Review Article

Oncologic benefits of laparoscopic and minimally invasive surgery: a review of the literature

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Objective: To determine the oncologic benefits of laparoscopic and minimally invasive surgery (MIS).

Background: Laparoscopy and MIS have been used increasingly in general surgery including surgical oncology. Early animal studies comparing the effect of laparoscopy and pneumoperitoneum on cancer development and progression suggested an oncological advantage with laparoscopy.

Methods: We conducted a review of the literature to examine the evidence and to establish the presence or absence of oncologic benefits in patients with cancer who underwent laparoscopic resections when compared to those who had open resections.

Conclusions: Laparoscopic surgery has well established short-term benefits in surgical patients, and in surgical oncology, the use of laparoscopy achieves equivalent technical aims such as margin adequacy and number of lymph nodes harvested, which are indirectly associated with oncologic outcomes. Survival and recurrence outcomes do not appear to be improved with laparoscopy, with the exception of a possible trend towards improved overall survival with laparoscopic liver resections. Unique benefits of laparoscopy in oncology include earlier access to adjuvant chemotherapy, less morbid multivisceral resections, staging, and more feasible metastasectomy (better visualization of areas of disease, and the ability to access and resect lesions in multiple locations with minimal invasiveness and tissue trauma). Definitive conclusions about the oncologic benefits of MIS will require more highly powered studies with adequate follow-up.

Keywords: Benefits; laparoscopy; oncology; survival

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Introduction

Since its introduction and subsequent widespread use across nearly all fields of general surgery, laparoscopy has been shown to confer multiple benefits to patient outcomes such as decreased pain, blood loss, length of stay (LOS), and reduced postoperative complications (1). Initial incorporation of laparoscopy into oncologic surgery raised concerns regarding the impact on tumor seeding, port-site metastases, ability to obtain adequate oncologic resections, inadequate lymph node harvesting, and effects on disease-free survival (DFS) as well as overall survival (OS) when compared to open procedures. While the short-term benefits of minimally invasive surgery (MIS) are well established the oncologic benefits of MIS in patients with cancer are still a subject of debate.

Theoretically, the better preservation of immune function following MIS, and its effect on tumor biology, should translate into better oncologic outcomes in patients with cancer. The early sections of our paper deal with

Table 1 Pros and cons of laparoscopic surgery on the immunologic environment

Pros
Decreased tissue trauma
Decreased systemic inflammation
Decreased post-operative pro-inflammatory cytokines (IL-6, IL-1, TNF-α, CRP)
Less depression of cell-mediated immunity
Decreased blood loss
Better preserved host peritoneal defenses
Cons
Increased operative time and exposure to general anesthetics which may affect the immune system negatively

IL, interleukin; TNF-α, tumor necrosis factor α; CRP, C-reactive protein.

understanding this complex interplay, while the latter sections deal with evaluating the animal (pre-clinical) and clinical studies examining the effects and outcomes of laparoscopy/MIS on cancer and patients with cancer. If MIS leads to less surgical stress, which in turn leads to better preserved patient immunity and decreased immunosuppression, hypothetically, this should lead to an oncologic advantage in patients with cancer. In this paper, we aim to evaluate the existing evidence, and to see if this theoretical advantage translates into actual, measurable oncologic benefits. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ales.amegroups.com/article/view/10.21037/ales-21-19/rc).

How does laparoscopic surgery preserve immune function

One of the benefits of laparoscopic surgery as described in the surgical literature is decreased tissue trauma resulting in less systemic inflammation and resultant immunosuppression (1).

This decreased tissue injury chemically demonstrated as relatively lower post-operative levels of pro-inflammatory cytokines, reduces the occurrence of exaggerated host immune responses (1). The greater degree of tissue trauma which occurs with laparotomy when compared to laparoscopy, leads to an activation of host inflammatory processes which are proportional to the surgical insult (2). The activated host responses are mitigated by negative feedback loops which in turn lead to immunosuppression (2,3). Several studies have demonstrated differences in the post-operative levels of interleukin 6 (IL-6) between patients who underwent certain laparoscopic operations compared to those who had laparotomies (4-6). IL-6 levels were found to correlate with tissue trauma, operative time, and blood loss (7). IL-6 levels were also associated with clinical deterioration in humans (8). In contradistinction, one study comparing laparoscopic to open hernia repairs, found no differences in post-operative IL-6 levels, which may be due to the relatively limited tissue damage which occurs in hernia repairs as compared to other operations which require more extensive tissue handling (9).

Using the post-operative levels of a pro-inflammatory cytokine such as IL-6 as an objective marker, laparoscopic surgery does have a demonstrable immunologic advantage (1). Other inflammatory markers and mediators shown to have higher blood levels following laparotomies when compared to laparoscopic surgery include interleukin-1 (IL-1), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP) (5,10-14).

Smit and colleagues postulated in 1996 that the decreased depression of cell-mediated immunity which occurs with the avoidance of laparotomy, may not only minimize infectious complications, but may also prevent peri-operative tumor implantation and growth (15). The expression of the major histocompatibility complex (MHC-II) molecule, human leucocyte antigen DR (HLA-DR) has been found to be relatively unaffected in patients who underwent laparoscopic surgery, but diminished after open surgery (7,16). This implies impaired antigen recognition and presentation in patients who had conventional surgery compared to patients who underwent laparoscopic surgery in the early post-operative period. Siestes and colleagues demonstrated depressed monocyte cytotoxic activity against tumor cells after open surgery, which was not observed following laparoscopy (17).

Several authors have demonstrated the effect of CO_2 pneumoperitoneum on peritoneal immunity and have suggested that avoiding exposure to atmospheric air is the mechanism by which host immunity is preserved rather than the magnitude of the surgical stress (18-20). One of these authors demonstrated increased TNF-α levels in mice who had air pneumoperitoneum and laparotomies, but normal levels in mice subjected to CO_2 pneumoperitoneum (20). Whether by better preservation of host peritoneal immunity, or decreased depression of cellular and/or humoral immunity, the immunologic benefits of laparoscopy are well established. Please see *Table 1* for the advantages

and disadvantages of laparoscopy on immune function. We will now evaluate if better preservation of immune function translates into better oncologic outcomes in cancer patients.

How does preserved immunologic function in laparoscopic surgery influence cancer biology

Impaired immune function after surgery has been thought to contribute to postoperative morbidity and mortality. Dampening the deleterious effects by the use of laparoscopy may play a role in faster recovery and thus lead to better outcomes in patients with cancer. The association between laparoscopy, immune function, cancer biology, and clinical outcomes is an area that is still under investigation with an overarching hypothesis that earlier restoration of immune competence can influence disease recurrence and prognosis.

A 2020 review by Onuma *et al.* explored the effects of surgical stress on tumor progression via its impact on the immune response (21). They showed that surgical injury (i.e., tumor resection) activates the host immune system and that the resulting procoagulant state may stimulate micrometastasis formation. Surgical stress can also alter the tumor microenvironment which promotes an immunosuppressive state via decreased recruitment of natural killer (NK) and regulatory T cells. The authors further reviewed several perioperative modalities that could counter the effects of surgical stress on tumor progression: inhibition of platelet activation using anticoagulation, use of phosphodiesterase inhibitors to enhance NK cell toxicity, use of beta blockers and cyclo-oxygenase (COX) inhibitors to enhance NK and cytotoxic T cell activity, decrease $CD4^+$ T cell activity, as well as the use of toll-like receptor (TLR) agonists to increase NK cell cytotoxicity.

A recently published randomized controlled trial used NK cell numbers and function to compare the postoperative immune function of patients with colorectal cancer who underwent either open or laparoscopic resection (22). NK cell quantity and lytic activity were assessed pre-operatively and on postoperative days 1, 4, and 7. The authors found that NK cell numbers decreased in both groups postoperatively; however, the laparoscopic group had a faster recovery of NK function and less impairment of function compared to the open group. The authors concluded that the number and activation of NK cells may serve as a prognostic indicator for postoperative recovery for patients. Future work would be needed to examine the long-term clinical benefits of NK cell function preservation.

Animal studies examining laparoscopic surgery and cancer

Numerous animal studies have explored the effects of laparoscopy on cancer immunology. One early landmark study by Allendorf *et al.* compared tumor growth in immunocompetent *vs* T-cell deficient mice following laparotomy, pneumoperitoneum, or no procedure (23). They found that tumors grew much larger after laparotomy versus laparoscopy in immunocompetent mice (23). However, there was no significant difference in tumor growth after laparotomy when compared to laparoscopy in athymic mice. The authors concluded that T-cell function plays a critically important role in the mechanism of tumor differences observed between mice who underwent laparotomy versus laparoscopy. Subsequent studies further examined the effects of laparoscopy on tumor growth in mice. In 2003, the influence of postoperative inflammatory responses on angiogenesis and tumor growth was examined (24). Cancer cells were injected into mice cecums followed by cecectomy two weeks later. The surgeries were performed open or laparoscopically with either CO_2 or helium insufflation. The mice were killed on postoperative day 12 and tumor load score, tumor weight, IL-6, vascular endothelial growth factor (VEGF), and microvessel density were all significantly higher in the open surgery group. The authors concluded that increased levels of cytokines and VEGF were associated with increased angiogenesis and tumor growth following laparotomy versus laparoscopy (24).

The long-term effects of surgery on cancer biology in the murine model was also studied (25). Kuntz *et al.* performed laparoscopic, open, or control (anesthesia only) procedures on male rats with colonic tumors and evaluated the stress and immune response postoperatively by measuring levels of corticosterone, neopterin, IL-1β, and IL-6 at one week after surgery. Long-term effects were evaluated in terms of survival time, tumor weight and the number of tumor infiltrated nodules at autopsy. They found significantly lower levels of stress and immune markers in the laparoscopic group; however, there was no difference in long-term markers (25).

Clinical studies examining laparoscopic surgery and cancer

A number of clinical studies have been performed, comparing outcomes in cancer patients who underwent MIS resections to outcomes in patients who had open

surgery for the same types of cancer. While MIS resections have well recognized advantages in pain control, LOS, and the occurrence of surgical site infections (SSI), the focus here will be specific to oncologic benefits. Nunobe and colleagues compared outcomes in patients with gastric cancer who underwent resection either laparoscopically or through an open incision (26). The authors found that laparoscopic surgery for gastric cancer had many benefits, but that differences in oncologic outcomes such as survival, recurrence, and type of recurrence were yet to be well established (26). The authors emphasized the fact that many studies reviewed had a follow up period of less than 5 years, and that studies examining the long-term survival outcomes between the groups were still ongoing (26). The article reiterated the decreased intraoperative bleeding, better post-operative pain control, earlier return of gastrointestinal motility and resumption of oral intake seen with laparoscopy (26).

In a study conducted using data from a randomized controlled multicenter trial comparing outcomes in patients who had laparoscopic versus open radical hysterectomies for early-stage cervical cancer, Zaccarini *et al.* found no difference in OS or DFS (27). Patients who had laparoscopic hysterectomies had a shorter LOS, but there was no statistically significant difference between the two groups in intra- and post-operative complication rates (27). Vennix and colleagues published a systematic review of randomized controlled trials comparing laparoscopic total mesorectal excisions to open total mesorectal excisions for rectal cancer, and found no difference in OS, 5-year DFS, local recurrence, number of resected lymph nodes and surgical margins (28). Kuhry *et al.* had performed an earlier systematic review comparing not just rectal resections, but laparoscopic and open colorectal resections, and found no difference in cancer-related mortality, and local or port-site recurrences (29). Kuhry's review did show short-term benefits of laparoscopy such as less post-operative pain, and faster recovery from ileus, etc. (29). A randomized controlled clinical trial: ACOSOG Z6051 studied and concluded that laparoscopic resections were not non-inferior to open resections for stage II and III rectal cancers with regards to oncologic markers of successful resections and could not recommend the use of laparoscopy based on these findings (30). The COREAN trial found similar DFS for patients with locally advanced rectal cancer who had neo-adjuvant therapy and therefore justified the use of laparoscopy for rectal cancer excision (31). The COLOR II trial demonstrated similar rates of locoregional recurrence, DFS and OS in laparoscopic compared to open resections for rectal cancer at 3 years from the index operation (32), and the ALaCaRT Randomized Clinical Trial, similar to ACOSOG Z6051, could not establish non-inferiority of laparoscopic resections compared to open resections when comparing a composite of oncological factors indicating an adequate surgical resection (33). Mirnezami reported on clinical trials comparing laparoscopic liver resections (LLR) to open liver resections (OLR) for malignant and benign liver diseases (34). The meta-analysis of pooled data carried out for cases of malignant disease showed equivalent rates of hepatic tumor recurrences, but also showed a statistically significant trend towards improved OS with LLR (34). Studies examining differences in outcomes between MIS and open resections have also been carried out for mesenchymal tumors such as gastrointestinal stromal tumors (GIST). Pelletier's meta-analysis and systematic review analyzed data from trials comparing open and laparoscopic resections for gastric GIST (35). Follow-up data was inconsistent across the trials analyzed, but the authors concluded that there were no differences in disease recurrence rates and OS (35).

Clinical studies comparing laparoscopic to open surgical resections for cancer consistently find no oncologic benefit with laparoscopic or MIS resections, with the possible exception of a trend towards improved OS with LLR (34). The mixed conclusions arrived at by these studies underscore the need for more research examining oncologic benefits of MIS with appropriate statistical power and adequate length of follow-up.

Other benefits of laparoscopic surgery in cancer patients

Beneficial uses of laparoscopy specific to patients with cancer can be seen in many important areas including minimally-invasive staging to avoid unnecessary open procedures and earlier initiation of chemotherapy secondary to decreased postoperative SSIs (36). The earliest published use of diagnostic laparoscopy for staging was in 1971. DeVita *et al.* used peritoneoscopy in 38 patients with Hodgkin's disease prior to induction of radiation therapy (36). They found that the ability to exclude patients with metastatic disease from radiation without having them undergo open liver examination to be a major benefit. Since that time, minimally-invasive diagnostic staging procedures have been established in multiple oncologic subspecialties. In 2016, Arumugam *et al.* discussed the role of laparoscopy

in hepatobiliary cancers and the fact that MIS staging remains crucial since non-invasive imaging may miss small liver or peritoneal tumors that would preclude curative operations and thus prevent futile laparotomies (37). In 2017, Mehta *et al.* reviewed staging in esophageal cancer and stated that two major advantages of MIS were the potential avoidance of a non-therapeutic laparotomy (and its associated mortality and morbidity) due to enhanced detection of distant metastases and the identification of more patients who might benefit from neoadjuvant therapy due to improved detection of locally advanced disease (38).

In metastasectomy procedures, LLR in comparison to the open technique and has been shown to be superior due to a decrease in the size of the surgical incision(s), length and trauma of surgery, blood loss, operating time, postsurgical pain, complications, LOS, and decreased time to recovery, and oral intake (39). The authors concluded that laparoscopic excision is a safe and feasible approach with near zero mortality with oncologic outcomes similar to open resection (39). A 2020 meta-analysis of LLR for colorectal metastases demonstrated superior short-term outcomes, with no differences in mortality rates compared to open resection (40). Oncologic outcomes such as R0 resection rates, OS and DFS rates were comparable to the open approach (40).

Metachronous or advanced cancers may require multivisceral resections, and these operations may be particularly morbid, especially as open procedures in patients debilitated from malignant disease. Piccoli in 2021 reported on fully robotic multi-visceral resections, and stated that they were safe and feasible with the added advantages of single exposure to anesthesia, reduced hospitalizations, decreased morbidity, and better cost-effectiveness (41).

For patients who would benefit from chemotherapy, a well-known barrier to the commencement of adjuvant chemotherapy is the presence of an active infection. Therefore, the decrease in post-operative infections seen with MIS would result in earlier initiation of adjuvant therapy, and the use of laparoscopy in colorectal surgery has been reported by Simpson *et al.* to be associated with a shorter time to adjuvant chemotherapy (42). While the clinical implementation of MIS approaches has not improved oncologic recurrence or survival, its use in patients with cancer does have unique benefits when compared to open surgery, which are distinct from the short-term benefits seen in general surgical patients as a whole.

Discussion

The aim of our paper was to review the surgical literature for oncologic benefits of laparoscopy. We expanded the subject matter to include MIS encompassing robotic and laparoscopic surgery and use the terms interchangeably, since the principles and minimally invasive nature remain the same. Our review of the literature reveals an equivalency with open resections with regards to the technical aims of oncologic surgery such as margins and lymph node harvests, but a lack of advantages when it comes to survival or recurrence. One notable exception was a trend towards improved OS with LLR compared to open resections (34). The trend in improved OS mentioned in LLR compared to open was based on meta-analyses of studies involving patients with hepatocellular carcinoma (HCC) alone (34). While it is reasonable to expect a more pronounced advantage of decreased immunosuppression in patients with systemic disease, the Mirnezami article was unable to analyze for differences in patients undergoing LLR or OLR for liver metastases (34).

Several explanations exist for the lack of clinical oncologic benefits with MIS. One possible explanation is that the immunological advantages of MIS described in our paper may not influence cancer cell biology in vivo as it they do in preclinical models. Oncogenesis and cancer progression involve a complex interplay of genetic, epigenetic, and environmental pathways and processes that go beyond the human immune system, and these processes may not be hindered by solely immunological changes. Meacham's paper "Tumor heterogeneity and cancer cell plasticity" discusses the phenotypic and functional heterogeneity among cancer cells in the same tumor which occur as a result of genetic change, environmental differences and reversible changes in cell properties (43). The authors contend that this heterogeneity and plasticity could explain resistance to treatment and progression (43). This underscores the complexity of cancer origination and progression, and it could be inferred that for any intervention (such as laparoscopy) to lead to a survival advantage, it would need to circumvent the complex mechanisms that are responsible for tumor progression. Another explanation may be the limited life expectancy in patients with cancer, who are more likely to be elderly and affected by other comorbidities. This limits to some extent, the duration for which patients with cancer could be studied, and as a result makes it difficult to detect a delayed survival advantage. While the cancer-specific outcomes may

be disappointing, the other benefits of MIS specific to patients with cancer are worthy of discussion. Laparoscopy does not appear to have a survival advantage in patients with cancer, but there are benefits of laparoscopy or MIS that are unique to patients with cancer which go beyond the short-term benefits seen in all surgical patients. Definitive conclusions about the oncologic benefits of laparoscopic or MIS will require further investigation using properly designed clinical studies with adequate power and follow-up.

Conclusions

Laparoscopic surgery has well established short-term benefits in surgical patients. In surgical oncology, the use of laparoscopy achieves equivalent technical aims such as margin adequacy and number of lymph nodes harvested, which are indirectly associated with oncologic outcomes. Survival and recurrence outcomes do not appear to be improved with laparoscopy, with the exception of a possible trend towards improved OS with LLR. Unique benefits of laparoscopy in oncology include earlier access to adjuvant chemotherapy, less morbid multivisceral resections, less invasive staging, and a trend towards improved oncologic outcomes for patients undergoing metastasectomy. Definitive conclusions concerning the oncologic benefits of MIS will require more highly-powered studies with adequate follow-up.

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Footnote

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