

Surgical management of colorectal cancer: A review of the literature

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Abstract

Background Colon cancer management continues to evolve with significant advances in chemotherapy, surgical technique and palliative interventions. As the options of therapy have improved, so have the challenges of management of primary colon cancer.

Review A review of historical and up to date literature was undertaken utilising Medline/PubMed to examine relevant topics of interest-related to the surgical management. Enhanced knowledge of genetics associated with colon cancer has improved our care of patients with hereditary colon cancer syndromes. Additionally, traditional approaches to surgical intervention for primary colon cancer have been questioned and will be discussed in this review including the role of laparoscopy, use of mechanical bowel preparation, management of the primary tumour in the face of metastatic disease, as well as the role of palliative intervention in select patients.

Conclusion Colon cancer has seen improvement and expansion of therapeutic approaches to primary colon cancer. Laparoscopy and palliative interventions have become widely accepted with level I evidence to demonstrate good patient outcomes. Traditional dogma with mechanical bowel preparation has been challenged and debunked with

regards to the efficacious benefits previously accepted. The management of the primary tumour has now become increasingly complex as it appears to be a reasonable approach to manage the primary tumour non-operatively in select cases of extracolonic disease requiring management.

Keywords Colorectal cancer · Bowel preparations · Minimally invasive colectomy · Stent

Introduction

Colorectal cancer (CRC) comprises 10% of the over 500,000 annual cancer deaths in the United States, making it the third most common cancer in men and women. In 2009, it is projected that 146,970 new cases of CRC will be diagnosed with 49,920 dying of disease [1]. Over the last 7 years, CRC death rates in men and women have decreased steadily (17% and 24%, respectively). These advances may be attributed to a better understanding of the disease genetics, improved surveillance, technical advances in the operations, increasing indications for the use neoadjuvant and adjuvant chemotherapy, and better palliation.

As operative and non-operative therapies have evolved and improved, the management of CRC has become multidisciplinary and more complex, particularly in the face of advanced disease. The role of surgical intervention, or at least the timing of it, is changing. Herein, we will review many of the evolving issues regarding surgery for CRC. Specifically, we will discuss the current recommendations related to role of colectomy in hereditary CRC syndromes, bowel preparations, laparoscopic surgery, management of the primary lesion in the face of metastatic disease, role of endoscopic interventions for palliation and treatment of

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obstructive symptomatology, and briefly discuss adjuvant and neoadjuvant therapies.

Hereditary colorectal cancer syndromes

The two major syndromes which make up approximately half of the familial cases of CRC are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). FAP is an autosomal dominant disease caused by mutations in the adenomatous polyposis coli (APC) gene. Polyps can be found anywhere throughout the gastrointestinal tract and the disease is characterised by the presence of hundreds of adenomatous polyps, 100% penetrance, and a 100% risk of developing colon cancer by age 40 [2, 3]. Screening for at risk family members should begin at puberty and consists of genetic testing to confirm risk and/or biennial flexible sigmoidoscopy [4]. The timing of surgery is often dependent upon the degree of polyposis [5]. Patients with mild polyposis may have their surgery delayed until their mid to late teens given the lower risk of earlier cancer development. However, patients with heavy polyp burden run a greater risk of the development of cancer and may need their surgery sooner [5, 6]. Surgical management options for these patients include total proctocolectomy with ileostomy (TPC), total abdominal colectomy with ileorectal anastomosis (IRA), and total proctocolectomy with ileal pouch anal anastomosis (IPAA). TPC is reserved for those patients who have poor sphincter function or patients who are not able to tolerate multiple bowel movements daily. IRA is occasionally offered to those patients who have less rectal disease, but it still carries an increased chance of developing a rectal cancer [7]. IPAA is considered the gold standard by removing all colorectal tissue at risk while maintaining sphincter function and bowel continuity. Lifelong surveillance for recurrence with flexible endoscopy is still required in patients undergoing IRA and IPAA [6].

HNPCC or Lynch syndrome, is an autosomal dominant disorder with high penetrance in mutation carriers caused by germline mutations in one of several DNA mismatch repair (MMR) genes. These are characterised by an early onset of CRCs, a predominance of developing right-sided colon cancers, metachronous lesions, and both benign and malignant extracolonic tumours [4]. Determining whether a patient has HNPCC is based on a thorough history utilising the Amsterdam criteria requirement that there be three relatives (one must be a first degree relative of the other two) with an HNPCC-related cancer, that two or more successive generations be involved, and that at least one relative have a CRC diagnosed before the age of 50 [8, 9]. CRC can occur in 80% of patients with MMR mutation and endometrial, gastric, urinary tract and ovarian cancers are also seen in this group [10]. Screening takes into account the possibility of both colonic and extracolonic malignancies with surveillance

colonoscopy every 1–2 years beginning at the age of 20–25 or 10 years prior to the age of CRC onset in a first degree relative, then annually after the age of 40. Females at 25–35 years of age should undergo annual transvaginal ultrasonography, endometrial aspirations, and have CA-125 levels checked. Oesophagogastroduodenoscopy can be utilised in patients to screen for gastric cancer and ultrasound and urine cytology can be utilised to screen for urinary tract malignancy [11]. Surgical management for patients with HNPCC, when elected, includes either a prophylactic total abdominal colectomy with IRA or a segmental colectomy with yearly colonoscopy [12]. Lifelong surveillance with flexible endoscopy is still required in both groups of patients because of the high chance of metachronous cancer.

Preoperative bowel preparation

The use of mechanical bowel preparation (MBP) in combination with oral antibiotics described by Nichols in 1973 was the first major stride in reducing wound infection and outcomes following colorectal surgery [13]. Since the subsequent introduction and routine use of perioperative intravenous antibiotics, however, the role of mechanical bowel preparation has been challenged. In fact, this specific issue has been addressed through more randomised controlled trials (RCTs) than virtually any other subject in colorectal surgery. Over the decades that followed Nichols' initial reports, mechanical bowel preparation continued to be widely used without any supporting data with regards to pelvic abscesses, wound infections, abdominal sepsis, reoperations or death. In a meta-analysis by Slim et al. in 2004, multiple RCTs were examined [14]. No benefit to MBP was seen and, in addition, several trials demonstrated increased morbidity with the use of MBP. In an updated 2009 meta-analysis, Slim et al. examined 14 RCTs with a total of 4,859 patients undergoing colonic resection exclusively without inclusion of rectal cancer patients [15]. These patients were divided into two groups; 2,452 who had MBP and 2,407 who did not. The primary endpoint was leak rate assessment. Secondary endpoints examined complications inclusive of abscesses, wound infections, sepsis, reoperations and death. Results demonstrated no statistically significant difference with respect to leak rates ($p = 0.46$), abdominal abscesses ($p = 0.75$), wound infections ($p = 0.11$), extra-abdominal sepsis ($p = 0.12$), reoperations ($p = 0.63$) or death ($p = 0.70$) [15]. The American Society of Colorectal Surgeons (ASCRS) support this by stating, "All types of mechanical preparation occasionally engender serious complications [16–18]. The balance remains tipped in favour of bowel preparation by the weight of tradition and by the procedure's intuitive appeal to surgeons and patients alike." The only use of routine MBP supported by the ASCRS website guidelines are in cases requiring intraoperative endoscopy.

Minimally invasive surgery

Technical advances in surgical techniques have developed over the last two decades for the treatment of colon cancers ranging from traditional open surgery to laparoscopic surgery and, most recently, robotic surgery. With the advent of these techniques, questions rightfully arise about their efficacy and safety. Robotic surgery for colon cancer is in its infancy and, hence, data is sparse. Therefore, for the purpose of this review, discussion will be limited to the role of laparoscopic surgery versus open surgery for colon cancer.

Three large multi-institutional prospective randomised trials beginning in the 1990s shaped our approach toward minimally invasive surgery for CRC. These included the Clinical Outcomes of Surgical Therapy (COST) Study Group trial in the United States and Canada, the Colon Carcinoma Laparoscopic or Open Resection (COLOR) trial in Europe, and the Medical Research Council Conventional versus Laparoscopic-assisted Surgery in Colorectal Cancer (MRC CLASICC) trial in the United Kingdom.

The COST trial started in August 1994 and ended in August 2001 with accrual of patients with histologically confirmed adenocarcinoma of the colon with the intent to show that laparoscopic colectomy and open colectomy have similar outcomes. The primary endpoint was time to tumour recurrence [19]. Secondary endpoints were disease-free survival, complications, variables related to recovery, and the quality-of-life. Eligible patients consisted of those with a histologically proven solitary colon adenocarcinoma amenable to curative resection by a formal haemicolectomy or sigmoidectomy. Patients were excluded on a basis of locally advanced or metastatic disease, synchronous or previous malignancies, pregnancy, inflammatory bowel disease, familial polyposis, concurrent or previous cancers, tumours located at the transverse colon or rectum, or severe medical illness. Surgery was conducted at 48 institutions by a total of 66 surgeons who demonstrated competency in advanced laparoscopic oncologic techniques. A total of 872 patients were randomised into two groups of laparoscopic versus open surgery. Of these, two patients refused surgery and seven others were ineligible leaving 432 patients in the open arm and 433 patients in the laparoscopic arm that underwent the intended operation. The findings showed that there were no significant differences between either group with respect to time to recurrence, disease-free survival, or overall survival for any stage. A significant difference was shown by shorter hospital stay in the laparoscopic group versus the open group (5 versus 6 days, $p < 0.001$), less use of intravenous narcotics (3 versus 4 days, $p < 0.001$), and less use of oral narcotics (1 versus 2 days, $p < 0.001$) [19]. The laparoscopic group did show a significantly longer operative time in comparison to the open group (150 versus 95 minutes, $p < 0.001$). These findings indicate that laparoscopic

colectomy is a safe, oncologic, operative approach for colon cancer and has other added benefits as well.

The COLOR trial started in March 1997 and ended March 2003. The primary endpoint of the study was disease-free interval at 3 years [20]. Secondary endpoints were short-term morbidity and mortality, number of positive resection margins, local recurrence, port-site or wound-site recurrence, and blood loss during surgery. Eligible patients consisted of those with a histologically proven solitary colon adenocarcinoma amenable to curative resection by a formal haemicolectomy or sigmoidectomy. Patients were excluded on a basis of locally advanced or metastatic disease, synchronous or previous malignancies, obesity (body mass index $>30 \text{ kg/m}^2$), pregnancy, tumours located at the transverse colon or rectum, or if resection of the splenic flexure was anticipated. Surgeons from 27 participating centres were required to have completed at least 20 laparoscopic colectomies to participate and the surgical technique was standardised. A total of 1,248 patients were randomised to open versus laparoscopic surgery, 172 were excluded after randomisation because of the presence of metastatic disease or benign disease. Of 1,076 remaining patients available for analysis (542 open surgery versus 534 laparoscopic surgery), there were no statistical differences in positive resection margins, number of lymph nodes removed, morbidity and mortality [20]. The combined disease-free survival at 3 years for all stages in the laparoscopic group was 74.2% and for the open group was 76.2%. The disease-free survival difference was small supporting the use of laparoscopic colectomy for colon cancer.

The MRC CLASICC trial started in July 1996 and ended June 2002 [21]. The primary endpoints were overall survival, disease-free survival, and local recurrence rates at 3 years. Secondary outcomes were distal recurrence rates, wound/port-site recurrence rates and quality-of-life. Eligible patients consisted of those with histologically proven adenocarcinoma amenable to curative resection by formal haemicolectomy, sigmoidectomy, anterior resection or abdominoperineal resection. Patients were excluded on the basis of tumours located at the transverse colon, contraindications to pneumoperitoneum, acute bowel obstruction, synchronous or previous malignancies in the past 5 years, pregnancy, and any other associated gastrointestinal disease requiring surgical intervention. Seven hundred and ninety-four patients from 27 centres were randomly assigned to 32 surgeons. Both the laparoscopic and open procedures were performed by each surgeon by random assignment. There was no statistical difference in the overall survival (68.4% versus 66.7%), disease-free survival (66.3% versus 67.7%), or 3-year local recurrence rate between laparoscopic and open groups, respectively (8.6% versus 7.9%). This trial concluded similar outcomes in patients undergoing laparoscopic surgery versus open surgery for colon cancer. These well-designed, closely

monitored trials show that laparoscopic resection for CRC is safe with oncologic outcomes similar to open surgery with the benefit of shorter hospital stays, less narcotic usage, and faster recovery. As such, minimally invasive techniques can be considered safe in patients with CRC when utilised by properly trained surgeons.

Unlike the widespread endorsement of many minimally invasive techniques such as laparoscopic cholecystectomy, fundoplication, and oesophageal myotomy, many surgeons were initially reluctant to openly accept laparoscopic colectomy for cancer without level 1 evidence. The above studies clearly show that there is no oncologic disadvantage to a laparoscopic approach and even suggest that there is a modest reduction in length of hospital-stay and postoperative pain. Thus, laparoscopic colectomy is an acceptable modality for the management of colon cancer primary. Its role in more advanced tumours or rectal tumours is still evolving.

Management of colorectal primary for stage IV disease

The management of patients with stage IV CRC has become increasingly challenging, particularly with regards to sequence of management of the primary tumour in lieu of metastatic disease. To date, there are no prospective RCTs examining treatment of these patients. Only retrospective reviews exist looking at the outcomes of patients treated operatively and non-operatively.

Two reviews demonstrate a survival benefit of initial resection of the colorectal primary in patients with metastatic disease. Konyalian et al. reviewed 109 patients over an 11-year period. These patients were divided into two groups, one of which underwent a surgical resection and the other underwent non-operative management [22]. Patients that underwent surgical resection were shown to have a survival of 375 days versus 138 days for the non-operative group ($p < 0.0001$). A similar retrospective study by Cook et al. reviewed 26,754 patients with CRC over a 12-year period. Of those patients, 17,658 were resected and demonstrated increased survival [23]. Survival in the group with colon cancer was 11 months following resection compared to 2 months when the primary was not removed ($p \leq 0.001$). In those with rectal cancer, survival was only 6 months in the resected group and 2 months in the non-operative group ($p < 0.001$). As one might expect, differences in survival in these retrospective studies likely reflect selection bias in favour of resection rather than true alteration in disease biology [24]. Accordingly, patients in these studies who were resected generally had a lower burden of disease, were of younger age, and had a higher performance status.

Conversely, other studies have shown a benefit to leaving the asymptomatic primary *in situ* in metastatic CRC. Scoggins et al. completed a retrospective review of 955 patients with CRC over a 12-year period of which 86

patients had incurable stage IV disease with an intact primary tumour [25]. These patients were divided into two groups based on initial management; 66 underwent resection of the primary while 23 did not. Median overall survival in the resected group was 14.5 months versus 16.6 months in the non-resected group ($p = 0.59$). These authors concluded that patients with asymptomatic primary colorectal tumours who present with incurable metastatic disease may safely avoid resection as the risk of these lesions becoming symptomatic before death from systemic disease is low. Damajanov et al. showed there was a selection bias to this study as well, elucidating the fact that 11 patients who were not resected had rectal cancer and 10 of those patients received radiation or chemoradiation [24]. Given that a prospective randomised trial comparing the operative and non-operative treatment of an asymptomatic primary in metastatic CRC is unlikely to occur, the controversy surrounding this issue will likely continue. Suffice it to say, traditional dogma mandating the removal of any CRC primary in patients with advanced malignancy has rightfully been called into question.

Perhaps a more vexing problem in the management of the CRC primary comes to light in patients with potentially curable synchronous liver metastases. Models of simultaneous colon and liver resection as well as resection of the primary followed by chemotherapy to stabilise the liver tumours with the intent to proceed to staged hepatectomy are being debated [26]. Studies have shown a survival benefit to neoadjuvant chemotherapy and resection of liver metastases prior to the resection of the colon primary [26–28].

Poultides et al. retrospectively reviewed prospective data on 233 patients over a 6-year period with synchronous metastatic CRC and an unresected primary who received neoadjuvant chemotherapy [27]. Of this group, 93% never required any surgical intervention for palliation of the primary. A small percentage of patients (4%) required non-operative intervention consisting of radiation or stent placement. Ultimately, 20% of patients went on to surgical therapy with removal of the primary and metastasectomy. The authors concluded that the use of chemotherapy without prophylactic colectomy as initial treatment is appropriate for patients with asymptomatic disease [27].

In a prospective study by Mentha et al. 20 patients over a 6-year period with stage IV CRC were treated with initial 2–6 cycles of chemotherapy prior to undergoing liver resection [26]. After hepatectomy, the colorectal primary resection was planned with addition of radiation therapy preoperatively for rectal cancers. Sixteen patients went on to hepatectomy. A curative strategy could not be pursued in the other four patients, of which two patients died of disease progression due to non-response, one died of septicemia, and the other patient of slowly progressive disease. Those patients who went on to hepatectomy were able to have their primary resected. The median survival of the resected group was 46 months with overall survival rates of 85%, 79%, 71% and 56% at 1, 2, 3 and 4 years, respectively. These are

improved in comparison to survival data of patients with similar severity of disease [29]. The authors suggest that neoadjuvant chemotherapy confers a treatment benefit to both the liver disease and the primary lesion. It is thought that it allows patients to be well selected from a biology standpoint, in which a curative resection could be attempted and avoids aggressive treatment in patients who would respond poorly. In addition, removal of the liver metastases protected against the growth of liver tumours while treating the primary. This is an important point to note because complications associated with colorectal surgery could delay the start of chemotherapy and allow progression of liver disease.

Symptom palliation

Large bowel obstructions are a significant problem in patients with colon cancer. It has been reported that approximately 15% of patients present with signs of obstruction [30]. Surgery was the primary means of management prior to the early 1990s. In 1991, Dohmoto described the use of endoscopic stent placement to traverse colonic malignancies [31]. Studies have shown that the use of colonic stenting is palliative for obstructions secondary to colon cancer [32]. A retrospective review encompassing 10 studies and a total of 451 patients has been reported. Malignant bowel obstructions were divided into two groups treated by either endoscopic stent or surgery. The stent group had a shorter length of stay by 7.72 days ($p < 0.001$), lower mortality ($p < 0.03$) and fewer medical problems ($p < 0.001$) [32]. Mortality rates of stent procedures vary between 1 and 5.7% [32, 33], whereas the mortality rate associated with open surgery was 12.1% [32]. There has been no data to indicate a difference in long-term survival between emergency surgery and stented patients at 3 and 5 years [34]. A significant cost reduction has also been associated with stent placement versus emergency surgery. The reduction is related to the decrease in hospital days and acuity of care required postoperatively [35]. In addition, the placement of stents allows patients to have a quicker recovery and expedite the administration of chemotherapy [36]. Chemotherapy administration sooner after surgery has been shown to be beneficial in quality-of-life and overall survival when compared to delayed administration [37].

Conclusion

The management of CRCs has been steadily changing as advances continue in medical and surgical techniques. The advent of new chemotherapeutic agents and minimally invasive procedures, including stenting and laparoscopy, have increased patients survival and quality-of-life. With

new advances, it is important to continue to investigate therapies with prospective randomised studies, when feasible, to provide the best outcomes for patients.

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