

# Current surgical considerations for colorectal cancer

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Submitted Mar 06, 2013. Accepted for publication Apr 08, 2013.

doi: 10.3978/j.issn.2304-3865.2013.04.01

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## Background

Colorectal cancer is the second leading cause of cancer-related deaths in the United States each year. Among men and women, it is the third most common cancer following lung cancer, prostate and breast cancers, respectively. In recent years, It has been estimated that in 2012 there were more than 100,000 new cases of colon cancer and more than 40,000 cases of rectal cancer (1,2). Fortunately, both the incidence and mortality of colorectal cancer have declined steadily in the past three decades. This has been largely attributed to more effective screening programs and improvements in treatment modalities (1,2). Surgical resection offers the best chance of achieving cure, but the management of colorectal cancer often requires a multidisciplinary approach, which has been pivotal in achieving better patient satisfaction and outcomes.

## Surgery for colon cancer

### Overview

The diagnosis of an invasive colon cancer requires a complete staging work up that includes endoscopic evaluation of the entire colon, baseline imaging of the abdomen and chest to rule out distant spread, and routine labs including a baseline carcinoembryonic antigen (CEA) level (1). Colectomy should be offered to those patients with resectable tumors that have no evidence of distant metastasis. The extent of the colectomy is primarily determined by the location of the tumor and the blood supply to that segment of bowel. Adequate margins ( $\geq 5$  cm) should be gained proximal and distal to the primary tumor and should include the associated mesentery containing regional lymph nodes. Tumors that are adherent to adjacent

structures should be resected *en bloc* to ensure complete removal of the cancer. Adjuvant chemotherapy is offered to patients with evidence of lymph node metastasis.

### Laparoscopy for colon cancer resections

Traditionally, colectomies have been approached via a laparotomy with good clinical outcomes. However, the advent of laparoscopy has revolutionized surgery and, in appropriate patients, is now a popular alternative for the surgical management of colorectal disorders. This has been primarily due to the substantial short-term benefits, which include less postoperative pain, earlier return of bowel function, and shorter hospital stays (3,4). While laparoscopy has been shown to be consistently safe and feasible for a variety of gastrointestinal pathology, initial enthusiasm about employing a minimally invasive approach for colorectal cancer was tempered by a steep learning curve as well as reports of wound and trocar site recurrences (4). Therefore, the steady implementation of this approach has required balance of the potential short-terms benefits with preservation of oncologic outcomes. These criticisms were addressed with initial data reported in retrospective studies and later confirmed by larger, randomized clinical trials, which demonstrated that laparoscopy does not compromise oncologic outcomes or increase perioperative complications (3,5-8).

The Barcelona trial was among the first randomized, prospective, single-institution trials, which compared laparoscopic colectomy to the conventional open approach. From 1993 to 1998, 206 patients were enrolled (105 patients in the laparoscopic arm) with cancer-related survival as the primary endpoint. The authors found that laparoscopy was more effective than open surgery with respect to morbidity,

hospital stay, tumor recurrence, and cancer-related survival. A follow up to this study with longer follow up data (median 95 months) comparing laparoscopic and open colectomies demonstrated that the overall survival and recurrence rates favored the laparoscopic group, but did not reach statistical significance (5,6).

A larger prospective, randomized, multicenter trial by the Clinical Outcomes of Surgical Therapy (COST) Study Group showed similar long-term results. Between 1994 and 2001, 872 patients (435 patients in the laparoscopic arm) were randomized. The median follow-up time was 52 months and the primary endpoint was time to tumor recurrence. Analysis at three years demonstrated similar recurrence rates in the laparoscopic and open groups, 16% and 18%, respectively. Additionally, there was no difference in overall survival (86% in the laparoscopic group *vs.* 85% in the open group). The authors have also recently published 5-year data from this original cohort demonstrating that overall and disease-free survival were similar between the two treatment groups. Additionally, overall recurrence rates remain similar (19.4% laparoscopic group; 21.8% open group) (7,9). These survival data have been confirmed in the slightly larger European multicenter Colon cancer Laparoscopic or Open Resection (COLOR) trial that was designed to evaluate disease-free survival and overall survival 3 years after laparoscopic or open resection for colon cancer. For all stages, the 3-year overall and disease-free survival rates were not significantly different between groups. Local and distant recurrence rates were also similar (8). It should be noted that lymph node harvest is also similar between open and laparoscopic groups. The main criticisms of these trials center on the probability of selection bias when offering a laparoscopic approach to those with cancer.

In fact, those with smaller tumors (amenable to smaller incisions) and those with tumors that involve only the colon (T3 and below) are most likely still the best candidates for laparoscopy.

#### ***Postoperative complications and quality of life (QOL)***

While the short-term benefits of laparoscopy have been well documented and reproducible across practices, many also postulate that laparoscopy also facilitates fewer complications than traditional open surgery. While the primary endpoints of the aforementioned clinical trials were tumor recurrence and survival, these initial data also offer some information on intraoperative and perioperative

complications. The Barcelona Trial found that the patients in the laparoscopic group had significantly less intraoperative blood loss and postoperative morbidity (5). However, the COST study and the COLOR trial did not demonstrate any significant difference in postoperative morbidity or 30-day mortality. The rates of intraoperative complications, rates or severity of postoperative complications, rates of readmission, and the rates of reoperation were similar between groups (7,8). Tjandra *et al.* recently published a systematic review of 17 randomized trials of laparoscopic resections for colon cancer, which analyzed 4,013 patients. The authors found that there were no significant differences in the overall complication rate. However, laparoscopic surgery had significantly lower perioperative mortality as well as lower wound complications (infection and dehiscence) (10).

Overall quality of life parameters after colorectal cancer resection have also been fertile ground for study and there is significant data to suggest that patients undergoing laparoscopic colectomies have modest improvements in these parameters. Analysis of the responders from the COST study (428 patients) showed short-term benefits according to the global rating scale score at 2 weeks after surgery. No difference was found between the groups using the other instruments or at other time points (2 days and 2 months) (11). Long-term follow up of the patients in this study found that at 18 months after surgery, patients who underwent laparoscopic resections had significantly greater improvement from baseline in the global QOL rating and total QOL index (QLI) (12).

#### ***The role of surgery in metastatic colon cancer***

Up to 25% of patients with colon cancer will present with synchronous colorectal cancer metastasis and of these, only approximately 10-20% will have lesions that are ultimately resectable (1,13). More commonly, patients will develop metastasis in the interval after resection of the primary colon tumor with the liver being the most commonly involved organ.

Patients with colorectal liver metastasis (CLM) should have a complete evaluation with the coordinated care of a multidisciplinary team—including oncologists, radiologists, colorectal and hepatobiliary surgeons in order to assess resectability. Surgical resection of these metastatic lesions should only be considered in medically fit patients with good performance status, if obtaining negative margins is feasible and adequate functional liver reserve (>20%) can be maintained. While surgery is the gold standard

for resectable disease, other potential treatment adjuncts, including radiofrequency ablation (RFA) and hepatic artery infusion (HAI) of chemotherapy, have been employed. Neither of these other modalities alone has been shown to be as effective as chemotherapy and surgical resection, which have reported 5-year survival rates up to 40% (1,14-16).

While the benefit of surgery and chemotherapy are clear, considerable controversy still remains in the optimal sequence of these treatments. Proponents for a surgery-first approach cite the potential for progression of disease and chemotherapy-associated liver injury as reasons to forego neoadjuvant chemotherapy; however, there is limited data that supports that this approach confers an advantage in overall survival (17). Contradictory data has been presented in the EORTC 40983 trial, which compared perioperative chemotherapy (pre- and postoperative) with surgery alone. The authors found that there was an 8.1% improvement in the 3-year progression-free survival with perioperative chemotherapy. However, postoperative complications were more frequent in the chemotherapy group (18).

The management of patients with synchronous, resectable CLM has also been subject to controversy. The traditional approach has been resection of the primary colon tumor followed by adjuvant chemotherapy and staged hepatic resection; however, more recent studies have shown that simultaneous colon and liver resections are safe in specialized centers and appropriately selected patients (19). This combined approach is advantageous in sparing the patient the morbidity of additional surgery and eliminating potential progression of liver disease during recovery from primary colorectal surgery. More recently, a reverse strategy, or liver-first approach, has been proposed for early management of metastatic liver disease, which proponents assert optimizes the potential for cure (20). While the data related to this approach is not as robust, the greater body of study on the management of synchronous CLM suggests that the approach should be individualized. The patient's functional status and burden of disease must be assessed in order to balance surgical risk and oncological benefit (21).

In patients with asymptomatic primary colon tumors and unresectable minimally symptomatic metastatic disease, chemotherapy is the mainstay of treatment. The available data supports that there is little benefit in resection of the primary tumor. Doing so risks delaying necessary chemotherapy and offers no survival advantage. In 2009, Poultsides *et al.* reported a series of 233 patients with unresected primary tumors and synchronous metastasis receiving chemotherapy. They found that 93% of patients

did not require any surgical palliation of their primary tumor (22). Clearly, if the patient is exhibiting signs and symptoms of obstruction, which cannot be controlled with dietary changes alone, then palliation with resection is required. This seems to be the minority of cases.

## **Surgery for rectal cancer**

### *Overview*

The surgical decision-making process for rectal cancer is complex and often requires a multidisciplinary approach. While the pathophysiology of rectal cancers is believed to be identical to that of colon cancers, the anatomic location within the bony pelvis offers unique surgical challenges. Over the past century, an improved understanding of the histopathology as well as patterns of recurrence has afforded significant strides in the treatment of rectal cancer (23).

The initial management of rectal cancer requires complete evaluation of the local extension as well as distant spread. Unlike colon cancers, rectal tumors are more easily accessible by physical examination, which can provide added information on size, the degree of fixation, and location (2). Ultimately, the choice of treatment hinges primarily on the location of the tumor in the rectum and the depth of local invasion. Therefore, modalities such as endorectal ultrasound (ERUS) and pelvic MRI are often used for local staging of tumor depth and nodal involvement (24,25). Patients with evidence of locally advanced cancers in the distal and mid rectum (defined as Stage IIA and beyond) are now routinely referred for neoadjuvant chemoradiation, which has been shown to decrease rates of local recurrence (23,26). This paradigm has been challenged and the Alliance for Clinical Trials in Oncology is currently accruing patients for a phase II/III trial of neoadjuvant chemotherapy with the selective use of radiation in locally advanced rectal cancer. Treatment of upper rectal cancers (those above the peritoneal reflection or at the rectosigmoid junction are more controversial. Data suggests that a more individualized approach may be needed for these patients, with bulky large tumors getting neoadjuvant and smaller ones getting treated primarily with surgery.

### *Total mesorectal excision*

Historically, local and radical resections for rectal cancers have been plagued by significant patient morbidity and high local failure rates (25). In 1982, Heald *et al.* named the concept of total mesorectal excision (TME), which has

drastically changed the surgical approach to proctectomy. An appropriate TME requires sharp dissection in the areolar, presacral plane between the mesorectal envelope (fascia propria) and the adjacent pelvic structures (27). For distal rectal cancers, TME is performed circumferentially down to the pelvic floor muscles incorporating the entire mesorectum. This allows complete removal of the rectal tumor and the regional lymph nodes while ensuring a negative radial margin and preserving the autonomic nerves (23,24,27). This has been shown to be an integral part of achieving lower local recurrence. A prospective, randomized trial, organized by the Dutch Colorectal Cancer Group, which was among the first to include surgical quality control for TME, reported a local recurrence rate of 8.2% at 2 years (10.9% at 6-year follow-up) in patients who underwent complete rectal cancer resection alone (28,29). Proximal rectal tumors, as mentioned, often do not require a total mesorectal excision since lymphatic spread is generally limited to within a few centimeters of the tumor. In these cases a partial mesorectal excision can be performed after ensuring an adequate distal margin. Bulky large proximal tumors may, however, benefit from preoperative chemotherapy and radiation in selected patients.

### ***Radial and distal margins***

Achieving the appropriate distal and radial margins is often not problematic in segmental colon cancer resection, but these are critical concepts in the surgical management of rectal cancer. A high-quality TME has improved our ability to achieve negative radial or circumferential resection margins (CRM), which has been shown to be an important predictor of local recurrence, distant metastasis, and survival (27,30,31). A positive CRM is defined as tumor extension to within 1 mm of the radial tissue edge and can occur due to direct tumor extension, mesorectal tumor deposits, involved mesorectal lymph nodes, or inadequate surgical dissection. In 2002, Wibe *et al.* reported a series of 686 patients who underwent proctectomy without adjuvant radiation, which underscored the significance of the circumferential margin. After a median follow up of 29 months, they found that the overall local recurrence rate for those with a positive CRM was 22% as compared to 5% for those with a negative margin (>1 mm). The CRM was also an independent risk factor for distant metastasis (hazard ratio 4.7) and mortality (hazard ratio 3.7) (32).

The ideal distal margin in rectal cancer surgery remains relatively controversial, especially in this era of sphincter-

preserving procedures. A 5-cm distal margin had been previously advocated; however, this has been largely refuted based on pathology data demonstrating limited intramural spread of low rectal cancers (33,34). The degree of intramural and extramural spread is crucial in determining the ideal distal resection margin. In one of the larger retrospective review on the subject, Shirouzu *et al.* reported a series of 610 patients who underwent rectal cancer resections and found that only 10% had distal intramural spread. Moreover, the majority of these cases were within 2 cm of the distal border of the primary tumor. As a result, the authors postulated that a distal margin of 1 cm would be appropriate for most rectal cancers (34). Based on the available data, current recommendations suggest that a 2-cm distal margin is adequate for most rectal cancers. Smaller tumors that are low in the rectum may be resected with an acceptable margin of 1 cm (35,36).

### ***Sphincter-preserving surgical procedures for rectal cancer***

The extent of surgical resection for rectal cancer largely depends on the location of the mass in the rectum, the degree of local invasion, and the patient's baseline sphincter function and medical co-morbidities (23,26,35). For tumors in the mid and upper rectum a low anterior resection (LAR) is generally the ideal approach. During the procedure, a TME dissection is carried out after the sigmoid colon and upper rectum are dissected free from the peritoneal attachments. The inferior mesenteric artery, which is the principal feeding vessel, is ligated and divided proximally. The distal rectum is left in place after ensuring a margin 4-5 cm distal to the inferior edge of the tumor. A colorectal anastomosis is then created using a circular stapler; however, a hand-sewn anastomosis is also possible. Tumors in the lower rectum can also be considered for LAR as long as a 1-2 cm distal margin can be obtained adequately. Intestinal continuity is then restored with a stapled or hand-sewn coloanal anastomosis. The potential for pelvic sepsis due to anastomosis leak can be mitigated by a temporary loop ileostomy in those patients with low pelvic anastomoses and those that have required preoperative radiation.

Many patients experience disordered bowel function after LAR, typically characterized by increased stool frequency, bowel fragmentation, fecal urgency, and incontinence, which has been termed "low anterior resection syndrome" (37). The incidence is variable, as there are no validated tools for diagnosis, and the etiology is likely multifactorial. Reported rates range from 20-50% and possible causes include sphincter

injury, decreased rectal compliance, or neuropathy (37). Alternative reconstructive techniques to the straight end-to-end anastomosis following TME with coloanal anastomosis including colonic J-pouch and transverse coloplasty have been explored in attempt to improve postoperative function. In these cases, randomized trials have shown that the colonic J-pouch results in superior postoperative bowel function for at least 18 months after surgery, after which function becomes similar to the end-to-end anastomosis (38). The ability to do this from a technical standpoint, however, is quite dependent upon the patient's body habitus with a narrow pelvis often precluding the safe formation of a colonic pouch.

### ***Abdominoperineal resection***

Patients with pre-existing fecal incontinence or with very low rectal cancers will ultimately require an abdominoperineal resection (APR). During the abdominal phase of the procedure, the TME dissection is carried out down to the pelvic floor muscles and a permanent colostomy is created using the descending colon. During the perineal dissection, the anus and the sphincter complex are excised widely in continuity with the proximal specimen. High rates of bowel perforation, positive circumferential margins, and subsequently local recurrence have been reported with conventional APR (39-41). Therefore, much emphasis has been placed recently on achieving a cylindrical resection, which avoids narrowing of the resected specimen at the level of the levator ani muscles. This approach has been shown to reduce the risk of local recurrence without increasing local complications (42).

The primary closure of the perineal wound has been plagued with significant complications, especially in the setting of preoperative radiation. Infection and wound dehiscence are among the most frequent complications with incidences that range from 10-40% in the existing literature (43). As a result, efforts to mitigate these complications with the routine use of rotational myocutaneous flaps have been proposed with variable success (43,44). Currently, there is no standard recommendation for the use of myocutaneous flaps in the reconstruction of the perineal wound. Individualizing treatment is required—those at higher risk of perineal wound complications (obese, diabetic, malnourished) may be selective candidates for flap closure.

### ***Minimally invasive surgery for rectal cancer resections***

Laparoscopy for rectal cancer resection has been approached with as much enthusiasm as initial studies for

colon cancer; however, the available data is not as mature. While a minimally invasive approach to proctectomy with laparoscopy, or even robotically, is more challenging and costly, the available technology offers the added benefit of better visualization and more precision than traditional open surgery. Initial nonrandomized studies demonstrated that laparoscopic proctectomy was safe and feasible with similar short-term benefits and oncologic outcomes (45). This has been confirmed in subsequent small, randomized trials; however, sufficient long-term data is lacking. The American College of Surgeons Oncology Group (ACOSOG) is nearing completion of a large phase III prospective randomized trial comparing laparoscopic-assisted resection versus open resection for rectal cancer which should further illuminate this subject. However, recent meta-analyses of the available randomized clinical trials comparing laparoscopic to open rectal cancer resections conclude that laparoscopy is associated with significantly lower rates of intraoperative bleeding and postoperative blood transfusion, quicker return of bowel function and shorter hospital admission (46,47). Additionally, when compared with open TME, there is no difference in the number of lymph nodes harvested, involvement of CRM, local recurrence, 3-year overall survival, and disease-free survival for rectal cancer (48). The results of larger multicenter, randomized clinical trials are pending. Complicating adoption of this technology is the large learning curve needed to implement these techniques in practice. Often “hybrid” open/laparoscopic approaches are utilized with some success to keep incision sizes small and mimic the advantages of a total laparoscopic approach in less time.

### ***Local excision for early rectal cancers***

In carefully selected patients, local excision has generally been considered as an acceptable treatment option for small, early (T1 and T2) cancers in the mid to distal rectum that have favorable histologic features (well-differentiated, absence of lymphovascular invasion, superficial submucosal invasion) (49,50). It has also been proposed in patients that are unsuitable for radical surgery as the resection of these lesions with traditional transanal surgery, or transanal endoscopic microsurgery (TEM) for more proximal tumors, is associated with lower patient morbidity.

Traditional transanal excision (TAE) is reserved for small tumors within 8 cm of the anal verge that are readily accessible. A full-thickness resection through the bowel wall into the perirectal fat is carried out with a minimum of

1-cm margins. In some cases, prominent lymph nodes can be resected but generally a thorough lymphadenectomy is not feasible, which is a major concern in more advanced tumors; therefore, preoperative patient selection and accurate staging is critical. The mucosal defect is then closed primarily. More proximal tumors can be accessed using TEM, which was introduced in the early 1980s as a minimally invasive alternative. The operating platform consists of an operating proctoscope and specialized microsurgical instruments that allow dissection in the upper rectum for lesions that previously could only managed with abdominal surgery (50).

The initial studies of local excision for early rectal cancers demonstrated that this procedure was associated with high local failure rates (17% for T1 tumors and up to 46% for T2 tumors) (51,52). In 2000, Mellgren *et al.* reported a retrospective study comparing 108 patients T1 and T2 rectal cancers excised locally with 153 patients who underwent radical resection. They found that local recurrence was significantly higher after local excision for both T1 and T2 cancers as compared with standard resection (T1: 18% *vs.* 0%, T2: 47% *vs.* 6%). Additionally, overall 5-year survival decreased significantly after local excision of T2 cancers as compared with standard resection (81% *vs.* 65%) (51). These findings were confirmed in a larger, retrospective study using the National Cancer Database. In this report, local recurrence after local excision was 12.5% for T1 cancers and 22.1% for T2 cancers. These were both statistically higher than rates for standard resection. Interestingly, despite these data, the authors also found that the use of local excision had increased significantly from 1989 to 2003 (53).

Salvage surgery may be possible for local recurrence after local excision but often not without significant morbidity. It often involves multimodality treatment including preoperative chemoradiation and extensive surgery (multivisceral resection or pelvic exenteration). Sphincter preservation is not always possible and overall 5-year survival is relatively poor (54).

These data suggest that in appropriately selected patients with T1 rectal cancers, local excision has similar acceptable overall survival rates as compared with standard resection. However, patients should be counseled that the reduced short-term morbidity of local excision is also associated with significantly higher rates of local and overall recurrence. Local excision of T2 rectal cancers has not been routinely recommended outside of clinical trials. The preliminary results of the ACOSOG Z6041 trial of

neoadjuvant chemoradiation followed by local excision of T2 cancers have just been reported. The authors found that this strategy resulted in high rates of complete response (44%) and 64% of patients had their tumors downstaged. Negative resection margins were achieved in 99% of the included patients; however, the chemoradiation toxicity and postoperative complications were not insignificant. Sixty-two patients (72%) were able to complete chemoradiation per protocol and 39% of patients developed grade 3 adverse events or higher. Perioperative complications occurred in 58% of study patients and the most common grade 3 adverse events included rectal pain, bleeding, infection, urinary retention, and anal incontinence (55).

### *Management of locally recurrent rectal cancer*

Despite the advances in chemoradiation therapy and surgical technique, local recurrence occurs in up to 10% of cases (56,57). The prognosis is generally poor and is only slightly improved with additional adjuvant treatment alone; therefore, radical surgical resection offers the only possibility for cure. The patterns of local recurrence are variable but may occur at the anastomosis or within the pelvis with attachments to the pelvic sidewall(s), bony structures, or adjacent pelvic organs. There is currently no accepted universal classification to define local rectal cancer recurrence; however, important features include patient symptoms, anatomic location, and the degree of fixation (57).

Patients who are suspected to have locally recurrent disease require a thorough endoscopic and radiographic evaluation to rule out distant metastasis and to define the degree of local involvement. Suspicious lesions should be biopsied with the help of useful diagnostic modalities including pelvic MRI, CT scan, or PET scan. Urologic and gynecologic exams should be performed as indicated.

Surgical resection is often complex and requires careful preoperative planning incorporating a multidisciplinary team (colorectal surgery, urology, gynecology, orthopaedics, and oncology). Patients that have not previously received chemoradiation should have neoadjuvant treatment followed by the anticipated resection, while those that have had previous radiation should proceed to surgery, if medically fit. Intraoperative radiation therapy (IORT) or brachytherapy may be indicated based on the degree of residual disease after resection. Extended resection should be performed *en bloc* with any contiguous organ to ensure no residual disease remains (57).

A recent series of 304 patients with locally recurrent rectal cancer undergoing subsequent curative resection found an overall 5-year survival rate of 25%. Preoperative external beam radiation was given in 244 patients (80%) and IORT in 131 patients (43%). Negative resection margins were achieved in only 138 patients and 5-year survival was significantly improved in these patients as compared with those that had residual gross or microscopic disease (32% vs. 16%). Extended resections (involving at least one surrounding organ) were performed in 130 patients and were associated with a higher complication rate; however, survival was not significantly different from those that underwent limited resections. Symptomatic pain and fixation in more than one location were associated with a poor prognosis (58).

## Conclusions

Colorectal cancer remains a significant cause of morbidity and mortality worldwide. Surgery is the mainstay of treatment for cure in these patients but the overall management of these cancers often requires a multidisciplinary approach. The advent of laparoscopy, robotic and other surgical technology, as well as an increased awareness of the importance of operative technique, have revolutionized the surgical management of this disease. Likewise, innovation in newer chemotherapy regimens and radiation therapy have increased median survival and decreased local recurrence in advanced disease. Despite these advances, there is ample room for further improvement.

## Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

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**Cite this article as:** Aarons CB, Mahmoud NN. Current surgical considerations for colorectal cancer. *Chin Clin Oncol* 2013;2(2):14. doi: 10.3978/j.issn.2304-3865.2013.04.01