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■ REVIEW ■

Is Laparoscopic Technique Oncologically Appropriate for Colorectal Cancer Surgery?

The role of laparoscopy for curative colorectal cancer surgery remains a topic of much debate. Even though, two oncologic issues, abdominal wall cancer recurrence and adequacy of intraperitoneal staging, are still of major concern, we believe that abdominal wall cancer recurrence may be largely avoidable using the appropriate surgical oncologic principles. In addition, laparoscopy appears to be quite valuable for accurate staging if used in combination with laparoscopic ultrasonography. The question, "Is laparoscopic technique oncologically appropriate for colorectal cancer surgery?", cannot be answered clearly until long-term recurrence and survival rates have been determined in a large number of patients undergoing curative laparoscopic cancer surgery. We, however, have still not had a single port-site recurrence at the Cleveland Clinic to date, having performed over eighty curative colectomies for cancer (performed only in a prospective randomized study) with a median follow-up of approximately two and half years.

Key Words : *Laparoscopy; Colorectal neoplasms; Recurrence; Neoplasm staging; Colectomy*

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INTRODUCTION

Since laparoscopic techniques have been employed in the surgical management of colorectal malignancy, several oncologic issues about whether these techniques are reasonable for the curative treatment of patients with colorectal cancer have been raised (summarized in Table 1). Initially, technical feasibility regarding adequacy of margins of resection and extent of lymph node dissection were at issue. Additionally, at least two other issues, abdominal wall cancer recurrence and adequacy of intraperitoneal staging, are of major concern. In this review, these oncologic issues are discussed.

Table 1. Oncologic issues regarding laparoscopic colorectal cancer surgery

- Adequacy of margins of resection
- Extent of lymph node dissection
- Abdominal wall cancer recurrence
- Intraperitoneal tumor staging

TECHNICAL FEASIBILITY

Because conventional surgical techniques are safe and acceptable methods for managing colorectal cancers, laparoscopic techniques for curative resection of colorectal malignancies must maintain the principles well-established in conventional surgery, without any significant changes in an oncologic basis.

However, some difficulties have arisen in proving that an oncologically "adequate" resection has been performed according to these principles. One approach to prove an adequate resection has been to examine the resected specimen with inspection of the resection margins and count the number of removed lymph nodes. Several reports of laparoscopic colectomy (1-4) have shown that the resection margins were acceptable and lymph node dissection was comparable to open colectomies even though the methods for these analyses were not standardized. However, tumor-free proximal and distal margins alone do not prove that an adequate oncologic resection has been accomplished, because wide and clear lateral margins are also mandatory especially in rectal cancers (5). Moreover, the length of the large intestine (6) and the number of

lymph nodes (7) vary individually; thus removal of a long specimen or merely counting the number of nodes in the resected specimen does not guarantee that an oncologic resection has been achieved. In addition, simple removal of a long segment with epicolic and paracolic nodes without performing a dissection of central nodes can theoretically show the same number of nodes as in the removal of a smaller colonic segment with central nodal harvest.

In our opinion, because an oncologic colorectal resection is defined in anatomic terms, the criterion that verifies whether oncologic resection is adequate is the anatomic extent of the resection. Therefore, at the Cleveland Clinic, we performed a series of laparoscopic right colectomies, proctosigmoidectomies (8), and abdominoperineal resections (9) in fresh human cadavers, and also performed a series of laparoscopic right colectomies (10) and total abdominal colectomies (11) in dogs. We measured the lengths of the remaining named mesenteric vessels, counted the number of lymph nodes remaining at the base of these main mesenteric vessels, and assessed the overall extent of mesenteric and pelvic dissection at a complete abdominal autopsy or zoopsy after the procedure. We were able to show that the anatomic extent of a laparoscopic oncologic resection could indeed be radical with removal of nearly all nodes at the base of the colonic mesentery, under these controlled experimental conditions.

We defined a curative oncologic resection as follows: 1) wide en bloc resection of the tumor-bearing bowel segment with adjacent soft tissue and mesentery, 2) resection of suitable margins of the normal bowel wall above and below the cancer, and 3) excision of draining regional lymph nodes accompanying the major vascular pedicle to the involved bowel. In addition, we believe the following are also mandatory for laparoscopic curative cancer surgery: 1) minimal manipulation of the tumor-bearing segment, 2) placement of the specimen in an endoscopic impermeable bag before delivery through the abdominal wall, and 3) thorough assessment of the abdominal cavity for metastatic disease. These are summarized in Table 2.

Table 2. Oncologic principles for laparoscopic colorectal cancer surgery

- Wide en bloc resection of the tumor-bearing bowel segment with adjacent mesentery
- Resection of suitable margins of the normal bowel wall above and below the cancer
- Excision of draining regional lymph nodes accompanying the major vascular pedicle
- Minimal manipulation of the tumor-bearing segment
- Placement of the specimen in an impermeable bag before delivery
- Thorough assessment of the abdominal cavity for metastatic disease

INTRAPERITONEAL STAGING

Theoretically, the lack of tactile feedback during laparoscopic colorectal surgery may limit the surgeon's ability to stage the disease adequately because palpation of the liver and the retroperitoneum is not possible. Thus, palpation of the abdominal cavity must be replaced by other methods that have the potential to provide the same information. For this purpose, preoperative and intraoperative ultrasonography, computed tomography (CT) scanning, and magnetic resonance imaging can be used. We prospectively evaluated the feasibility and efficacy of intraoperative laparoscopic ultrasonography to completely evaluate the liver (12). This technique was a safe, quick, and useful tool for hepatic evaluation that permits identification of all important anatomic structures in the liver. It also provided a valuable means for intraoperative evaluation of the liver parenchyma during laparoscopic resection of colorectal cancer. At the Cleveland Clinic, the accuracy of intraoperative laparoscopic ultrasonography compared to preoperative contrast enhanced CT in the detection of liver metastases in patients with colorectal cancer is currently being evaluated.

If there is a difference in the extent of lymphadenectomy between laparoscopic and open colectomy, then understaging of the disease may occur. The incidence of such understaging is unknown. We believe, however, if laparoscopic technique does strictly adhere to well-established oncologic principles, it will not compromise the adequacy of staging.

CONCERN ABOUT ABDOMINAL WALL CANCER RECURRENCE

Since Alexander et al. (13) first reported the case of port site cancer recurrence after laparoscopic colectomy, many others (14-26) have reported the same complication. Direct tumor implantation to the minilaparotomy incision used to remove the specimen may lead to abdominal wall recurrence, as had been seen historically after the Mikulicz operation where the tumor-bearing bowel segment was brought directly out through an abdominal wall incision (27). Some authors (14) argued that this recurrence may be due to the advanced nature of the disease and peritoneal carcinomatosis rather than the technique. However, several other mechanisms have

been postulated because trocar site implantation has occurred even with early stage cancers and in sites not used for specimen extraction (28). One hypothesis is increased exfoliation of malignant cells induced by traumatic manipulation of the cancer specimen with laparoscopic instruments (15, 16, 21, 22). Limited working space and lack of tactile sense in laparoscopy may mean that tumors are manipulated more extensively than in open surgery, and subsequently more malignant cells can be dislodged into the peritoneal cavity (21, 22). Yet another hypothesis is the influence of pneumoperitoneum (19, 21, 22, 26, 29, 30). Cirocco et al. (19) speculated that remote port site recurrence may be due to the liberation of cancer cells facilitated by intraperitoneal carbon dioxide insufflation. Jacquet et al. (26) suggested the sustained intraabdominal pressure of pneumoperitoneum may favor extrusion of tumor cells from the specimen and dissemination of tumor emboli within the peritoneal cavity. Nduka et al. (21) speculated that pneumoperitoneum may allow concentration of airborne exfoliated tumor cells in a closed ventilation system to become trapped on moist intraperitoneal surfaces. Pressure gradients induced by pneumoperitoneum, as during removal of laparoscopic ports ("chimney effect"), may contribute to this phenomenon (29).

In a hamster model, after injection of human colon cancer cells into both the cecal mesentery and free peritoneal cavity, Jones et al. (31) observed that CO_2 pneumoperitoneum (10 mmHg for ten-minute duration) enhanced the incidence of tumor implantations in the cecal mesentery (10 vs. 28 percent), the midline abdominal incision (29 vs. 68 percent) and at trocar sites (26 vs. 75 percent). The authors suggested that the mechanical force of pneumoperitoneum might have disseminated tumor cells and seeded trocar sites as carbon dioxide leaked around the ports, and postulated stretching the abdominal wall during pneumoperitoneum may augment release of growth factors from the wound and subsequently promote tumor progression. However, they could not explain why tumor implantation was also enhanced in the cecal mesentery. It might mean that carbon dioxide has unknown trophic effects on tumor growth. They also observed that there was a definite dose-response relation between trocar implantation and an increasing number of cells in the inoculum. They stated that this dose-related response may explain why expert laparoscopic surgeons who have performed hundreds of colectomies have still not had a single recurrence to date.

We assessed whether pneumoperitoneum enhances tumor growth or incidence in the abdominal wall wound after intraperitoneal cancer cell injection and, if so, to determine which of the above two suggested mechanisms ("chimney effect" and trophic effect) is most likely responsible (32). After making a 0.5-cm laparotomy in a syngeneic immunocompetent rat, colon cancer cells were injected intraperitoneally (Experiment I: 1×10^5 cells per rat for assessing tumor growth, Experiment II: 1×10^4 cells per rat for assessing tumor incidence). Rats were assigned into one of the 3 groups: control (no pneumoperitoneum, wound left open), CO_2 and air pneumoperitoneum. For pneumoperitoneum groups, one 5-mm cannula was inserted into the wound and secured loosely with a purse-string to permit a gas leak around the cannula. Gas insufflation was continued for 30 minutes at 6 mm-Hg. Two weeks later, the abdominal wound tumor weight or incidence were compared between groups. In the Experiment I, tumor developed in the abdominal wound in all groups, without carcinomatosis. Mean tumor weight ($\pm$SD) in the abdominal wall wound was 7.0 ± 5.4 mg in the CO_2 group, 5.9 ± 3.5 mg in the air group, and 7.0 ± 5.5 mg in the control group ($n=25$ each group, $p=0.95$ by analysis of variance). In the Experiment II, abdominal wall tumor incidence was 40% in the CO_2 group, 33% in the air group, and 33% in the control group ($n=15$ each group, $p=0.91$ by Chi-square). In our experimental model, pneumoperitoneum with a gas leak around the abdominal wall cannula did not enhance abdominal wall tumor growth or incidence. CO_2 vs. air had no trophic effects. Large numbers of intraperitoneal cancer cells led to tumor development in the abdominal wall wound, irrespective of CO_2 pneumoperitoneum. This study may support the importance of surgical techniques in avoiding the spillage of malignant cells during any type of cancer resection.

In our opinion, abdominal wall recurrence after laparoscopic colectomy is likely closely related to surgical technique. The wide variation of reported incidences of port site recurrence within one review article (25), ranging from 1.5 to 21 percent, after a curative resection of colorectal carcinoma strongly implies this may be the case. This statement is supported by recent clinical data (33, 34) showing a very low incidence of port site metastases (less than 1 percent) in large numbers of patients undergoing laparoscopic colorectal cancer surgery by experienced surgeons. Even in conventional colectomy, the experience of the surgeon performing the operation, 'surgeon-related variability', appears to influence a local recurrence rate (35-37). Abulafi and Williams (36) divided factors that influence local recurrence after conventional colectomy into three groups: patient, tumor and surgery-related. The third factor is unquestionably related to the technique in surgery.

A cutaneous metastasis from colorectal cancer is an uncommon, but a well-known feature (38-52), having been reported in less than 4% of patients with colonic cancer coming to autopsy (50, 51). In a large series of

724 cases of metastatic tumors of the skin reported by Brownstein and Helwig (42), cutaneous metastatic lesions from carcinoma of the large intestine were most often located in the skin of the abdominal wall. Although some authors (25) mentioned that there had been no case reports of abdominal wound recurrence after standard laparotomy searched in the medical literature except one series (46), we found many reported cases of abdominal wall scar recurrence of colorectal cancer (27, 38, 39, 43, 45-47, 52). Surprisingly, most cases were isolated lesions located in the previous incision scar tissue without any systemic or intraperitoneal disseminations (39, 43, 45-47). Even though Hughes et al. (46) insisted that the development of an incisional scar tissue malignant nodule is much more likely to be an early manifestation of incurable systemic malignant disease because of poor outcome for these patients, we believe that many of these recurrences should be categorized as locoregional recurrence as suggested by Galandiuk et al. (48). In the study from the Roswell Park Memorial Institute (45), ten of 22 patients who underwent radical surgical excision for abdominal wall recurrence were alive at the five-year follow-up mark. In fact, Hughes et al. (46) did not perform excisional surgery in most patients in their series even though most of them (11 of 16 patients) had apparently isolated recurrence in the abdominal incisional scar. The favorable outcome after excisional therapy may support the concept that abdominal wall scar recurrence should be considered as a part of locoregional recurrence. Again, any locoregional recurrence can be affected by surgeon-related variability. In most series (38, 39, 43, 45) of abdominal wall scar recurrence of colorectal cancer, the total number of cancer patients seen was not mentioned, thus an estimate of the incidence of abdominal wall metastases could not be made. By only one series (46), the incidence of tumor recurrence in the abdominal wall scar tissue after open colectomy could be determined, which was less than 1 percent (11 of 1,603 patients). However, the incidence of incisional recurrence after open colectomy is likely underestimated. In one prospective study, the incidence and clinical features of wound recurrence following open colectomy were examined (52). Eleven (0.6 percent) of 1,711 enrolled patients documented incisional recurrences. Only four were identified on physical examination before reoperation, and the remaining seven were discovered incidentally at the time of abdominal exploration for clinically suspected recurrent disease. Because only a portion of the patients underwent reoperation, the authors suggested that true incidence of wound recurrence may be underestimated.

Abdominal wall recurrence after laparoscopic colon cancer surgery seems to be an unusual pattern of recurrence, yet it is uncertain whether there is truly an increased recurrence rate compared to open surgery. If abdominal wall recurrence after laparoscopic colon cancer surgery is closely related to surgical technique, and if it is results from either traumatic manipulation of the cancer specimen during laparoscopic dissection or direct contact between the specimen and the margins of the incision during specimen removal, this complication may be largely avoidable using the appropriate surgical oncologic principles.

We prospectively evaluated whether or not laparoscopic techniques, carefully performed according to oncologic principles during resection of colon cancer, increases the exfoliation of malignant cells into the peritoneal cavity compared with conventional surgical techniques (53). The results demonstrated that laparoscopic techniques in curative colorectal cancer surgery did not lead to an increased risk of intraperitoneal cancer cell spillage, compared to conventional techniques. This study decreased some of the concerns of the possibility of tumor cell spillage and seeding during laparoscopic surgery. Although controversy is still present regarding whether or not exfoliated malignant cells are viable and whether these free floating cells have the clinically relevant affect on the incidence of tumor implantation of wounds, one study (54) demonstrated 70% of exfoliated colonic cancer cells obtained by preoperative lavage and irrigation of the cut ends of the operative specimen were viable. Also, some studies demonstrated that exfoliated colon cancer cells have the proliferative and metastatic potential in vivo (55) and the capacity for in vitro growth (56).

Additionally, many surgeons argue port site recurrence is not unique to laparoscopic surgery for colorectal cancer. These recurrences have also been reported after laparoscopic procedure for other cancers such as biliary (57, 58), gastric (59, 60), gynecologic (61, 62), hepatocellular (63), pancreatic (64, 65), and urinary bladder (66) carcinomas. However, we would point out that tumor implants have also been reported in incisional scars after conventional surgery for breast (67), gastric (68), hepatocellular (63), pancreatic (69), endometrial (70), and re-

Table 3. Reported cases of incisional scar recurrence following conventional and laparoscopic manipulation of malignancy

Malignancy	Conventional*	Laparoscopic*
Colorectal	27, 38, 39, 43, 45-47, 52	14-26
Biliary		57, 58
Gastric	68	59, 60
Gynecologic	70	61, 62
Hepatocellular	63	63
Pancreatic	69	64, 65
Urinary/renal	71	66

*Number of reference cited in the text

nal cell (71) cancers. Reported cases of incisional scar recurrence after conventional and laparoscopic manipulation of malignancy are summarized in Table 3.

CONCLUSION

Technical feasibility regarding adequacy of margins of resection and extent of lymph node dissection, which were initially at issue of laparoscopic colorectal cancer surgery, seem not to be a problem anymore. Even though, two other oncologic issues, abdominal wall cancer recurrence and adequacy of intraperitoneal staging, are still of major concern, we believe that abdominal wall cancer recurrence may be largely avoidable using the appropriate surgical oncologic principles. In addition, laparoscopy appears to be quite valuable for accurate staging if used in combination with laparoscopic ultrasonography.

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