

Systemic Therapy for Colon Cancer

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Colorectal cancer (CRC) is a common and frequently fatal disease in North America. In the United States, 106,680 new cases of colon cancer and 41,930 new cases of rectal cancer were reported in 2006, with an estimated 55,170 deaths attributed to CRC [1]. In Canada, there were approximately 20,000 new cases of CRC, with an estimated 8500 deaths in 2006 [2].

RISK FACTORS

Many environmental and hereditary factors are associated with an increased risk for developing CRC. There are multiple genetic predispositions to CRC. The genetic condition associated with the highest risk for developing CRC is familial adenomatous polyposis (FAP) caused by germline mutation of the tumor-suppressor adenomatous polyposis coli (APC) gene. FAP is transmitted in an autosomal dominant fashion. Individuals who have FAP virtually always develop CRC by the age of 40 years if not treated by prophylactic removal of the colon and rectum [3].

A more common genetic disorder that increases the risk for CRC is hereditary non-polyposis colorectal cancer (HNPCC), characterized by dysfunction in DNA mismatch repair genes. HNPCC is inherited in an autosomal dominant manner [4]. It is associated with an early age of colon cancer diagnosis and right-sided colon cancer. The diagnosis of HNPCC is suspected by either the Amsterdam or the more recent and more liberal Bethesda Criteria, which identify individuals who have a strong likelihood of mismatch repair gene mutation. Such individuals should be referred for genetic counseling and evaluation.

Other individual risk factors for CRC include a personal history of adenomatous polyps, a personal or family history of colon cancer, and a personal history of ulcerative colitis, especially pancolitis for more than 10 years. Protective factors that may reduce the risk include a diet high in fruits and vegetables [5] and low in animal fat and red meat [6]. Other suggested protective factors include dietary calcium, nonsteroidal antiinflammatory drugs, and frequent

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physical activity. Postmenopausal women administered hormone replacement therapy have a decreased incidence of CRC [7].

Screening the general population for CRC reduces disease morbidity and mortality [8]. Various screening tools have been recommended, including colonoscopy, double contrast barium enemas, sigmoidoscopy, annual fecal occult blood test (FOBT), and CT virtual colonoscopy. Of these screening tests, colonoscopy is considered the gold standard because it directly visualizes the entire colon, provides biopsy capability, and is therapeutic in the removal of precancerous polyps. The American Cancer Society (ACS) recommends that all asymptomatic individuals undergo initial screening colonoscopy at age 50. Individuals at a higher-than-average risk, on the basis of family history, genetic screening, or other risk factors, should begin screening before age 50. Routine screening colonoscopies should be repeated every 10 years in asymptomatic individuals who have a negative index colonoscopy.

Patients who have first-degree relatives who had CRC should undergo CRC screening beginning at age 40, or 10 years earlier than the age of onset of the CRC in their first-degree relative [9]. Our practice is to initiate colonoscopic screening at either age 40, or 20 years younger than the index case, whichever occurs sooner.

Despite the established benefit and clear guidelines for screening, the North American population is underscreened. More than 70 million people in the United States are 50 years of age or older and thus eligible for screening. Yet as of 2004, only 28.3 million (40.4%) have been screened for CRC, including 21.6 million by colonoscopy and 6.7 million by FOBT [10]. In Canada, only about 20% of individuals aged 50 to 59 years have been screened for CRC [11] by any screening method, with a mere 4% of the screen-eligible population aged 50 to 74 years undergoing screening colonoscopy in 2001 [12].

PRESENTATION AND EVALUATION

Patients typically present with nonspecific symptoms, including abdominal pain, change in bowel habits, melena, hematochezia, or fatigue. Patients frequently are anemic. Approximately 20% of patients initially present with metastatic disease. Preoperative staging routinely includes an abdominal and pelvic CT scan. The role of preoperative chest roentgenogram versus chest CT is controversial. The current American Society of Clinical Oncology (ASCO) surveillance guidelines, however, recommend chest CT [13]. Because of the emerging role of metastasectomy for liver metastasis and the increasing role of neoadjuvant systemic therapy, a baseline chest CT is reasonable. Measurement of a carcinoembryonic antigen (CEA) level is recommended preoperatively.

NUTRITIONAL STATUS

Optimizing the nutritional status of the patient who has CRC is an important concern of the surgeon, gastroenterologist, and medical and radiation oncologist. Many solid tumors, including CRC, are associated with obesity and the metabolic syndrome of hyperglycemia and insulin resistance [14].

Paradoxically, malignancy and its various treatment modalities induce a catabolic state and impair the function of the GI tract, resulting in weight loss. These metabolic abnormalities increase surgical complication rates, including impaired wound healing and thromboembolism. An increased body mass index (BMI) also presents challenges to the medical and radiation oncologist when calculating the ideal dose of therapy. Patients who have CRC should work with their physicians and dietitians to develop a customized dietary plan to maintain an ideal BMI. Patients who have CRC who consume a diet high in fruits, vegetables, and non-red meats have an improved outcome when compared with those who consume a traditional Western diet high in red meat and refined grains [15].

SURGERY

The primary curative therapy is surgery, either by traditional open colectomy or, most recently, laparoscopically assisted colonic resection. These two techniques were reported as equivalent in efficacy in a large randomized trial performed by experienced surgeons [16]. Surgical resection optimally includes complete resection of the primary tumor and sampling of at least 12 regional lymph nodes. The surgeon should also inspect the entire abdominal cavity, palpate for evidence of metastatic disease, and obtain biopsies should a questionable metastatic lesion be encountered.

The optimal locoregional management of rectal cancer is more complex and anatomically more difficult than that for colon cancer because of its location within the bony pelvis, as opposed to the abdomen, and its location below the peritoneal reflection. Endorectal ultrasound or pelvic MRI should be standardly performed preoperatively. Tumors that are imaged as non–full thickness (T1–2, N0) should undergo initial surgical resection. If the final pathology remains non–full thickness and node-negative, no further therapy is routinely indicated. If the final pathology demonstrates full thickness, or if lymph nodes contain cancer, then postoperative chemoradiotherapy is indicated. If the initial endorectal evaluation indicates a full-thickness tumor (T3–4), preoperative chemoradiotherapy should be administered. Appropriate surgical treatment includes total mesorectal excision.

Metastasectomy is well established. Single or few metastatic lesions confined to either lung, liver, or ovary are potentially curable and should be considered for resection. A dedicated hepatic surgeon can aggressively resect liver metastases. Patients who have liver-only metastases deserve evaluation by a hepatic surgeon unless there is multifocal spread to all hepatic lobes. In patients who have surgically resectable hepatic metastases, 5-year survival approaches 40% [17].

Postoperative Management of Stage II and III Disease

Postoperative, or adjuvant, systemic therapy has become routine and standard for stage III colon cancer. Adjuvant therapy should also be strongly considered in stage II patients. It is generally recommended for any medically fit patient

who has stage II cancer with unfavorable factors, including colonic perforation, unfavorable histology, colonic obstruction, or lymphovascular invasion. The optimal choice of adjuvant chemotherapy has recently changed from a 6-month course of 5-fluorouracil (5FU)-based chemotherapy alone to a 6-month course of infusional 5FU plus leucovorin (LV) and oxaliplatin (FOLFOX) based on

Table 1
Systemic therapy for colorectal cancer

Therapy	Mechanism of action	Indications	Potential common toxicities
5- Fluorouracil (5-FU)	Blocks the enzyme thymidylate synthase, which is essential for DNA synthesis	Multiple uses in combination with other agents in the adjuvant (postoperative) and palliative settings	Nausea, diarrhea Myelosuppression Fatigue
Capecitabine	Blocks thymidylate synthase (orally administered prodrug converted to 5-FU)	Multiple uses in combination with other agents in the adjuvant (postoperative) and metastatic setting	Nausea, diarrhea Myelosuppression Fatigue Palmar-plantar syndrome (hand-foot syndrome)
Oxaliplatin	Inhibits DNA replication and transcription by forming inter- and intra-strand DNA adducts/cross-links	Used in combination with 5FU, LV (FOLFOX) in the adjuvant (postoperative) and metastatic setting	Peripheral neuropathy Nausea, diarrhea Fatigue Myelosuppression Hypersensitivity
Irinotecan	Inhibits topoisomerase I, an enzyme that facilitates the uncoiling and recoiling of DNA during replication	Used alone or in combination with 5FU, LV (FOLFIRI) in the metastatic setting	Cholinergic (acute diarrhea) Nausea, late diarrhea Fatigue Myelosuppression Alopecia
Bevacizumab	Monoclonal antibody that binds to VEGF ligand	Used in combination with either FOLFOX or FOLFIRI in the metastatic setting	Hypertension Arterial thrombotic events Impaired wound healing Gastrointestinal perforation
Cetuximab	Monoclonal antibody to EGFR (chimeric) that blocks the ligand-binding site	Used with irinotecan or as a single agent in the metastatic setting	Acneform rash Hypersensitivity Hypomagnesemia Fatigue
Panitumumab	Monoclonal antibody to EGFR (fully humanized) that blocks the ligand-binding site	Used as a single agent in the metastatic setting	Acneform rash Hypomagnesemia Fatigue

Abbreviations: EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

a large trial of adjuvant systemic therapy for resected stage II or III colon cancer (Table 1) [18]. This trial demonstrated an increase in disease-free survival at 3 years from 72.9% to 78.2% ($P = .002$) with addition of oxaliplatin to FU/LV. Toxicities were comparable between the two groups, with the exception that oxaliplatin is associated with a much higher rate of paresthesia: 12.4% versus 0.2% grade 3 (serious) toxicity. This neurotoxicity persisted at a grade 3 level in 1.1% of treated patients at 1 year of follow-up.

In addition to adjuvant chemotherapy, patients should undergo follow-up for recurrent disease and metachronous cancer. Follow-up guidelines are somewhat controversial. A typical approach used at Memorial Sloan Kettering, and endorsed by ASCO, is to examine the patient every 3 to 4 months for the first several years postoperatively, with CEA monitoring at each visit, and annual CT scans of the chest, abdomen, and pelvis for the first 3 years. Full colonoscopy should be performed at 1, then 3, and then every 5 years after resection, unless colonoscopic findings or other factors necessitate more frequent colonoscopy.

CHEMOTHERAPY FOR METASTATIC DISEASE

Approximately 20% or more of patients who have CRC initially present with metastatic disease (mCRC). Approximately 35% of patients who present with stage III, 20% of patients with stage II, and 5% to 10% of patients with stage I cancer eventually relapse and subsequently die from mCRC. The most common sites of metastases are the liver, lung, peritoneum, and retroperitoneum.

Many advances have occurred recently in the treatment of mCRC. Active agents, in addition to the original 5FU, that have been approved by the US Food and Drug Administration (FDA) for mCRC include irinotecan, capecitabine, oxaliplatin, bevacizumab, cetuximab, and panitumumab. The goals of systemic therapy of mCRC include palliation of symptoms, prolongation of life, and, in selected cases of liver-only metastases, tumor regression to facilitate surgical resection of these metastases. The median survival of a patient who has mCRC has improved during the last decade from less than 1 year (with only 5FU-based therapy) to approximately 2 years (with multiagent systemic therapy).

Several factors help guide the selection of the appropriate first-line therapy for mCRC. The efficacy of systemic therapy is usually established in patients who have a good “performance status,” or general medical status, at therapy initiation. A patient who has good performance status can provide for his or her own care and is active for most of the day. A patient who spends more than half of waking hours confined to a bed or chair has a poor performance status. Clinical trials for efficacy of chemotherapy and other systemic agents are restricted to patients who have a good performance status. The benefit of systemic therapy in patients who have poor performance status has not been well established and therefore should not be assumed. In patients who have poor performance status, initial efforts should focus on improvement of performance status through ambulation, nutrition, pain control, and medical treatment of

underlying conditions, to render the patient a better candidate for chemotherapy. Patients receiving chemotherapy should also have adequate liver, kidney, and bone marrow function, or dose modifications may be required.

To determine the efficacy of chemotherapy for metastatic cancer, several measures are used. The definition of a response to therapy is a reduction, usually by at least some prespecified percentage, in cancer size. Reduction in the serum level of a tumor marker, such as CEA, can be confirmatory, but is an inadequate criterion. A partial response is defined as a 30% decrease in the longest dimension of each measurable tumor deposit, using unidimensional, or response evaluation criteria in solid tumors (RECIST), criteria [19]. A complete response is complete disappearance of all clinically detectable disease. The response rate (RR) is the percentage of patients who meet either criterion. Measures used to determine the duration of benefit include: (1) progression-free survival, which is the time from the start of treatment to the date the disease worsens, and (2) overall survival, which is the length of time patients are alive after diagnosis.

5FU, often modified by LV, has been clinically used for half a century [20] as a standard agent for mCRC. It was the only available agent until 1996, when irinotecan was approved. Over the last decade, oxaliplatin, capecitabine, bevacizumab, cetuximab, and most recently panitumumab have also been approved. 5FU blocks the enzyme thymidylate synthase, which is essential for DNA synthesis. LV, also known as folinic acid, enhances the antineoplastic effects of 5FU. Both LV (FOL, folinic acid) and 5FU (F, fluorouracil) can be combined with irinotecan (IRI) or oxaliplatin (OX) with the treatment acronyms FOLFIRI or FOLFOX, respectively. These alternative treatments consist of administration of a bolus of 5FU, LV, and either oxaliplatin or irinotecan. The patient is then sent home with a 2-day infusion of low-dose 5FU, administered by a small, lightweight, portable pump, usually worn on a belt or shoulder strap, infused through a centrally placed catheter. The patient or health care provider can simply disconnect the catheter after the 2-day infusion. Capecitabine is an oral fluoropyrimidine with a similar mechanism of action and similar efficacy as 5FU.

Irinotecan is a derivative of camptothecin, found in *Camptotheca acuminata*, a plant native to China. It potently inhibits topoisomerase I, an enzyme that facilitates the uncoiling and recoiling of DNA during replication by cleaving one strand and subsequently reattaching that strand. Oxaliplatin is a platinum chemotherapy that inhibits DNA replication and transcription by forming inter- and intra-strand DNA adducts/cross-links.

In patients who have mCRC, optimal chemotherapy consists of initial administration of a fluoropyrimidine and oxaliplatin or irinotecan (eg, FOLFOX or FOLFIRI). Tournigand and colleagues [21] and Colucci and colleagues [22] performed randomized trials in which patients received either FOLFIRI followed by FOLFOX, or vice versa. In the Tournigand and colleagues study, FOLFIRI was found to have an RR of 56% and an 8.5-month median progression-free survival (mPFS), whereas FOLFOX had an RR of 54% and an mPFS of 8 months. Colucci and colleagues found that FOLFIRI had an RR of 31%

and FOLFOX had an RR of 34%. Both regimens had an mPFS of 7 months. Both investigators concluded that the regimens had similar efficacy when used as first-line therapy. Either FOLFOX or FOLFIRI can therefore be considered standard options for first-line treatment of mCRC. These regimens are typically given with bevacizumab.

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor ligand to inhibit angiogenesis. Its antineoplastic effect is ascribed to regression of microvascular density, inhibition of neovascularization, and normalization of grossly abnormal tumor vasculature that permits more effective chemotherapy delivery to the tumor. The FDA recently approved bevacizumab in combination with 5FU-based chemotherapy for mCRC based on findings that addition of bevacizumab to irinotecan, FU, and LV for mCRC improved progression-free survival from 6.2 months to 10.6 months, improved the response rate from 35% to 45% [23], and improved overall survival from 15.6 to 20.3 months. Most recently, Saltz and colleagues [24] reported on a randomized trial that found that the addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved progression-free survival from 8.0 to 9.4 months. The addition of bevacizumab did not improve the response rate, however.

In 2004, the FDA approved cetuximab, the chimeric (human/mouse) monoclonal antibody targeting epidermal growth factor receptor (EGFR), for treatment of mCRC with irinotecan and as a single agent for patients intolerant of irinotecan-based therapy. In a single-arm, nonrandomized trial, cetuximab as a single agent had a 9% RR and a 35% rate of minor response or disease stability for at least 12 weeks [25]. When cetuximab was combined with irinotecan, the response rate was 22.9% versus 10.8% for irinotecan alone [26]. Cetuximab causes an acneform rash on the face and upper body in more than 80% of patients. The rash is associated with RR. Although the FDA approved cetuximab for use in EGFR-expressing mCRC, there is no evidence that the presence or absence of EGFR expression influences RR, and routine testing for this is unnecessary.

In 2006, the FDA approved panitumumab, a monoclonal antibody to EGFR, that unlike cetuximab is fully humanized (not chimeric). It is indicated for patients who have mCRC that has progressed on or following 5FU, oxaliplatin, and irinotecan-containing regimens. In a large randomized trial of panitumumab versus best supportive care for mCRC, a response rate of 8% was found [27]. Like cetuximab, panitumumab causes an acneform skin rash. As a fully human monoclonal antibody, panitumumab entails a lower risk for serious infusion reactions than the 3% rate observed with cetuximab. The relative activity of cetuximab versus panitumumab and the relative activity of panitumumab when given with chemotherapy are currently unknown.

SUMMARY

The prevention, treatment, and posttreatment care of colorectal cancer is a multidisciplinary process that involves surgeons, radiation therapists, and medical

oncologists, along with gastroenterologists, radiologists, pathologists, and primary care physicians. The care of patients who have colorectal cancer is rapidly evolving. Despite numerous recent advances, the gains have been modest and incremental; CRC still remains the number two cause of cancer mortality in the United States. The mortality and morbidity from CRC can be dramatically reduced with effective implementation of universal screening. Further advances in medical oncology will result from better understanding of tumor genetics and biology and of host response to cancer that will allow therapy tailored to critical tumor-specific molecular targets while minimizing toxicity to normal tissue. With these advances it is hoped that CRC will become a rare disease, presenting in a small unscreened segment of the population, but treatable with highly effective, low-toxicity medical treatments.

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