, and remains, establishing clinical relevance. In fact, in some cases, it is difficult to even determine whether a given change is “bad” or “good.”

Immunologic Consequences Of Surgical Approach

Prior to the laparoscopic era it had been well established that major open surgery is associated with the temporary suppression of a variety of cells that are involved with both innate and specific immunity including lymphocytes, neutrophils, monocytes, and macrophages. In addition, interactions between cells and other cellular functions are negatively influenced by open surgical trauma. Further, the ability to mount a positive response to a delayed type hypersensitivity (DTH) recall antigen challenge is suppressed after surgery.¹⁻⁵

The relative contribution of each part of an abdominal procedure (abdominal wall access incision versus intra-abdominal dissection and resection) to the post surgical immunosuppression had not been assessed prior to the advent of advanced

laparoscopic methods. The results of recent studies suggest that the method of entry into the abdomen is an important determinant of postoperative immune function. Minimally invasive methods, for a variety of immune parameters, have been shown to be associated with significantly better preserved function when compared to the equivalent open procedure. Of note, in many cases the differences are small and short lived, on the order of a day, and sometimes less for several variables. For a number of parameters no differences have been noted.

DTH Testing:

One of the simplest methods is to evaluate immune function via delayed-type hypersensitivity (DTH) testing. The ability to mount a delayed-type hypersensitivity (DTH) response to an intradermally injected antigen to which the subject has been previously exposed verifies that several important elements of the immune system are functioning (antigen presentation, proliferation of the memory CD4 lymphocyte, cytokine elaboration, and the effector response which results in the wheal at the injection site). By administering a series of DTH challenges, one before (which establishes the baseline response) and several after surgery (postop responses are compared to the preoperative result), it is possible to assess the functional state of the immune system.

Animal studies have shown that laparoscopic colectomy is associated with significantly better preserved DTH responses than the open equivalent.⁶ A small human nonrandomized DTH study was carried out in the late 1990's on colectomy patients. In this study, serial DTH challenges were given before and after surgery to both open and closed colorectal resection patients. The study demonstrated that open colectomy was associated with a significant decrease in the size of the mean DTH response when patients were challenged on the day of surgery and postoperative day 3, whereas the minimally invasive colectomy group's post-surgery responses were not significantly smaller than their preop results.⁷ A just completed randomized human study that assessed the impact of perioperative GM-CSF in the setting of minimally invasive colorectal cancer surgery has confirmed that there is no significant decrease in DTH response to Tetanus or Candida on POD 1 and POD3 after minimally invasive colorectal resection (control group results).⁸

Cytokines:

Surgical trauma evokes a potent local and systemic inflammatory response manifested by rapid changes in the plasma concentration of various acute-phase proteins and pro-inflammatory cytokines. Although increased levels of cytokines and acute-phase proteins reflect an inflammatory response, they do not directly correlate with the status of the immune system. Plasma levels of acute phase proteins such as C-reactive protein (CRP), which is the most widely measured marker of the acute-phase response, and the pro-inflammatory cytokines IL-1 β , IL-6, IL-8 and TNF α are, typically, transiently increased following significant tissue injury. IL-6, the best studied cytokine, has been consistently found to be transiently increased in response to injury.

Pre- and postoperative plasma levels of all the above inflammatory mediators have been compared in patients undergoing laparoscopic and conventional surgery. Most reports on the stress response following open and laparoscopic surgery have shown that open cholecystectomy is associated with higher postoperative plasma levels of CRP, TNF α , IL-1 β , and/or IL-6 relative to laparoscopic cholecystectomy, suggesting that open surgery is associated with a greater inflammatory response.⁹⁻¹³ Significantly higher levels of some or all of these proteins were also found postoperatively in patients following conventional Nissen fundoplication^{14,15} and colorectal cancer resection relative to patients undergoing laparoscopic surgery.¹⁶⁻²⁰ Other studies have shown that while both open and laparoscopic colorectal surgery are associated with elevated plasma CRP levels, there is a more prompt return of CRP levels to baseline preoperative values following laparoscopic than open surgery.²²

Specifically in regards to IL-6 levels, conflicting results have been reported, though the discrepancy between various studies may be the result of differences in the sampling times. Those investigators that have measured IL-6 levels in the first 24 hours after surgery have almost always found significantly higher levels in the open patients.^{17, 21,23,24} However, in a number of studies, the differences between the open and closed colectomy patients were lost within 24 hours. Several of the papers that reported no difference between groups did not obtain the first sample until at least 24 hours after surgery.²⁵

Lymphocytes:

Studies assessing the number of circulating lymphocytes of different subtypes have, with rare exception, found no significant differences between open and closed groups.³¹ A randomized cholecystectomy study which indirectly assessed the ratio of Th-1 / Th-2 lymphocytes by measuring levels of **Interferon γ** (Th-1) and IL-4 (Th-2) that were elaborated by peripheral blood monocytes in vitro, after stimulation, found a significant difference between the laparoscopic and open groups only 2 hours after the operation; all other sampling points yielded similar result between groups.²⁶ A recent colectomy study analyzed CD31 expression on circulating T lymphocytes before and after surgery. Efficient killing of tumor cells or other pathogens depends on, among other things, T cell migration from the circulation to peripheral tissues. T cells migrating from the circulation to the peripheral tissues express the CD31 antigen. CD31 expression was found to be significantly decreased from preoperative baseline levels in the open group on the first and third postoperative day; this was not the case in the laparoscopic group. Furthermore, there was a significant correlation between the decrease in CD31 expression and the incision length in the open group.²⁷

Some insight into the specific molecular effects of laparotomy and laparoscopy on T cells comes from a microarray analysis on the time course of the differential effects of sham laparotomy vs. CO₂ pneumoperitoneum on splenic T cell gene expression in mice.²⁸ Relative to anesthesia control, 12 hours after surgery, sham laparotomy resulted in notable alterations (greater than 2 fold differences in expression in 398 T cell genes compared with 116 genes following pneumoperitoneum). At 24 hours, the differences between the two surgical methods were less marked, with alterations in expression

noted in 157 genes following laparotomy as opposed to 132 genes after pneumoperitoneum. When global gene expression was compared between laparotomy and pneumoperitoneum, expression of 177 genes was increased following laparotomy relative to pneumoperitoneum at 12 hours, a difference that was reduced 4-fold at the 24 hour time point.²⁸ Functional differences in gene expression between 12 and 24 hours after surgery were also noted in both groups. These transient but substantial alterations in splenic T cell gene expression profiles following laparotomy provide a molecular basis for the observation that open surgery is associated with transient but marked immune alterations. Ongoing functional analysis of those genes with differential expression in response to laparotomy and pneumoperitoneum will not only uncover the biological significance of these differences, but may identify genes that can be used as clinical markers of the effect of surgery on the immune system.

Monocytes/Macrophages:

Results regarding the in vitro function of circulating monocytes and peritoneal macrophages conflict and are difficult to interpret. As per some studies, CO₂ pneumoperitoneum may inhibit or down-regulate peritoneal macrophage function. However, in a rodent study carried out by the author's lab comparing open vs closed cecectomy, it was demonstrated that open surgery was associated with significantly lower H₂O₂ release (a reflection of respiratory burst activity) from peritoneal monocytes on POD 1 when compared to anesthesia control results. These results suggest that the peritoneal macrophages are less ready and able to function after open surgery.⁴⁷

Collet et al, in a pig study that compared open and closed Nissen fundoplication, assessed the ability of the peritoneal cavity to clear 10⁹ *E. coli* introduced into the abdomen at the end of the operation. Bacterial counts of samples of peritoneal fluid were taken 1, 2, and 8 hours after surgery. The open group bacterial count was dramatically higher than the closed group results 8 hours after the operation. However, when assessed in vitro after recovery, no differences in the ability of peritoneal or circulating monocytes to phagocytize *S. aureus* in vitro was noted between the open and closed groups.²⁹

A recently published large animal study of peritoneal macrophages (PM's) compared the impact on macrophage IL-6 and TNF production of open, hand-assisted, and laparoscopic nephrectomy. PM's were harvested 4, 12, and 24 hours after surgery, after which the PM's were cultured and then stimulated with lipopolysaccharide, after which the levels of the fore mentioned cytokines were determined. All three types of surgery were associated with increased TNF and IL-6 levels. However, the open nephrectomy group results at the 12 and 24 hour timepoints were significantly greater than either the hand or the laparoscopic groups whose results were similar to each other.³⁰ These results imply that open methods are associated with peritoneal macrophage activation to a greater extent than the minimally invasive surgery methods. As can be seen from the above 3 studies, the literature is conflicting in regards to peritoneal macrophages. Thus, it is not clear what the "take home" message is regarding peritoneal macrophages; similarly, the clinical relevance of these results, if any exists, is unknown.

In regards to peripheral blood mononuclear cells (PBMC's), a randomized study of human colectomy patients demonstrated a small but significant difference in the expression of the marker HLA-DR on circulating monocytes in favor of the laparoscopic patients on the 4th day after surgery.¹⁷ This is an activation marker for monocytes; decreased expression rates have been associated with worse outcome in trauma patients.

Clinical Import:

It should be realized that the clinical significance, if any exists, of the immune function differences has not been determined. Better preserved postoperative cell-mediated immune function, in theory, may have an impact on the rate of infections and, possibly, tumor recurrence rates and survival. The low rate of port-site wound infections that has been noted for most laparoscopic procedures and the significantly better disease free survival of laparoscopic patients after colectomy for cancer noted by Lacy in his randomized study would seem to support this notion.⁴⁸

Etiology of Surgery-related Immunosuppression:

What is it about abdominal surgery that causes temporary suppression of the immune system? There are probably a number of contributing factors. There is evidence that the overall length of an abdominal wall incision is an important factor. Others, based on the results of a murine study, believe that the exposure of the abdominal cavity to air is the cause of the immunosuppression after open surgery. These latter investigators believe that small amounts of lipopolysaccharide(LPS) in the air cause immunosuppression by stimulating bacteria in the intestine to elaborate LPS which then translocates across the bowel wall after which it is absorbed systemically.³²

Possible Future Immunotherapies:

The controversy surrounding laparoscopic surgery for cancer has led to studies that have significantly increased our understanding of surgery's impact on the body. This will hopefully lead to new perioperative pharmacologic therapies that will lessen the deleterious immunologic effects of all types of surgery. An example of this type of approach is to administer immunostimulatory agents perioperatively to cancer patients. Such treatment in small animal studies has been shown to be associated with significantly lower tumor recurrence and metastases rates.^{33,34} Mels et al in a small randomized trial of 16 open surgery patients demonstrated that 7 perioperative doses of GMCSF (granulocyte-macrophage colonystimulating factor) was associated with significantly better preserved postoperative DTH responses and HLA-DR expression on monocytes than placebo.³⁵ (GMCSF is usually used as a bone marrow rescue agent in chemotherapy patient.)

A similar randomized human study of perioperative immunomodulation study in the setting of colorectal cancer has just been completed at Columbia University (59 patients total).⁸ GMCSF was given daily 3 times before surgery and then for the first 4 postoperative days to patients undergoing minimally invasive surgery. The goal was to up-regulate immune function perioperatively and also to determine the impact of this treatment. The drug was well tolerated and was not associated with any discernible complications. Unlike the Mels et al study mentioned above, the Columbia study did not

demonstrate significantly better immune function after GMCSF treatment as measured by serial DTH responses, number of DR+ monocytes, an array of Th1/Th2 cytokines, or plasma IFN- γ levels. One possible reason for these findings may be that it was much harder to demonstrate immune benefits for the GMCSF group because the immune function of the control patients (all laparoscopic patients) was better preserved than in the open surgery control of the Mels et al study which demonstrated more dramatic decreases in the immune parameters followed. An unexpected and noteworthy finding of this GMCSF study was that it clearly demonstrated that GMCSF results in significantly higher soluble VEGF-Receptor 1 levels and a significantly higher Angiopoetin 1 /Angiopoetin 2 ratio on POD 5 than in the control group. Further, post-GMCSF blood on POD 5 was shown to significantly decrease endothelial cell proliferation and invasion in in vitro cultures. These results suggest that angiogenesis is inhibited by GMCSF. ⁴⁹

Another possible immunotherapy would be to give preoperative tumor vaccines in order to encourage the development of an active immune response against the tumor prior to resection. Then, in the early postoperative period when the tumor burden is at its lowest, the patient would have a means of eliminating any viable tumor cells that may remain. In small animal studies this approach has been successful in lowering the rate of metastases.³⁵ There are no human preoperative vaccine trials underway presently, to the authors knowledge.

Surgery Related Protein Alterations:

Not surprisingly, surgery impacts the composition of the plasma which contains a countless number of different proteins. Since the blood stream is “downstream” to all the bodies organs, it is difficult to determine the source(s) of the protein changes detected in the plasma or serum. Further, although there is some in vitro data which assesses the impact of surgery-related plasma protein alterations, in general, it is difficult to determine the clinical significance of many of the alterations that have been documented. Whereas the function and effects of most of the proteins assessed has been well studied in vitro and, in some cases, in vivo, there is little data regarding the import of temporary and, in some cases, modest changes in the plasma levels of these parameters. Also, pre-cancer resection plasma levels of some of the parameters, VEGF is a prime example, have been shown to be significantly higher in cancer patients than in control patients without tumors; high blood VEGF levels correlate with advanced disease stage and a worse prognosis. Plasma VEGF levels increase after open and closed colorectal resection and remain increased for at least 3 weeks (see below).⁴⁴ This is a very interesting finding; however, it has not been established that this sustained increase has any bearing on the oncologic outcome. Thus, similar to the situation with the immune parameters, the burden of proof remains with the laparoscopic enthusiasts to demonstrate clinical outcome benefits for the closed patients. The blood protein alterations that might impact tumor growth will be emphasized in this brief review.

IGFBP3:

Perhaps the best evidence, albeit it in vitro data, regards insulin-like growth factor binding protein 3 (IGFBP-3). This protein has been well studied and has been

show to inhibit tumor growth via several mechanisms. Besides binding and essentially "tying up" IGF-1, a major cell growth factor (an indirect effect), IGFBP-3 also induces apoptosis in most tumor cell lines. This protein also inhibits DNA synthesis in poorly differentiated cell lines. Thus, IGFBP-3 is an endogenous inhibitor of tumor growth. At baseline, the vast majority of people have fairly high levels of this protein. Of note, only the intact protein has the tumor inhibitory effects. In contrast, the partially degraded IGFBP-3 protein does not have this effect.

Major abdominal surgery, open significantly more so than laparoscopic, is associated with a 1-3 day significant decrease in plasma levels of intact IGFBP3.³⁷ In the laparoscopic patients, a non-significant decrease was observed. The duration of the larger decrease in the open patients was associated with the incision length. Furthermore, postoperative day 1 plasma (with decreased intact IGFBP-3 levels) from open colectomy patients has been shown to stimulate *in vitro* tumor cell growth when compared to culture results obtained when preoperative plasma from the same patients is assessed. The fact that when exogenous IGFBP-3 is added to the postoperative plasma no increase in the *in vitro* tumor growth rate over baseline is observed, suggests that the decrease in IGFBP-3 levels is responsible for the tumor growth stimulation noted with the "raw" postoperative plasma.³⁸

MMP-9:

Several of the matrix metalloproteinases are thought to play an important role in tumor growth and spread. Plasma MMP levels have been shown to be elevated in patients with a variety of different cancers. These proteolytic enzymes are capable of degrading connective tissue at the border of tumors, thus permitting the spread and growth of the tumor in question. In the plasma, MMP-9 has been demonstrated to degrade IGFBP-3 and is thought to be the mechanism by which open surgery results in a decrease in IGFBP-3 levels. In a study of 88 open and closed colorectal cancer patients, a significant increase in plasma MMP-9 levels was noted on POD 1 in the open group, whereas there was no sizable change in the laparoscopic group's levels. The decrease in MMP-9 levels is very transient and by POD 2 and 3 levels have returned to normal.³⁹

TIMP-1 (Tissue Inhibitor of Metalloproteinases-1):

The most likely reason why the above noted MMP-9 decrease is so short lived is that plasma TIMP-1 levels also rise after open surgery and remain significantly elevated over baseline for at least the first 3 days after surgery. Laparoscopic patients manifest a smaller yet still significantly increased TIMP-1 level after surgery.³⁹ Similar to the situation with the MMP's, TIMP-1 levels have been shown to be elevated in the setting of several different cancers. The clinical import of these transient increases is uncertain.

VEGF (Vascular Endothelial Growth Factor):

Vascular endothelial growth factor (VEGF) is a potent inducer of angiogenesis, which is critical for wound healing, and plays a crucial role in the early steps in angiogenesis. It is logical to anticipate that plasma levels increase after major surgery. VEGF has also been shown to facilitate

and promote tumor growth. It has been demonstrated that many tumors, including colonic adenocarcinoma, cannot grow beyond 2-3 mm in size without the development of new blood vessels. When groups of cancer patients have been evaluated pre-resection, their mean serum and plasma VEGF levels have been shown to be significantly greater than the mean values of control populations without tumors.^{40,41,43} The height of the elevation for some tumors, including colon, correlates with the stage of disease and/or prognosis in some series.

What impact does surgery have on blood VEGF levels? A postoperative increase in plasma VEGF levels may facilitate tumor growth early after surgery. In a study published this past fall, early postoperative plasma VEGF levels were studied in the setting of both open and minimally invasive colorectal resection for cancer and for benign indications. In the open cancer patients, a significant and stepwise increase was noted on POD 1 and POD3 when compared to preoperative levels. In the laparoscopic patients, on POD3 a significant VEGF increase was also noted over baseline. However, of note the mean laparoscopic value, although increased, was significantly lower than that noted in the open group at the same timepoint. Also, no increase was noted on POD1 in the closed group. Although the benign colorectal resection group's baseline VEGF levels were lower than the cancer group, their response to surgery was very similar; steady increase in the open group and a delayed and blunted increase in the laparoscopic group.⁴²

A more recent study assessed plasma VEGF levels for the first postoperative month after laparoscopic colorectal resection for benign (30 pts) and malignant disease (49 pts). In the cancer patients, VEGF levels continued to rise and peaked during the 3rd postoperative week. Significant elevations were noted from POD 3 through the 4th postoperative week. Similar, yet lower and less persistent elevations were noted in the patients with benign disease (values peaked during the second week).⁴⁴ To date, to the author's knowledge, this is the first surgery-related plasma protein alteration that has been demonstrated to persist for this length of time. Given the fact that these were minimally invasive patients, the findings came as somewhat of a surprise. Whether levels for open colorectal resection patients would be similar remains to be shown. In the authors view, although it is possible that open patients will manifest even greater plasma VEGF elevations, it is more likely that open patients will demonstrate similar elevations. Thus, the transient, 1-2 day delay in VEGF increase observed after closed surgery may be of little significance in light of the long duration of the effect.

Angiopoetin 1 (Ang 1) and Angiopoetin 2 (Ang 2):

These proteins play important yet conflicting roles in regards to VEGF-mediated angiogenesis. Both bind to the Tie-2 receptor. Whereas Ang 1 stabilizes mature vessels and inhibits VEGF-mediated angiogenesis, Ang 2 is thought to encourage and promote VEGF-mediated angiogenesis. The ratio of plasma Ang 1 to Ang 2 levels is thought to be a measure of the body's tendency towards VEGF-mediated angiogenesis. A high ratio would encourage blood vessel stabilization whereas a low ratio would favor the VEGF stimulated effects which stimulate new vessel formation.

In a study of benign pathology open and closed colon and rectal resection patients it was demonstrated that both surgical methods are associated with a decrease in Ang 1 and an increase in Ang 2 levels on POD 1 and 3 such that a significantly greater Ang 1/ Ang 2 ratio was noted at both time points. The magnitude of the Ang 2 and Ang 1/ Ang 2 ratio changes were significantly greater in the open resection group.⁴⁵

In a recently completed study of over 100 colorectal resection patients it was demonstrated that following either open or minimally invasive resection, (on both POD 1 and 3), Ang 1 levels were significantly lower and Ang 2 levels significantly higher when compared to the preoperative results for both benign indications and for cancer patients. Similarly, the Ang 1/ Ang 2 ratio on POD 1 and 3 following both types of surgery was significantly lower (favoring VEGF mediated angiogenesis). Although both surgical methods had similar effects on Ang 1, Ang 2, and the Ang 1 / Ang 2 ratio, the extent of the changes (decrease in Ang 1, increase in Ang 2, and the decrease in the Ang 1/ Ang 2 ratio) were significantly greater following open colorectal resection. Thus, surgery in general results in similar effects, however, open surgery has a notably greater impact.⁴⁶

Summary:

Clearly minimally invasive surgery is associated with less marked perturbations of the immune system. It makes sense that it is desirable to maintain baseline immune function and status; thus laparoscopic surgery is preferable to open methods from this vantage point. What is needed is better clinical data, in regards to short term or long term outcome measures, that demonstrate advantages for the minimally invasive patients. Lower wound infection rates and morbidity rates have been reported by some investigators; these may be the clinical reflection of better preserved immune function. The shorter length of stay may also, in some way, be related, however, this has not been proven and would be hard to demonstrate.

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Role of Minimal Access Surgery in Staging of Malignancies

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Preoperative imaging continues to improve rapidly with technology developments. Currently surgeons can precisely judge the local, regional, and metastatic behavior of specific cancers with an abundance of studies. We have all become familiar and increasingly rely upon high grade functional and anatomic imaging studies such as multi slice CT, endoscopic ultrasonography (EUS), MRI, and PET imaging alone or in combination with CT. The role of laparoscopy in the staging of gastrointestinal cancers is evolving rapidly as these other imaging techniques improve. Laparoscopy can also be augmented with intraoperative ultrasound to look at the liver parenchyma and local tumor characteristics. The intellectual case for staging laparoscopy can be made for cancers where other imaging modalities may understage disease by either missing metastatic implants due to location, size, or inability to delineate a tumor's local extent. Initially, staging laparoscopy was described primarily in patients with esophageal, gastric, and pancreatic primaries. Diagnostic laparoscopy has also been useful in staging of gallbladder cancer or establishing a diagnosis in cases of peritoneal disease with an unknown primary. There are currently no evidence based medical (EBM) guidelines, such as a Cochrane analysis, to guide surgeons in this decision. The best evidence available to surgeons in real time are the National Comprehensive Network Practice Guidelines (NCCN), which are consensus documents updated yearly and give cancer specific algorithms that cover from workup through treatment¹.

Pancreatic Malignancy

Laparoscopy for staging of pancreatic malignancy is considered a Category 2B recommendation as defined by a “nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate”². This opinion was based on a literature review of primarily small clinical single institution reports. In these studies laparoscopy was reported to be helpful in identification of peritoneal implants, or surface studding on the liver or intestinal serosa. Many surgeons consider tumor location (body or tail lesions), significant CA 19-9 elevations, and large primaries as an indication for laparoscopy because the potential to identify unresectable patients is greater in this subset of patients. Peritoneal washings for cytologic examination have been performed by multiple groups but there is no consensus as to whether this should be done routinely if laparoscopy is performed. There is agreement though that if washings are done and are positive for malignancy that this would be considered metastatic disease and the patient should not undergo resection³. Ultrasonography is advocated by some surgeons as an additional way to get more information about the location and relationship of the primary cancer to surrounding vascular structures. This has not been critically examined in a large trial and no EBM recommendations can be made in support of the addition of laparoscopic ultrasonography.

Gastric Cancer

Laparoscopy is also considered a Category 2B recommendation in the NCCN practice guidelines⁴. It is recommended for patients prior to resection or referral for chemoradiation protocols. Gastric cancer has a greater likelihood of peritoneal implants than other cancers for an unknown reason and this may explain why many centers use laparoscopy in the operative staging algorithm of these patients. A series from Memorial Sloan Kettering examined the role of laparoscopy in detection of unknown metastatic disease in patients with advanced gastric cancers with no evidence of metastatic disease on preoperative

imaging. More than one third (37%) of the patients were found to have unsuspected metastatic disease at time of laparoscopy and were not resected⁵. In my opinion diagnostic laparoscopy in gastric cancer represents one of the best case types for routine laparoscopy in all patients except those with early Tis or T1 lesions.

Esophageal Cancer

Initially there was a lot of enthusiasm for laparoscopy in the staging of esophageal malignancies but some of the enthusiasm waned after the development of endoscopic ultrasound with end fire fine needle aspiration (FNA) which can definitively determine nodal status. In the most recent NCCN practice guideline there is no mention or recommendation of laparoscopy in the document⁶. This is counter distinction to the opinion held by the group at the University of Pittsburgh who has the largest US experience in minimally invasive esophagectomy. In a recent study they compared EUS with FNA to laparoscopic staging with examination of the peritoneum, liver capsule, stomach, and lesser sac. Results demonstrated that 17% of patients were found to have metastatic disease at the time of laparoscopy that was not suspected and that laparoscopy was able to correctly stage patients who had suspicious nodes on imaging but could not be biopsied by EUS⁷. Their conclusion was that staging laparoscopy should be performed in patients who are being considered for neoadjuvant protocols and in those referred directly for resection. It will be interesting to see if this data becomes incorporated into the next version of the NCCN guidelines.

Gallbladder Cancer

Patients who are found to have incidental cancers at the time of cholecystectomy that are T1b (invasion of muscle layer) or greater on pathologic exam should be strongly considered for diagnostic laparoscopy prior to definitive resection. Gallbladder cancer has a proclivity to seed the peritoneum, surgical wounds, and laparoscopic port sites and can be overlooked in working up advanced cases. Peritoneal seeding from spillage of gallbladder contents can also lead to the

finding of extensive seeding throughout the peritoneal cavity at the time of operation. The NCCN current practice guideline recognized this finding and recommends strong consideration of laparoscopy before resection⁸. In my personal practice I routinely perform a diagnostic laparoscopy prior to any resection for T1b or greater gallbladder cancer.

Summary

The definitive role of diagnostic laparoscopy with or without ultrasonography is evolving quickly as other non invasive examinations such as CT, EUS, and PET/CT progress in their resolution and detection. It is my opinion that diagnostic laparoscopy has a role where there is a significant chance of peritoneal implants or surface hepatic lesions that are not well imaged with current techniques. Gastric and gallbladder cancer represent the "best case" examples for the role of laparoscopy in staging of these malignancies. I do not think a surgeon would ever be considered unreasonable for using laparoscopy to stage a patient in any of the malignancies listed above. One of the most difficult things can be scheduling issues because if it is done as the first portion of a planned resection and found to preclude a resection then a large block of operating room time was not utilized and administrators complain. On the other hand if it is done as its own operative procedure on a day preceding the resection date it means that the patient has to undergo two general anesthetics and incur increased costs which make insurance carriers unhappy. Diagnostic laparoscopy can be an important staging tool, especially in advanced cases where identification of patients with metastatic disease without a laparotomy saves the patient a prolonged recovery and the system the cost of an unnecessary laparotomy.

¹ http://www.nccn.org/professionals/physician_gls/f_guidelines

² http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf

³ Ferrone CR, Haas B, Tang L, et al. The influence of positive peritoneal cytology on survival on patients with pancreatic adenocarcinoma. *J Gastrointest Surg* 2006;10:1347-1353

⁴ http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf

⁵ Burke EC, Karpeh MS, Conlon KC, Brennan MF. Laparoscopy in the management of gastric adenocarcinoma. *Ann Surg*. 1997 Mar;225(3):262-7.

⁶ http://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf

⁷ Kaushik N, Khalid A, Brody D, Luketich J, McGrath K. Endoscopic ultrasound compared with laparoscopy for staging esophageal cancer *Ann Thorac Surg*. 2007 Jun;83(6):2000-2

⁸ http://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf

Minimal Invasive Access Surgery for Esophageal Cancer

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Introduction

The incidence of esophageal cancer (EC) has increased dramatically in the Western population in the last 2 decades. The reason for this dramatic increase is not entirely clear, but gastroesophageal reflux disease, obesity and Barrett's esophagus have been identified as risk factors. The annual rate of malignant transformation in Barrett's is approximately 0.5 percent. In this talk, we will discuss the development and technique of minimally invasive esophagectomy (MIE), and recent developments in technique including minimally invasive Ivor-Lewis esophagectomy.

Minimally Invasive Esophagectomy

We have published our analysis of 222 consecutive patients who have undergone minimally invasive esophagectomy at the University of Pittsburgh. Esophagectomy was performed with thoracoscopy, laparoscopy and cervical anastomosis. We have detailed our technique of minimally invasive esophagectomy. Although early in the series we selectively performed MIE on patients with smaller tumors and no previous therapy, 35% of the patients in this series had been treated with chemotherapy and 16% with radiation. In addition, 25% of patients had undergone prior open abdominal surgery.

MIE was able to be completed as planned in 206 (93%) patients. No emergent conversions to an open procedure were necessary for bleeding. Overall there were three deaths in the series (1.4% mortality). This very low mortality rate compares favorably with the largest series of open esophagectomy. The survival Stage for Stage was comparable to open series. We now have an extensive experience with MIE at our institution.

New Developments in Minimally Invasive Esophagectomy

Minimally Invasive Ivor Lewis Esophagectomy

The standard minimally invasive esophagectomy performed at the University of Pittsburgh is a three-field operation, with a cervical anastomosis. Many open esophageal surgeons prefer an intrathoracic anastomosis, as it avoids another incision, lowers the likelihood of recurrent nerve injury, and may be associated with a lower leak rate. The significant drawback of the standard operation is the need for both a thoracotomy and laparotomy, which may increase the incidence of pulmonary complications.

We have reported our initial experience with a minimally invasive Ivor Lewis esophagectomy at the University of Pittsburgh. Early on the operation was a hybrid procedure, combining laparoscopic mobilization of the stomach with a mini-thoracotomy for creation of the anastomosis. With increasing experience we have turned to a completely minimally invasive approach. We perform esophageal dissection as high up into the thoracic inlet as possible to allow some mobility of the proximal esophagus while the anastomosis is being created. The esophagus is then divided at the level of the azygos vein, and the anvil of a 25mm EEA stapler is introduced into the lumen, and is secured using a purse string suture. We then enlarge one of the posterior ports to introduce the stapler into the chest. An end-to-side anastomosis is then created, and the distal tip of the stomach is amputated using a liner stapler. We now have a growing experience with minimally invasive Ivor Lewis esophagectomy and is our current preferred approach. It is particularly useful option, especially for patients with extensive involvement of the cardia in whom the conduit may not reach to the neck.

Prone Positioning

For several reasons, the learning curve associated with the thoracoscopic mobilization of the esophagus is quite steep. For one, the chest wall is far more rigid than the abdomen. Port placement, therefore, is critically important during VATS. Improper port placement will lead to significant torque when using the instruments and operator fatigue. In addition, unlike laparoscopy, the surgeon is often operating in a plane perpendicular to the view of the camera. This makes disorientation far more likely when the surgeon is first learning the technique. Finally, the esophagus is at the bottom of the operative field when the patient is in the lateral position. Consequently the view tends to be obscured by pooled blood and the collapsed lung.

A modification to address these concerns is to perform the thoracoscopic mobilization in the prone position¹. The potential advantage of this technique is that the lung and blood do not obscure the view of the esophagus. In fact single

lung ventilation may be used with CO₂ insufflation, as the ipsilateral lung will fall away from the field due to gravity. In addition the surgeon is operating in a plane parallel with the camera, improving the ergonomics of the procedure.

To date the largest experience with prone positioning is from C. Palanivelu, a surgeon practicing in Coimbatore, India. All patients in his series of 130 cases had squamous cell cancer of the mid-thoracic esophagus and only one patient received neoadjuvant therapy. In his technique the esophagus is first mobilized thoracoscopically using three ports, in the prone position. The patient is then turned to the lithotomy position, and mobilization of the esophageal hiatus and stomach is done laparoscopically. A mini-laparotomy is then performed for tumor extraction, creation of the gastric tube and pyloroplasty. The procedure is then concluded with a cervical anastomosis.

Early results after this procedure are encouraging. There were no conversions to an open procedure, the median ICU stay was one day, and the overall mortality was 1.5%. The mean number of lymph nodes harvested was 18, and the mean operative time was 220 minutes. The major morbidity rate was 11%, with an anastomotic leak rate of 3%. Stage-specific survival following this procedure was equivalent to that of open series. Certainly the benefits of this technique await confirmation in larger series and other centers. However this report clearly serves to emphasize the low morbidity and mortality that can be achieved with a minimally invasive approach in a dedicated center.

Conclusion

In summary, Minimally invasive esophagectomy can be performed with acceptable morbidity, low mortality and potentially equivalent oncologic results. A multi-institution trial is underway to document the potential advantages of minimally invasive esophagectomy. This trial is sponsored by the Eastern Cooperative Oncology Group (ECOG 2202), with participation of multiple centers across the United States, with the University of Pittsburgh serving as the coordinating center. The completion of this study will hopefully demonstrate the benefits of the procedure, and document that its advantages can be realized at other centers.

Minimal access surgery (MAS) in Gastric Cancer: Current Status

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I. Introduction

Gastric cancer is one of the major malignant diseases with high mortality in the world. Recently, as diagnostic modalities for gastric cancer have been developed, the frequency of early gastric cancer (EGC) has been increasing. For the treatment of patients with EGC, minimal access surgery (MAS), such as laparoscopic surgeries, has been used to improve patient's quality of life (QOL).

Since the laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection for EGC was first performed in 1991 in Japan¹⁾, several laparoscopic procedures including laparoscopic wedge resection (LWR) and intragastric mucosal resection (IGMR) have been developed. During the last 20years, laparoscopic surgery for gastric cancer has rapidly become popular, especially in Japan and Korea. A number of surgeons in their countries have started to feel that laparoscopic surgery is a preferred choice of treatment for the patients with gastric cancer. In my lecture, the present status of laparoscopic gastrectomy for cancer is going to be presented.

II. Present status of laparoscopic surgery in Japan

LWR was developed by M. Ogami et al. in 1992, and LADG by S. Kitano et al. in 1991. The indication of LWR is EGC without risks of lymph node

metastasis and that of LADG is EGC with risks of lymph node metastasis and advanced gastric cancer (AGC) without serosal exposure. Recently, as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) has been developed, the number of LWR has decreased while LADG with lymph node dissection has become rapidly popular

According to the national survey conducted by Japan Society of Endoscopic Surgery (JSES)²⁾, the total number of LWR and LADG from 1991 to 2005 in Japan is about 1844 and 9063 as shown in Fig.1. In LADG, the perigastric lymph nodes and the lymph nodes around the common hepatic artery are usually dissected (D1+ β). The number of patients underwent LADG occupied over 78% of the total number of patients underwent laparoscopic gastrectomies in 2005.

III. Techniques of LADG

Under general anesthesia, the Hasson type cannula is inserted at subumbilical portion and CO₂ pneumoperitoneum is created. After the other 4 ports are placed at the upper abdomen, the greater and lesser omentums and gastrocolic ligament are dissected. The right gastroepiploic vessels are divided to dissect the subpyloric lymph nodes (No.6). The suprapyloric lymph nodes (No.5) are dissected after dividing the right gastric vessels, and the duodenum is transected by using linear cutter. After the lymph nodes along the common hepatic artery (No.8) are dissected, the left gastric vessels are divided to dissect the lymph nodes along the left gastric artery (No.7). Then, the cardiac and superior gastric lymph nodes are then dissected (No.1, 3). After the mobilization of the stomach and the D1+ β lymph node dissection, a 5-cm laparotomy is created below the xyphoid. The bulbus of the duodenum and the distal portion of the stomach are exteriorized through this mini-laparotomy.

Distal gastrectomy is performed with a linear stapler, and then the reconstruction by Billroth-I method is carried out as the same manner of open surgery.

III. Safety and curability in LADG

According to the national survey, the incidence of intraoperative and postoperative complications associated with LADG was 1.3% and 9.0%. The most frequent intraoperative and postoperative complications were bleeding and anastomotic troubles respectively.

There are few reports about the long-term outcome of patients undergoing LADG. Japanese Laparoscopic Surgery Study Group (JLSSG, 2001~) reviewed the operative results of 1763 LADGs for cancer, which were collected from 15 surgical units from 1994 to 2003. According to the staging system of the Japanese Gastric Cancer Association³⁾, the 5-year disease free survival rate was 99.6% for stage IA disease, 98.5% for stage IB disease, 92.0% for stage II disease and 57.3% for stage IIIA, during the median follow-up period of 36 months⁴⁾.

These data demonstrates the same safety level and curability in LADG as conventional open distal gastrectomy (ODG).

IV. LADG with minimal access

There are several reports to clarify some advantages of LADG over open distal gastrectomy (ODG) from the viewpoint of short-term clinical outcome. Table 1 is summarized to show the results from these reports⁵⁾. Although most of these studies are retrospective studies, these studies shows the advantages of LADG over conventional ODG as follows: less surgical trauma, less impaired nutrition, less pain, rapid return of gastrointestinal function and shorter hospital stay. We also showed the less invasiveness of LADG and better QOL of patients after

LADG in comparison with conventional ODG. Furthermore, our RCT with small series of patients shows that LADG has several advantages over ODG as follows: less pain, less impaired respiratory function and patient's quality of life (QOL). Thus, better short-term results showed the feasibility of LADG for the management of gastric cancer.

V. Conclusions

LADG with minimal access is a preferred choice in the treatment of gastric cancer, when it is performed by experienced surgeons.

Fig.1 Lap. Surgery for Gastric Cancer

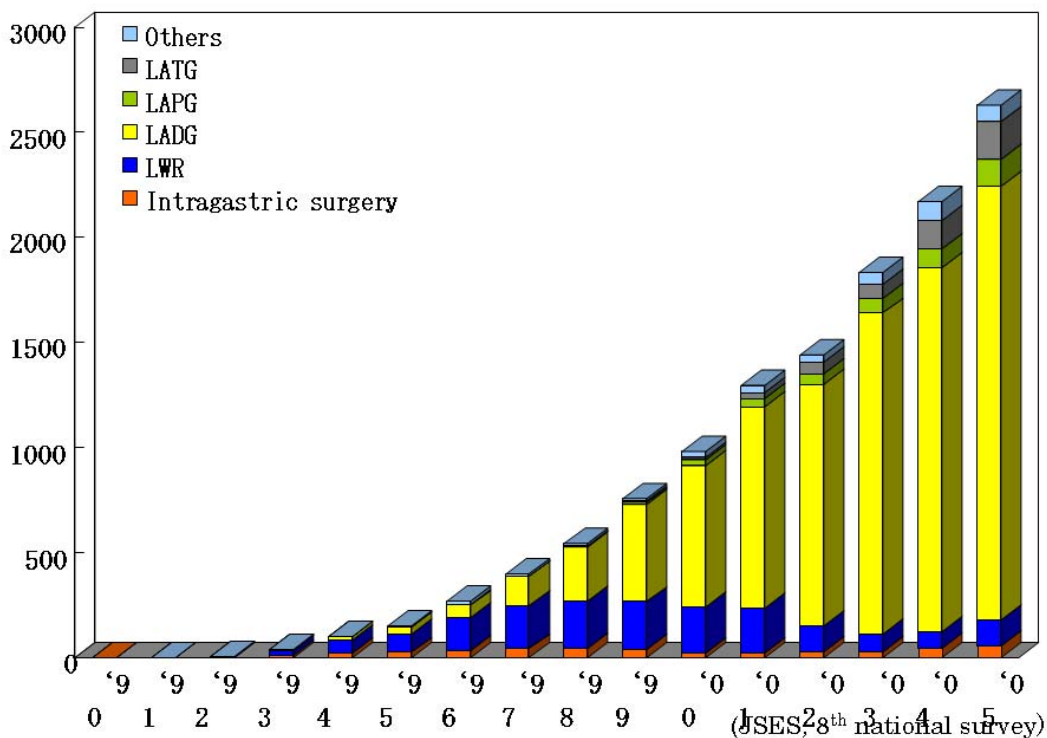


Table 1 Evaluation of LADG for Cancer

Author	Report	Cases (LADG/DG)	Advantage of LADG
Short-term clinical outcome			
Kitano S	Surg (2002)	14/14 (RCT)	less pain, less impaired pulmonary function
Adachi Y	Arch Surg (2000)	49/53 (case)	less surgical trauma, less impaired nutrition less pain, shorter hospital stay
Yano H	Gastric Cancer (2001)	24/35 (case)	shorter times to the first passing of flatus, first walking, restarting of oral intake, shorter hospital stay, less pain
Reyes CD	Surg Endosc (2001)	18/18 (case)	earlier return to bowel function, shorter hospital stay
Mochiki E	World J surg (2002)	24/31 (case)	shorter hospital stay, rapid recover of bowel function lower rate of postoperative complication
Migo S	Hepato-gastro (2003)	10/17 (case)	earlier start of liquid diet, lower level of serum CRP
Weber KJ	Surg Endosc (2003)	12/13 (case)	earlier return to bowel function, shorter hospital stay

(be continued)

(From ref.5)

Table 1 Evaluation of LADG for Cancer

Author	Report	cases (LADG/DG)	Advantage of LADG
Immunofunction			
Fujii K	Surg Endosc (2003)	10/10 (case)	preservation of postoperative Th1 cell function
Cost			
Adachi Y	Surg Endosc (2001)	48/43 (case)	less expensive
Patient's QOL (questionnaire)			
Adachi Y	Ann Surg (1999)	41/35 (case)	better patient's QOL
Goh PMY	Surg Endosc (1997)	16 surgeons	superior to the open techniques (10 of 16 surgeons)

(From ref.5)

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Tips to Obtain an Oncologic Resection for Colon Cancer

James Fleshman, M.D.

Locoregional Recurrence and Survival after Curative Resection of Adenocarcinoma of the Colon

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- BACKGROUND:** There is wide variability in reported locoregional recurrence rates after curative resection of adenocarcinoma of the intraperitoneal colon, and there is no universally accepted surgical technique regarding length of the resected specimen or extent of lymphadenectomy. The aim of this study was to determine the disease-free survival, locoregional failure, and perioperative morbidity of patients undergoing curative resection of colon adenocarcinoma.
- STUDY DESIGN:** The records of 316 consecutive patients undergoing curative resection for primary adenocarcinoma of the intraperitoneal colon between 1990 and 1995 were reviewed. Locoregional recurrence was defined as disease at the anastomosis or in the adjacent mesentery, peritoneum, retroperitoneum, or carcinomatosis. The product-limit method (Kaplan-Meier) was used to analyze survival and tumor recurrence.
- RESULTS:** The study population comprised 167 men and 149 women, mean age 70 ± 12 years (range 22 to 95 years). Median followup was 63 ± 25 months. Five-year disease-free survival was 84% overall. Disease-free survival paralleled tumor stage: stage I, 99% (n = 73); stage II, 87% (n = 151); stage III, 72% (n = 92). The predominant pattern of tumor recurrence was distant failure only. Overall locoregional recurrence (locoregional and locoregional plus distant) at 5 years was 4%. Locoregional recurrence paralleled tumor stage: stage I, 0%; stage II, 2%; stage III, 10%. Of the 12 patients who suffered locoregional recurrence, 9 (75%) had T4 primary tumors, N2 nodal disease, or both. Major and minor complications occurred in 93 patients (29%) including: anastomotic leak or intraabdominal abscess (n = 4, 1%); hemorrhage (n = 8, 3%); cardiac complications (n = 17, 5%); pulmonary embolism (n = 4, 1%); death (n = 2, 1%). Multivariate analysis (Cox proportional hazards) revealed that the only independent predictor of disease-free survival and locoregional control was tumor stage.
- CONCLUSION:** Longterm survival and locoregional control can be achieved for patients with colon cancer, with low morbidity. In the absence of adjacent organ invasion and N2 nodal disease, locoregional recurrence should be a rare event. Just as for rectal cancer, the technical aspects of colectomy for colon cancer deserve renewed attention. (*J Am Coll Surg* 2002;195:33–40. © 2002 by the American College of Surgeons)
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In the past decade, there has been renewed interest in the technical aspects of proctectomy for rectal cancer,

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spurred by wide surgeon-to-surgeon variability in both local recurrence and survival rates demonstrated in recent series^{1–4} and high pelvic recurrence rates (25% to 35%) in most of the early multiinstitutional trials after proctectomy alone.^{2,5–9} Performance of a more complete lymphadenectomy by removal of the mesorectum in its fascial envelope for a distance of approximately 5 cm distal to a rectal cancer has been shown to reduce local recurrence rates to the 5% to 10% range, and has gained acceptance as the preferred technique of proctectomy for patients with adenocarcinoma of the rectum.^{10–15}

Despite the interest in proctectomy for adenocarcinoma of the rectum, technical aspects of resection for

adenocarcinoma of the intraperitoneal colon have not received the same level of attention. Although surgical extirpation of the tumor and adjacent segments of colon and mesentery remains the cornerstone of initial treatment, there is no standard surgical technique that is universally accepted regarding the length of the resected specimen or the extent of lymphadenectomy.¹⁶ Several authors have demonstrated excellent long-term disease-free survival and low local recurrence after wide lymphadenectomy, especially in patients with left-sided tumors,^{17,18} and other investigators have found that the rate of local recurrence was dependent on the extent of lymphadenectomy, margins of resection, or specialty training of the surgeon.^{17,19-22} Alternatively, a prospective, randomized evaluation of patients with left colon tumors showed no improvement in crude survival when patients underwent extended resection of the splenic flexure region.²³

Further complicating the issue is the lack of standardization in reporting "local" recurrence, with some authors reporting only intraluminal anastomotic recurrences as local failure^{24,25} and others reporting regional recurrences. Regardless, the variability in locoregional recurrence rates after curative resection of colon cancer in the literature (6% to 28%)^{17,18,20,22,24-35} indicates that the technique of colectomy for cancer deserves renewed scrutiny.

The purpose of this study was to examine long-term disease-free survival and locoregional recurrence rates in a large group of patients undergoing curative colectomy for adenocarcinoma of the intraperitoneal colon. We attempted to identify technical variables influencing prognosis. Locoregional recurrence was defined as disease at the anastomosis or in the adjacent mesentery, peritoneum, retroperitoneum, or carcinomatosis.

METHODS

The medical records of 316 consecutive patients undergoing curative treatment for primary colon adenocarcinoma during the period 1990 to 1995 were reviewed. Patients were identified from a prospective database of all patients undergoing treatment in the Section of Colon and Rectal Surgery at Washington University. The collection of clinical data and organization in a computerized colorectal cancer database received approval from the Human Studies Committee of Washington University Medical Center. Patients with adenocarcinoma of the rectum were excluded, as were patients with meta-

static disease undergoing palliative procedures. Tumor stage, lymph node count, and margins of resection were obtained from the pathologic report after colectomy. Specimens were processed in routine fashion; lymph nodes were obtained by dissection of the mesentery by the pathologist. Tumors were staged according to the International Union Against Cancer/American Joint Committee on Cancer TNM staging system: stage I, T1 or T2 primary tumor with no nodal or distant metastasis; stage II, T3 or T4 primary tumor with no nodal or distant metastasis; stage III, any stage of primary tumor with nodal metastasis but no distant metastasis; and stage IV, any stage of primary tumor or regional lymph node involvement with distant metastasis.

Surgical procedures performed included right colectomy (n = 165), left-sided colectomy (left colectomy, sigmoid colectomy, or anterior resection of rectosigmoid, n = 131), total abdominal colectomy/subtotal colectomy/proctocolectomy (n = 17), and transverse colectomy (n = 3). All procedures were performed by surgeons with specialty training and board certification in colon and rectal surgery.

Primary end points of the study were survival and tumor recurrence. Followup was through office records, telephone, or written contact with the patient or primary care physician, the cancer registry of Barnes-Jewish Hospital and State of Missouri, and the Social Security Death Index. Overall survival was defined as the time from the date of primary treatment to the date of death. Patients who died in the postoperative period were included in the survival analysis. Disease-free survival was defined as the time from the date of primary treatment to the date of first recurrence. The presence of recurrent disease was confirmed by histology or clinical course (tumor that was palpable or evident on radiographic studies with subsequent progression or accompanied by rising carcinoembryonic antigen level). Locoregional recurrence was defined as disease at the anastomosis or in the adjacent mesentery, peritoneum, retroperitoneum, or carcinomatosis. Tumor recurrence at other sites was labeled as distant. Locoregional tumor recurrence was classified as local failure whether it occurred in the presence or absence of distant disease.

Postoperative mortality was defined as death occurring during the hospitalization for, or within 30 days of, the primary operative procedure. Anastomotic leak was defined as contrast extravasation on contrast enema, the presence of perianastomotic abscess or phlegmon on ab-

dominopelvic CT, or both. These radiographic studies were obtained for clinical suspicion of pelvic sepsis, not as a matter of routine. Wound infection was defined by the presence of purulent discharge necessitating opening the wound, or by the presence of serous discharge with documented bacteriologic culture.

Statistical analyses were performed using specifically designed and commercially available software (Statview 5.0.1; SAS Institute, Inc, Cary, NC). The product-limit method (Kaplan-Meier) was used to analyze survival and tumor recurrence. The two-tailed log-rank test was used to assess the effect of individual variables on disease-free survival and locoregional control in univariate analysis. Risk factors were assessed for their effect on disease-free survival and locoregional control by multivariate analysis using the Cox proportional hazards method. When data were missing about whether the inferior mesenteric artery (IMA) was divided at its origin with the aorta or whether the splenic flexure was completely mobilized, both were considered to have not occurred for the purposes of multivariate analysis. Age of the patient at time of operation and date of the operation were entered into the multivariate analysis as continuous variables. All mean numbers are expressed as mean ± standard deviation.

RESULTS

The study population consisted of 316 patients, mean age 70 ± 12 years, range 22 to 95 years. There were 167 men and 149 women. Median followup was 63 months. Stage of tumor at diagnosis was stage I (n = 73), stage II (n = 151), and stage III (n = 92). Chemotherapy was given to 81 patients (26%) postoperatively. Tumors were classified as obstructing in 61 cases and perforating in 9 cases.

Five-year Kaplan-Meier disease-free survival was 84% overall (95% confidence interval [CI] 0.89, 0.81), as shown in Figure 1. Disease-free survival at 5 years paralleled tumor stage: stage I, 99% (95% CI 1.0, 0.96); stage II, 87% (95% CI 0.93, 0.81); stage III, 72% (95% CI 0.82, 0.63), as shown in Figure 2. Tumor recurred in 45 of 316 patients (14%). The predominant pattern of recurrence was distant failure only (10%). The Kaplan-Meier overall locoregional control rate at 5 years was 96% (95% CI 0.98, 0.94), as shown in Figure 3. Locoregional control at 5 years also paralleled tumor stage: stage I, 100% (95% CI 1.0, 1.0); stage II, 98% (95% CI

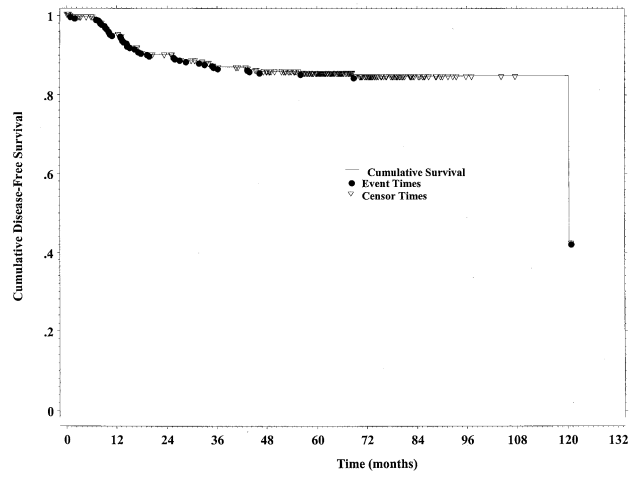


Figure 1. Disease-free survival of 316 patients undergoing curative colectomy for adenocarcinoma of the colon.

1.0, 0.96); stage III, 90% (95% CI 0.97, 0.84), as shown in Figure 4.

The stage at initial diagnosis of the 12 patients who suffered locoregional recurrence was: T3N0 (n = 2); T3N1 (n = 1); T3N2 (n = 4); T4N0 (n = 1); T4N1 (n = 2); T4N2 (n = 1); T4N3 (n = 1). So 9 of the 12 patients (75%) who suffered locoregional recurrence had either T4 primary tumors, N2 nodal disease, or both. One patient had an isolated pelvic recurrence of tumor 10 years after low anterior resection of the rectosigmoid for a T4N1 adenocarcinoma of the sigmoid colon invasive into the pelvic sidewall, accounting

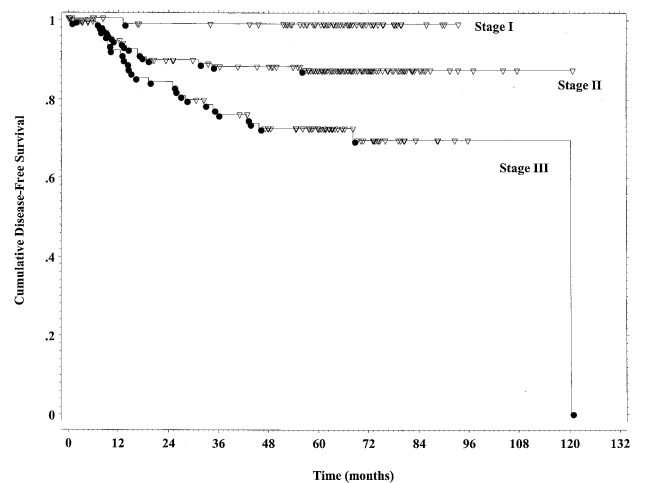


Figure 2. Disease-free survival versus histologic stage in 316 patients undergoing curative colectomy for adenocarcinoma of the colon.

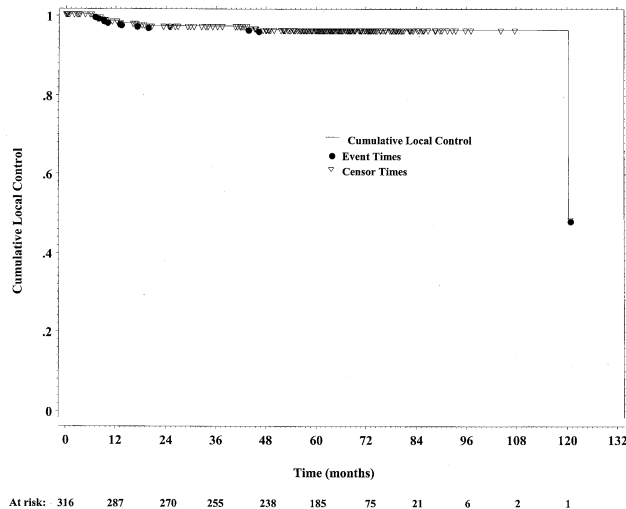


Figure 3. Locoregional control in 316 patients undergoing curative colectomy for adenocarcinoma of the colon.

for the apparent precipitous drop in disease-free survival and locoregional control in stage III patients at 10 years of followup.

Mean lymph node harvest was 14 ± 12 in the 287 of 316 patients (91%) in whom accurate nodal number was obtained. Mean proximal margin was 16 ± 14 cm (296 of 316 patients evaluable, 94%); mean distal margin was 15 ± 10 cm (303 of 316 patients evaluable, 96%). Of the 131 patients who underwent left colectomy, sigmoid colectomy, or anterior resection of rectosigmoid, data were available regarding the site of transection of the inferior mesenteric artery in 129

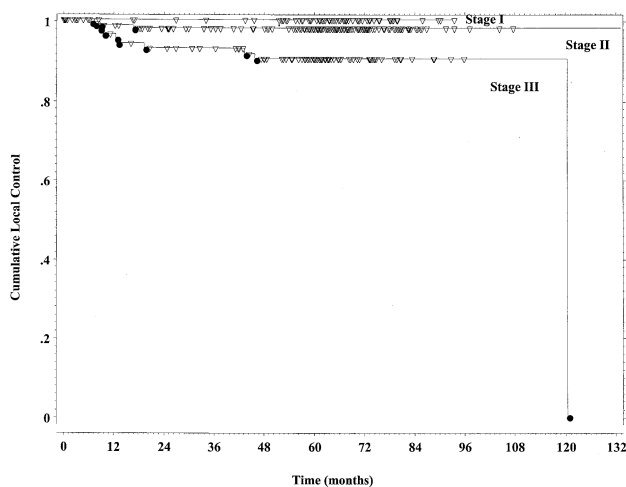


Figure 4. Locoregional control versus histologic stage in 316 patients undergoing curative colectomy for adenocarcinoma of the colon.

(98%) and whether the splenic flexure was completely mobilized in 121 (92%). The inferior mesenteric artery was ligated at the aorta in 86% and the splenic flexure completely mobilized in 84% of these patients.

Advanced tumor stage was associated with a poor prognosis in both univariate ($p < 0.001$) and multivariate analysis ($p = 0.016$). There were no statistically significant differences in disease-free survival in univariate or multivariate analysis for the following variables: individual surgeon, age at operation, date of operation, obstructing tumor, perforating tumor, gender, margins, or number of lymph nodes analyzed (Table 1). There was a trend toward poor prognosis in patients with obstructing tumors, but this did not reach statistical significance in multivariate analysis ($p = 0.14$). The small number of patients with perforating tumors ($n = 9$) may have precluded accurate analysis of the prognostic effect of this variable. The multivariate analysis was repeated, stratifying for tumor stage with equivalent results for all variables (data not shown).

In an attempt to test our hypothesis that wide mesenteric resection may improve locoregional control and disease-free survival, multivariate analysis (stratified by tumor stage) was performed for the 131 patients undergoing left-sided operations on the effect of five variables related to surgical technique (Table 2). There was a trend toward poor prognosis for both locoregional control and disease-free survival if the IMA was not divided at the aorta, but this did not reach statistical significance. The other variables did not affect outcomes in this analysis.

Major and minor complications occurred in 93 patients (29%) and are detailed in Table 3. The 30-day postoperative mortality rate was 1% (2 of 316). One patient died as a consequence of severe postoperative pneumonia; a second patient suffered from sudden death of unexplained cause. Anastomotic leak, intraabdominal abscess, or both occurred in four patients (1%).

DISCUSSION

This study demonstrates that longterm survival and low locoregional recurrence can be achieved in patients with adenocarcinoma of the colon. These goals can be obtained with low morbidity and mortality. Our data suggest that locoregional recurrence after curative colectomy should be a rare event; it occurred in only three patients in the absence of primary T4 or N2 disease.

Our study cannot prove that wide resection of the mesocolon results in low local recurrence and longterm

Table 1. Estimated Hazards Ratios for Clinical Prognostic Factors of Disease-Free Survival (Multivariate Analysis Using Cox's Proportional Hazards Method) in 316 Patients Undergoing Curative Colectomy for Adenocarcinoma of the Colon

Variable	Hazards ratio (95% confidence interval)	p Value
Stage: I versus II versus III	n/a	0.016
Stage: I versus III	0.06 (0.008–0.46)	0.007
Stage: II versus III	0.61 (0.30–1.22)	0.16
Surgeon	n/a	0.50
Age at operation	0.996 (0.967–1.025)	0.99
Date of operation	1.00 (1.00–1.00)	1.00
Gender: female versus male	0.83 (0.42–1.66)	0.84
Tumor obstructing	2.10 (0.78–5.67)	0.14
Tumor perforating	0.81 (0.10–6.41)	0.84
Distal margin	0.99 (0.96–1.03)	0.60
Proximal margin	1.0 (0.97–1.02)	0.91
Number of lymph nodes	1.03 (0.99–1.08)	0.14

disease-free survival. Although there was a trend toward better prognosis for both locoregional control and disease-free survival if the IMA was divided at the aorta in patients with left-sided tumors, this did not reach statistical significance. But because the overwhelming majority of patients underwent division of the IMA at the aorta, it would be difficult to demonstrate the prognostic significance of this variable in the context of our study. The mean resection margins of 16 cm proximal to and 15 cm distal to the tumor (as measured by the pathologist) and the mean lymph node harvest of 14 would suggest that the majority of patients had removal of mesocolon at risk for lymphatic metastases. These data, and those of others,^{17-22,36,37} suggest that the technical aspects of colectomy for adenocarcinoma of the intraperitoneal colon, specifically the extent of mesenteric resection, may have an effect on prognosis.

The only prospective, randomized study of resection margins in patients with colon cancer to date was performed by the French Association for Surgical Re-

search.²³ Although the authors found no improvement in crude survival when patients with left-sided tumors underwent additional resection of the splenic flexure region, the trial had several shortcomings that make definitive conclusions regarding extent of mesocolic resection difficult. The authors did not report disease-free survival, disease-specific survival, or locoregional control, so conclusions about the oncologic benefit of extended resection could not be made. The group undergoing segmental colectomy (the lesser resection) may have undergone what many surgeons would consider a wide mesenteric resection, in that the splenic flexure was mobilized in all cases and the IMA was divided at the aorta and inferior mesenteric vein divided at the ligament of Treitz in some (number not stated in the article).²³ In addition, the margins of resection were not appreciably different between the hemicolectomy and the segmental colectomy groups (proximal margin 22 cm versus 15 cm, distal margin 10 cm versus 7 cm, respectively). Finally, the large number of centers con-

Table 2. Estimated Hazards Ratios for Clinical Prognostic Factors of Disease-Free Survival and Locoregional Control (Multivariate Analysis Using Cox's Proportional Hazards Method) in 131 Patients Undergoing Left-Sided Colonic Resection for Adenocarcinoma of the Colon, Stratified by Tumor Stage

Variable	Disease-free survival		Locoregional control	
	Hazards ratio (95% CI)	p Value	Hazards ratio (95% CI)	p Value
Number of lymph nodes	1.04 (0.98–1.10)	0.24	1.07 (0.98–1.18)	0.13
Inferior mesenteric artery divided at aorta: No	2.68 (0.74–9.66)	0.13	12.13 (0.16–922.34)	0.25
Splenic flexure mobilized: No	1.26 (0.30–5.37)	0.75	1.47 (0.07–29.45)	0.80
Proximal margin	1.0 (0.94–1.06)	0.98	1.09 (0.90–1.32)	0.38
Distal margin	0.96 (0.88–1.04)	0.29	0.90 (0.69–1.18)	0.44

CI, confidence interval

Table 3. Major Perioperative Complications in the 93 of 316 Patients (29%) Overall Who Suffered Major or Minor Complications after Curative Colectomy for Adenocarcinoma of the Colon

Complication	n	%
Anastomotic leak/intraabdominal abscess	4	1
Cardiac complications	17	5
Cerebrovascular accident	2	1
Death	2	1
Duodenal perforation	1	0.3
Hartmann stump fistula	1	0.3
Hemorrhage	6	2
Multiorgan system failure	1	0.3
Pancreatitis	2	1
Pneumonia	2	1
Prolonged ileus/small bowel obstruction	20	6
Pulmonary embolism	2	1
Renal failure	3	1
Ureteral injury	1	0.3
Urinary tract infection/urinary retention	19	6
Wound complications (infection or dehiscence)	13	4

tributing patients (26 centers, 270 patients) with an unknown number of surgeons performing the operations makes it difficult to ensure standardization of operative technique.

Unfortunately, the French study did not compare one of the most common methods of performing colectomy, that is, a short segmental resection with limited resection of the mesentery. Although not frequently described in the literature, data from a large tumor registry of almost 19,000 patients who underwent colectomy for cancer would indicate that such a practice is widespread.³⁸ In this registry, the number of lymph nodes found in the colectomy specimens varied widely, from zero to four nodes (32% of patients) to more than nine nodes (36% of patients).³⁸ Although the number of nodes examined can depend on the technique of specimen processing, such large differences suggest that the extent of mesenteric resection varied as well. The finding that one-third of specimens contained fewer than five nodes suggests that some surgeons perform a limited segmental colectomy for cancer. Given data suggesting that prognosis is related to margins of resection and the number of nodes in the resected specimen,^{17,19-22} differences in extent of mesenteric resection may explain the surgeon-to-surgeon variability in outcomes demonstrated by some investigators.²⁰

The key question when operating for left-sided colonic lesions is whether wide resection of the mesentery

by ligating the IMA at the aorta and removing the entire sigmoid and descending mesocolon at risk for nodal spread imparts benefit by improving locoregional control and disease-free survival as compared with performing a segmental colectomy. Historically, several authors have demonstrated excellent results with such techniques.^{17,18,39} Other investigators have shown that the local recurrence rate after colectomy for intraperitoneal colon cancer was dependent on the extent of lymphadenectomy, margins of resection, or specialty training of the surgeon.^{17,19-22} Turnbull and associates³⁹⁻⁴¹ attributed their excellent results to the use of a “no-touch” technique, but they are more likely related to the wide mesocolic resection they routinely performed. Although removal of nodes infiltrated with tumor at the origin of the IMA has not been shown to be of oncologic benefit, division of the IMA at the aorta and dissection in the avascular plane posterior to the superior hemorrhoidal vessels ensures that the entire sigmoid mesocolon is removed. If the apical nodes are not involved with tumor, it is possible to encompass all gross and nodal disease in the resection. Hohenberger and coworkers³⁷ have demonstrated by angiography that lesser mesenteric resections were performed in 79% of cases of anastomotic recurrence in the left colon.

The most obvious beneficiaries of wide mesenteric resection are patients with stage III disease in whom nodal involvement with tumor can be completely encompassed by the resection. In addition, the subgroup of patients originally thought to have stage II disease, who have occult nodal metastases (as demonstrated by microsection or molecular techniques),⁴²⁻⁴⁴ may also benefit from wide mesenteric resection. Recent data from Burdy and colleagues²² and Caplin and associates²¹ support this view, in that the prognosis of patients with stage II adenocarcinoma of the colon in both studies was dependent on the number of nodes found in the specimen. Local control may be improved by removal of tumor present in the lymphatics of the mesocolon, which is where most local recurrences are thought to originate.^{31,45} Just as for rectal cancer,⁴⁶ it is possible that improved local control may also translate into improved disease-free survival overall.

It has been our routine to completely mobilize the side of the colon involved with tumor, including the flexures, and divide the major vessels at their origins. On the left side, this technique involves mobilization of the splenic flexure and division of the IMA at the aorta and

division of the inferior mesenteric vein adjacent to the ligament of Treitz. This method is used for technical reasons because it allows soft proximal descending colon to reach easily into the pelvis for a tension-free colorectal anastomosis with excellent proximal blood supply from the middle colic vessels. It also ensures complete removal of the sigmoid mesocolon. Although some surgeons have expressed concern regarding perfusion of the proximal colon after division of the IMA at the aorta, this technique did not result in a high anastomotic leak rate in our series.

There is currently pressure on surgeons in the United States to limit length of hospital stay and improve short-term outcomes after operations. The performance of short segmental colectomy may allow surgeons to limit incision size, retroperitoneal manipulation, and duration of ileus. Although this may improve short-term outcomes by limiting length of stay, such a practice may jeopardize long-term oncologic cure. The use of laparoscopic techniques to perform colectomy may allow surgeons to achieve adequate resection margins while minimizing the physiologic insult to the patient. But mobilization of the flexures and dissection of the transverse colon are often the most challenging aspects of any laparoscopic resection of the intraperitoneal colon. It is also unlikely that surgeons will adopt a more rigorous method of mesenteric resection using laparoscopic techniques if it is not their routine during open colectomy.

We believe that the technical aspects of colectomy for intraperitoneal adenocarcinoma of the colon deserve renewed scrutiny. It may be difficult to design a trial examining different techniques for right colectomy because the level of division of the ileocolic pedicle or the amount of mesentery resected does not easily lend itself to anatomic differentiation. But intraperitoneal left colon lesions account for about one-third of all colorectal adenocarcinomas encountered.⁴⁷ It may be feasible to perform a prospective, randomized trial comparing wide mesenteric resection (with division of the IMA at the aorta and complete mobilization of the splenic flexure) and segmental colectomy for left colon tumors.

Author Contributions

Study conception and design: Read

Acquisition of data: Read, Mutch, Chang, McNevin,

Fleshman, Birnbaum, Fry, Kodner

Analysis and interpretation of data: Read

Drafting of manuscript: Read

Critical revision: Caushaj

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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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AQ: 1

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.

(*Ann Surg* 2007;246: 000–000)

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 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

From the The Writing Committee of the Clinical Outcomes of Surgical Therapy Study Group responsible for the reporting of the Laparoscopic Colectomy Trial.

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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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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; Pri-

mary 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 noninferior. 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 distributions¹⁸; 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

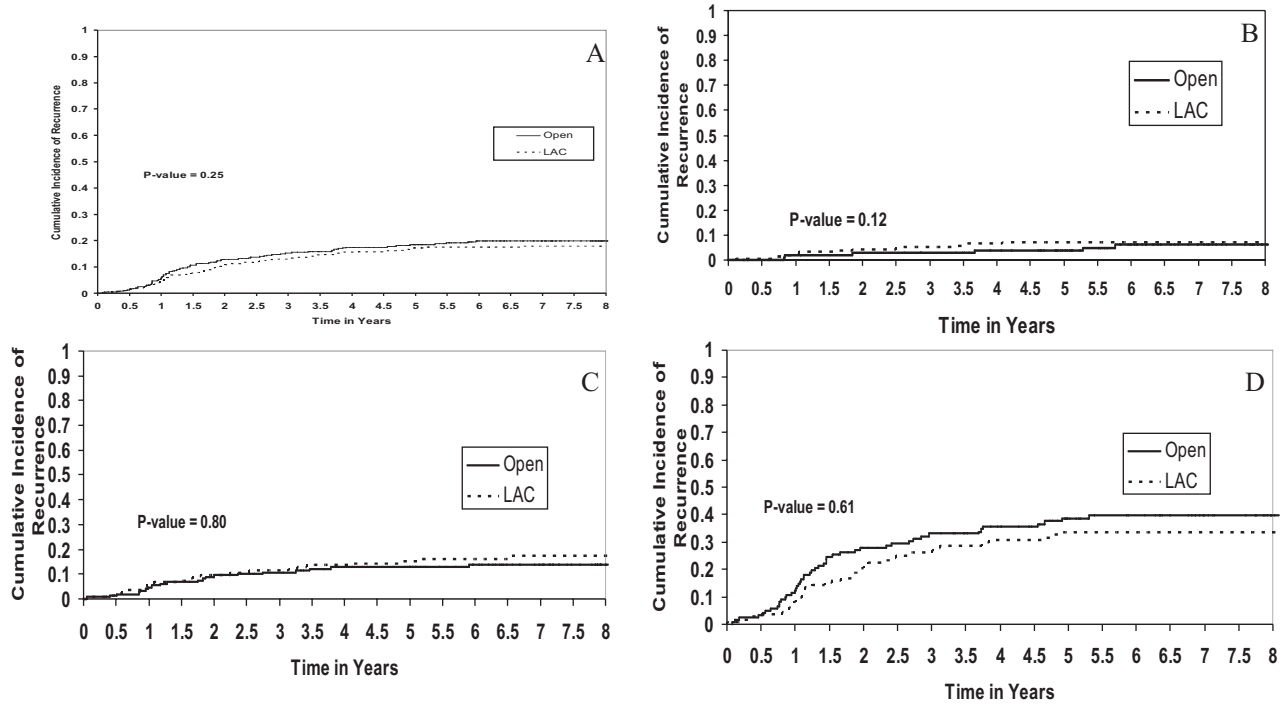
As of March 1, 2007, 170 patients have recurred and 252 have died. Disease-free 5-year survival, overall 5-year survival, overall recurrence rates and sites of first recurrence (including wound recurrences) were similar for the 2 groups (Table 1). The one-sided *P* value for time to recurrence in favor 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 class²⁰ 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 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%) com-

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

Outcome	Open (n = 428)	LAC (n = 435)	<i>P</i>
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.

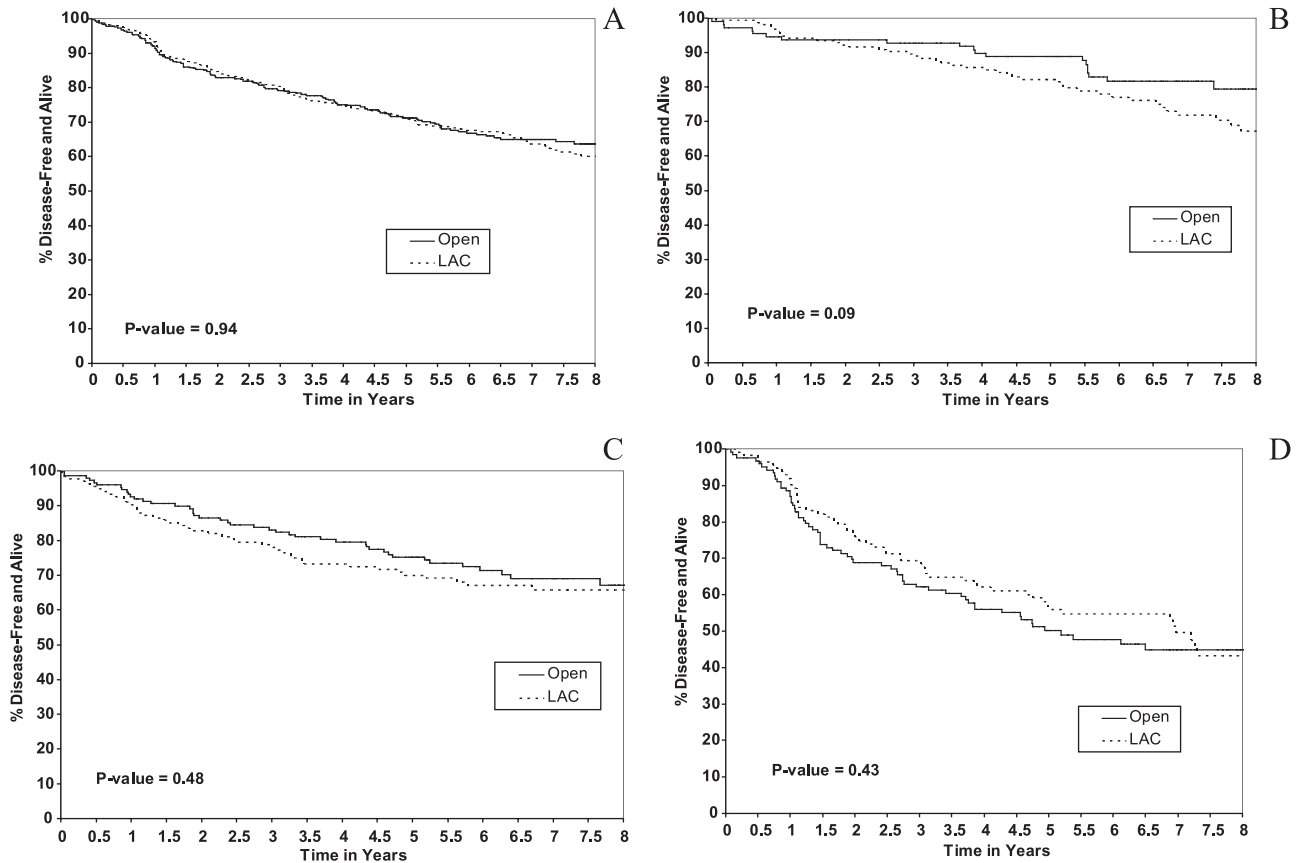
pared with those converted to open (69%) ($P = 0.04$). Reasons for conversion are diverse and included conversions encouraged or protocol mandated for safety or oncologic purposes including presence of advanced disease, complicating diseases, or inadequate margins (Table 3). Conversion to an open operation 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 laparoscopic 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.



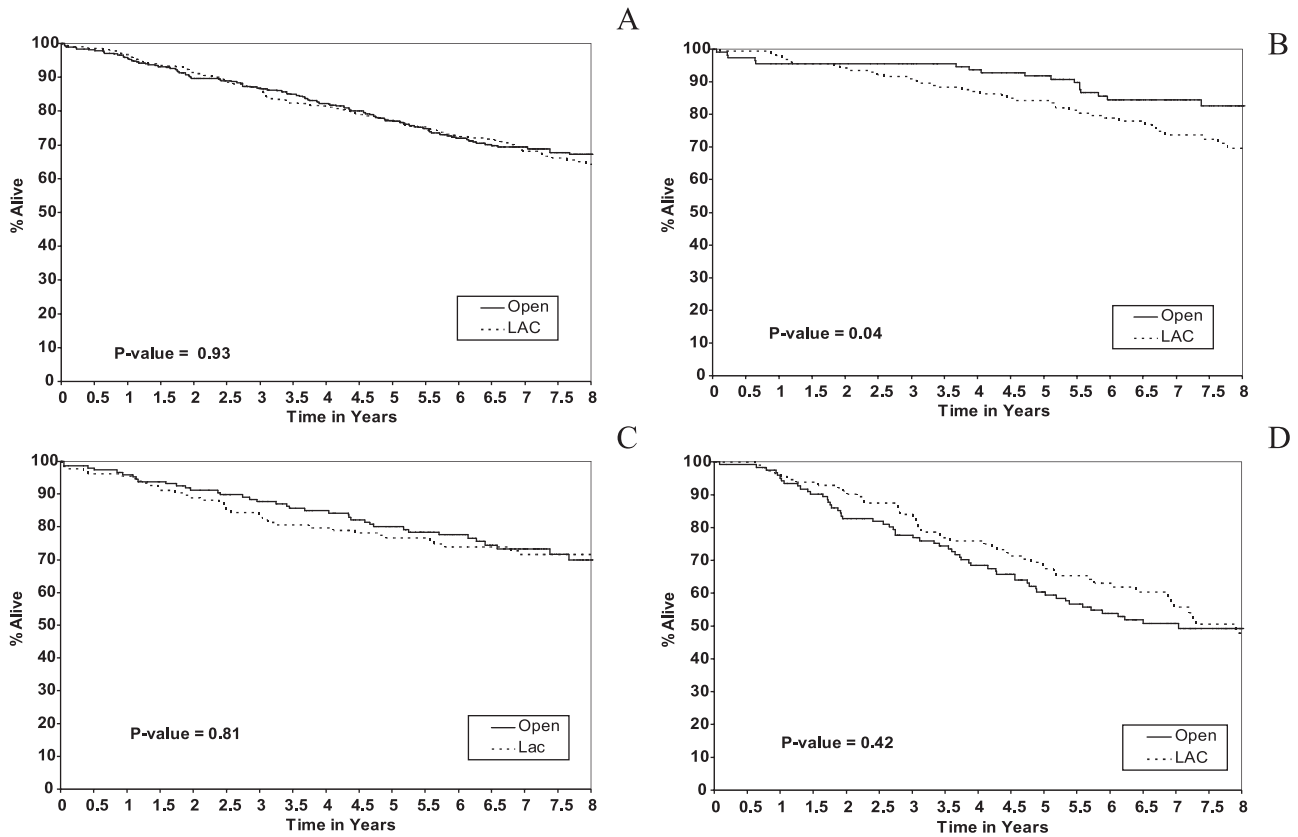
5-yr Disease-Free Survival for:
 A: All Stages; B: Stage I; C: Stage II; D: Stage III

FIGURE 2. Five-year disease-free survival.

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 T₄ 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 recom-

mend 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 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



5-yr Overall Survival for:

A: all Stages; B: Stage I; C: Stage II; D: Stage III

FIGURE 3. Five-year overall survival.

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 adequate 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

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

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

The members of the Clinical Outcomes of Surgical Therapy Study Group were the following, in order of accrual contribution by institution, principle investigator, and associate(s):

Clinical centers: *Mayo Clinic, Minnesota*—H. Nelson [North Central Cancer Treatment Group (NCCTG)], D. Sargent, T. Young-Fadok, G. Schroeder; *Washington University School of Medicine, Missouri*—J. Fleshman [Radiation Therapy Oncology Group (RTOG)], E. Birnbaum; *St. Joseph’s HealthCare, McMaster University, Ontario, Canada*—M. Anvari [National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG)], D. Birch; *Northwestern University/Feinberg School of Medicine, Illinois*—S.J. Stryker [Eastern Cooperative Oncology Group (ECOG), RTOG]; *University of Southern California, Keck School of Medicine, California*—R.W. Beart, Jr. [Southwest Oncology Group (SWOG)], A. Ortega; *University of Miami/Jackson Memorial Medical Center, Florida*—M. Hellinger (ECOG), R. Hartmann (ECOG), L. Sand; *St. Joseph Mercy Hospital, Michigan*—R. Flanagan, Jr. (NCCTG), R. Cleary (NCCTG); *Boone Hospital Center, Missouri*—W. Peters [The Cancer and Leukemia Group B (CALGB)]; *IHC Cancer Services, LDS Hospital, Utah*—B. Christensen (RTOG); *Columbia Presbyterian Hospital, New York*—R. Whelan (SWOG); *University of Missouri, Missouri*—D. Ota (CALGB); *Midwest Surgical, P.A., Kansas*—J. Hyder (SWOG); *Group Health Cooperative, Washington*—D. Lauter (SWOG), E. Froines; *Lahey Clinic, Massachusetts*—P. Marcello (CALGB); *MD Anderson Orlando Cancer Center, Florida*—S. Larach (RTOG), A. Ferrara; *Cleveland Clinic Florida, Florida*—S. Wexner (SWOG); *University of Texas Health Sciences Center, Texas*—J. Stauffer (SWOG); *University of Kentucky, Kentucky*—A. Park (SWOG); *The Lankenau Hospital Institute for Medical Research, Pennsylvania*—J. Marks [National Surgical Adjuvant Breast and Bowel Project (NSABP)]; *Ottawa Regional Cancer Center, Ottawa, Canada*—H. Stern (NCIC-CTG); *Creighton University, Nebraska*—A. Thorson (NCCTG); *Lehigh Valley Hospital, Pennsylvania*—R. Boorse (ECOG); *Cleveland Clinic Foundation, Ohio*—A. Senagore (SWOG), C. Delaney (SWOG); *St. Joseph Medical Center, Maryland*—H.C. Kim (RTOG); *Norfolk Surgical Group, LTD/Eastern Virginia Medical School, Virginia*—W.K. Ruffin (CALGB), G. Hoffman, G.W. Hubbard II, R. Gould, S. Wohlgenuth; *St. Luke’s Hospital, Pennsylvania*—J. Lukaszczuk (ECOG), W.T. Reilly; *Mercy Health Center, Oklahoma*—R.C. Thomas, Jr. (SWOG); *Mayo Clinic, Arizona*—R. Schlinkert (NCCTG); *Massachusetts General Hospital, Massachusetts*—D. Rattner (CALGB); *Swedish Medical*

Center, Colorado—R. Bell (ECOG); Centre Hospitalier Universitaire de Quebec, Quebec, Canada—C. Thibault (NSABP); East Carolina University/Brody School of Medicine, North Carolina—W. Chapman III (NSABP); Mount Sinai Hospital, New York—B. Salky (CALGB), L.B. Katz; Jefferson Regional Medical Center, Pennsylvania—A. Fine (ECOG); St. Joseph Mercy Hospital, Michigan—A. Tootla (NCCTG); Abington Memorial Hospital, Pennsylvania—R. Josloff (ECOG); Brigham and Women's Hospital/Boston Medical Center, Massachusetts—R. Bleday (CALGB), R.A. Forse (CALGB); Dartmouth-Hitchcock Medical Center, New Hampshire—J. Sutton, Jr. (CALGB); USAF Wilford Hall Medical Center, Texas—T. Brown; University of Virginia, Virginia—B. Schirmer (ECOG); Legacy Health System, Oregon—L. Swanstrom (SWOG); Allegheny General Hospital, Pennsylvania—D. Fowler (NSABP); Mt. Diablo Medical Center/John Muir/Mt. Diablo Health System, California—S. Oommen (RTOG), H. Asbun (RTOG); Huntington Memorial Hospital, California—E. Suddleson; Kaiser Permanente Medical Center, California—J. Greif (NSABP); University of Massachusetts Memorial Medical Center, Massachusetts—D. Litwin (CALGB); University of Texas Southwestern Medical Center, Texas—C. Simmang (NSABP).

Other participants: T. Julian (NSABP), M. O'Connell (NSABP) (Allegheny General Hospital, Pennsylvania); H.S. Wieand (NSABP) (University of Pittsburgh, Pennsylvania); J. Weeks (CALGB) (Dana-Farber Institute, Massachusetts).

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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 unfounded 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 impor-

tant 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.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

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AQ1—AQ: Kindly provide the degree/educational qualification of Erin Green.

AQ4—AQ: Kindly check whether the affiliation is OK as given. Also kindly provide the affiliation and academic degrees of Erin Green and the department/division names for all the affiliations.

AQ2—AQ: Please provide the expansion for the abbreviation CIR.

AQ3—AQ: Please check whether the ref. 11 is OK as edited.

Pancreatic Malignancies: *What is the role of MIS?*

***Horacio J. Asbun, MD
Director, HPB Program
John Muir Health Cancer Institute***

Introduction

Minimal access surgery techniques have rapidly evolved to include a variety of complex surgical procedures. However, the role of minimal access surgery for resection of malignant neoplasms has been widely debated and remains an area of controversy for surgical oncologists. Since the early years of advanced laparoscopic procedures, concerns about port-site metastases [1-3] and dissemination of tumor cells via CO₂ insufflation [3] prevented laparoscopic surgeons from further developing innovative new approaches for oncologic resections. More recent prospective, randomized trials have nevertheless shown that the laparoscopic approach can be done in a safe manner [4]. The key issue is to ensure safe, complete oncologic resection, and at the same time provide the additional benefits such as decreased pain, shorter hospital stay, fewer incisional hernias and earlier return to work. Added advantages of the minimal access approach over open surgery that are of particular potential benefits to cancer patients are decreased blood loss and possibly a reduced immunosuppressive impact from the surgical intervention [5]. These advantages however are present only when the operator is an experienced laparoscopic surgeon with extensive expertise in open pancreatic surgery and a clear understanding of pancreatic diseases.

Over the past several years, improvement in open surgical techniques have decreased the mortality and morbidity of pancreatic surgery. The overall prognosis of pancreatic cancer however remains quite poor. In this scenario were the development of innovative minimal access procedures may find increased acceptance with surgeons and affected patients by way of providing less traumatic and debilitating surgery when life span is limited and surgery likely non-curative. This however requires a responsible approach to ensure that the results of the laparoscopic technique in regards to morbidity, mortality and oncologic resection match or improve the results obtained in the open technique.

Distal and subtotal distal pancreatectomy

Even though laparoscopic pancreatic surgery is still not universally practiced, distal resections are now proven to be safe and readily feasible. In experienced hands, the procedure has striking advantages over its open counterpart. The minimal access approach suits distal pancreatectomy well because of the advantages in visual magnification, the inherent delicate manipulation of tissues,

the decreased blood loss, the enhanced access to the pancreas and the absence of need for reconstruction.

Indications for the procedure are in general, equal to an open distal pancreatectomy. [6-7]. In selected cases however, there could be a more liberal indication to do the procedure with a palliative intent in patients with malignancies of the body and tail. This is based on the lesser negative impact that the minimal access approach has in the patient's quality of life.

In the presence of a small lesion, the laparoscopic approach is limited by the inability to palpate the lesion and surgeons dealing with the procedure must have experience in the use of intraoperative ultrasound. Even though not commonly needed, the operation can also be performed in a hand-assisted manner. The surgery can be done either with spleen preservation or with a splenectomy. The indications to include or not to include a splenectomy should not be affected by the fact that the procedure is being done using the minimal access method. Robotic assisted laparoscopic distal pancreatectomy has been described and may have a role in the splenic preserving procedure. However, its advantages over the traditional laparoscopic technique done by an experienced surgeon are still to be proven.

The laparoscopic approach is not limited to distal pancreatectomy of the pancreatic tail. When a more proximal resection to include the neck, body and tail of the pancreas can be safely done. In fact, in experienced hands, the laparoscopic approach to the area of the neck of the pancreas may be even safer than its open counterpart.

Conditions that may preclude a laparoscopic approach include: presence of portal hypertension, either generalized, or limited to the splenic circulation as well as prior episodes of pancreatitis

Technique [7]

The patient is placed in a modified right lateral decubitus position that would allow for rotation to the left or right during the procedure. This facilitates the exposure of the operative area by allowing gravity do a significant portion of the retraction of the neighboring organs . The surgeon stands to the right of the operating table.

Dissection is started by performing a wide mobilization of the splenic flexure as well as the descending colon. Given the lateral position of the patient, this dissection allows for displacement of the colon and omentum medially by gravity. The lesser sac is entered from its lateral aspect, and the gastrocolic omentum is divided and ligated from lateral to medial. This maneuver readily exposes the distal pancreas. Once the distal pancreas has been exposed, the dissection is continued in a clockwise manner, starting at the lower edge of the pancreas from

lateral to medial. When in the right plane, this dissection is readily done with ultrasonic or similar energy in a relatively avascular plane. When more medial dissection is needed, the first named vascular structure that is found is the inferior mesenteric vein. Depending on the indications for the procedure, the dissection is stopped here and attention paid to the division of the pancreas or the dissection continued further medially. When needed, the inferior mesenteric vein is ligated. If more of a subtotal pancreatectomy is necessary, the dissection is continued medially along the lower edge of the pancreas. The area of the ligament of Treitz and the fourth portion of the duodenum are exposed and care is taken to avoid injury. Following the lower edge of the pancreas, the next vascular structure that is evident is the superior mesenteric vein heading cephalad to travel under the neck of the pancreas. The posterior aspect of the tail and body of pancreas has been exposed during the dissection of the lower edge of the pancreas and partially separated of its posterior attachments by gentle blunt dissection. This aids in further facilitating the dissection and exposure of the inferior edge when going from lateral to medial. At the chosen site of pancreatic division, additional posterior dissection is performed from caudad to cephalad up to the superior edge of the pancreas. The splenic vein is exposed and if needed isolated. Passing a Penrose drain to encircle the pancreas aids in its retraction when a splenic preserving procedure is planned.

If the pancreatic parenchyma is thin a stapler technique is used. The use of bioabsorbable staple reinforcement could be of benefit. When the pancreatic parenchyma is too thick at the division site, the use of a stapler is not advised. In that situation, our preference is to divide the pancreas with ultrasonic shears in a fish mouth fashion. The proximal divided edge is then sutured with a running non-absorbable monofilament suture. Particular care is taken to suture shut the pancreatic duct opening. This is done in similar manner as in an open procedure.

After the posterior dissection and ligation of the vessels is completed, attention is paid to the dissection of the superior edge of the pancreas that is now done from medial to lateral, continuing in a clockwise manner. Up to this stage, the superior attachments of the body and tail of the pancreas lateral to the division site had been kept intact. The dissection of the superior edge is continued reaching the end of the tail of the pancreas laterally. The pancreatic mobilization is then completed.

If a splenectomy is performed, a small serosal band between the upper pole of the spleen and the diaphragm can be left undivided until the specimen is within the retrieval bag. This facilitates the manipulation and placement of the specimen in the bag by keeping the specimen anchored superiorly. As described by the author, when retrieving the specimen, care should be taken to preserve the pancreatic specimen intact for pathologic examination.

Even though unusual, the procedure can always be converted to an open procedure if felt needed. As in any other advanced laparoscopic procedure, and

experienced operator will not hesitate to do so when he/she feels that the quality or safety of the operation can be compromised by continuing with the minimal access approach.

Laparoscopic Pancreaticoduodenectomy

When dealing with proximal resections, the need for reconstruction significantly prolongs its learning curve and questions the advantages over its open counterpart. Visual magnification, delicate manipulation of tissues, decreased blood loss are still an advantage but the magnitude of the operation is such that operative times are usually longer and patients hospital stay and recovery are not as shorten as for distal resections. Over recent years however, several authors have acquired the surgical skills and the procedure is being performed safely for selected patients. The operator embarking in this procedure does not only need to have mastered advanced laparoscopic skills, but also have extensive expertise in open pancreatic surgery and a clear understanding of pancreatic diseases.

The surgical technique follows the same general principles of its open counterpart . As mentioned above, the laparoscopic approach is limited by the inability to palpate the lesion. Surgeons embarking in this procedure must have experience in intraoperative ultrasound. The hand-assisted approach is strongly considered for patients with lesions in close proximity to the portal/SMV confluence in which pa. Robotic assisted laparoscopic pancreaticoduodenectomy has also been described and may have a role in facilitating the reconstruction. However, its advantages over the traditional laparoscopic technique done by an experienced surgeon may not justify its cost.

In despite of the above-mentioned limitations of the technique, recent series of laparoscopic pancreaticoduodenectomy appear to show significant advantages over the open counterpart and the oncologic principles of resection practiced on the open procedure are preserved. [8]

Since these series contain only a limited number of patients, further studies are needed to assess if laparoscopic pancreaticoduodenectomy will become a standard procedure.

Nonetheless, as more expertise is being gained, the advantages over its open counterpart appear more evident. Given the poor prognosis of patients with adenocarcinoma of the head of the pancreas and based on the lesser negative impact that the minimal access approach has in the patient's quality of life; the laparoscopic approach could become the procedure of choice once becomes more established as a safe and feasible procedure.

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MIS for Splenic Malignancies

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Introduction: Major surgical procedures are rarely required in management of hematological malignant diseases, although minor interventions such as peripheral lymph node biopsy or catheter placement are not infrequent. When major surgery is needed, it can be classified into two categories, spleen removal and deep intraabdominal/retroperitoneal lymph node sampling for staging. The advantages of MIS for cancer are widely recognised and as hematological patients requiring laparoscopic splenectomy (LS) are usually elderly and frail, any less invasive approach may in itself be beneficial, at least from a conceptual viewpoint.

Hematological malignancies: Classification and current therapy:

Medical therapy has improved considerably in recent years and few hematological malignancies require splenectomy as first-line treatment. Those in which a splenectomy may be considered within the treatment strategy can be classified in six groups: Hodgkin lymphoma, non-Hodgkin lymphoma and chronic lymphocytic leukemia, chronic myeloid leukemia, myelofibrosis and splenic metastasis

Indications for splenectomy: Splenectomy has 4 clinical indications in the malignant hematological setting 1. - Diagnosis: In cases of splenomegaly when additional findings suggesting malignancy are lacking. 2. Therapeutic splenectomy: A primary splenic lymphoma may occasionally be found and LS may be curative. Cytopenia secondary to hypersplenism or autoimmune cytopenias are good indications. 3. Palliation of symptoms secondary to the massive enlargement of the spleen. 4. - Staging or re-staging may be indicated on occasions.

The most frequent indication for LS is non-Hodgkin lymphoma (NHL) Diagnosis is made by biopsy of a peripheral adenomegaly, and primary splenic NHL is infrequent. The spleen is involved in more than 70% of patients. Standard treatment is chemotherapy and LS is indicated only in cases of clinical suspicion without peripheral tissue or in relation to massive splenomegaly. After NHL is diagnosed, LS may be indicated in cases of symptomatic splenomegaly or symptomatic cytopenia. It is not associated with an improvement in the natural history of the disease but cytopenia improves in up to 75% of patients. Therapeutic LS may also be beneficial in the case of primary spleen lymphoma or splenic marginal zone lymphoma.

The second most frequent indication is myelofibrosis, a malignant condition without definitive cure. It is characterized by bone marrow fibrosis, pancytopenia, extramedullar hematopoiesis and hepatosplenomegaly. It is associated with a massive spleen enlargement, and repeated transfusions are needed. Surgery is performed to palliate symptoms and in cases of massive enlargement and portal hypertension.. A potential risk that should be taken in account is postoperative portal vein thrombosis.

LS may be indicated for Hodgkin disease. The laparoscopic approach for staging is currently indicated in very few cases. Indications for LS in this

subset correspond to patients with clinical suspicion of lymphoma without peripheral disease, or patients requiring re-staging after chemotherapy due to imaging or PET suspicion of residual disease. Hodgkin's disease patients are younger and spleen size is usually normal.

Chronic lymphocytic leukemia, currently considered an NHL subtype, is an incurable disease, and LS is mainly indicated to treat cytopenia, massive spleen enlargement, or progressive splenomegaly refractory to treatment. Waldstrom's macroglobulinemia is a rare disorder and 40% of these patients present splenomegaly. LS is indicated in cases that are refractory to systemic therapy.

Chronic myeloid leukemia is an infrequent indication for LS. It is most common in males in their sixth decade of life. Splenomegaly appears in 55%-70% of patients, and its rapid development predicts a blast crisis. Splenectomy may be indicated in advanced disease, providing some benefit in up to 15% of patients, but the risk of blastic crises does not decrease. In chronic myeloid leukemia the spleen is often massively enlarged (median 3675 gr, range 3200-4500 gr in our group). Surgical risk in this subgroup is high because the disorder is associated with coagulation disorders and platelet malfunction. Splenic metastasis is an infrequent indication for LS as it is usually a sign of systemic cancer dissemination. It is feasible, however, in the few cases where metastasis is limited to the spleen. The most frequent origins are lung or breast cancer, or melanoma.

Intra-abdominal sampling of enlarged retroperitoneal masses may be indicated when CT-guided needle biopsy is not available, when percutaneous sampling is insufficient, or when a large biopsy specimen is required for immunohistochemical study

SURGICAL TECHNIQUE: Laparoscopic splenectomy

Preoperative work-up: Patients undergoing elective LS for malignancy require special preparation. A physical examination will allow the surgeon to determine the size of the spleen. Normal spleens are not felt below the lower costal margin. Moderate splenomegaly is disclosed by palpation of a lower pole in the left hypocondrium. Massive spleen with a main diameter over 30 cm may occupy the entire abdominal cavity. Abdominal examination reveals mobility of the spleen, distensibility of the abdominal wall, and margins in the lower pole of the spleen at midline. These data will determine patient positioning on the operative table (supine, semi-supine or lateral), guide placement of a hand-assisted device, or reveal the need for an open approach. A preoperative blood transfusion should be considered in view of the cytopenia and the spleen blood sequestration expected in an enlarged spleen. Coagulation tests should be performed and intraoperative fresh frozen plasma or platelet can be administered if required. A preoperative CT or ultrasonography [US] is recommended to evaluate the size and shape of the spleen.

Preoperative splenic artery embolization [SAE] to occlude terminal vascular branches and diminish the risk of bleeding as well as to reduce spleen size has been proposed. However, SAE is associated with pain, hemorrhage and hepatic or splenic abscesses and is an invasive treatment. Although preoperative SAE is not recommended routinely for LS it may play a role in spleens larger than 25 centimeters in maximum dimension. Polyvalent vaccines are administered prior to surgery.

Technological requirements for LS: LS can be performed in any operating room in which conventional laparoscopy is conducted. The use of two video monitors improves operator comfort and efficiency. LS is usually performed using three or four trocars. An angled [30°] laparoscope is most commonly used for LS.. Most grasping, dissecting and cutting instruments used in this procedure are 5 mm in diameter. In case of hemostasis, mechanical methods such as clip applicators, endovascular stapling devices, electrocautery, bipolar cautery, and ultrasonic dissector are helpful. Clips should be placed with care, avoiding sites where an endovascular stapler may also be applied as they can block the functioning of the stapler. Endovascular staplers are useful, particularly for the control of splenic hilar structures. A durable nylon sack should be considered key equipment for LS. It must be able to withstand the rigors of the final morcellation process.

Surgical techniques: I. anterior approach: The patient is placed supine or in the Fowler position. . A sand bag is placed below the left hypochondrium. After establishing the pneumoperitoneum, the first trocar is inserted in an umbilical port and an exploratory laparoscopy is performed. Trocars are then inserted in the subxiphoid and midepigastrium areas, and a fourth in the left iliac fossa. The scope is introduced through the midepigastric trocar and the subxiphoid area and umbilical ports are used for placement of grasping and dissecting instruments. The table is then placed in a right lateral tilt and reverse Trendelenburg position. After opening the omental pouch, the short gastric vessels are divided with the harmonic or bipolar cautery device.

Several techniques have been proposed for the dissection of the splenic hilum. The splenic vessels can either be controlled at the main trunk or a segmental devascularization can be performed near the splenic parenchyma.. Once the main vessels have been divided and the pancreas dissected away the remaining short gastric vessels can be controlled. The splenic flexure is then liberated and the posterior attachments to the spleen are sectioned until the viscus is completely freed.

Surgical techniques: II. lateral approach: The patient is placed in the right lateral decubitus position over the break in the operating table. The table is broken 20° to 30° below level in both its cephalad and caudad portions and the patient is placed in moderate reverse Trendelenburg position. Three or four trocars are then inserted in the patient's left upper quadrant. A 12 mm port is inserted in the anterior axillary line superior to the patient's anterior superior iliac spine. The endovascular stapler is inserted through this trocar. The trocar through which the camera is most frequently used is placed in the rim of the umbilicus in pediatric and non-obese patients. A left subcostal or subxiphoid trocar is also inserted for the use of a retracting or grasping instrument. Finally, a dorsal trocar is placed under direct vision below the twelfth rib in the mid- to post-axillary line. Retracting forceps are passed through this trocar, elevating the lower pole of the spleen

Dissection commences with mobilization of the splenic flexure of the colon. The lateral peritoneal attachments of the spleen are then incised. The retracting forceps can be used to grasp the peritoneal cuff or mobilize the spleen medially, or placed under the inferior pole to elevate it. In this way the spleen is never directly grasped. Dissection of the splenic hilum is initiated from the lower pole and progresses cephalad. A lower pole splenic vessel is

often present and should be divided between clips or by using the ultrasonic dissector.

Once the lower pole of the spleen has been mobilized and the polar vessels are divided, access to the lesser sac is facilitated. With the spleen elevated, the short gastric vessels and main vascular pedicle are tented. The short gastric vessels are divided. The tail of the pancreas is often visible at this point of the dissection. The splenic pedicle is well exposed and easily accessed and is divided by applications of the endovascular stapler.

Extraction of the specimen:

After the remaining splenic hilar and short gastric vessels are divided, a small cuff of avascular splenophrenic ligament is temporarily left in situ. This serves to hold the spleen in its normal anatomic position and facilitates introduction in the retrieval bag. The specimen retrieval bag is introduced, unfurled and maneuvered over the relatively immobile spleen. The final splenophrenic attachments are then divided and the drawstring on the device is closed. The neck of the bag is withdrawn through the 12 mm trocar site. The spleen is morcellated within the sack and extracted piecemeal. Great care is needed to insure the bag is not ruptured so as to avoid spillage and subsequent splenosis. Once the entire specimen and bag are removed, a final laparoscopic revision is made and irrigation is performed.

In the event that it is necessary to extract the spleen intact, an accessory incision must be used. This can be made in various locations on the abdomen or through the widening of a trocar incision.

Surgical technique: III. Hand-assisted laparoscopic splenectomy: In the HALS procedure, the patient is placed in right lateral decubitus position. In the case of a massive splenomegaly, the lateral position is reduced to 30-45° to prevent the spleen from falling. A pneumoperitoneum is created with a Veress needle inserted into the right iliac fossa, a good distance from the spleen. A 12 mm. trocar is inserted in the periumbilical area to perform an exploratory laparoscopy and to select the best site for an accessory incision (7-7.5 cm) to insert the hand. It is usually made in the right hypogastrium, but in cases of massive splenomegaly it is performed in the right subcostal area or in the right iliac fossa. Once the incision is made, the device is introduced. The left hand is then inserted into the abdomen to examine the shape of the spleen. A second 12-mm trocar is inserted laterally to the laparoscope under manual control. All the instruments are introduced using this trocar. When additional retraction is needed, a 5 mm trocar is placed in the left flank and an endoretractor is introduced. The first step in the procedure is to access the retrogastric pouch through the gastrosplenic omentum. The whole of the great curvature of the stomach is freed until the short vessels are sectioned with the ultrasonic shears or bipolar device). The splenic artery is located in the upper border of the pancreas and a clip is placed to interrupt the inflow of blood into the spleen. The hand then mobilizes the spleen medially to expose its posterior surface and the retroperitoneal adhesions are sectioned. The splenic hilum and pancreatic tail are bluntly dissected with the hand, and the endostapler can be placed in the splenic hilum without tension, sparing the pancreatic tail. Once the hilum is controlled, the upper pole is dissected from the posterior attachments and the spleen is freed. In most cases, the spleen is retrieved intact through the accessory incision. However, in cases of massive splenomegaly, a sterile plastic bag is introduced in the abdomen, and the spleen is placed inside this

and then morcellated. It is then removed in large pieces through the 7 cm. incision.

Complications of LS: Apart from any complications inherent to laparoscopic surgery in general, in cases of malignancy there are several potential perioperative complications. The most likely problem is hemorrhage, from small calibre vessel [short gastric or polar vessels], a larger vessel of the hilum, or the splenic parenchyma.. Another potential complication of LS is injury to the tail of the pancreas. Other pitfalls reported include deep vein thrombosis, portal vein thrombosis, pulmonary embolus and wound infection. Recent reports have suggested a higher incidence of portal thrombosis when LS is performed. No clear relation to pneumoperitoneum has been stated, but close monitoring of postoperative thrombocytosis and preoperative anti-aggregant therapy is warranted, especially in patients with additional risk factors such as myelofibrosis

Comment: In conclusion, malignancy and splenomegaly is not a contraindication for the laparoscopic approach. However, LS in the case of splenomegaly is an advanced laparoscopic procedure that will only be necessary in a small subgroup of patients. Surgeons undertaking this procedure should be aware of the medical characteristics of hematological patients requiring splenectomy in the case of splenomegaly, and be familiar with hand-assisted techniques. However, further information from comparative studies is needed to determine the exact role of the laparoscopic approach in this setting.

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ROLE OF MAS IN PEDIATRIC MALIGNANCY

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The role of Minimal access surgery in pediatric oncology patients has expanded significantly over the last decade. There is now extensive use in both thoracic and abdominal malignancies ranging from biopsy to complete resection. The only caveat is to not compromise basic oncology surgical principles.

Role of Thoraacoscopy:

The most common procedure performed on the pediatric age group is lung biopsy for presumed primary, metastatic, or infectious disease. The most common metastatic lesions are Rhabdo and Osteosarcomas. Other common metastatic lesions include Wilm's , neuroblastoma, primary liver tumors, leukemic infiltrates, and other more rare malignancies. Early biopsy in immunocompromised hosts with undiagnosed infiltrates has also proven to be extremely beneficial to help direct antibiotic therapy Wedge resection of all of these lesions has proven to be a safe and effective technique. Depending on the experience of the surgeon and the type of primary tumor single or multiple lesions can safely be resected using a thoracoscopic technique. In cases of bilateral disease both sides maybe approached in the same operative setting or in staged procedures. The procedure requires 3 ports. In larger patients an endoscopic stapler can be used and therefore 2- 5mm and one 12mm port are placed. In smaller patients

(<10-15 kg) the biopsies are performed with endoloops and 2 – 3mm and 1-5mmport. This has proven to be a safe and effective technique providing an air and water tight seal.

In cases where the nodules are smaller than 5mm or are deep in the parenchyma of the lung pre-operative localization is recommended. We use a blood patch technique where 1 cc of the patient's blood is injected just under the visceral pleural under CT guidance. A blind wedge is then performed over the site. This technique has an over 95% success rate. Others have used methylene blue or wire placement as a localizing technique.

Another very effective application of thoracoscopy is in diagnosing and resection of mediastinal masses. Biopsy of anterior mediastinal masses for lymphoma has been reported in a number of series with excellent results.

Thoracoscopy is also effective for post therapy evaluation to evaluate for residual tumor. Resection of anterior teratomas and thymomas is also well documented. Posterior mediastinal masses are also treated well by thoracoscopy. The majority of the solid tumors are neurogenic in origin. There are a number of series reporting complete resection of ganglioneuromas, ganglio-neuroblastomas, and neuroblastomas with excellent results and recurrence rates comparable to open thoracotomy.

There are reports of port site recurrences after thoracoscopic resection of metastatic lesions. Therefore care must be taken to avoid any contamination during tumor extraction. Specimens must either fit through the trocar or be placed in a specimen bag to avoid tumor seeding.

Role of Laparoscopy:

The use of laparoscopy to evaluate, biopsy, and resect pediatric abdominal tumors is also well documented.

Evaluation and resection of lymphomas has been well documented in a number of series. While in most cases complete resection is not appropriate, biopsy and staging laparoscopically can result in quicker post-operative recovery and allow for earlier onset of adjuvant therapy. In some cases localized intestinal obstruction has been by laparoscopic resection and primary anastomosis with excellent results. Laparoscopy has also been used for post-treatment evaluation in cases of lymphoma to determine if there is any remaining viable tumor.

The treatment of abdominal neurogenic tumors has also been shown to be highly successful and beneficial. Laparoscopic adrenalectomy has been shown to be effective in resecting both benign and malignant neurogenic tumors. Other neurogenic tumors of the sympathetic chain are also approached safely laparoscopically.

Large abdominal tumors are somewhat more controversial. The benefits of a laparoscopic biopsy of a large tumors such as wilm's is not clear. Biopsy of large liver and renal tumors may help establish a clear diagnosis prior to resection as many of these tumors are pre-treated with chemotherapy. In case such as these an individual approach should be taken in each case. Laparoscopy can also be used to biopsy liver nodules or suspected metastatic nodules. This has been accomplished using a wedge or tru-cut biopsy with good result.

Pelvic teratomas are usually well suited to laparoscopic resection as are other ovarian masses. Laparoscopy has also been used to safely mobilize the intra-abdominal portion of sacro-coccygeal teratomas in a combined abdominal perineal approach. These techniques have been used to do as little as ligate the feeding middle sacral artery to a complete mobilization of the intra-abdominal mobilization.

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