Immunologic and Oncologic Implications of Laparoscopic Surgery: What Is the Latest?

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ABSTRACT

Laparoscopic surgery has been associated with many short-term benefits such as a shorter time to recovery, return of bowel function, less pain, and a decrease in wound infection rate. Several animal and human experiments have demonstrated an immunologic and oncologic benefit of minimally invasive surgery. Whether these results will translate into similar results in human settings is unclear. Although the first published prospective randomized clinical trial suggests better long-term outcomes for patients undergoing laparoscopic surgery, results from other ongoing randomized, controlled clinical trials are needed to verify this controversial result.

KEYWORDS: Laparoscopy, immunology, oncology

Objectives: On completion of this article, the reader should be familiar with the current immunologic and oncologic implications of laparoscopic surgery.

Laparoscopic surgery has been associated with many short-term benefits such as a shorter time to recovery, return of bowel function, less pain, and a decrease in wound infection rate. These benefits are more apparent in patients who are undergoing relatively minor intra-abdominal procedures such as laparoscopic cholecystectomy or Nissen fundoplication than in patients who are undergoing major procedures such as laparoscopic colectomy. Although similar short-term advantages may benefit patients who are undergoing laparoscopic colectomy for cancer, concern that this approach may have an adverse impact on tumor-free survival and tumor recurrence led to a delay in wide implementation of the technique.

What is interesting is the vast amount of basic science data that have accumulated over the past 10 years, which suggest that immunologic and oncologic functions are significantly better preserved after laparo-

scopic surgery. This has significant oncologic implications: in the right setting, laparoscopic surgery may result in better long-term oncologic outcome. Until recently, this has been demonstrated only in animal studies. In 2002, Lacy et al reported the results of the first prospective randomized study that showed that patients who underwent laparoscopic colectomies for cancer had significantly longer cancer-related survival and less tumor recurrences than their counterparts who underwent open surgeries.¹ Since then, two additional large multicenter prospective randomized studies have demonstrated equivalent long-term outcomes of patients undergoing either laparoscopic or conventional surgery for colon cancer.^{2,3} On the basis of current data, we can finally make a cogent argument for performing laparoscopic colectomy for cancer and expect at least equivalent if not better long-term outcomes with potential short-term benefits. A fundamental question then becomes,

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"why would different surgical exposure methods lead to different cancer outcomes?" Ever expanding basic science data regarding this subject are very revealing.

The aim of this article is to review current literature regarding immunologic and oncologic basic science data regarding laparoscopic surgery. Several years ago, we published a review on this subject matter. Our goal is to summarize previously reported data and update several recently published studies.

ONCOLOGIC AND IMMUNOLOGIC BASIC SCIENCE DATA

Systemic Oncologic Implications of Surgery

Over the past several decades, there has been a paradigm shift in the way we view and treat cancer. The classic Halstedian approach to cancer treatment with extensive surgical therapy has given its way to multimodal systemic therapy. In the 1970s, Fisher argued that microscopic metastases may already be present at the time of initial diagnosis and thus intensive local therapy would be ineffective.⁴ Fisher further noted that the surgical procedure itself might have a negative influence on residual cancer cells by accelerating postoperative tumor growth. Not only is extensive local therapy not effective in preventing tumor recurrence but also, in some cases, it may have a detrimental effect.

With the introduction of minimal access surgery, some investigators questioned whether a less traumatic approach to surgery might result in a better oncologic outcome. Using a murine model, Allendorf et al demonstrated that tumors grow larger and are more easily established following sham laparotomy than CO₂ pneumoperitoneum.⁵ Similar results were noted for multiple tumor cell lines and seemed to persist in the setting of bowel resection.⁶ In most of these studies, there were stepwise increases in both tumor growth and establishment rates from the control to the laparoscopy and, finally, to the laparotomy group. These studies suggest that minimal access surgery may result in a better long-term oncologic outcome than traditional laparotomy.

The exact mechanism underlying differences in tumor growth following laparotomy versus laparoscopy is unclear. Because changes in tumor size reflect the net balance between the tumor proliferation rate and the tumor cell death rate, accelerated tumor growth in animals undergoing open surgery may be due to an increased tumor cell death rate in the minimally invasive surgery animals or increased tumor proliferation in animals undergoing open surgery, or both. Lee et al determined the proliferation and apoptotic rates of tumors 2 weeks following sham laparotomy or CO₂ insufflation.⁷ Tumor cells were injected subcutaneously into the dorsal surface of the mice just prior to surgical

procedures. Tumors from laparotomy group mice had significantly greater proliferation rates than those of the insufflation group. Conversely, the laparotomy group tumors had significantly lower rates of apoptosis than the tumors from the CO₂ insufflation group. Although the rates of tumor cell necrosis following different access methods have not been studied, a decrease in tumor cell death rate after laparotomy is most likely due to associated immune suppression resulting in decreased tumor cell killing. On the other hand, increased tumor proliferation is likely to be due to trophic effects of growth factors and angiogenesis.

Immunology

Major surgery results in impairment of immunologic function. In particular, surgery is known to inhibit the cell-mediated immune response, resulting in subsequent morbidity and mortality related to sepsis. The cellular immune response consists of three phases: cognitive, activation, and effector (Fig. 1). In the cognitive phase, macrophages display foreign antigens on their surface in a form that can be recognized by antigen-specific T_H1 (T helper 1) lymphocytes. In the activation phase, T_H1 cells produce cytokines that promote the proliferation and differentiation of the T cells as well as other cells, including macrophages. Finally, in the effector phase of the cell-mediated response, activated macrophages carry out phagocytosis and cytolysis. Interruption of any of these steps results in significant cellular immune suppression.

Postsurgical immune suppression occurs as a consequence of complex events that are not yet well understood. The extent of suppression roughly correlates with the degree of trauma caused by the operation. Several studies have demonstrated that immune function is better preserved following laparoscopic surgery than open surgery. These studies have demonstrated that laparoscopic surgery results in better preservation of lymphocyte and macrophage function and lower serum levels of potentially harmful cytokines such as tumor necrosis factor (TNF) and interleukin 1 (IL-1). The implications of such differences may be far reaching. Improved postoperative immune function may translate into lower rates of postprocedure infectious complications and more rapid healing. In this section, we review what is presently known about immune function after open and laparoscopic surgery by presenting the results of recent human and animal studies.

Delayed-Type Hypersensitivity Testing

Probably one of the most global indicators of the cellular immune system is the delayed-type hypersensitivity (DTH) response. In order for DTH response to occur, all three phases of cellular immunity have to be intact.

Figure 1 The cellular immune response consists of three phases: cognitive, activation, and effector. In the cognitive phase, macrophages display foreign antigens on their surface in a form that can be recognized by antigen-specific T_H1 (T helper 1) lymphocytes. In the activation phase, T_H1 cells produce cytokines that promote the proliferation and differentiation of the T cells as well as other cells, including macrophages. Finally, in the effector phase of the cell-mediated response, activated macrophages carry out phagocytosis and cytolysis. Interruption of any of these steps results in significant cellular immune suppression.

DTH testing involves the intradermal injection of specific antigens that elicit an immune response leading to an accumulation of inflammatory cells in the injected area, causing erythema and induration in the overlying skin. A decrease in the size of the reaction correlates with a decrease in the functional status of the cell-mediated immune system.

Using DTH testing in rats, Trokel et al assessed the effects of sham laparotomy, CO_2 insufflation, and anesthesia alone.⁸ All animals underwent DTH challenges preoperatively, immediately after surgery, and on postoperative day 2. Although all groups had an equal response preoperatively, the laparotomy group demonstrated a significantly smaller postoperative DTH response than either the pneumoperitoneum or anesthesia group for both postoperative challenges. There were no significant differences between the insufflation and anesthesia control groups at any time point. Similar results persisted in the setting of bowel resection in rats.⁹ These studies suggest that the extent of surgery correlates with postoperative suppression, with minimally invasive surgery leading to less suppression than open surgery.

Two nonrandomized studies in humans have been conducted to compare the effects of open versus minimally invasive surgery on postoperative DTH responses. Kloosterman et al investigated DTH responses after laparoscopic versus open cholecystectomy. DTH challenges were administered 1 day before surgery and on postoperative days (PODs) 1 and 6. The open group demonstrated a significant decrease in the DTH response on POD1, but there was no significant difference on POD6. The laparoscopic group, however, had no significant change for either of the postoperative challenges.¹⁰ This study suggests that open but not laparo-

scopic surgery reduces the DTH response in the immediate postoperative period.

Whelan et al performed a similar study comparing the DTH response in patients undergoing laparoscopic or open colectomies. Injections were administered preoperatively, immediately after surgery, and on POD3, and the response was measured at 48 hours. The percentage changes from baseline were averaged for each antigen after each postoperative challenge, allowing comparison between individual patients. The laparoscopic group did not have significant differences between the preoperative and postoperative challenges, but the open group had a significantly smaller response to the POD3 challenge.¹¹ Both of these human studies are consistent with the animal DTH studies, suggesting that laparoscopy preserves cellular immune function better than open surgery.

The advantage of DTH testing is that there is a correlation between the results of DTH challenges and clinically significant endpoints. In surgical patients, preoperative anergy to DTH testing is associated with higher rates of postoperative sepsis and infection. In a study by Christou et al, the rates of postoperative sepsis or mortality were higher in patients anergic to DTH testing (30% and 23%) than in patients with normal DTH responses (7.5% and 4.6%).¹² Responsiveness to DTH testing also correlates with resectability of the tumors. In a study performed by Trokel et al, the antigen 2,4-dinitrochlorobenzene was used to assess the DTH response in preoperative patients with cancer. Patients anergic to this challenge were found to have a higher rate of inoperative cancer (93%) than patients with normal responses (5%).⁸ These results suggest that deficiencies in the immune system may be associated with increased tumor growth and metastatic spread.

COGNITIVE PHASE

The cognitive phase of the immune response consists of the binding of foreign antigens to specific receptors on mature lymphocytes. T lymphocytes express receptors that recognize only short peptide sequences in protein antigens. T lymphocytes have the unique property of recognizing and responding only to peptide antigens that are present on the surfaces of other cells. The factors that favor immune responses in the cognitive phase include diversity of lymphocyte receptors for foreign antigens and the presence of major histocompatibility complex (MHC) molecules capable of binding processed antigens.

Monocyte Antigen Expression

Monocytes play a central role in both innate and cell-mediated immune functions. Monocytes play an important role in the presentation of antigens to T cells and, thus, are also involved in the afferent arm of cell-mediated immune responses.

The ability to process foreign antigen and to present peptide segments to T helper lymphocytes is one of the most important functions of monocytes and tissue macrophages. T helper lymphocytes can recognize foreign antigen peptide segments only when they are presented in conjunction with MHC class II surface protein (HLA-DR) on the surface of monocytes, macrophages, or other antigen-presenting cells. Only monocytes or other antigen-presenting cells that express HLA-DR molecules are capable of presenting antigen to CD4⁺ helper T lymphocytes, and this interaction is essential to generate an effective immunologic response. Changes in the percentage of circulating monocytes expressing HLA-DR have been shown to correlate with short-term outcome after major elective surgery and trauma. In a study by Hersman et al, patients who had postoperative sepsis or mortality were found to have lower postoperative HLA-DR expression than patients who had an uneventful recovery.¹³ Decker et al investigated HLA-DR expression in a nonrandomized study of patients after cholecystectomy. They reported that patients in both the open and laparoscopic groups had significantly lower HLA-DR levels 2 hours and 24 hours after surgery. The decrease in HLA-DR expression was greater in the open than the laparoscopic group, but they did not comment on whether the difference between groups was significant.¹⁴ Bolla and Tuzzato also found a significant decrease in HLA-DR expression in patients undergoing laparotomy compared with laparoscopy.¹⁵ It should be noted, however, that a study by Klava et al yielded slightly different results. In a nonrandomized study, Klava obtained whole blood monocytes from patients within 24 hours after either laparoscopic or open surgery and found that both open

and laparoscopic surgery decreased HLA-DR expression to a similar extent. They also reported that this down-regulation was refractory to treatment *in vitro* with either interferon- γ (IFN- γ) or lipopolysaccharide, two well-established stimulators of HLA-DR expression.¹⁶ One limitation of both of these studies was that they examined HLA-DR expression only within the first 24 hours after surgery, but an additional experiment by Brune et al investigated these changes over 7 days. In a nonrandomized study of open or laparoscopic cholecystectomy patients, they reported that surgery down-regulated HLA-DR expression for the first 24 hours in both groups, but levels in the laparoscopic group returned to normal by seven days. There was no difference, however, in the antigen-presenting capacity of the monocytes from either group.¹⁷

Minimally invasive surgery may confer an advantage to the macrophages within the peritoneal cavity. In theory, regional trauma or the exposure to either the room air or the insufflation gas may alter the function of peritoneal macrophages differently than that of the monocytes in the systemic circulation, which are not exposed to those influences. Efficient recognition of tumor cells by macrophages within the peritoneal cavity may be crucial in eradicating tumor cells liberated at the time of surgery.

Lee et al investigated MHC class II expression in peritoneal macrophages after open cecectomy, laparoscopic cecectomy, or anesthesia alone in rats.¹⁸ They found that a significantly lower percentage of macrophages in the open group expressed MHC class II antigen than in the anesthesia group. Also, MHC class II expression was higher in the laparoscopic group compared with the open group, but the difference was not statistically significant. They did not find significant differences in MHC class II expression in peripheral blood monocytes from the groups. Overall, this study suggests that a greater number of peritoneal macrophages from the laparoscopic group are capable of presenting antigen to CD4⁺ helper T lymphocytes, which may help with the clearance of tumor cells released in the abdomen at the time of resection.

ACTIVATION PHASE

The activation phase of the immune response is the result of a sequence of events triggered by lymphocytes in response to specific antigen recognition. During this phase, lymphocytes undergo two major changes: clones of antigen specific lymphocytes proliferate and lymphocytes transform from cells whose primary function is to recognize antigens to cells that function to eliminate foreign antigens. Under specific circumstances, T helper cells differentiate into one of the two subsets in such a way that cell-mediated immunity is more effective against intracellular microbes. The three factors that

play major roles in determining the nature and magnitude of the immune response during this phase are cytokines, the type of antigen-presenting cells, and the nature and amount of antigen.

Lymphocyte Proliferation Assays

There are several different methods of assessing lymphocyte function. Lymphocyte proliferation assays (LPAs) assess the ability of lymphocytes to replicate in vitro. The rate of lymphocyte replication correlates with the level of activity of the immune system but does not provide information about either lymphocyte subpopulations or cytokine expression. Horgan et al investigated the lymphocyte proliferation rates of mice undergoing air pneumoperitoneum, sham laparotomy, or anesthesia alone. They found that open surgery caused a significant reduction of proliferation rates compared with anesthesia controls but that no significant differences existed between the pneumoperitoneum group and either the control or the laparotomy group.¹⁹ In a similar study, Lee et al investigated the time course of the changes in LPA. They reported that the lymphocyte proliferation rates were significantly lower in the sham laparotomy group compared with the pneumoperitoneum and anesthesia control groups on POD3, 4, and 5 but that these differences disappeared by the POD8.²⁰ Similar findings were noted by Griffith et al in a nonrandomized study of cholecystectomy patients. They reported that patients with open surgery had significantly lower proliferation rates 24 hours after surgery compared with their preoperative results, but laparoscopic cholecystectomy patients did not have a significant difference between their preoperative and postoperative proliferation rates.²¹ These studies indicate that, using LPA, there is less suppression of the immune system following minimally invasive surgery.

Lymphocyte function can also be assessed using lymphocyte subpopulation studies. Several investigators have determined the ratios of several different subpopulations following minimally invasive surgery. Vallina et al evaluated changes in the number of CD4+ (T helper) and CD8+ (T suppressor) cells in patients at different time points following laparoscopic cholecystectomy. They reported a nonsignificant decrease in the number of T helper lymphocytes and a nonsignificant increase in the T suppressor lymphocytes on POD1 and on POD5–7. Although the absolute numbers did not reach statistical significance, the CD4+/CD8+ cell ratio at 24 hours after surgery was significantly lower (13%) than the preoperative value.²² Although this study did not have an open group for comparison, these findings are consistent with earlier reports of significantly lower CD4+ and significantly higher CD8+ cell counts postoperatively in open cholecystectomy patients.²³ Vallina

et al concluded that there is probably less immunosuppression after laparoscopic cholecystectomy than after open surgery.

T Helper Lymphocyte Subpopulation (T_H1/T_H2) Study

It has been recognized that there are subsets of CD4+ helper T cells that produce distinct cytokines in response to antigenic stimulation. Because most of the effector functions of helper T cells are mediated by cytokines, helper T cells with distinct cytokine profiles perform different functions. It is thought that naive T cells in response to antigenic stimulation differentiate into either T_H1 or T_H2 subsets with relatively restricted profiles of cytokine production. T_H1 cells produce IL-2 and INF- γ , which activates macrophages, and they are the principal effectors of cell-mediated immunity and of the DTH reaction. Th2 cells produce IL-4, IL-5, and IL-10, which activate antibody production by B cells and suppress cell-mediated immunity. In human studies, decreased production of T_H1-type cytokines and increased production of T_H2-type cytokines by peripheral blood monocytes have been noted following major trauma, burns, or hemorrhagic shock. Decker et al studied the T_H1 and T_H2 balance or ratio by following peripheral blood mononuclear cell (PBMC) cytokine production, in vitro, after stimulation. They found that phytohemagglutinin-induced IL-4 production by PBMCs from patients increased more after open cholecystectomy than laparoscopic cholecystectomy. Decker et al also assessed T_H1/T_H2 balance by determining and comparing the level of CD23 expression on circulating B cells and HLA-DR expression on PBMCs. CD23 expression is up-regulated by IL-4 that is produced in response to T_H2 stimulation. Monocytes elaborate HLA-DR in response to T_H1-induced INF- γ elaboration. Significantly higher levels of CD23 antigen and significantly lower HLA-DR levels were noted after surgery in both groups. Furthermore, significant HLA-DR and CD23 differences between the open and laparoscopic groups were noted at 2 and 24 hours postoperatively. The HLA-DR/CD23 ratio was shifted toward the T_H2 side at all time points; only at 2 hours was the difference between these ratios significant.¹⁴

A similar study by Fujii et al also showed increased production of INF- γ representing T_H1 function and decreased production of IL-4 representing T_H2 cell function after laparoscopic distal gastrectomy in gastric cancer patients. The authors concluded that laparoscopic distal gastrectomy contributes to the preservation of postsurgical TH1 cell-mediated immune function.²⁴ The results of these studies support the concept that, after major trauma, a shift toward increased T_H2 function occurs.

EFFECTOR PHASE

The effector phase of the immune response is the stage in which lymphocytes that are stimulated in response to a specific antigen carry out functions that lead to elimination of the antigen. Activated lymphocytes also stimulate a nonspecific inflammatory response by phagocytes, complement, mast cells, and leukocytes. Although these inflammatory responses are also functional in the absence of lymphocyte activation, antigen-specific immune responses amplify and focus onto the antigens in a variety of effector mechanisms.

Monocyte Function

Monocytes play a central role in both innate and cell-mediated immune functions. Monocytes phagocytize infected or altered cells and are also the principal source of TNF and IL-1 following T cell stimulation. The literature regarding the impact of open and laparoscopic abdominal surgical methods on peritoneal macrophage and PBMC function and surface antigen expression has been confusing and subject to very different interpretations. One reason for this uncertainty is that, whereas the results regarding one parameter suggest that monocytes are stimulated, the results of another parameter suggest the opposite. Also, it is not clear, in some cases, whether a given result is beneficial or detrimental.

TNF- α is the principal proinflammatory cytokine released by several types of cells but especially by macrophages. The low levels of the cytokine may help maintain homeostasis. Lee et al studied TNF- α release by macrophages and PBMCs from rats undergoing anesthesia, laparoscopic, or open cecal resection. The authors found that the open group rats produced significantly more TNF- α than cells from the laparoscopic or anesthesia control group.¹⁸ These results are in agreement with the monocyte/macrophage TNF findings of two murine studies and one human study that assessed this parameter.²⁵⁻²⁷

Lee et al also evaluated H₂O₂ release by macrophages and PBMCs in the same study. The open group macrophages released less H₂O₂ than both the anesthesia and laparoscopy groups.¹⁸ It is possible that the laparoscopic group peritoneal macrophages are primed to a greater extent than the open cells for phagocytic activities and that animals in the open group might be less prepared or "armed" to deal with a load of bacteria or tumor cells released into the peritoneal cavity at the time of surgery. It should be noted that the present study's H₂O₂ results do not agree with the findings of the one previous study that assessed a related parameter for peritoneal macrophages. Watson et al, in a murine study, measured superoxide anion release after PMA stimulation and found significantly increased elaboration in peritoneal macrophages from the laparotomy animals compared with the anesthesia control groups results.²⁷

Similar findings have been noted in regard to circulating monocyte release of superoxide anion after in vitro stimulation by the same group in both a murine and a human study.^{26,27} As discussed previously concerning TNF- α , increased H₂O₂ elaboration after stimulation can be interpreted as beneficial or detrimental. Additional studies, however, are required to determine what, if any, effect these changes have on the ability of the peritoneal macrophages to clear tumor cells released locally at the time of surgery.

Natural Kill Cell Function

In addition to macrophages, natural killer (NK) cells are involved in nonspecific immune function. Numerous studies have identified NK cells as playing a significant role in the natural antitumor defense, especially in the clearance of potentially metastatic tumor cells from the circulation and capillary beds.²⁸⁻³⁰ Numerous studies have also demonstrated a reduction of NK cell numbers and function after surgical trauma.³¹ There have been only a limited number of studies investigating the effect of laparoscopy on NK cells, and the results are inconclusive. Hewitt et al investigated the changes in NK cell subpopulation in patients randomly assigned to receive either open or laparoscopy-assisted colon resection. They reported that both groups had significant reductions of NK cell numbers up to 7 days after surgery but that levels returned to normal by 3 weeks.³² Similar findings were reported by Griffith et al in a study comparing patients after either open or laparoscopic cholecystectomy.²¹

A different conclusion, however, was drawn in two animal studies by Da Costa et al. Instead of investigating changes in the numbers of the NK cell subpopulation, they examined NK cell cytotoxicity (NKCC) after either laparotomy or laparoscopy in mice. They reported that laparotomy caused a significant reduction of NKCC compared with laparoscopy or anesthesia controls, and this difference persisted up to 14 days after surgery. Laparoscopy, however, was found to cause a less substantial decrease in NKCC, and function returned to nearly normal by the fourth postoperative day.^{33,34} On the basis of these studies, one cannot say definitively whether minimally invasive surgery significantly alters NK cell function differently than open surgery; however, the importance of NK cells in preventing the formation of metastases by circulating tumor cells suggests that any improvement in NK cell activity may lead to decrease recurrence after cancer resection.

Growth Factor Studies

Lee et al examined the possibility that a postsurgical plasma factor may exist that influences tumor growth. It was determined that cancer cells incubated in vitro with

plasma from mice that had undergone sham laparotomy proliferated significantly faster than cells incubated with plasma from the insufflation group.³⁵ These results suggest that a plasma soluble factor was responsible, in part, for the increase in tumor growth seen after laparotomy. Lee et al in a different study showed that laparotomy in mice is associated with higher levels of heparin-binding plasma factor consistent with platelet-derived growth factor (PDGF).³⁶ The enhanced mitogenic effect of the open group plasma was neutralized with anti-PDGF antibody, suggesting that the increased plasma level of PDGF after laparotomy may be partly responsible for accelerated tumor growth in mice.

Kirman et al performed a similar study in a human setting. In this study, HT29 human colon cancer cells proliferated significantly faster when incubated with plasma collected postoperatively from patients undergoing open abdominal surgery compared with laparoscopic surgery. Significantly lower postoperative plasma insulin-like growth factor binding protein 3 (IGF-BP3) levels were detected in the open surgery group compared with the laparoscopic surgery group. This effect disappeared when neutralizing antibody to IGF-BP3 was applied to the laparoscopic group, suggesting that this effect is due, at least in part, to surgery-related depletion of IGF-BP3 in peripheral blood.³⁷

SUMMARY

Several animal and human experiments have demonstrated an immunologic and oncologic benefit of minimally invasive surgery. Whether these results will translate into similar results in human settings is unclear. Although the first published prospective randomized clinical trial suggests better long-term outcomes for patients undergoing laparoscopic surgery, results from other ongoing randomized, controlled clinical trials are needed to verify this controversial result.

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