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Surgical Treatment for Colorectal Cancer

Art Hiranyakas, Yik-Hong Ho

Department of Surgery, James Cook University, Townsville, Queensland, Australia

The rapid in development of surgical technology has had a major effect in surgical treatment of colorectal cancer. Laparoscopic colon cancer surgery has been proven to provide better short-term clinical and oncologic outcomes. However this quickly accepted surgical approach is still performed by a minority of colorectal surgeons. The more technically challenging procedure of laparoscopic rectal cancer surgery is also on its way to demonstrating perhaps similar short-term benefits. This article reviews current evidences of both short-term and long-term outcomes of laparoscopic colorectal cancer surgery, including the overall costs comparison between laparoscopic surgery and conventional open surgery. In addition, different surgical techniques for laparoscopic colon and rectal cancer are compared. Also the relevant future challenge of colorectal cancer robotic surgery is reviewed.

Key words: Colorectal cancer – Laparoscopic colorectal surgery – Treatment of colorectal cancer – Colorectal cancer surgery

In 1987[1] the success of laparoscopic surgery for gallbladder disease had a major effect on the development of present day laparoscopic surgery for various organs of benign and malignant diseases. The first series laparoscopic colonic surgery was reported in 1991 by Jacob *et al.*[2] Twenty patients with both benign and malignant colorectal diseases were safely resected laparoscopically with acceptable outcomes. With the aim to enhance postoperative recovery, reduce postoperative morbidity, reduce overall cost of treatment, and improve long-term survival for colorectal cancer patients, laparoscopic colorectal surgery had become a popular treatment option for colorectal cancer. A few years later, the interesting results from the first randomized controlled trial in 2002, emphasizing on the late outcomes of laparoscopic surgery for colonic cancer by Barcelona trial, Lacy *et al*[3] stated the significant advantages of reduced blood loss, early return of intestinal motility, lower overall morbidity, and shorter duration of hospital stay in the laparoscopic-assisted group. Subgroup analysis from the study also revealed survival benefit that was mainly limited to stage III (Dukes' C) disease. Although this finding might be explained by statistical phenomenon on subgroup analysis, it had already started the hope for this novel surgical approach on potential outcome improvement.

The objective of this review is to describe the comparison of available evidence between the conventional open approach and laparoscopic resection on short-term and long-term outcome of colorectal cancer treatment.

Reprint requests: Art Hiranyakas, MD, Department of Surgery, James Cook University, Townsville, Queensland, Australia. Tel.: +61 7 47961417; Fax: +61 7 47961401; E-mail: art.hiranyakas@jcu.edu.au

Short-Term Outcome

Laparoscopic colorectal surgery has a steep learning curve due to its unique technique of working in multiple abdominal quadrants, control of vascular structures, creation of anastomosis, as well as retrieving large specimens in some patients.[4,5] Early randomized controlled trials suggest that the short-term outcomes of laparoscopic colorectal surgeries are probably marginally better than the traditional open approach. However, after laparoscopic technique had been widely accepted, later reports[6,7] demonstrated clear superiority of short-term outcome for the laparoscopic approach, including a reduction in postoperative ileus, less postoperative pain and a concomitant reduction in the need for analgesics, earlier tolerance of diet, shortened hospital stay, quicker return to premorbid functional activity, less wound-related morbidity, improved cosmetic results, and a possible reduction in adhesion formation.

The Clinical Outcomes of Surgical Therapy (COST) study group[8] (1994–2001) reported the outcome from 48 institutions of 872 patients with colon cancer who were randomized to two groups: 435 laparoscopic resections and 437 open resections. The results from experienced surgeons who had done 20 or more laparoscopic resections showed longer operating time, but shorter recovery time and hospital stay, and trend toward lower intraoperative complications. There was no significant difference in morbidity and mortality, tumor recurrence, or overall survival after 4.4 years of follow-up. The COlon cancer Laparoscopic or Open Resection (COLOR) trial[9] is also a multicenter study that enrolled 1248 patients with colon cancer randomized to two groups: 627 laparoscopic resections and 621 open resections. The laparoscopic group had longer operating times but less blood loss, early recovery of bowel function, fewer analgesics requirement, and shorter hospital stay. There was no significant difference in radicality of resection and postoperative morbidity and mortality. The Medical Research Council (MRC) Conventional vs. Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial[10] included 794 patients who were diagnosed with colon and rectal cancer (526 laparoscopic resections and 268 open resections) from 27 United Kingdom centers between 1996 and 2002. Recent evidence from the meta-analysis of 12 randomized controlled trials on short-term outcome comparing laparoscopic resection for colorectal cancer to open resection reported by Abraham *et al*[11] in 2004 showed that it took 30% longer to perform the operation in the laparoscopic group, but there was less morbidity, earlier return of bowel function (33%), reduced analgesia requirements (37%), and reduced hospital stay (20%). There was no difference in perioperative mortality or oncologic clearance in either group.

The superior short-term outcomes with laparoscopic resection is supported by the reports on perioperative immunologic response. A recent prospective study from China[12] on 68 colorectal cancer patients (35 laparoscopic resections and 33 open resections) showed significant earlier return of bowel function and reduction of hospital stay in the laparoscopic resection group. Total lymphocytes, CD4 T cell, and CD8 T cell levels were significantly higher in laparoscopic resection compared with open resection, especially on postoperative day 4. This study confirmed the results from other studies[13–16] for better reserved cellular immune responses in patients undergoing laparoscopic colorectal resections. In addition, more aggressive phenotype of cancers also found with more profound immunosuppression demonstrated after open surgery.[17] Milašien *et al*[18] also reported that better cellular immunity correlated with higher postoperative survival rates. However, we are still anticipating stronger evidence supporting improvement of long-term oncologic advantages.

Cost

The concern about potential increased cost of laparoscopic colorectal resections has always been considered. However, laparoscopic colorectal resections were found to be significantly cheaper than conventional open resections because of the reduced hospital stay, despite higher operative spending.[19] A recent report from Australia by Norwood *et al*.[20] compared hospital cost using Hospital Patient Costing System, including costs from nursing interventions (calculated in minutes). Ninety-seven patients (53 laparoscopic resections, 44 open resections) were analyzed. The median total cost of the procedure was equivalent: AUS$9698/£5631 (AUS$3862–90,397) in the open group and AUS$10,951/£6219 (AUS$2337–66,237) in the laparoscopic group. The laparoscopic group showed more benefit in reduction of nursing intensity (80 versus 58.5 hours), and the significant reduction of nursing intensity was demonstrated after exclusion of laparoscopic patients who underwent conversion (80 versus 54 hours; $P = 0.01$).

Long-Term Outcome

Several evidences from early basic science studies suggested that in the right setting, laparoscopic surgery will result in a better long-term oncologic outcome by more preservation of immunologic functions.[21–23] Preservation of the body's immunologic function, particularly cellular immunity immediately after surgery, is an essential defense to potentially prevent cancer recurrence.[24] Significantly less physiologic alterations during this critical perioperative period can be achieved by laparoscopic surgery, which is relating to less tissue trauma.[21–23] Interestingly, these potential advantages have not been translated into better long-term outcomes in human settings.

Jayne *et al*[25] reported the evidence on long-term outcomes of the UK MRC CLASICC trial after 5 years of follow-up. They described no difference in the overall survival, disease-free survival, local or distant recurrence between laparoscopic resection and open resection. Long-term quality of life was also comparable between groups. These data, together with other multicenter randomized trials[9,10,26] and meta-analyses[12,27,28], are applied not only for colonic caner but also for rectal cancer. As already mentioned, the steep learning curve for laparoscopic colorectal surgery may have a major effect on unimproved oncologic outcomes. Expert surgeons who participated in the trials at that time were relatively inexperienced. Unexpectedly very high conversion rates from the 3 multicenter prospective trials also confirmed this hypothesis: COST, 21%; COLOR, 17%; CLASICC, 29%.[29–31] However, the up-to-date trial by more experienced laparoscopic surgeons is still debatable if better cancer long-term outcome can be expected from laparoscopic colorectal surgery.

There is conflicting data on the conversion rate, which may affect morbidity, mortality, and overall survival. Some studies have suggested that conversion does not influence outcome.[32] Casillas *et al*[33] reported a case-match study from the Cleveland Clinic with 51 (12%) cases converted to open surgery from 430 laparoscopic colectomies performed between 1999 and 2002. The converted cases were matched for operation and age. They found that conversion does not result in inappropriately prolonged operation times, increased morbidity or length of stay, increased direct costs, or unexpected readmissions compared with similarly complex laparotomies. Other investigators[34,35] found a correlation between conversion and survival disadvantages. Data from 5 years of follow-up in the CLASICC trial[25] also demonstrated this clear survival disadvantage. The adverse impact of conversion was significant only for overall survival not disease-free survival. This finding is not attributable to a surgeon-related factor. Although advanced cancer pathology, which was cited as the most common reason for conversion, other reasons (*e.g.*, obesity, technical difficulties, complication) appear to have a bad outcome independent of surgical experience.

Port site recurrence had been one of the major concerns for laparoscopic surgery for colorectal cancer. This unusual pattern of recurrence was first reported in 1991.[36,37] The incidence from case series ranged from 1% to 21%, and 80% of cases presented within 12 months of surgery.[38] The incidence from open surgery is 1.1% ± 1.5%.[39] This type of recurrence in laparoscopic colorectal surgery for malignancy might be overstated. Data reported from prospective voluntary audit from 1992 to 1995 showed an incidence of 1.1%, which is similar to open surgery.[40] It also appeared that these types of recurrences are not observed in the latest updates from large randomized control trials: COST, 0.5%; COLOR, 1.3%; Barcelona trial, 0.9%.[29,31,41]

Experimental[42] and clinical data from single-center, nonrandomized, and largely heterogeneous studies[43–47] support that adhesion formation was reduced after the laparoscopic procedure. Incisional hernia is also a cause of postoperative morbidity and mortality. Several studies have suggested that the rate of incisional hernia was reduced after laparoscopic colorectal surgery[43,45] owing to the absence of a large abdominal wound.[48,49] The MRC CLASICC[50] reported long-term complications in 411 patients—adhesive intestinal obstruction and incisional hernia. The results did not confirm that laparoscopic surgery reduced the rate of adhesive intestinal obstruction and incisional hernia after colorectal cancer surgery. Trends suggested that a reduction in conversion to open surgery and elimination of port site hernias may produce such an effect.

Rectal Cancer

According to anatomic limitation, laparoscopic surgery for rectal cancer involves several challenges that lead to a longer learning curve when compared with laparoscopic colonic surgery. Laparoscopic surgery for rectal cancer is limited to specially trained surgeons, as a result the reports for this procedure are scanty. Better visualization with the

laparoscopic approach for rectal dissection reduced blood loss and surgical stress, which also leads to faster recovery.[51] However, laparoscopic surgery for rectal cancer is still not universally accepted and concerns persist regarding the adequacy of oncologic resection. The CLASICC trial[25] reported a nonsignificant increased rate in radial resection margin positive in patients undergoing laparoscopic anterior resection (6.3% for open resection versus 12.4% for laparoscopic resection). This also did not affect the difference in local recurrence rate at the 5-year follow-up. These data are reassuring—laparoscopic surgery for rectal cancer is feasible with benefits of shorter outcomes and comparable long-term oncologic outcomes.

Many investigators have called for a change in the technical approach of the abdominoperineal resection (APR). The remaining difference in local recurrence rate between rectal cancer treated by an anterior resection and those patients undergoing APR, which carries an 8.8% increased risk, relates to the anatomic location of the tumor. The introduction of cylindric APR is now well recognized to rectify the situation.[52] This difference has been attributed, in part, to the smaller tissue volume around the tumor and the higher rate of cancer at circumferential resection margins (CRM) after APR.[53–55] A recent multicenter study reported by West *et al*[56] comparing 176 extralevator APR from 11 European colorectal surgeons to 124 standard APR from 1 United Kingdom center demonstrated significant more removed tissue from outside the smooth muscle layer per slide (median area 2120 versus 1259 mm^2; $P < 0.001$) leading to a reduction of circumferential involvement (from 46.6% to 20.3%; $P < 0.001$), and intraoperative perforation (from 28.2% to 8.2%; $P < 0.001$). However, extralevator surgery was associated with an increase in perineal wound complications (from 20% to 38%; $P = 0.019$). This is interesting when compared to a report from Memorial Sloan-Kettering[57] in 2007. One hundred nine patients with locally advanced rectal cancer who underwent preoperative chemoradiotherapy followed by total mesorectal excision (TME) were studied. A complete pathologic response was found in 16% of patients. In patients with residual tumor, the median CRM was 10 mm. This was similar to the patients undergoing either low anterior resection or standard APR. There were only 2% of patients who had CRM of less than 1 mm.

Genitourinary dysfunction results in significant morbidity when it occurs after rectal resection. Studies comparing differences in rates of genitourinary dysfunction after laparoscopically assisted or open rectal cancer resections are limited. Quah *et al*[58] reported no statistically significant difference in bladder dysfunction between laparoscopically assisted and open TME for rectal cancer. However, impotence and ejaculation dysfunction had significantly higher rates with the laparoscopic resection. A study from the United Kingdom[59] also reported a trend toward male sexual dysfunction. However, it was also stated that laparoscopic rectal resection did not adversely affect bladder function. Nerve identification during resection may reduce the rate of postoperative genitourinary dysfunction.[60–62] Junginger *et al*[60] demonstrated in their study of 150 patients who underwent TME for rectal cancer that intraoperative visual inspection of the pelvic autonomic nervous system was achieved 72% of the time. Patients who had complete identification of the pelvic autonomic nerves experienced a significant reduction in postoperative urinary dysfunction.

Robotic Surgery

Limitations inherent in conventional laparoscopic surgery can be overcome by the use of robot. The clear advantages of robot are increased dexterity of instruments, precision, 3-dimensional visuals, a steady camera, and intuitive movements that may help obtain better oncologic and overall surgical outcomes.[63,64] It has been well documented that robotic surgery has passed it infancy for some subspecialties (*e.g.*, urology and gynecology). The data have shown the equality and sometimes superiority of robotic surgery versus conventional laparoscopic surgery.[65–69]

Reports on robotic surgery for colorectal cancer are still limited. Potential advantages of the robot in colorectal surgery are similar to those in other fields: less operative blood loss, better oncologic technical dissection in rectal cases, and increased ease of dissection in a confined space. Laparoscopic TME is limited both by the rigidity of the instruments and the restricted range of motion for the surgeon. The robot overcomes these limitations and allows for more precise oncologic dissection.[70] The high conversion rate of laparoscopic surgery for rectal cancer ($\leq$30%)[10] may have an advantage in implementing robot surgery. Three-dimensional visualization also is providing the ability of better nerve sparing TME.[71] Baik *et al*[72] reported on a randomized controlled trial of 36 patients: 18 who underwent robotic low anterior resection using the da Vinci Surgical System, and 18 patients who under-

went conventional laparoscopic low anterior resection. No difference was found in operating time, hemoglobin level change, conversion rate, or quality of the specimen between the 2 groups. The significant difference was demonstrated in the average length of stay (6.9 ± 1.3 days in robotic resection group; 8.7 ±1.3 days in laparoscopic group; $P < 0.001$).

Repositioning is a major obstacle for robotic surgery when more than 1 field of dissection is required. The hybrid procedure—laparoscopic splenic flexure mobilization and vascular pedicle transection combined with robotic total mesorectal excision—may be 1 solution to be considered. However, operative time may be reduced by an experienced team or by using the nonrepositioning technique, as reported by Hellan *et al.*[73]

In conclusion, laparoscopic surgery for colorectal cancer has become popular among patients and surgeons. In recent years, it has been confirmed that laparoscopic surgery for colon cancer demonstrates better short-term outcome, oncologic safety, and equivalent long-term outcome. For rectal cancer, laparoscopic surgery can be more complex depending on the tumor location. TME, sphincter preservation, and autonomic pelvic nerve preservation provide even more challenge for colorectal surgeons to minimize local recurrence, and at the same time, to maximize quality of life for the patients. Unlike laparoscopic surgery for colon cancer, there is not enough evidence to reach any conclusion on its long-term oncologic outcome. Large randomized control trials need to be conducted to assess the long-term outcome of laparoscopic surgery for rectal cancer to reach the same conclusions.

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