Chapter 153: Colorectal Cancer

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 62, Colorectal Cancer.

KEY CONCEPTS

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1. Advancing age, high-risk adenomatous polyps, inherited and acquired genetic susceptibilities, inflammatory bowel disease, diabetes mellitus, and lifestyle factors are associated with colorectal cancer risk.

2. Regular use of aspirin and other nonsteroidal anti-inflammatory drugs reduces the risk of colorectal cancer, but it is not recommended for routine cancer prevention, nor are any other therapies.

3. Effective colorectal cancer detection programs incorporate routine screening starting at the age of 45 years for average-risk individuals. Colorectal adenomas can progress to cancer and should be removed.

4. The treatment goal for stages I, II, and III colon cancer is cure; surgery should be offered to all eligible patients. Six months of fluoropyrimidine-based adjuvant systemic therapy reduces the risk of cancer recurrence and overall mortality in patients with stage III and select patients with stage II colon cancer; 3 months may be considered in select patients with stage II and III colon cancer. An oxaliplatin-containing regimen further reduces risk as compared with fluoropyrimidine alone in stage III patients.

5. Adverse drug reactions with the most common drugs used in the treatment of colorectal cancer include fluorouracil/capecitabine: palmar-plantar erythrodysesthesia, stomatitis, diarrhea, leukopenia; oxaliplatin: acute and persistent peripheral neuropathies; irinotecan: diarrhea, neutropenia. Deficiencies in dihydropyrmidine dehydrogenase (DPD) and uridine diphosphate-glucuronosyltransferase (UGT1A1) may increase adverse drug reactions with fluorouracil/capecitabine and irinotecan, respectively.

6. Combined modality neoadjuvant therapy consists of fluoropyrimidine-based chemosensitized radiation therapy (XRT) and surgery for patients with stage II or III cancer of the rectum and is considered the standard of care to decrease risk of local and distant disease recurrence.

7. Chemotherapy is palliative for metastatic disease. A fluoropyrimidine with oxaliplatin or irinotecan improves survival compared to fluoropyrimidine monotherapy and should be offered to patients who are candidates for aggressive treatment. The ability for patients to receive all active cytotoxic agents (eg, fluoropyrimidine, oxaliplatin, and irinotecan) during the course of their disease improves their overall survival.

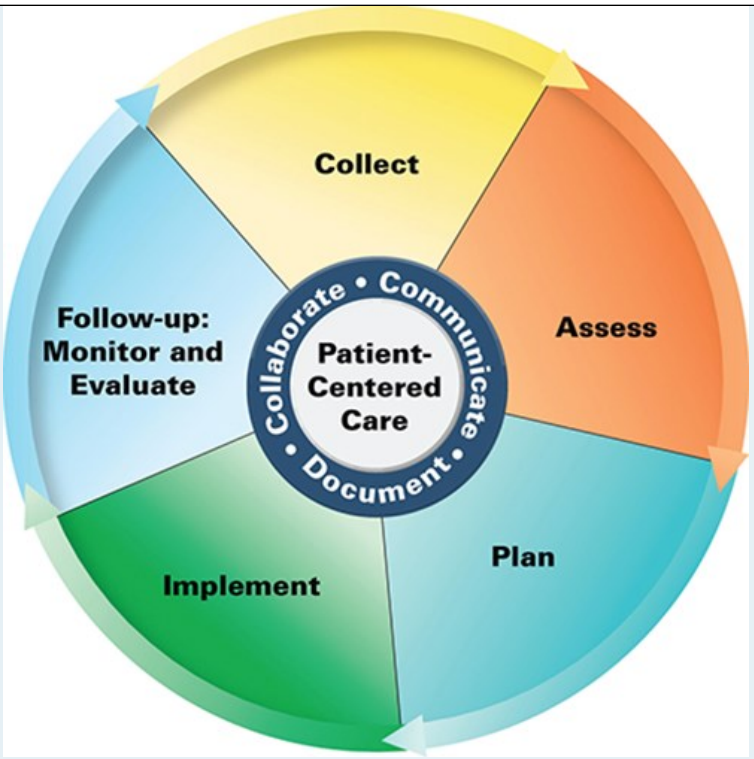
8. Bevacizumab plus fluoropyrimidine-based chemotherapy as initial therapy for metastatic disease is considered standard of care and provides a survival benefit compared with combination chemotherapy alone. Hypertension, proteinuria, and impaired wound healing are common adverse drug reactions.

9. The addition of an epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumumab) to initial treatment for *RAS* and *BRAF* wild-type, left-sided advanced or metastatic disease may improve tumor response rates (RRs) and survival. Papulopustular skin rashes, diarrhea, and hypomagnesemia are common, and infusion-related reactions may also occur.

10. Immune checkpoint inhibitors can provide benefit to patients with metastatic colorectal cancer when a deficiency in DNA mismatch-repair (MMR) genes or high microsatellite instability (MSI) is present. These agents are associated with immune-mediated adverse drug reactions.

PATIENT CARE PROCESS

Patient Care Process for Colorectal Cancer



Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (lifestyle factors—alcohol use, tobacco use, physical activity)
- Patient characteristics (eg, social history/situation, insurance coverage) and treatment preferences
- Patient medical and family history (eg, performance status, concurrent disease states [inflammatory bowel disease, colorectal cancer, polyps])
- Clinical presentation signs and symptoms (see Clinical Presentation box)
- Current signs and symptoms and evaluation of tumor growth (for follow-up visits)
- Current medications (prescription, over-the-counter, and complementary alternative)
- Objective data
  - BP, heart rate (HR), height, weight, and BSA
  - Labs (eg, serum electrolytes, renal function, liver chemistries, complete blood count, coagulation studies, carcinoembryonic antigen [CEA] level—see Workup)
  - Physical examination data (eg, hepatomegaly, lymphadenopathy, ascites)
  - Colorectal cancer staging (see Table 153-4)
  - Colorectal tumor genomics (eg, *KRAS*, *NRAS*, MMR/MSI, *BRAF, PIK3CA, NTRK*)

Assess

- Risk factors for treatment-related toxicities (eg, *UGT1A1*28* genotype, DPD deficiency, poor nutritional intake, uncontrolled blood pressure or

hypertension, baseline peripheral neuropathy)

- Type of and response to prior treatments
- Potential for disease responsiveness to specific agents and risk factors for disease recurrence
- Potential problems with medication adherence to oral treatment regimens
- Need for drug dose reductions or supportive care

Plan*

- Goals of treatment
- Drug therapy regimen including specific anticancer agent(s), dose, route, frequency, and duration (see Tables 153-5, 153-6, and 153-7)
- Supportive care plan (eg, antiemetics, prophylactic antidiarrheals, infusion reaction prophylaxis)
- Monitoring parameters including efficacy (eg, cancer imaging studies-chest, abdominal, and/or pelvic CT scans and radiographs, CEA if previously elevated, symptoms of recurrence), safety (medication-specific adverse drug reactions, including major-dose limiting toxicities), and time frame (see Tables 153-5, 153-6, and 153-7)
- Patient education (eg, goals of treatment, expected and potential serious toxicities, drug therapy, monitoring and management plan)

Implement*

- Provide patient education regarding all elements of treatment plan
- Survivorship care plan (eg, primary prevention of other diseases, such as infections, and other cancers; support systems for maintaining healthy lifestyle choices and BMI)

Follow-Up: Monitor and Evaluate

- Determine disease response to treatment (see "Evaluation of Therapeutic Outcomes" section) and occurrence of disease progression or recurrence (cancer imaging studies, CEA if previously elevated)
- Presence of adverse drug reactions (see "Evaluation of Therapeutic Outcomes" section and Tables 153-5, 153-6, and 157-7)
- Patient adherence to treatment plan using multiple sources of information (eg, patient self-report, medication administration records or refill data)
- Patient's satisfaction with treatment, including understanding of adherence

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

For each of the available antiangiogenic inhibitor and EGFR inhibitors, describe when in the treatment of colorectal cancer (ie, neoadjuvant, adjuvant, first-line metastatic, second- or greater-line metastatic treatment) it is appropriate to use the drug, including the rationale and whether the drugs within a class are interchangeable. This activity is useful to enhance student understanding of the ASSESS, PLAN, and FOLLOW-UP steps in the patient care process.

INTRODUCTION

Colorectal cancer involves the colon, rectum, and anal canal. It is one of the three most common cancers in adult men and women in the United States.[1] In 2021, an estimated 149,500 new cases were diagnosed, of which 104,270 involves the colon and 45,230 involves the rectum. An additional 9,090 new cases of cancer involve the anus, anal canal, or anorectum. For both adult men and women, colorectal cancer is the third leading cause of cancer-related death in the United States. An estimated 52,980 deaths from cancer of the colon or rectum occurred during 2021.

Colorectal cancer mortality and incidence rates in the United States have decreased steadily over the past two decades. Incidence rates vary worldwide, with the highest incidence rates in countries with a high human development index (HDI).[2] The decline in colorectal cancer mortality rates is likely due to increased screening and/or improved treatments, but mortality rates continue to increase in low-income and middle-income countries in eastern Europe, Asia, and South America.

Multiple factors are associated with the development of colorectal cancer, including inherited susceptibility, lifestyle factors, and certain disease states. About 73% of affected individuals are diagnosed at an early stage of disease, which can potentially be cured with surgery alone or surgery followed by adjuvant XRT, chemotherapy, or both.[3] Five-year survival rates are about 91% for persons with early stages of colon and rectal cancer. Once the tumor has spread regionally to adjacent lymph nodes or tissues, the 5-year survival rate drops to 72% for both colon and rectal cancer. Five-year survival for individuals with metastatic disease is about 15%.

Treatment modalities for colorectal cancer include surgery, XRT, chemotherapy, targeted molecular therapies (eg, angiogenesis inhibitors and EGFR inhibitors), and immune checkpoint inhibitors. Surgery is the definitive procedure associated with cure. XRT can improve curability following surgical resection in rectal cancer and can reduce symptoms and complications associated with advanced disease. Chemotherapy is used in the adjuvant setting to increase cure rates and in treatment for advanced stages of disease to prolong survival. Some patients with metastatic disease who receive aggressive preoperative chemotherapy and targeted therapies experience higher resection rates and can be potentially cured. Much progress has been made in the treatment of advanced disease and the availability of active drug regimens that improve patients' survival.

EPIDEMIOLOGY

Colorectal cancer is the third most common diagnosed malignancy worldwide and the fourth most common cause of cancer-related deaths, accounting for about 1.9 million new cases and 935,000 deaths annually.[2] Although the highest incidence and mortality rates are found in economically developed countries, such as the United States, Australia, New Zealand, and Western Europe, where the HDI is highest, rates have stabilized or are decreasing. This is in contrast to countries with a medium-to-high HDI, such as Eastern Europe, Asia, and South America, where colorectal cancer incidence and mortality rates are increasing rapidly. These increases are believed to be associated with an increased prevalence of risk factors associated with westernization, such as unhealthy diet, obesity, and smoking. The lowest incidence rates are observed in less-developed areas such as sub-Saharan Africa and South Central Asia.

The incidence of invasive colon cancer is greatest among men, who have an age-adjusted incidence rate of 29.1 per 100,000, as compared with women for whom the rate is 24.3 per 100,000.[3] Invasive cancer of the rectum occurs less frequently, with an incidence rate of 14.1 and 9.0 per 100,000 for men and women, respectively. Differences in colorectal cancer incidence exist among ethnic groups in the United States, where incidence is highest among non-Hispanic Black individuals followed by American Indian/Alaska Native individuals, non-Hispanic White individuals, Hispanic individuals, and Asian/Pacific Islander individuals. Cultural and genetic factors as well as disparities in access to healthcare services may influence risk among population groups.

The overall incidence of colon and rectal cancers in the United States has steadily decreased since the mid-1980s, with an annual decline by 3.7% among individuals aged 65 years and older from 2009 to 2018.[3] However, the incidence rate increased by 1% per year in adults between 50 and 64 years of age and in adults younger than 50, the incidence of colorectal cancer increased by 2.2% annually. The incidence of colorectal cancer in adults younger than 55 has been increasing since the mid-1990s, with the most rapid increase in metastatic disease.[4]

Cancer incidence rates have been declining among every broadly defined racial/ethnic group since the mid-1990s, except in American Indian/Alaska Natives, for whom cancer incidence rates remain stable.[3]

Cancer of the colon and rectum accounts for about 8% of all cancer deaths in the United States.[1] The median age for death from cancer of the colon or rectum is 72 years. An estimated 52,980 individuals died of colorectal cancer in the United States in 2021, which represents a continued decline in overall combined mortality for both colon and rectal cancer. Overall mortality rates are highest among non-Hispanic Black individuals, although a steep rate of decline began in the late 1990s.[3] Colorectal cancer death rates are decreasing among all ethnic groups, but mortality rates are not lower in American Indian/Alaska Native individuals. Factors contributing to the overall decline in colorectal cancer mortality include decreasing incidence rates, screening programs with early polyp removal, and more effective and better tolerated treatments. Differences among different world geographic regions, and in population groups in the United States, may also reflect more unfavorable tumor characteristics, late stage at diagnosis, decreased access to screening programs, comorbidities, and lower availability or utilization of effective treatments.

ETIOLOGY AND RISK FACTORS

The development of colorectal cancer is related to both uncontrollable and modifiable risk factors. Age, family history, and clinical and genetic susceptibilities cannot be controlled by individuals. Modifiable lifestyle factors are responsible for more than half of the colorectal cancers.[4,5]

Personal Medical History

Age

1 An individual's risk of developing cancer of the colon or rectum increases with advancing age, rising progressively after age 50.[4] The median age at colon cancer diagnosis is 67 years in men and 71 years in women and 62 years in men and 63 years in women for rectal cancer. The proportion of individuals diagnosed with colorectal cancer who were younger than 50 increased from 6% to 11% between 1990 and 2013, with the majority of cases diagnosed in adults in their 40s.[3] The increase in colorectal cancer incidence in younger adults may reflect trends in obesity and detrimental lifestyle factors, but the role of modifiable and non-modifiable risk factors in early-onset colorectal cancer remains unclear.

Adenomatous Polyps or Colorectal Cancer

A prior history of high-risk adenomatous polyps, particularly multiple adenomas or size 1 to 2 cm or more, is associated with an increased risk of colorectal cancer.[4,5] Individuals with a prior diagnosis of colon or rectal cancer have a greater risk of developing a new malignancy at another area in their colon or rectum as compared to individuals without a prior history of colorectal cancer.

Inflammatory Bowel Disease

Individuals with chronic inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, have about a twofold greater risk of developing colorectal cancer than the average individual.[4-6] This risk rises with increasing extent, duration, and severity of disease, a familial history of colorectal cancer, and coexistent primary sclerosing cholangitis. Persons diagnosed with chronic inflammatory bowel disease constitute about 1% to 2% of all new cases of colorectal cancer each year.

Diabetes Mellitus

Individuals with type 2 diabetes mellitus have an increased risk of developing colorectal cancer, independent of body mass size and physical activity level. Epidemiologic studies show that diabetes is associated with 26% to 53% increase in risk of colorectal cancer, as well as a higher risk of colorectal cancer-related and all-cause mortality.[7] Metformin use may improve survival outcomes in patients with colorectal cancer and diabetes, but further study is needed.

Family History and Inherited Genetic Risk

Colorectal Cancer or Adenomatous Polyps

Three specific patterns of colon cancer occurrence are generally observed: sporadic, familial, and recognized hereditary syndromes. Although most cases of colorectal cancer are sporadic in nature, about 30% of patients who develop colorectal cancer will have a family history of colorectal cancer

that is not associated with an inherited syndrome.[4,5] First-degree relatives of patients diagnosed with colorectal cancer have an increased risk of the disease (two times the risk), which is higher if the relative was diagnosed at age 45 or younger (three to six times higher). Similarly, parents and siblings of relatives diagnosed with adenomatous polyps are at increased risk for developing colorectal cancer.

Hereditary Syndromes

Colorectal cancer is a consequence of several well-defined genetic syndromes.[4,5] The two most common forms of hereditary colon cancer are familial adenomatous polyposis (FAP) and Lynch syndrome, historically known as *hereditary nonpolyposis colorectal cancer* (HNPCC). Both forms result from a specific germline mutation. FAP is a rare autosomal dominant trait caused by inactivating mutations of the adenomatous polyposis coli (*APC*) gene and accounts for about 1% of all colorectal cancers. The disease is manifested by hundreds to thousands of tiny sessile adenomatous polyps that carpet the colon and rectum, typically arising during adolescence. The polyps continue to proliferate throughout the colon, with eventual transformation to malignancy. The risk of developing colorectal cancer for individuals with untreated FAP is virtually 100%; most will develop colorectal cancer by the fourth and fifth decades of life.

Lynch syndrome is an autosomal dominant inherited syndrome and is the most common hereditary predisposition for colorectal cancer.[4,5] Patients with Lynch syndrome are predisposed to many types of cancer (eg, endometrial, stomach, and ovarian), but the risk of colorectal cancer is the highest.[4] Germline mutations in one of the DNA mismatch-repair (MMR) genes, most commonly *MLH1*, *MSH2*, *MSH6*, or *PMS2*, or rarely, epithelial cell adhesion molecule *(EpCAM)*, are responsible for Lynch syndrome, which accounts for 3% to 5% of overall colorectal cancer cases.[4,8] The estimated lifetime risk of developing colorectal cancer for carriers of germline MMR mutations is about 13% to 57%, depending on the specific affected gene.[8] Multiple generations within a family are affected, and colorectal cancer develops early in life, with a mean age at the time of diagnosis of about 44 to 61 years.[5] If Lynch syndrome is suspected in a patient diagnosed with colorectal cancer, typically due to early age at diagnosis or family cancer history, the tumor is examined for evidence of deficient MMR to distinguish between sporadic or germline genetic mutations. Clinicians should identify carriers of these MMR mutations so that they can be counseled and followed appropriately.[4,8]

Lifestyle Factors

Nonsteroidal Anti-inflammatory Drug and Aspirin Use

2 Several lifestyle factors influence colorectal cancer risk (Table 153-1). Regular (at least two doses/week) nonsteroidal anti-inflammatory drug (NSAID) and aspirin use is associated with a reduced risk of colorectal cancer. In an average-risk individual, regular aspirin use is associated with a 20% to 40% reduction in the risk of colorectal adenoma and colorectal cancer.[9]

TABLE 153-1

Lifestyle Factors Associated with Colorectal Cancer Risk

Factor	Comments
Elevated Risk	
Physical inactivity	Sedentary lifestyle associated with a 25%-50% increased risk of colorectal cancer compared with the risk in physically active individuals
Obesity	Elevated BMI, waist circumference, and waist-to-hip ratio directly associated with increased cancer risk
Alcohol intake	Moderate and heavy alcohol consumption associated with 20% or greater cancer risk compared to light drinking (<1 drink/day)
Smoking	Prolonged tobacco smoking increases risk of large adenomas and carcinoma; higher colorectal cancer mortality in current smokers; risk persists after smoking cessation
Western diet	High red meat, processed meat, and saturated fat dietary consumption increases cancer risk; cancer risk lower with diets high in whole fiber grains and cereals, fruits, and vegetables
Reduced Risk	
Aspirin and non-aspirin NSAID use	Regular aspirin or NSAID use associated with 20%-45% reduction in adenoma recurrence and colorectal cancer risk. Benefit in risk reduction may require at least 5-10 years of use
Postmenopausal hormone use	Exogenous hormone intake decreases the risk of adenomas, colon, and rectal cancer by about 35%
Calcium and vitamin D intake	Vitamin D 400 international units and calcium intake of 1,000 mg/day (adults <50 years) or 1,200 mg/day (adults >50 years) may help reduce colorectal cancer risk but data remain unclear

BMI, body mass index.

Benefit is also seen with NSAID and cyclooxygenase-2 inhibitor (COX-2) use. NSAID use over a 10- to 15-year period is associated with protection against adenomas and colorectal cancer, with a 30% to 45% reduction in the risk of colorectal cancer.[9] The protective effects of these agents are related to their inhibition of COX-2, which is overexpressed and elevated in up to 50% of colorectal adenomas and 85% of sporadic colon carcinomas.[10] Inhibition of COX-2 also downregulates the phosphatidylinositol 3-kinase (PI3K) signaling pathway, which plays an important role in carcinogenesis and cancer cell resistance to apoptosis.[11]

Postmenopausal Hormone Replacement Therapy

Exogenous postmenopausal oral hormone replacement therapy is associated with a significant reduction in colorectal cancer risk.[9,12] Risk reduction is seen in postmenopausal individuals receiving combined estrogen and progestin therapy and persists for about 10 years after therapy is discontinued. However, because of the harmful risks associated with postmenopausal hormone replacement therapy, its use is not recommended to prevent colorectal cancer.

Obesity and Physical Inactivity

1 Physical inactivity and elevated BMI are associated with an elevated risk of colon adenoma, colon cancer, and rectal cancer.[4,5,9] Compared to

physically active individuals, physically inactive people have up to a 50% higher risk of developing colorectal cancer.[5]

Elevated BMI and higher general and abdominal body fatness are risk factors for colorectal cancer in adults, although the associations are weaker and less consistent for women.[4] The risk of colon cancer is about 50% higher in obese men, who also have a 25% higher risk of rectal cancer as compared to men of normal body weight. Obese women have about 10% increased risk of colon cancer, and even a higher body weight within the normal range appears to be associated with an increased risk of early onset colorectal cancer.

The relationship between physical inactivity and cancer risk is incompletely understood, but may be related to oxidative stress and immune dysfunction.[13] Obesity promotes insulin resistance, chronic inflammation, elevated insulin-like growth factor-1 levels, and altered levels of circulating sex hormones, which can contribute to tumorigenesis.[5,13]

Alcohol and Tobacco Use

1 Moderate and heavy alcohol consumption is a major risk factor for colorectal adenomas and colorectal cancer.[4,5,14] Individuals with an intake of two to three alcoholic beverages per day have a 21% higher risk of developing colorectal cancer, and heavier drinking further increases cancer risk.[4,14] This association is stronger in men than in women, perhaps due to differences in drinking patterns or alcohol metabolism.

An estimated 12% of colorectal cancer deaths are attributed to cigarette smoking.[4,5] Cigarette smoking is associated with an increased risk of colorectal cancer (about 38% and 18% in current and former smokers, respectively) and mortality than in nonsmokers.[15] The risk of colorectal cancer development increases with longer duration of smoking and number of cigarettes consumed daily, and persists after smoking cessation.

Gut Microbiota

The gut microbiota could play an important role in the development of colorectal adenomas and adenoma progression to colorectal cancer.[4,5] The gut microbiome is involved in absorption and metabolism of nutrients, drug metabolism, elimination of xenobiotics, and immune cell function.[5] Certain bacterial species, such as *Fusobacterium nucleatum* and *Bacteroides fragilis*, produce bacterial metabolites that promote and sustain local inflammation, cause DNA damage, alter the immune response, and affect pro-tumorigenic cell signaling pathways.[16] Factors that alter the composition and function of normal gut microbiota, such as diet, lifestyle, obesity, and drug therapy (eg, antimicrobials, antacids, and proton pump inhibitors), may be associated with increased risk of colorectal cancer.

Dietary Intake and Nutrients

1 Epidemiologic studies of worldwide incidence of colorectal cancer suggest economic development and dietary habits strongly influence its development. Dietary characteristics of economically developed countries and increased colorectal cancer risk include higher intake of red and processed meat, fat, and refined grains, and a lower intake of fruit, vegetables, and whole grains.

Many large epidemiologic studies have identified a positive association of a high consumption of red and processed meat with the risk of developing colorectal cancer.[4,5] Potential underlying mechanisms for this association include carcinogenic chemicals formed during the cooking process or the presence of specific fatty acids in red meat.[5] Processed meat products may increase exposure to carcinogenic nitrates and *N*-nitroso compounds.[5]

Worldwide, high-fiber dietary patterns have been associated with a low incidence of colorectal cancer.[2,5,9] Foods that are high in fiber include fruit, vegetables, whole grains, and cereals. Fruit and vegetables are rich in soluble fiber, vitamins, minerals, flavonoids, and other micronutrients that may be protective for colorectal cancer risk. However, the role of dietary fiber with regard to amount, source, and type and colorectal cancer risk has not been defined.

Dietary and supplemental calcium consumption is associated with a decreased risk of adenomas and colorectal cancer.[2,4,5,17] The protective effects of calcium may be due to antiproliferative, proapoptotic actions, and reduced colonic epithelial cell exposure to mutagens.[5,9] High levels of circulating 25-hydroxyvitamin D_3 are also associated with a reduced risk of colorectal cancer.[4,5,18] Vitamin D has antiproliferative, anti-inflammatory, and immune regulatory effects.[5,9,18] Vitamin D and calcium appear to interact synergistically to protect against adenoma recurrence and colorectal cancer, but large

clinical trials have yet to confirm that supplementation with calcium and vitamin D in individuals with adequate dietary calcium and vitamin D intake reduces colorectal cancer risk.[4,5,9]

An association between folate intake through diet or supplements and colorectal cancer is complex, as data have shown both protective and tumor promoting effects.[4,9,19] However, the underlying basis for this is complex, particularly because alcohol use, smoking, genetic variants of the *methylenetetrahydrofolate reductase* gene, and other factors can interfere with folate metabolism. Thus, an adequate dietary folate intake may be enough to lower the risk of colorectal cancer, and exceeding normal intake may not be beneficial.

Deficiencies in other dietary micronutrients and antioxidants, including vitamin B_6, selenium, vitamin C, vitamin E, and carotenoids, may increase colorectal cancer risk, but there is no convincing evidence that the risk of colorectal cancer is greater in patients with low serum levels than in patients with adequate levels.[17,19]

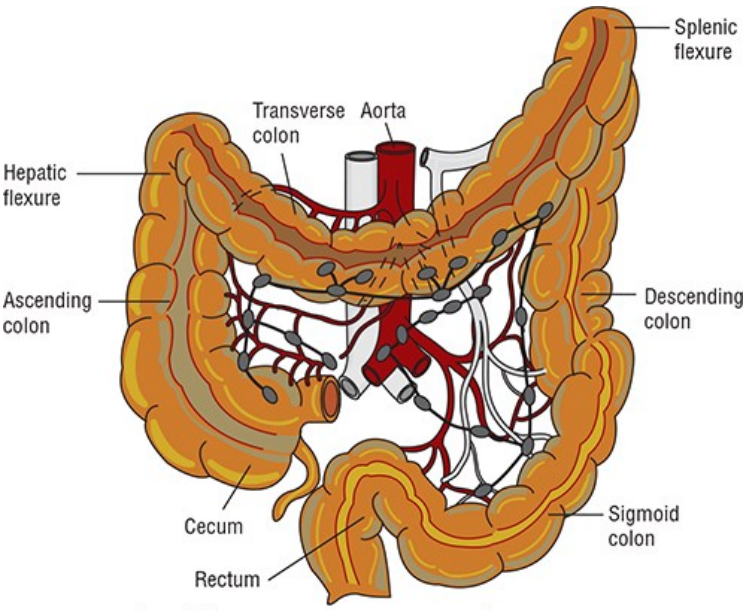
PATHOPHYSIOLOGY

Anatomy and Bowel Function

The large intestine consists of the cecum; the ascending, transverse, descending, and sigmoid colon; and the rectum (Fig. 153-1). In adults, it extends about 1.5 m and has a diameter ranging from 8 cm in the cecum to 2 cm in the sigmoid colon. Absorption of fluid and solutes occurs in the right colon or the segments proximal to the middle of the transverse colon, with movement and storage of fecal material in the left colon and distal segments of the colon. Mucus secretion from goblet cells into the intestinal lumen lubricates the mucosal surface and facilitates movement of the dehydrated feces. It also serves to protect the luminal wall from bacteria and colonic irritants such as bile acids.

FIGURE 153-1

Colon and rectum anatomy.



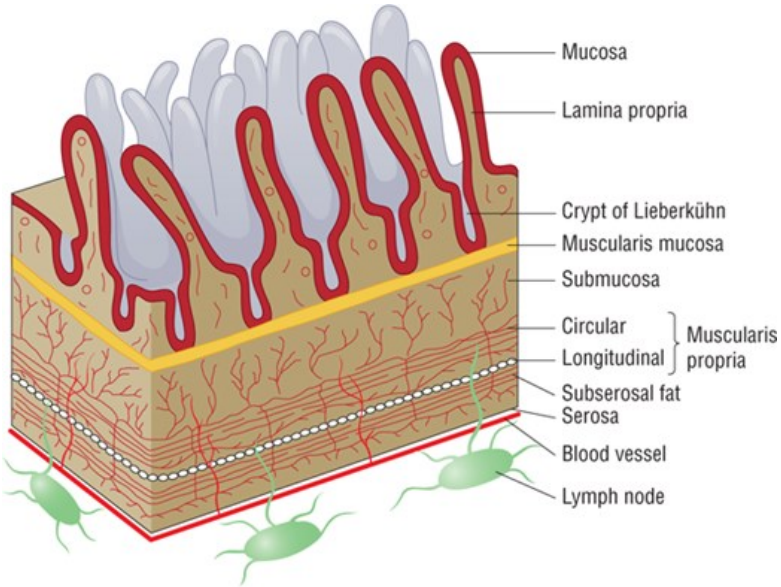
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Four major tissue layers, from the lumen outward, form the large intestine: the mucosa, submucosa, muscularis propria, and serosa (Fig. 153-2). Embedded in the submucosa and muscularis propria is a rich lymphatic capillary system. Lymphatic channels do not extend into the mucosa. The muscularis propria consists of circular smooth muscle and outer longitudinal smooth muscle bands. Contraction of these muscle groups moves colonic material toward the anal canal. The outermost layer of the colon, the serosa, secretes a fluid that allows the colon to slide easily over nearby structures within the peritoneum. The serosa covers only the anterior and lateral aspects of the upper third of the rectum. The lower third lies

completely extraperitoneal and is surrounded by fibrofatty tissue as well as adjacent organs and structures.

FIGURE 153-2

Cross-section of bowel wall.



The surface epithelium of the colonic mucosa undergoes continual renewal, and complete replacement of epithelial cells occurs every 4 to 8 days. Cell replication normally takes place within the lower third of the crypts, the tubular glands located within the intestinal mucosa. The cells then mature and differentiate to either goblet or absorptive cells as they migrate toward the bowel lumen. The total number of epithelial cells remains relatively constant as the number of cells migrating from the crypts is balanced by the rate of exfoliation of cells from the mucosal surface. This two-phase process is critical to the malignant transformation of the epithelial cells. The number of dysplastic and hyperplastic aberrant crypt foci increases with increasing age; as the mass of abnormal cells accumulates at the top of the crypt and starts to protrude into the stream of fecal matter, their contact with fecal mutagens can lead to further cell mutations and eventual adenoma formation.

Colorectal Tumorigenesis

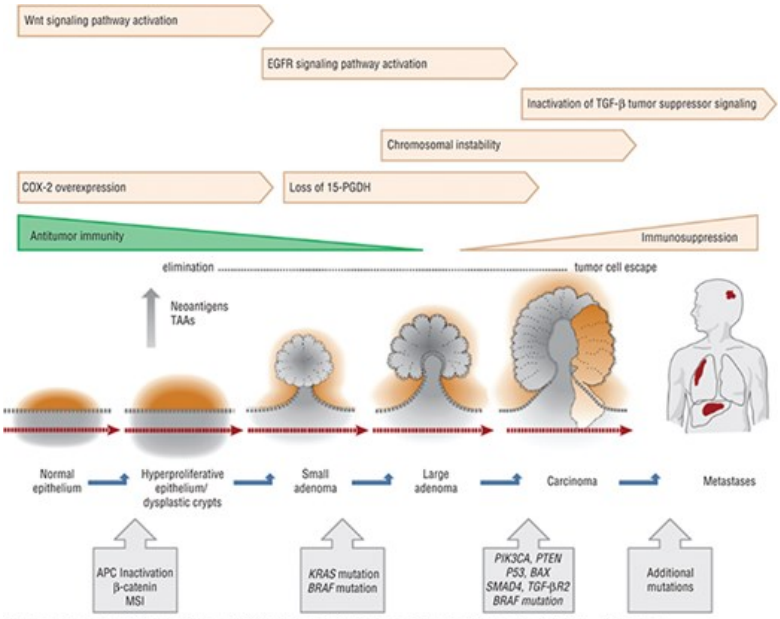
The development of a colorectal neoplasm is a multistep process involving several genetic and phenotypic alterations of normal bowel epithelium structure and function, leading to dysregulated cell growth, proliferation, and tumor development. Because most colorectal cancers develop sporadically, with no inherited or familial disposition, efforts have been directed toward identifying these alterations and learning whether detection of such changes may lead to improved cancer detection or treatment outcomes.

Features of colorectal tumorigenesis include genomic instability, activation of oncogene pathways, mutational inactivation or silencing of tumor-suppressor genes, genes associated with DNA repair, and activation of growth factor pathways.[20] During the early stages of tumorigenesis, emerging tumor cells expressing tumor antigens are eliminated by the immune system, which serves as an initial barrier to cancer progression.[21] These cells eventually escape immune surveillance as the tumor microenvironment becomes progressively immunosuppressive.

Genetic models have been proposed for colorectal tumorigenesis that describe a process of transformation from adenoma to carcinoma (Fig. 153-3).[20,22,23] The adenoma to carcinoma sequence of tumor development reflects an accumulation of mutations within colonic epithelium that confers a selective growth advantage to the affected cells. Key elements of this process include hyperproliferation of epithelial cells to form a small benign neoplasm or adenoma in conjunction with acquisition of various genetic mutations and epigenetic alterations that promote transformation to adenocarcinoma.[5,20,22]

FIGURE 153-3

Genetic changes associated with the adenoma–carcinoma sequence in colorectal cancer. The accumulation of genetic changes in the pathogenesis of colorectal cancer includes initiated by aberrant DNA methylation or MMR gene mutation with subsequent disruption in transforming growth factor-β receptor type II (TGF-β2R) and BAX signaling; mutation in the *APC* gene or abnormalities in β-catenin leading to inappropriate activation of the Wnt signaling pathway; mutational activation of COX-2 and impaired prostaglandin degradation from loss of 15-prostaglandin dehydrogenase (15-PGDH); *KRAS*, *PIK3CA*, or *BRAF* oncogene activation; increased EGFR signaling; and deletions or mutations of tumor suppressor genes *SMAD4*, *PTEN*, *P53*. Chromosomal instability (CIN) is a common feature of sporadic disease, but causative factors are not defined. Tumor-associated antigens (TAAs) expressed by emerging tumor cells are eliminated by the immune system during early tumorigenesis but eventually escape immune surveillance. The sequence of molecular events may differ between somatic and inherited genetic alterations. *(Data from References 20, 22, and 23.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Two discrete adenoma to carcinoma progression sequences have been described, a traditional adenoma-carcinoma pathway (referred to as the chromosomal instability pathway) and the serrated neoplasia pathway.[5,22] Although both pathways share several genetic alterations, each has unique molecular and phenotypic characteristics. Table 153-2 lists important genetic mutations that are associated with colorectal cancers.[20,22,23]

TABLE 153-2

Genetic Mutations Associated with Colorectal Cancer

Type of Mutation	Disease	Genes	Comments
Germline	FAP	*APC*	Multiple adenomas and carcinomas in colon and rectum
	MYH-associated polyposis	*MYH*	Autosomal recessive syndrome; wide spectrum of degree of polyposis; frequent *KRAS* mutations
	Lynch syndrome	DNA MMR genes: *MSH2*, *MLH1*, *MSH6*, *PMS2*, *EpCAM*	Colorectal cancer in the absence of extensive polyposis; predisposition for endometrial, ovarian, gastric, hepatobiliary, urothelial, pancreatic, brain, and skin cancers
Somatic	Sporadic colorectal cancer	Oncogenes	
		KRAS	Mutations found in about 30%-50% of cancers
		NRAS	Mutations found in <5% of cancers
		BRAF	*BRAF* V600E mutation found in 5%-15% of cancers
		PIK3CA	Activating mutations found in 10%-20% of cancers
		EGFR	Gene upregulation in 30%-70% of cancers
		c-MYC	Elevated expression in 70%-80% with gene amplification/rearrangement in 10%-30% of cancers
		ERBB2 (known as HER2)	Gene amplification or mutation in 2%-7% of cancers
		SRC	Gene deregulated in up to 80% of cancers
		Tumor suppressor genes	
		P53	Loss or mutation in up to 60% of cancers
		SMAD4	Mutations in 3%-18% of cancers
		APC	Inactivated in up to 80% of sporadic cancers
		TGF-βR2	Inactivating mutations present in 20% of cancers; mutations in more than 90% of cancers with MSI
		PTEN	Frequency of inactivating mutations about 10% but loss of PTEN protein expression evident in 15%-20% of cancers

HER-2, human epidermal growth factor receptor 2; TGF-βR2, transforming growth factor-β receptor type II.

Data from References 20, 22, and 23.

Genomic Instability

Genomic instability is a hallmark of colorectal carcinogenesis, and presents as chromosomal instability (CIN) or MSI.[20] Three molecular pathways that lead to genomic instability are CIN, MSI, and CpG island methylator phenotype (CIMP) pathways. The CIN pathway accounts for about 85% of colorectal cancers, and typically follows genomic events initiated by a sporadic APC mutation, with subsequent activation of *RAS* or loss of *P53*.[22] Features of CIN include a high frequency of gene DNA amplifications/gains or deletions/losses and copy number alterations. Important consequences of CIN include imbalanced chromosome number (aneuploidy), chromosomal gene amplification, and loss of a wild-type allele of a tumor-suppressor gene, also referred to as loss of heterozygosity (LOH).

Up to 15% of colorectal cancers arise though the MSI pathway, which is caused by a disruption of DNA repair genes.[22] Microsatellites are a series of repeat nucleotide sequences that are spread out across the entire genome. Microsatellite replication errors within tumor DNA occur frequently, and mutations of the MMR genes that recognize and regulate DNA MMR errors contribute to MSI and colorectal tumorigenesis. Mutations in MMR genes can be inherited or developed by somatic causes. Germline mutation of MMR genes is an important characteristic of Lynch syndrome.

Alterations in gene expression or function in the absence of DNA sequence alterations are referred to as epigenetic changes, and these are usually due to methylation of DNA gene promoter regions or histone modifications.[22] The serrated neoplasia pathway (also referred to as the CIMP pathway) can lead to microsatellite stable and instable cancers. It accounts for 10%-20% of colorectal cancers, and is associated with epigenetic instability, *RAS* and *RAF* mutations. CIMP is characterized by hypermethylation of a panel of multiple genes that are associated with gene silencing and subsequent loss of tumor suppressor gene function.[5]

Growth Factor Signaling Pathways

Aberrant signaling of growth factor pathways plays an important role in colorectal tumorigenesis. Activation of prostaglandin signaling is an early step in the adenoma to carcinoma transformation process and is induced by upregulated expression of COX-2 and inflammation.[24] COX-2 mediates the synthesis of prostaglandin E2, which stimulates cancer growth. Furthermore, 80% of colorectal cancers have loss of 15-prostaglandin dehydrogenase, or 15-PGDH, the rate-limiting enzyme responsible for prostaglandin degradation. Dysregulated intracellular signal transduction from EGFR, a transmembrane glycoprotein involved in signaling pathways that affects cell growth, differentiation, proliferation, and angiogenesis, plays a key role in colorectal cancer pathogenesis and immune evasion in colorectal cancer. *EGFR* activation enables downstream signaling through the mitogen-activated protein kinase (MAPK)/RAS/RAF/MEK/ERK and PI3K/AKt/mTOR pathways, thereby promoting tumor differentiation, proliferation, progression, and survival.[22,24] EGFR is overexpressed in most colorectal cancers and high tumor EGFR overexpression is associated with a worse prognosis.[24] These mechanisms are relevant because of the availability of pharmacologic agents that can influence these signaling pathways and affect cell growth.

Oncogene and Tumor Suppressor Gene Alterations

Mutation or loss of the *APC* tumor suppressor gene is a key factor involved in tumor formation through constitutive activation of the Wnt signaling pathway, a mediator of cell-cycle progression, cell proliferation, differentiation, and apoptosis.[22] The *APC* gene encodes for APC protein that binds to and degrades cytoplasmic β-catenin, a downstream component of the Wnt signaling pathway. Inactivation of the *APC* gene is the single gene defect responsible for FAP and is frequently an initiating event in sporadic colorectal cancer.

Mutational inactivation of *P53* represents a frequent and key step in colorectal tumorigenesis, occurring in the majority of colorectal cancers.[22] Normal *P53* gene expression is important for G_1 cell-cycle arrest to facilitate DNA repair during replication and to induce apoptosis. An additional step in tumor progression is the mutational inactivation of the transforming growth factor-β (TGF-β) signaling pathway, which facilitates adenoma transition to high-grade dysplasia or carcinoma and also inactivates *SMAD4.* In normal epithelium, TGF-β has an antiproliferative role and induces growth arrest and apoptosis. Alterations in *SMAD4* or TGF-β receptors lead to a loss of the normal growth inhibitory response to TGF-β.

Several oncogene-activating mutations play an important role in promoting colorectal cancer.[22] Mutations in members of the *RAS* gene family—*KRAS*, *HRAS*, and *NRAS*—in addition to *BRAF*, activate the MAPK signaling pathway, which stimulates cell proliferation and other activities that promote

carcinogenesis. *HER2* gene amplification/overexpression occurs infrequently in colorectal cancer, although *RAS* and *BRAF* wild-type tumors have a greater likelihood of having HER2 overexpression.[24] Mutations of *PIK3CA*, which encodes the catalytic subunit of the PI3K survival pathway, increase production of phosphatidylinositol-3,4,5-triphosphate, which influences cell growth, proliferation, and survival. Mutation or loss of *PTEN*, a tumor suppressor gene that antagonizes PI3K signaling, produces similar effects. Multiple additional genetic alterations contribute to carcinoma formation and metastases by altering cellular growth, metabolism, migration, and invasive capabilities, and angiogenesis.[22,24]

Histology

Adenocarcinomas account for about 92% of tumors of the large intestine and about 7% are classified mucinous adenocarcinoma.[4] The other histologic types, such as signet-ring adenocarcinoma, squamous cell carcinoma, and neuroendocrine carcinomas, are rare. Adenocarcinomas are assigned one of the three tumor grade designations based on the degree of cellular differentiation, the degree to which the tumor resembles the structure, and the function of its cell of origin. The most differentiated adenocarcinomas are low-grade tumors, whereas high-grade tumors are the most undifferentiated, and have frequently lost the characteristics of mature normal cells. Poorly differentiated tumors are associated with a worse prognosis than those that are relatively better differentiated.

Mucinous adenocarcinomas possess the same basic structure as adenocarcinomas but differ in that they secrete an abundant quantity of extracellular mucus. They tend to be frequent in patients with MMR tumor mutations. Signet-ring adenocarcinomas also have a characteristic appearance but are uncommon. Signet-ring histology occurs more frequently in individuals younger than 50 years of age, patients with ulcerative colitis, and tends to be present at a more advanced stage of disease at diagnosis. Both mucinous and signet-ring adenocarcinoma histologies confer a poor prognosis. Patients with neuroendocrine tumors and squamous cell carcinoma often present with distant metastases and also have a poor prognosis.

PREVENTION AND SCREENING

Cancer prevention efforts can be either primary or secondary. Primary prevention strategies aim to prevent the development of colorectal cancer in a population at risk. Secondary prevention approaches are undertaken to prevent malignancy in a population that has already manifested an initial disease process.

Chemoprevention

2 Several agents have been evaluated as chemoprevention strategies for colorectal cancer, including prospective population-based screening trials of dietary fiber intake, and randomized controlled trials of calcium, vitamin D, and folate supplementation.[25-27] However, findings do not support their use now. Additional intervention trials of various micronutrients, epigenetic modulators, and other chemopreventive agents have been completed or are ongoing.[9,21,26,28-30] In addition, the most widely studied agents for the chemoprevention of colorectal cancer are aspirin, non-aspirin NSAIDs, and COX-2 selective inhibitors, but only aspirin is recommended for chemoprevention in some patients.[10,27,29] The effectiveness of these agents has been studied in high-risk individuals and within the general population.

In individuals with FAP, celecoxib, NSAIDs, and aspirin have been studied to delay the development of adenomatous polyps and to reduce polyp recurrence following colectomy with a retained rectum, but they are not viewed as alternatives to surgery.[25,26,29] In randomized controlled trials, celecoxib 400 mg orally twice daily as an adjunct to usual care significantly reduced the mean size and number of colorectal polyps after 6 to 9 months of treatment. However, the US Food and Drug Administration (FDA) approval for celecoxib was withdrawn because of lack of data showing long-term benefit. Sulindac induces adenoma regression but does not appear to delay or prevent malignancy. The benefits of these agents are transient because polyps increase in size and number within a few months after discontinuing treatment. These agents may be useful to reduce adenoma recurrence following surgery, but they are not recommended for chemoprevention.

2 Non-aspirin NSAIDs and COX-2 inhibitors reduce the risk of sporadic and recurrent colorectal adenomas in cohort and case-control studies, and COX-2 inhibitors were also effective in controlled trials.[31] Celecoxib is associated with a 34% relative risk reduction in adenoma recurrence and 55% risk reduction in the incidence of advanced adenomas.[29,31] Optimal dosing, agents, and duration of treatment remain to be determined, and cardiovascular events in addition to the risk of gastric ulceration and bleeding with these agents are of concern. Although NSAIDs may be appropriate for selected individuals at high risk for colorectal cancer but low risk for cardiovascular disorders, the US Preventive Services Task Force (USPSTF) has

concluded that potential harms associated with NSAID use (other than aspirin) outweigh benefits for prevention of colorectal cancer in the general population.[32]

The use of aspirin as both a primary and a secondary chemopreventive agent remains controversial. In patients with prior adenomas or diagnosis of colorectal cancer, regular daily aspirin use reduces colorectal adenoma recurrence, and colorectal cancer incidence and mortality.[29,30]

Aspirin reduces the risk of sporadic and recurrent adenomas by about 17% and advanced adenomas by 28%.[29,31] Higher aspirin doses reduced the risk of colorectal cancer over a 23-year follow-up period by 26% among the general population, but lower doses (75-300 mg) of daily aspirin for 5 years were also associated with a reduction in the risk of colorectal cancer and in 20-year mortality from colorectal cancer by 34%.[29,30] Individuals with Lynch syndrome who received aspirin 600 mg daily for at least 2 years experienced a 59% reduction in colorectal cancer risk that became evident 5 years after the aspirin was first started and had been discontinued.[29]

Although the optimal aspirin dose and treatment durations are unknown, increasing evidence supports a chemoprotective effect of aspirin in select high-risk individuals and in the general population. The extent of risk reduction appears to be inversely related to the duration of therapy and the chemopreventive effects of aspirin may be delayed by 5 to 10 years. However, the balance of risks and benefits with long-term aspirin use is unclear, and aspirin is only recommended for chemoprevention in some patients. The USPSTF guidelines endorse daily low-dose aspirin for at least 10 years in adults aged 50 to 59 years with a ≥10% 10-year cardiovascular disease risk, a life expectancy of at least 10 years, and who are not at risk for bleeding, for primary prevention of both cardiovascular disease and colorectal cancer.[32] Adults of age 60 to 69 years may also receive low-dose-daily aspirin for at least 10 years if the benefits outweigh the risks, and an individual risk calculation model could be useful to identify those individuals who would benefit most.[33] *PIK3CA* mutations, which are present in up to 20% of colorectal cancers, may also be a useful biomarker.[29] Among aspirin users with a history of colorectal cancer, those with tumor *PIK3CA* mutations experienced longer survival times compared to individuals without *PIK3CA*-mutated tumors.

Randomized controlled trials of calcium, vitamin D, and folate supplementation as chemoprevention have also been conducted, but findings do not support their use now.[28-30] Despite data from epidemiologic and preclinical studies that suggest a benefit from calcium and vitamin D supplementation, data from randomized clinical trials have been inconsistent. Individuals with adequate vitamin D levels and no known increased risk of colorectal cancer do not appear to benefit from calcium or vitamin D supplementation.[29] In two trials, folate supplementation was associated with a nonsignificant increase in adenoma recurrence. Based on these results, the use of folate supplementation to reduce colorectal cancer risk is not recommended now.[26]

Newer preventive strategies include metformin chemoprevention and gut microbiota modulation using prebiotics, probiotics, and other approaches. Metformin reduced risk of adenoma and colorectal cancer in patients with type 2 diabetes, but definitive randomized clinical trials are needed to establish its effects among populations with different risk.[29] Findings from two randomized, controlled trials of prebiotics and probiotics have shown beneficial alterations in colorectal cancer biomarkers, and further studies are warranted to confirm clinical benefit in colorectal cancer prevention.[34]

Surgical Resection

Surgical resection remains an option to prevent colon cancer in individuals at extremely high risk for its development.[35] Despite the effects of NSAIDs and COX-2 selective inhibitors on adenoma development and recurrence in individuals with FAP, their effects are incomplete, and surgical resection is necessary for cancer prevention for these high-risk individuals. Individuals with FAP who have polyposis on lower endoscopy screening examinations should undergo colectomy or proctocolectomy, typically starting around the age of 20 years. Because of the high incidence of metachronous (ie, consecutive development) cancers (45%) in patients with Lynch syndrome, prophylactic subtotal colectomy is recommended for individuals who are not candidates for routine close follow-up. Colonoscopic polypectomy, removal of polyps detected during screening colonoscopy, is considered the standard of care for all individuals to prevent the progression of premalignant adenomatous polyps to adenocarcinomas.

Screening

Colorectal cancer screening decreases mortality by detecting cancers at an early, curable stage, and by detecting and removing adenomatous polyps. Effectiveness of screening programs relies on participation, which is influenced by test access, costs, risk of complications, technical aspects, expected and perceived burden of the test, and the socioeconomic status and cultural beliefs of the participating individual.[33] Multiple screening

recommendations for early detection of colorectal cancer have been established; differences exist in specific screening guidelines published by various organizations.[36-41] Structural (visual) tests detect colorectal polyps and cancer while fecal-based tests detect early cancer. This section reviews available screening techniques for colon and rectal cancer.

Colonoscopy

Colonoscopy facilitates examination of the entire large bowel to the cecum in most patients and allows for simultaneous removal of premalignant lesions. Although no randomized trials show that colonoscopy directly decreases colorectal cancer mortality, observational studies show that screening colonoscopy and polypectomy reduces the incidence in colorectal cancer by about 80%, with a 50% to 60% reduction in colorectal mortality.[25,39] Colonoscopy allows for greater visualization of the colon, but it involves sedation, complete bowel preparation, and is associated with greater risk and inconvenience to patients. Colonoscopy is considered the gold standard for colorectal screening because of its ability to detect and remove lesions in the proximal as well as distal colon.[25,39,42]

Flexible Sigmoidoscopy

Flexible sigmoidoscopy (FSIG) uses a 60-cm flexible sigmoidoscope to examine the lower half of the bowel to the splenic flexure for most patients and is thus capable of detecting 50% to 60% of cancers.[39] According to some randomized trials, FSIG may decrease colorectal cancer incidence and mortality by 23% and 31%, respectively.[36,39] The combination of FSIG and a fecal-based test appears to improve sensitivity for lesions that will be missed by sigmoidoscopy alone, but the true benefit of this approach to general practice has not been established.[39] FSIG offers the advantage of not requiring sedation or extensive bowel preparation, but the entire colon cannot be examined with FSIG and suspicious lesions must be evaluated by colonoscopy.[42]

Computed Tomography Colonography

Computed tomography colonography, also referred to as *virtual colonoscopy*, is an imaging procedure that creates two- or three-dimensional images of the colon by combining multiple helical computed tomography (CT) scans.[36] Sedation is not required and initial tests show high sensitivity and specificity for detecting adenomas of at least 6 mm in size. However, the procedure requires complete bowel preparation and is associated with radiation exposure, and colonoscopy will still be necessary to remove detected lesions.[39,42] Individuals may find this method as a more acceptable option to colonoscopy or sigmoidoscopy, although the insufflation procedure can be associated with some discomfort.[5]

Fecal Occult Blood Tests

Fecal occult blood tests (FOBTs) detect occult blood in the stool that may be associated with bleeding adenomas or cancer. Results from randomized controlled trials of annual FOBT screening show a reduction in colorectal cancer mortality by 33%.[39] Unlike structural tests, FOBTs are noninvasive and do not require bowel preparation. However, they will not detect most polyps and may produce false-positive or false-negative results.[36,39] Two main methods are available to detect occult blood in the feces: guaiac-based FOBT (gFOBT) and fecal immunochemical tests (FITs), also known as immunochemical FOBT. gFOBTs detect pseudoperoxidase activity of heme in human blood. Because gFOBTs detect blood from any sources and some foods affect peroxidase activity, patients are instructed to avoid NSAIDs, red meat, vitamin C, and large amounts of citrus for at least 3 days before and through the testing period.

Several limitations associated with gFOBT screening are of concern. Many early-stage tumors do not bleed, or bleed intermittently, and therefore the false-negative rates can be high and are variable depending on the gFOBT product used. In addition, the test results may not be valid because the test is often poorly performed both in the home and in physician office settings.[36,39] However, these concerns are addressed by testing three successive stool samples. False-positive results can prove to be very expensive and inconvenient for a patient because of the follow-up tests required to confirm a positive result. Annual screening, preferably using a high-sensitivity gFOBT (eg, Hemoccult SENSA), is an acceptable option for individuals at average risk for colorectal cancer. It should be noted that FOBT conducted in conjunction with a digital rectal exam during an office visit is not considered adequate colorectal screening.

FITs were developed to reduce false-positive and false-negative test results associated with the gFOBT. FIT uses antibodies to detect the globin protein

portion of human hemoglobin. Since globin is degraded by enzymes in the upper gastrointestinal tract, FIT is more specific for lower gastrointestinal bleeding. Also, no diet or medication restrictions are necessary and testing involves a single stool sample collection annually.[38] FIT is more accurate than gFOBT for detecting cancer and advanced adenomas, although colonoscopy identifies more adenomas.[39,42]

Stool DNA Screening Tests

Molecular screening strategies analyze stool samples for the presence of potential markers of malignancy in cells that are shed from premalignant polyps or adenocarcinomas in the bowel.[36,39] Adenomas and carcinomas can contain certain DNA mutations and markers of MSI that can be detected using multi-target stool DNA (mt-sDNA) testing. A combined FIT and mt-sDNA test is available that has improved sensitivity for advanced adenomas and sessile serrated polyps, but lower specificity compared to FIT.[33,36,39] The optimal appropriate screening interval is unclear, although it may be less frequent than annual FIT.[39] Like other stool-based tests, patients with positive test results should be followed up with a colonoscopy.

Capsule Colonography

Capsule colonography (CapC) is not approved for screening average-risk patients, but it is approved for colorectal imaging in patients who are not candidates for sedation or colonoscopy or who had a previous incomplete colonoscopy.[37,39] This procedure uses a wireless capsule device that is swallowed by the patient to examine the gastrointestinal tract, thereby avoiding risks associated with sedation and colonoscopy.

Serology Test

A *SEPT9* DNA methylated polymerase chain reaction (PCR)-based blood test is approved for colorectal cancer screening but is not recommended in US cancer screening guidelines. Methylated *SEPT9* DNA is a form of the *SEPT9* gene that distinguishes colorectal cancer from normal tissue and is found in circulating plasma with some colorectal cancers.[36] Although the test has low sensitivity for detecting colorectal cancer, it may be an alternative for individuals who refuse to undergo other screening tests.[39]

Screening Summary

Table 153-3 shows US screening guidelines for early detection of colorectal cancer with the goal of cancer prevention.[36-41] In recognition of the increasing incidence of colorectal cancer in adults younger than 50 years, the American Cancer Society, the National Comprehensive Cancer Network (NCCN), and the USPSTF recommend initiating colorectal cancer screening for individuals at average risk for colorectal cancer (their only risk factor is age greater than or equal to 45 years) at the age of 45 years.[36,38,39,42] Recommended programs for regular screening include a colonoscopy every 10 years, annually with a high-sensitivity gFOBT or FIT, or an FSIG every 5 years. Recommendations for screening procedures and schedules vary among organizations. The US Multi-Society Task Force on Colorectal Cancer, the American College of Gastroenterology, and the American College of Physicians recommend colorectal cancer screening in adults at average risk beginning at the age of 50 years, except in Black individuals, for whom evidence supports screening starting at the age of 45 years.[37,40,41]

Several screening methods are available, which have the potential to reduce colorectal cancer mortality, and because each method is associated with different benefits and potential harms, patient preferences and available resources should be considered for individual patients.[36,42] More aggressive (usually starting at an earlier age) screening recommendations are given for moderate-to-high risk individuals and colonoscopy is generally preferred for initial screening and surveillance following polyp removal in this population.[5,39] Most organizations recommend discontinuing screening and surveillance in populations when risk may outweigh benefit. Routine colorectal cancer screening is recommended for individuals up to the age of 75 years with a life expectancy ≥10 years, with individualized screening decisions made for individuals aged 76 to 85 years and discontinuing screening in adults older than 85 years.[36-42]

TABLE 153-3

Guidelines for Colorectal Cancer Screening in the United States for Individuals at Average Risk, 45-50 Years of Age and Older[a,b]

	ACS	USPSTF	USMSTF	NCCN	ACP	ACG
Fecal-based Tests						
FIT	Annually	Annually	Annually	Annually	Every 2 years	Annually
gFOBT	Annually	Annually	Not recommended	Annually	Every 2 years	Not recommended
mt-sDNA	Every 3 years	Every 1 to 3 years (with FIT)	Every 3 years	Interval uncertain but every 3 years suggested	Not recommended	Every 3 years
Structural (visual) Tests						
Colonoscopy	Every 10 years	Every 10 years	Every 10 years	Every 10 years	Every 10 years	Every 10 years
CTC	Every 5 years	Every 5 years	Every 5 years	Every 5 years	Not recommended	Every 5 years
FSIG	Every 5 years	Every 5 years	Every 5-10 years	Every 5-10 years	Not recommended	Every 5-10 years
Others	----------	FSIG every 10 years + FIT *annually*	CapC every 5 years if patient declines other options	----------	FSIG every 10 years + FIT every 2 years	CapC every 5 years if patient declines other options

[a]Starting at the age of 45 years (ACS, USPSTF, NCCN).

[b]Starting at the age of 45 years if Black individual (USMSTF).

ACP, American College of Physicians; ACG, American College of Gastroenterology; ACS, American Cancer Society; CapC, capsule colonography; CTC, computed tomography colonography; USMSTF, US Multi-Society Task Force on Colorectal Cancer; USPSTF, US Preventive Services Task Force.

Data from References 36-41.

CLINICAL PRESENTATION AND DIAGNOSIS

Signs and Symptoms

The signs and symptoms associated with colorectal cancer can be extremely varied and nonspecific. Patients with early-stage colorectal cancer are often asymptomatic, and lesions are usually found through screening studies. Any change in bowel habits (eg, constipation, diarrhea, alteration in size or shape of stool), abdominal pain, or distension may be warning signs of a malignant process. Obstructive symptoms and changes in bowel habits frequently develop with tumors located in the transverse and descending colon. Rectal cancer may be associated with tenesmus, though bleeding is the most common symptom. Bleeding may be acute or chronic and can appear as bright red blood mixed with stool or melena. Iron-deficiency anemia, presenting as weakness and fatigue, can develop from chronic occult blood loss.

About 20% of patients with colorectal cancer present with metastatic disease.[1] Metastatic spread occurs in the setting of direct tumor invasion of the peritoneum or by lymphatic or hematogenous spread. The venous drainage of the colon and rectum influences the pattern of metastases most commonly seen. The most common site of metastasis is the liver followed by the lungs, and then bones, specifically the sacrum, coccyx, pelvis, and lumbar vertebrae. Liver metastases are present in 25% of patients at presentation, with another 25% to 30% of patients developing liver metastases in the following 2 to 3 years from diagnosis.[43]

CLINICAL PRESENTATION: Colorectal Cancer

General

- Patient symptoms are usually nonspecific and can vary drastically among patients.
- Most patients are asymptomatic.

Symptoms

- Change in bowel habits (generally an increase in frequency) or rectal bleeding.
- Constipation, depending on the location of the tumor.
- Nausea, vomiting, and abdominal discomfort.
- Fatigue may be present if anemia is severe.

Signs

- Blood in the stool is the most common sign in symptomatic patients.
- Hepatomegaly and jaundice in advanced disease.
- Leg edema is a consequence of lymph node involvement, thrombophlebitis, fistula formation, weight loss, and pain in the lower back or radiating down the legs may be indicative of widespread disease.

Laboratory Tests

- Positive guaiac stool test and anemia (iron deficiency) from blood loss.
- Elevated carcinoembryonic antigen (CEA; more likely in patients with higher stages at presentation).
- Elevated liver enzymes may be present with metastatic disease.

Workup

When a patient is suspected of having colorectal carcinoma, a complete history and physical examination should be performed. The patient history should include a past medical history and family history, especially noting the presence of inflammatory bowel disease, colorectal cancer, polyps, and familial clustering of cancers to assess risk for an inherited colorectal cancer syndrome, as well as a full medication history, including prescription, over-the-counter (OTC), and complementary or alternative therapies. A complete physical examination includes careful abdominal examination for the presence of masses or ascites, a rectal examination, and an assessment for possible hepatomegaly and lymphadenopathy. A breast and pelvic examination is recommended in all women.

Evaluation of the entire large bowel requires a total colonoscopy, which allows for tissue collection for histologic evaluation to provide a tissue diagnosis following the procedure. Patients with invasive cancer of the colon or rectum require a complete staging workup, which includes laboratory testing and imaging of the abdomen, pelvis, and chest. Baseline laboratory tests should be obtained and include a complete blood cell count, platelet

count, international normalized ratio, prothrombin time, activated partial thromboplastin time, liver chemistries, renal function tests, and CEA level. Abnormal liver chemistry test results may suggest liver involvement with tumor, though normal levels do not preclude metastatic involvement. Iron studies (eg, serum ferritin, serum iron, and total iron-binding capacity) may identify iron deficiency in patients with anemia.

CEA belongs to a group of cell-surface glycoproteins termed *oncofetal proteins*, which are expressed during embryonic development and re-expressed on the cell surfaces of many carcinomas, particularly those originating from the gastrointestinal tract. CEA concentrations can be measured in the blood and can, therefore, potentially serve as a marker for colorectal cancer. Elevated CEA levels are more frequent in patients with metastatic disease, but not all colorectal cancers produce CEA. Several concomitant disease states are associated with an elevated CEA: liver diseases, gastritis, peptic ulcer disease, diverticulitis, chronic obstructive pulmonary disease, chronic or acute inflammatory conditions, and diabetes.[44] Most commercially available assays list a value of less than 5 ng/mL (µg/L) as the upper limit of normal. Although CEA measurement is too insensitive and nonspecific to be used as a screening test for early-stage colorectal cancer, it is the surrogate marker of choice for monitoring colorectal cancer response to treatment, particularly if the pretreatment concentration is elevated.[44] The CEA test may have preoperative prognostic implications because it correlates with the size and degree of differentiation of the carcinoma. Elevated preoperative CEA levels correlate with poor survival and may predict the likelihood of recurrence, regardless of tumor stage at diagnosis. However, it should not be used as an indication for adjuvant therapy. After a potentially curative resection, CEA levels should return to normal within 4 to 6 weeks. Persistently elevated CEA levels may indicate residual disease, while elevations after normalization may indicate relapsed disease.

Radiographic imaging studies are used to evaluate the extent of disease involvement for initial staging, and subsequently to monitor disease response to therapy. Contrast dye-enhanced CT scans of the chest, abdomen, and pelvis are performed to evaluate pulmonary, hepatic, and retroperitoneal involvement as well as occult abdominal and pelvic disease. In certain cases, such as patients with contrast dye allergies, magnetic resonance imaging (MRI) of the abdomen and pelvis may be substituted. A glucose analog [^{18}F]-fluorodeoxyglucose-positron emission tomography (PET) scan may also be performed as the primary imaging modality or to confirm metastatic disease if findings from CT or MRI scans are not conclusive. PET imaging may provide functional information to assist in discriminating between benign and malignant disease by detecting tumor-related metabolic alterations in affected tissues. PET scans are commonly used for the detection of recurrent colorectal cancer in patients with rising CEA levels and inconclusive findings on standard imaging studies. A PET scan is often performed in conjunction with a CT scan for anatomical localization of a lesion(s). For initial rectal cancer staging, assessment of the extent of tumor spread into the surrounding mesorectum and depth of invasion within the bowel wall may be performed using MRI or endorectal ultrasound.

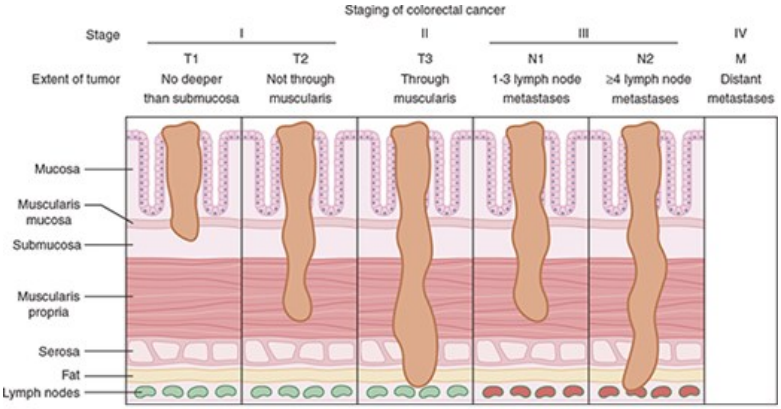
Because of the increased likelihood of Lynch syndrome in patients diagnosed with colorectal cancer younger than the age of 50 years, MMR protein testing on the cancer specimen is recommended. The level of MMR protein expression can be determined by immunohistochemistry, which is decreased with MMR gene mutations. Gene sequencing can also be performed to detect MSI. If immunohistochemical analysis of the tumor reveals the absence of MLHI protein expression, *BRAF* gene mutation testing is recommended to distinguish between somatic and germline *MLH1* gene mutation. Individuals with abnormal MMR protein expression or MSI should be referred for genetic counseling as additional testing and cancer susceptibility risk assessment may be appropriate for themselves and family members.

Staging

Staging examinations determine the extent of disease, which allows the clinician to develop treatment plans and estimate overall prognosis. The same TNM classification system is used for both cancers of the colon and rectum since the categories reflect similar survival outcomes.[44,45] This classification assesses three aspects of cancer growth: T (tumor size or penetration), N (lymph node involvement), and M (presence or absence of metastases). The TNM classification also allows for various subdivisions within each of the three categories, which is then used to determine the disease stage. Table 153-4 summarizes the staging definitions used in the TNM system and corresponding 5-year survival rates.[44-46] Figure 153-4 shows the various stages of cancer based on cancer penetration through the bowel wall and extension to regional lymph nodes. An individual patient's stage is determined at the time of the initial diagnosis and does not change with progression of disease or recurrence. For example, if a patient is diagnosed with stage II colon cancer and later recurs with metastases to the liver, that patient is in stage II now with metastatic disease to the liver, not stage IV.

FIGURE 153-4

TNM staging for colorectal cancer. *(Reproduced with permission from Mayer RJ. Lower Gastrointestinal Cancers. In: Jameson J, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine, 20e. McGraw Hill; 2018.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 153-4

Colon Cancer by TNM Classification and Associated 5-Year Survival Rate

Stage	T	N	M	Survival (%)
0	T_{is}	N_0	M_0	95.6
I	T_1	N_0	M_0	97.4
	T_2	N_0	M_0	96.8
IIA	T_3	N_0	M_0	87.5
IIB	T_{4a}	N_0	M_0	79.6
IIC	T_{4b}	N_0	M_0	58.4
IIIA	T_1-T_2	N_1/N_{1c}	M_0	71.1
	T_1	N_{2a}	M_0	68.5
IIIB	T_3-T_{4a}	N_1/N_{1c}	M_0	60.6-68.7
	T_2-T_3	N_{2a}	M_0	53.4-81.7
	T_1-T_2	N_{2b}	M_0	62.4
IIIC	T_{4a}	N_{2a}	M_0	40.9
	T_3-T_{4a}	N_{2b}	M_0	21.8-37.3
	T_{4b}	N_1-N_2	M_0	15.7
IVA	Any T	Any N	M_{1a}	11.5[a]
IVB	Any T	Any N	M_{1b}	11.5[a]
IVC	Any T	Any N	M_{1c}	11.5[a]

Primary Tumor (T)

T_{is}, Carcinoma in situ: intraepithelial or invasion of lamina propria with no extension through muscularis mucosae.

T_1, Tumor invades submucosa through the muscularis mucosa but not into the muscularis propria.

T_2, Tumor invades muscularis propria.

T_3, Tumor invades through the muscularis propria into pericolorectal tissues.

T_{4a}, Tumor invades through the visceral peritoneum, including bowel perforation through tumor and invasion of tumor through inflammatory surface of visceral peritoneum.

T_{4b}, Tumor directly invades or is adherent to other organs or structures.

Lymph Nodes (N)

N_0, no regional lymph node metastasis.

N_1, metastasis in 1-3 lymph nodes.

N_{1a}, metastasis in 1 lymph node.

N_{1b}, metastasis in 2-3 lymph nodes.

N_{1c}, tissue tumor deposits without lymph node metastasis.

N_2, metastasis in 4 or more lymph nodes.

N_{2a}, metastasis in 4-6 lymph nodes.

N_{2b}, metastasis in more than 7 lymph nodes.

Distant Metastasis (M)

M_0, no distant metastasis

M_{1a}, metastasis confined to one site or organ without peritoneal metastasis.

M_{1b}, metastasis in two or more sites or organs without peritoneal metastasis.

M_{1c}, metastasis to the peritoneal surface with/without metastasis to another site or organ.

[a]Survival for Stage IVA-C.

Data from References 44-46.

Prognosis

The stage of colorectal cancer upon diagnosis is the most important independent prognostic factor for survival and disease recurrence. Five-year survival is about 90% for individuals who present with a localized tumor stage at diagnosis as compared with about 14% for individuals with metastatic disease at diagnosis.[1]

Clinical factors present at the time of diagnosis that are associated with a poor prognosis and decreased survival include bowel obstruction or perforation, high preoperative CEA level, distant metastases, and location of the primary tumor in the rectum or rectosigmoid area.[47] Along with resection of the primary tumor, a minimum of 12 lymph nodes must be examined to accurately determine regional lymph node involvement and predict lymph node-negative disease. The pathologic assessment also includes determination of TNM stage, tumor type, and histologic grade, presence of venous, and lymphatic invasion, and whether the resected margins are free of tumor.[44] Consideration of these factors plays an important role in determining optimal strategies for treatment and appropriate follow-up. Additional morphologic tumor features that have been associated with adverse clinical outcome include infiltrative tumor border configuration, evidence of perineural invasion, extranodal tumor deposits, and presence of tumor budding, characterized by clusters of cells that possess properties of malignant stem cells and are associated with increased risk of local and distant spread.

Certain molecular markers, particularly MSI, 18q/*DCC* mutation or LOH, *BRAF V600E* mutation, and *RAS* mutations, are also associated with colorectal cancer prognosis, although the pathologic stage of disease remains the primary prognostic assessment.[44,48] Colorectal cancers with allelic LOH on chromosome 18q or absent DCC protein are associated with a worse prognosis within stages II and III disease, but data are insufficient to warrant use

of this test in practice now.[49] MSI can be determined through DNA sequencing or by immunohistochemistry staining for protein products of the MMR genes. Colorectal cancers that demonstrate MSI-H appear to be associated with a more favorable outcome and do not benefit from adjuvant fluoropyrimidines for early-stage disease. Tumor DNA *BRAF* and *RAS* mutation status appears to be associated with overall survival but is not used to determine prognosis.

Although multiple prognostic biomarkers for colorectal cancer have been identified, single molecular tests other than MSI are not used routinely in clinical practice. However, several multigene assays have been developed that provide prognostic information to assist in identifying individuals at high risk for cancer recurrence from early-stage disease.[44,48] The Onco*type* DX colon cancer assay is commercially available and has been validated in several trials as a prognostic test for stages II and III colon cancer.[50,51] Gene expression profiles classify risk of recurrence as low, intermediate, or high, and these scores are prognostic for recurrence, disease-free survival, and overall survival. The ColoPrint gene expression assay characterizes the risk of recurrence as low or high, and is undergoing further validation in clinical trials.[44] The ability for these and other gene signature assays in development to predict which patients may benefit from adjuvant chemotherapy has not been well established.

TREATMENT

Desired Outcomes

Treatment goals for cancer of the colon or rectum are based on the stage of disease at presentation. Stages I, II, and III disease are considered potentially curable and the goal of management is to eradicate potential micrometastases after surgical resection. Based on the numbers and site(s) of metastases, about 20% to 30% of patients with metastatic colorectal cancer may be cured, if their metastases are considered resectable.[44] Most patients with stage IV disease are not curable, and treatments for metastatic disease are considered palliative to reduce symptoms, avoid disease-related complications, and prolong survival. However, special attention should be given to those with oligometastatic lesions in the liver or lung since potential cure is still possible for some of these patients.

General Approach

Performance status, concomitant disease states, lifestyle factors, patient preferences, and patient age (although advanced age is not an absolute contraindication for aggressive therapies) must be considered in the treatment planning process. Special or emergent conditions, such as bowel obstruction or perforation, severe pain, anemia, or other symptomatic problems, need to be addressed acutely, after which time a more long-term disease-specific plan can be developed. The treatment approaches for cancer of the colon or rectum reflect two primary treatment goals: curative therapy for localized disease and palliative therapy for metastatic cancer.

For patients for whom treatment intent is curative, surgical resection of the primary tumor is the most important component of therapy. Depending on the extent of disease and whether the tumor originated in the colon or rectum, further adjuvant chemotherapy or chemotherapy plus XRT (chemoradiation) may be appropriate. For selected patients with resectable metastases, surgical resection may be an option. However, for most patients with metastases, systemic chemotherapy is the mainstay of treatment; XRT may also be useful for disease palliation of localized symptoms. Patients with metastatic disease who are asymptomatic may benefit from initiation of therapy and continuous treatment should be considered.

Operable Disease

Surgery

4 Individuals with operable—stages I, II, and III—cancer of the colon or rectum should undergo complete surgical resection of the primary tumor mass with regional lymphadenectomy as a curative approach for their disease.[33] The surgical approach for colon cancer generally involves complete resection of the tumor with at least a 5-cm margin of tumor-free bowel and regional lymphadenectomy of at least 12 lymph nodes.

The preferred surgical procedure for rectal cancer is total excision of the mesorectum, the surrounding tissue containing perirectal fat and draining lymph nodes.[33,45] If the distal margin clear of tumor is at least 1 cm, sphincter-preserving surgery may be possible for patients with cancers in the middle and lower portion of the rectum. Individuals who are not candidates for sphincter-sparing resections or have extensive local spread of tumor will require an abdominoperineal resection. This involves removal of the distal sigmoid colon, rectosigmoid colon, rectum, and anus with the

establishment of a permanent sigmoid colostomy.

Colectomies for colon cancer can be performed as open procedures or laparoscopically. Laparoscopic colectomy has become an accepted procedure for colon cancer.[44] This technique appears to produce similar results to conventional surgery, with the benefits of a smaller surgical incision, shorter hospital stay, shorter duration of ileus, and reduced pain. Complications associated with colorectal surgery include infection, anastomotic leakage, obstruction, adhesion formation, sexual dysfunction, and malabsorption syndromes, depending on the site and extent of resection. Complications affecting bowel function associated with surgery for rectal cancer increase as the level of anastomosis approaches the anus.

Neoadjuvant XRT for Colon Cancer

XRT has a limited role in colon cancer because most recurrences are extrapelvic and occur in the abdomen. A subset of patients with recurrent disease or with T_4 tumors that have penetrated fixed structures may benefit from neoadjuvant (preoperative) fluorouracil-based chemoradiation to improve resectability.[44] Adverse reactions associated with XRT in colon cancer can be acute or chronic. Acute effects primarily include hematologic depression, dysuria, diarrhea, abdominal cramping, and proctitis. Chronic symptoms that sometimes persist for months following discontinuation of XRT include persistent diarrhea, proctitis or enteritis, small bowel obstruction, perineal tenderness, sexual dysfunction, and impaired wound healing.

Adjuvant Chemotherapy for Colon Cancer

Adjuvant chemotherapy in colorectal cancer is administered after complete tumor resection in an attempt to eliminate residual micrometastatic disease, thereby decreasing tumor recurrence and improving survival rates. Patients should start adjuvant therapy as soon as they are medically stable following surgery because each 4-week delay results in a 14% decrease in overall survival.[44] Because more than 90% of patients with stage I colon cancer are cured by surgical resection alone, adjuvant therapy is not indicated.

Patients with stage II disease who are at higher risk for relapse should be offered adjuvant therapy, with a detailed discussion regarding the potential benefits versus treatment-related toxicities.[44] High-risk features include those with inadequate lymph node sampling, perforation of the bowel at presentation, poorly differentiated tumors, lymphovascular invasion, perineural invasion, inadequately sampled lymph nodes (<12 evaluated), T_4 lesions (stage IIB/IIC), and lesions with localized perforation or close or indeterminate margins. Individuals with MSI-H tumors have a better prognosis compared to those with MSI-L and may not benefit or even be harmed from adjuvant chemotherapy.

The presence of lymph node involvement with tumor places patients with stage III colon cancer at high risk for recurrence, and the risk of death within 5 years of surgical resection alone is as high as 70%, depending on the number of lymph nodes involved.[4] In this group of patients, adjuvant chemotherapy significantly decreases risk of cancer recurrence and death and is standard of care.

4 Standard adjuvant chemotherapy regimens include a fluoropyrimidine (fluorouracil [with leucovorin] or capecitabine) in combination with oxaliplatin (FOLFOX or CAPEOX) or administered alone (Table 153-5).[52-56] The addition of oxaliplatin is superior to fluoropyrimidines alone in stage III colon cancer, but this benefit has not been observed in stage II colon cancer.[44]

TABLE 153-5

Chemotherapy Regimens for the Adjuvant Treatment of Colorectal Cancer

Regimen	Agents	Comments
FOLFOX[52,53]	Oxaliplatin 85 mg/m^2 IV on day 1 Leucovorin 400 mg/m^2 IV on day 1 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin on day 1, then 1,200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46-48 hr) Repeat every 2 weeks × 24 weeks[a,b]	Preferred regimen for stage III colon and rectal cancer high-risk stage colon cancer; common toxicities: sensory neuropathy, neutropenia
CAPEOX[53,54]	Oxaliplatin 130 mg/m^2 IV day 1 Capecitabine 1,000 mg/m^2 twice daily orally days 1 through 14 Each cycle lasts 3 weeks × 24 weeks[a,b]	Improved DFS in patients with stage III colon cancer compared to capecitabine alone or Roswell Park Regimen; common dose-limiting toxicities: neuropathies and hand-foot syndrome. A preferred regimen for adjuvant rectal therapy
Capecitabine[55]	Capecitabine 1,000 mg/m^2 to 1,250 mg/m^2 PO twice daily on days 1 through 14 Each cycle lasts 14 days and is repeated every 3 weeks × 24 weeks	Hand-foot syndrome common, useful for patients without vascular access or who have difficulties with travel to infusion center
Roswell Park Regimen[56]	Leucovorin 500 mg/m^2 IV day 1 over 2 hr Fluorouracil 500 mg/m^2 IV bolus 1 hr after leucovorin Repeat weekly for 6 of 8 weeks × 4 cycles	Leukopenia common dose-limiting toxicity, diarrhea, and stomatitis common
Simplified Biweekly[44]	Leucovorin 400 mg/m^2 per day IV Fluorouracil 400 mg IV bolus, after leucovorin, then 1,200 mg/m^2/day days 1 and 2 (total 2,400 mg/m^2 over 46-48 hr) for 2 consecutive days Repeat every 2 weeks × 12 cycles	Hand-foot syndrome common

[a]Known as mFOLFOX6; survival benefit has not been demonstrated for patients 70 years and older.

[b]In patients with low-risk stage III (T1-3, any N), 3 months of CAPEOX is non-inferior to 6 months of CAPEOX for DFS but this has not been proven for FOLFOX. In patients with high-risk stage III disease (T4, N1-2, or any T, N2), 3 months of FOLFOX is inferior to 6 months of FOLFOX for DFS, but this has not been proven with CAPEOX. Grade 3 neuropathy is lower with 3 months of CAPEOX or FOLFOX.

CIV, continuous intravenous infusion; DFS, disease-free survival; OS, overall survival; PO, by mouth.

Data from References 44 and 52-56.

Fluorouracil Plus Oxaliplatin Regimens

4 NCCN guidelines recommend the FOLFOX (fluorouracil/leucovorin and oxaliplatin) regimen as the preferred treatment for patients with stage III colon cancer who can tolerate combination therapy.[44] These recommendations are based on results from the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, where the addition of oxaliplatin resulted in a 20% risk reduction in disease recurrence and increased 5-year disease-free survival (73% vs 67%) as compared with fluorouracil plus leucovorin alone.[52] With a median follow-up of 82 months, the addition of oxaliplatin resulted in an absolute 6-year overall survival difference of 2.5%. FOLFOX was associated with increased risk of paresthesia, neutropenia, and gastrointestinal toxicity (nausea, vomiting, and diarrhea) but toxicities were manageable with supportive care. This initial trial was performed with FOLFOX4 dosing schedule. Studies have further modified the regimen to improve tolerability and mFOLFOX6 regimen is now used.[44] A survival benefit has not been demonstrated for FOLFOX in patients with stage II colon cancer, but it is often used in stage II patients with multiple high-risk factors.[57]

5 Toxicity associated with fluorouracil differs based on the dose, route, and schedule of administration. Leukopenia is the primary dose-limiting toxicity of IV bolus fluorouracil, although diarrhea, stomatitis, and nausea and vomiting can also occur.[58] The incidence and severity of stomatitis can be significantly reduced with the use of oral cryotherapy. In this approach, the patient is instructed to chew and hold ice chips in the mouth during the period between 5 minutes prior to and 30 minutes following the bolus injection of fluorouracil. The protective effects of this procedure are probably related to the local vasoconstriction caused by the ice chips, which temporarily reduces blood flow to the oral mucosa, thereby reducing drug exposure to the oral mucosa.

5 Although continuous IV infusion fluorouracil is generally well tolerated, dose-limiting toxicities can be substantial. A distinct toxicity, palmar–plantar erythrodysesthesia (“hand-foot syndrome” or PPE), and stomatitis occur most frequently with this route of administration.[58] Hand-foot syndrome occurs in 24% to 40% of patients receiving extended continuous IV infusions and is characterized by painful swelling and erythroderma of the soles of the feet, palms of the hands, and distal fingers. The skin toxicity is fully reversible on interruption of therapy or dose reduction and is not life-threatening, but it can be significant and acutely disabling. The risk of stomatitis, diarrhea, and hematologic toxicity is not substantial at standard doses, but it increases with increasing fluorouracil doses. No significant difference is noted in the incidence of mucositis, diarrhea, nausea and vomiting, or alopecia between continuous and bolus IV fluorouracil administration.

5 An additional determinant of fluorouracil toxicity, regardless of the method of administration, is related to its catabolism and pharmacogenomic factors. DPD is the main enzyme responsible for the catabolism of fluorouracil to inactive metabolites. A rare pharmacogenetic disorder characterized by complete or near-complete deficiency of this enzyme has been identified in patients with cancer. Patients with this enzyme deficiency develop severe toxicity, including death, after fluorouracil administration. Molecular studies have identified a relationship between allelic variants in the *DPYD* gene (the gene that encodes DPD) and a deficiency in DPD activity.[44] An approved genetic test for *DPYD* polymorphisms is available to identify patients who would require lower fluorouracil doses to avoid severe toxicity, but pretreatment DPYD genotyping is not recommended.

The addition of leucovorin to fluorouracil regimens increases the binding affinity of the active fluorouracil metabolite to thymidylate synthase (TS), thus enhancing its cytotoxic activity. Leucovorin administration prior to fluorouracil is the most effective approach to enable intracellular-reduced folates to accumulate prior to fluorouracil administration. When leucovorin is unavailable, levoleucovorin, the active isomer of racemic leucovorin, can be substituted as an alternative. The recommended levoleucovorin dose is 50% of the leucovorin dose.[59]

5 Oxaliplatin has minimal renal toxicity, myelosuppression, and nausea and vomiting when compared with other platinum-based drugs. Oxaliplatin is associated with both acute and persistent neuropathies.[60] The acute neuropathies occur within 1 to 2 days of dosing and resolve within 2 weeks. The neuropathies usually occur peripherally, but may also occur in the jaw and tongue. A rare acute syndrome of pharyngolaryngeal dysesthesia (1%-2% of patients) is characterized by subjective sensations of difficulty in swallowing and shortness of breath. Overall, acute neuropathies occur in about 90% of patients, and are precipitated or exacerbated by exposure to cold temperatures or cold objects. Thus, patients should be instructed to avoid cold drinks and use of ice, and to cover skin before exposure to cold environments or cold objects. Several prophylactic and treatment strategies have been studied with varying degrees of success. Persistent neuropathy is typically a cumulative adverse drug reaction occurring after 8 to 10 cycles. The neuropathy is characterized by paresthesia, dysesthesia, and hypoesthesia, but may also include deficits in proprioception that can interfere with daily activities (eg, writing, buttoning, swallowing, and difficulty walking as a result of impaired proprioception). Persistent neuropathy occurs in about one-half of patients receiving oxaliplatin but may improve or resolve with dosage reductions or cessation of oxaliplatin therapy.[44,60] Prophylaxis with calcium and magnesium infusions has not been proven effective. A “stop-and-go” approach where oxaliplatin is temporarily discontinued after 3

months of therapy (or sooner with significant neuropathic symptoms) with the other drugs continued reduces neurotoxicity without compromising antitumor activity and has been advocated.[44] Oxaliplatin can be reinitiated at disease progression in those patients who experience near complete resolution of neurotoxicity. Duloxetine may be used to treat painful neuropathy.

Fluorouracil/Leucovorin Regimens

The efficacy of bolus and continuous infusion schedules generally favor continuous infusion of fluorouracil, which is probably related to its short plasma half-life and S-phase specificity for optimal TS inhibition. Continuous IV infusions also permit increased fluorouracil dose intensity, which may account for the higher response rates observed with prolonged infusions of fluorouracil. Most commonly, fluorouracil is administered by both IV bolus injection and continuous IV infusion (eg, FOLFOX and simplified biweekly regimens; see Table 153-5).

Capecitabine Regimens

4 Capecitabine can be used as an alternative for fluorouracil in an attempt to improve the safety and ease of administration of the chemotherapy regimen. Capecitabine is converted to fluorouracil through a three-step activation process, the final step being activation by thymidine phosphorylase, which is present in greatest concentrations at the tumor site. These activation steps lead to about a threefold increase in tumor fluorouracil levels. CAPEOX prolonged 3-year disease-free survival (71% vs 67%) as compared to bolus fluorouracil alone in patients with stage III disease, but did not prolong overall survival.[61] Capecitabine is non-inferior to bolus fluorouracil and leucovorin in patients with stage III colon cancer.[55] Disease-free survival between the groups was equivalent, and safety was improved with capecitabine.

5 The toxicities differ for the two regimens, with increased risks of neuropathies and hand-foot syndrome with CAPEOX and increased risk of neutropenia/neutropenic fever with fluorouracil-based regimens. The incidence of diarrhea and stomatitis is also decreased with capecitabine. Doses may need to be reduced in patients who experience adverse drug reactions. Patients with renal dysfunction can accumulate drug and often require dose modification. Capecitabine-based regimens are recommended when patients are unable to tolerate fluorouracil-based therapy.[44]

Selection of an Adjuvant Regimen

Selecting a specific regimen from those listed in Table 153-5 requires an assessment of several patient-specific factors, including the performance status of the patient, comorbid conditions that may exist, and patient preferences for treatment based on lifestyle factors that are important to the patient. If a clinical trial is not an option, most patients with a good performance status will receive FOLFOX. Some patients prefer to not receive IV chemotherapy and may choose CAPEOX. Single-agent capecitabine may be the preferred option for patients with preexisting neuropathies, such as diabetic patients, or those patients wishing not to receive IV chemotherapy for any other reason. Fluorouracil and leucovorin have limited use now but are an acceptable option for patients, with low risk or average-risk stage II disease or those who cannot receive oxaliplatin and are unable to tolerate or take oral capecitabine. For example, patients who develop severe hand-foot syndrome may tolerate IV bolus fluorouracil/leucovorin because the risk of this toxicity is minimal with this administration method.

Patient age should also be considered when selecting an appropriate regimen. Subset analysis of the MOSAIC and National Surgical Adjuvant Breast and Bowel Project (NSABP)-C07 trials have demonstrated no overall survival benefit from adding oxaliplatin to patients older than 70 years and these patients may be appropriate for fluoropyrimidine-based therapy alone.[52,62]

The usual length of adjuvant therapy is 6 months. Non-inferiority studies have compared 3 versus 6 months of therapy in an effort to minimize long-term toxicities, particularly neuropathy associated with FOLFOX and CAPEOX. According to the results of two meta-analyses, 3 months of CAPEOX is non-inferior to 6 months of CAPEOX in terms of disease-free survival in patients with low-risk stage III disease, but the same results have not been proven for FOLFOX and overall survival results were not evaluated.[53] In patients with high-risk stage III disease, 6 months of FOLFOX is superior to 3 months (3-year disease-free survival 76% vs 72%; hazard ratio [HR] 1.27; 95% confidence interval [CI], 1.07-1.51), but this has not been evaluated with CAPEOX.[63] The incidence of grade 3 neuropathy is lower with 3 months of CAPEOX or FOLFOX. Therefore, it remains controversial whether 3 months of adjuvant therapy is appropriate for all individuals.

Adjuvant and Neoadjuvant Therapy for Rectal Cancer

6 Rectal cancer involves those tumors found below the peritoneal reflection in the most distal 15 cm of the large bowel, and as such it is distinct from colon cancer in that it has a propensity for both local and distant recurrence. The higher incidence of local failure and overall poorer prognosis associated with rectal cancer is a result of anatomic limitations in excising adequate radial margins around the rectal tumor. Most patients with stage II or III rectal cancer should receive combined-modality therapy consisting of chemoradiation and fluoropyrimidine-based chemotherapy perioperatively for a total of 6 months.[45]

6 Perioperative treatment can be accomplished with the use of neoadjuvant (preoperative) chemoradiation followed by surgery and adjuvant (postoperative) chemotherapy or total neoadjuvant therapy (fluoropyrimidine-based chemotherapy followed by chemo XRT [or vice versa] followed by surgery). FOLFOX or CAPEOX are the preferred fluoropyrimidine-based chemotherapy regimens, but fluorouracil and leucovorin combination regimens and capecitabine can be used.[45] Neoadjuvant chemoradiation significantly reduces local recurrence and has fewer toxicities, and improved sphincter-preserving surgeries as compared to postoperative chemoradiation.[45,64] However, some patients are unable to tolerate a typical 5- to 6-week chemoradiation regimen and may be more appropriate candidates for a short course of preoperative XRT alone.[45] Chemotherapy combined with XRT typically involves continuous infusion fluorouracil, oral capecitabine, or bolus fluorouracil and leucovorin; the addition of oxaliplatin to either fluoropyrimidine was associated with increased toxicities without clear improvements in complete remission rates or survival benefit.[45,64]

Metastatic Disease: Initial Therapy

Patients are generally classified as having resectable, potentially resectable, or unresectable metastatic disease. Surgery and XRT are used to manage isolated sites of tumor. Chemotherapy is used for disseminated disease and the primary treatment modality for unresectable metastatic colorectal cancer. Patients with resectable or potentially resectable metastases are candidates for multimodality therapy.[44,45] Tumor genotyping for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutation status, *HER2* amplification, and determination of tumor MMR or MSI status (if not previously done) are recommended for patients at the time when metastatic disease is diagnosed to identify appropriate treatment options. Testing can also be performed on archived tissue samples obtained when the cancer was initially diagnosed.

Resectable (or Potentially Resectable) Metastatic Colorectal Cancer

7 Patients present with metastatic disease isolated to the liver or lung and who undergo resection of all metastatic and primary lesions (metastasectomy) have an increased probability of survival compared with those whose metastatic lesions remain unresected.[44] Therefore, strategies to increase the success rate of these resections (or convert unresectable lesions to resectable) are used in these patients. Neoadjuvant chemotherapy, also referred to as conversional chemotherapy, is the primary method to increase complete resection rates in both patients with resectable or potentially resectable liver or lung lesions. In some cases, individuals with metastatic disease initially deemed unresectable may achieve significant tumor regression following neoadjuvant chemotherapy to then be considered for surgery.

The optimal sequencing of chemotherapy for patients with initially resectable metastatic disease is controversial, as treatment options include surgery followed by chemotherapy or perioperative (pre- and postoperative) chemotherapy with surgery.[44,45] Because of the high risk of recurrence following resection of metastases, postoperative chemotherapy is always recommended. Administration of both pre- and postoperative chemotherapy is common practice, but the risk of hepatotoxicity associated with preoperative chemotherapy should be considered. Irinotecan-containing regimens can cause steatohepatitis and oxaliplatin-containing regimens can cause vascular sinusoidal obstructive liver injury.[44] Therefore, surgery is performed as soon as possible after the disease becomes resectable and preoperative chemotherapy is limited to a 2- to 3-month time period while patients undergo close monitoring.

The choice of neoadjuvant therapy depends on patient-specific factors and includes regimens such as FOLFOX, CAPEOX, FOLFIRI (infusional fluorouracil, leucovorin, and irinotecan), or FOLFOXIRI (infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan). It is typically administered for 2 to 3 months before surgery. Adjuvant chemotherapy (preferably FOLFOX or CAPEOX) should be administered to patients to complete a total of 6 months of chemotherapy (pre- and postoperative).[44]

Patients with unresectable lesions are eligible for the same chemotherapy regimens. However, because the primary goal is surgical resection whenever possible, patients should be evaluated for possible resection after every 2 months of therapy. If resection occurs, adjuvant chemotherapy should be administered to complete a total of 6 months of chemotherapy.

Hepatic-Directed Therapies

Hepatic-directed therapy, in addition to or as an alternative to surgical resection, can be considered in individuals with liver-only or liver-predominant metastatic disease. Hepatic artery infusion involves the placement of a permanent access catheter to the hepatic artery through which chemotherapy can be infused directly into the liver.[44] This approach offers the advantage of delivering high drug concentrations to tumors locally, thereby limiting systemic toxicities. Floxuridine with dexamethasone and fluorouracil with or without leucovorin are the most commonly used agents. Hepatic artery infusion is associated with potential biliary toxicity and the technical expertise required warrants use in selected patients by experienced practitioners. XRT can also be given to sites of hepatic tumor with external beam XRT or percutaneous arterial injection of micron-sized embolic particles loaded with a radioisotope (radioembolization). Other less common methods include tumor ablation procedures using radiofrequency ablation or microwave energy to generate heat that destroys localized tumor cells. Cryoablation can also be used, which includes placement of a cryoprobe into the tumor, either percutaneously or intraoperatively, and then lowering the probe temperature to −20°C to −40°C and rewarming it in cycles, resulting in formation of an ice ball that causes tumor destruction. These strategies may be useful for patients who have very small hepatic lesions and are unable to undergo liver resection surgery, but they are less successful than surgical interventions.

Unresectable Metastatic Colorectal Cancer

Unless the primary tumor is causing an obstruction, surgery in patients with established unresectable disease is rarely indicated. XRT may be useful to control localized symptoms in patients with metastatic colorectal cancer. Systemic chemotherapy palliates symptoms and improves survival in patients with unresectable disease. Common treatment regimens include combination of cytotoxics and a biologic agent.

Chemotherapy

7 Several chemotherapy regimens are acceptable for initial treatment of metastatic colorectal cancer.[44] The goals of therapy, history of prior chemotherapy, tumor genotype status, performance status/comorbidities, and risk of drug-related toxicities should be considered when an appropriate management strategy is defined for each individual. Treatment regimens are the same for metastatic cancer of the colon and rectum. Table 153-6 lists common initial chemotherapeutic regimens for metastatic disease.[44,45]

TABLE 153-6

Initial Chemotherapeutic Regimens for Metastatic Colorectal Cancer[a]

Regimen	Agents	Major-Dose Limiting Toxicities	Comments
Patients Appropriate for Intensive Therapy with *RAS* Mutations			
FOLFOX +/− bevacizumab	Oxaliplatin 85 mg/m^2 IV day 1 Leucovorin 400 mg/m^2 IV day 1 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin day 1, then 1,200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46-48 hr) Repeat every 2 weeks +/− Bevacizumab 5 mg/kg IV day 1 before FOLFOX Repeat cycle every 2 weeks	FOLFOX: sensory neuropathy, neutropenia Bevacizumab: hypertension, thrombosis, proteinuria	Most commonly used first-line regimen
CAPEOX +/−	Oxaliplatin 130 mg/m^2 IV day 1	CAPEOX: diarrhea, hand-	Reduced capecitabine dose better

bevacizumab	Capecitabine 1,000 mg/m^2 orally twice a day, days 1-14 Repeat cycle every 3 weeks +/− Bevacizumab 7.5 mg/kg IV day 1 Repeat cycle every 3 weeks	foot syndrome, neuropathies Bevacizumab: hypertension, thrombosis, proteinuria	tolerated; patient must be able to be adherent and report adverse drug reactions in a timely fashion
FOLFIRI +/− bevacizumab	Irinotecan 180 mg/m^2 IV day 1 Leucovorin 400 mg/m^2 IV day 1 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin day 1, then 1,200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46-48 hr) +/− Bevacizumab 5 mg/kg IV day prior to FOLFIRI Repeat cycle every 2 weeks	FOLFIRI: diarrhea, mucositis, neutropenia Bevacizumab: hypertension, thrombosis, proteinuria	May be preferred in patients who have preexisting neuropathy or those in which neuropathy may be debilitating to their line of work (eg, musician)
FOLFOXIRI +/− bevacizumab	Irinotecan 165 mg/m^2 IV day 1 prior to oxaliplatin Oxaliplatin 85 mg/m^2 IV prior to leucovorin day 1 Leucovorin 400 mg/m^2 IV day 1 prior to fluorouracil Fluorouracil 1,200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 48 hr) Repeat cycle every 2 weeks +/− Bevacizumab 5 mg/kg IV day 1 before FOLFOXIRI Repeat cycle every 2 weeks	FOLFOXFIRI: neutropenia, diarrhea, stomatitis, peripheral neurotoxicity, thrombocytopenia Bevacizumab: hypertension, thrombosis, proteinuria	[b]More neutropenia and peripheral neurotoxicity compared to FOLFIRI; often used in medically fit individuals with diffuse aggressive disease to palliate symptoms and as potential conversion therapy
Patients Appropriate for Intensive Therapy with *RAS* or *BRAF* Wild-Type and Left-Sided Colon Tumors			
FOLFOX + cetuximab or panitumumab	FOLFOX regimen + cetuximab (400 mg/m^2 IV loading dose, then cetuximab 250 mg/m^2 IV weekly thereafter OR cetuximab 500 mg/m^2 IV every 2 weeks) before FOLFOX OR FOLFOX regimen + panitumumab 6 mg/kg IV day 1 before FOLFOX Repeat cycle every 2 weeks	FOLFOX: sensory neuropathy, neutropenia Cetuximab: Papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia Panitumumab: rash, diarrhea, hypomagnesemia	Only *RAS* or *BRAF* wild-type and left-sided tumor
FOLFIRI + cetuximab or panitumumab	FOLFIRI + cetuximab (400 mg/m^2 IV loading dose, then cetuximab 250 mg/m^2 IV weekly thereafter OR cetuximab 500	FOLFIRI: diarrhea, mucositis, neutropenia Cetuximab:	Only *RAS* or *BRAF* wild-type and left-sided tumor; preferred for patients with preexisting neuropathy or those in whom

	mg/m^2 IV every 2 weeks) before FOLFIRI OR FOLFIRI + panitumumab 6 mg/kg IV day 1 before FOLFIRI Repeat cycle every 2 weeks	papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia Panitumumab: rash, diarrhea, hypomagnesemia	neuropathy may be debilitating to their line of work (eg, musician)
Patients NOT Appropriate for Intensive Therapy with *RAS* Mutations			
Infusional fluorouracil + leucovorin +/− bevacizumab	Fluorouracil 400 mg/m^2 IV bolus, after leucovorin on day 1, then 1,200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46-48 hr) Repeat cycle every 2 weeks +/− Bevacizumab 5 mg/kg IV day 1 prior to fluorouracil and leucovorin Repeat cycle every 2 weeks	Infusional fluorouracil/leucovorin: neutropenia, diarrhea Bevacizumab: hypertension, bleeding, proteinuria	Infusional fluorouracil/leucovorin regimen preferred to bolus fluorouracil regimen
Capecitabine +/− bevacizumab	Capecitabine 850-1,250 mg/m^2 orally twice a day, days 1-14 +/− Bevacizumab 7.5 mg/kg IV day 1 Repeat cycle every 3 weeks	Capecitabine: hand-foot syndrome, diarrhea, hyperbilirubinemia Bevacizumab: hypertension, thrombosis, proteinuria	
Patients NOT Appropriate for Intensive Therapy with *RAS* or *BRAF* Wild-Type and Left-Sided Tumors			
Cetuximab[c]	Cetuximab 400 mg/m^2 IV loading dose, then cetuximab 250 mg/m^2 IV weekly thereafter Or Cetuximab 500 mg/m^2 IV every 2 weeks	Papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia	Only *RAS* or *BRAF* wild-type and left-sided tumor
Panitumumab[c]	6 mg/kg IV over 60 minutes every 2 weeks	Rash, diarrhea hypomagnesemia, rare allergic reactions	Only *RAS* or *BRAF* wild-type and left-sided tumor
Patients with dMMR or MSI-H			
Pembrolizumab	2 mg/kg IV every 2 weeks or 200 mg IV every 3 weeks or 400 mg IV every 6 weeks[d]	Immune-mediated adverse drug reactions (most common: skin, liver, kidney, gastrointestinal tract, lung and endocrine systems)	Only in MMR-d or MSI-H tumors. Patients should be closely monitored for adverse drug reactions and report any adverse drug reactions immediately as interruption of treatment or initiation of corticosteroids may be needed

Nivolumab +/- ipilimumab	Nivolumab 3 mg/kg IV over 30 minutes and ipilimumab 1 mg/kg IV over 30 minutes every 3 weeks × 4 doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks[d]	Immune-mediated adverse drug reactions (most common: skin, liver, kidney, gastrointestinal tract, lung and endocrine systems)	Only in MMR-d or MSI-H tumors. Patients should be closely monitored for adverse drug reactions and report any adverse drug reactions immediately as interruption of treatment or initiation of corticosteroids may be needed
Patients NOT Appropriate for Intensive Therapy with *HER*-Amplified and *RAS* and *BRAF* WT			
Trastuzumab + (pertuzumab or lapatinib) or fam-trastuzumab deruxtecan-nxki	Trastuzumab 8 mg/kg IV day 1 of cycle 1 then 6 mg/kg IV every 21 days + pertuzumab 840 mg IV day 1 of cycle 1 then 420 mg IV every 21 days OR trastuzumab 4 mg/kg IV day of cycle 1 then 2 mg/kg IV weekly + lapatinib 1,000 mg po daily OR fam-trastuzumab deruxtecan-nxki 6.4 mg/kg IV on day 1 every 21 days	Trastuzumab + pertuzumab: hypokalemia, abdominal pain, diarrhea, fatigue, nausea; trastuzumab + lapatinib: fatigue, elevated liver enzymes, diarrhea, and rash; fam-trastuzumab deruxtecan-nxki, interstitial pneumonitis	Only in *HER*-amplified and *RAS* and *BRAF* WT tumors. Evaluate all patients for left ventricular ejection fraction at baseline and monitor closely throughout therapy. Do not substitute conventional or biosimilar trastuzumab with ado-trastuzumab emastine, fam-trastuzumab deruxtecan or trastuzumab/hyaluronidase

[a]NCCN Guideline recommendations for initial therapy. All recommendations are category 2A unless otherwise noted. Category 2A: based on lower-evidence, there is uniform NCCN consensus that intervention is appropriate.

[b]Original dosing was 1,600 mg/m^2/day but it is recommended that US patients use this dose as they do not tolerate fluorouracil as well.

[c]NCCN Category 2B: based upon lower-evidence, there is NCCN consensus that this intervention is appropriate.

[d]Flat dosing is preferred.

Data from References 44,45.

Most metastatic colorectal cancers are incurable, and treatment goals are to control cancer growth, reduce patient symptoms, improve quality of life, and extend survival. The benefit of palliative chemotherapy for metastatic colorectal cancer as compared to observation or supportive care alone with regard to these treatment goals has been established. According to results from multiple randomized trials and meta-analyses, chemotherapy prolongs life and improves quality of life of patients with metastatic colorectal cancer.[33,44,45]

Most first-line chemotherapy regimens for metastatic colorectal cancer incorporate a fluoropyrimidine. Irinotecan or oxaliplatin added to a fluoropyrimidine-based regimen significantly improves response rates, progression-free survival, and median survival.[44,45] The addition of the targeted anti-angiogenesis agent bevacizumab further improves response rate and survival. Patients considered appropriate for initial intensive chemotherapy usually receive an oxaliplatin or irinotecan-containing regimen with infusional fluorouracil plus leucovorin and bevacizumab (unless contraindicated) or an EGFR inhibitor (if their tumors are left-sided and express *RAS* and *BRAF* wild-type). Capecitabine can be substituted for fluorouracil and leucovorin. If the patient has dMMR or MSI-H, they may receive immunotherapy. Patients who are not appropriate candidates for initial intensive therapy may be treated with fluoropyrimidine monotherapy with or without bevacizumab, EGFR inhibitor monotherapy (if their tumors are left-sided and express *RAS* and *BRAF* wild-type) immunotherapy if they have dMMR or MSI-H, or trastuzumab + pertuzumab or lapatinib or fam-trastuzumab deruxtecan-nxki (if their tumors have human epidermal growth factor receptor-2 [HER2] amplification and *RAS* and *BRAF* wild-type), as appropriate.[44] Patients may receive multiple different regimens; the sequence of drugs used appears less important than exposure to all active agents during the course of cancer treatments. Please refer to "Adjuvant Chemotherapy for Colon Cancer" section for more information on the toxicities of the regimens used in both the adjuvant and metastatic settings.

Fluorouracil can be administered as an IV bolus, a continuous infusion, or a combination of the two in the metastatic setting. Continuous IV infusion

fluorouracil regimens increase the duration of drug exposure during the S-phase of the cell cycle, increase cytotoxicity, and are better tolerated than bolus administration. When combined with irinotecan or oxaliplatin, infusional fluorouracil is recommended because of improved efficacy.[44]

Unlike in the adjuvant setting, irinotecan added to fluorouracil plus leucovorin as initial therapy for metastatic disease improves tumor response rates, time-to-progression, and overall survival.[65] 5 The most common adverse drug reactions of irinotecan in these regimens are diarrhea, neutropenia, nausea and vomiting, dehydration, asthenia, abdominal pain, and alopecia; diarrhea and neutropenia are dose limiting. Two distinct patterns of diarrhea have been described. Early-onset diarrhea occurs during or within 2 to 6 hours after irinotecan administration and is characterized by lacrimation, diaphoresis, abdominal cramping, flushing, and/or diarrhea. These cholinergic symptoms, thought to be caused by inhibition of acetylcholinesterase, respond to atropine 0.25 to 1 mg given IV or subcutaneously. About 10% of patients experience acute symptoms during or shortly following the irinotecan. More commonly, late-onset diarrhea occurs 1 to 12 days after irinotecan administration and may last for 3 to 5 days. Late-onset diarrhea may require hospitalization or discontinuation of therapy, and fatalities have been reported. The risk of late-onset diarrhea can be decreased with aggressive antidiarrheal intervention. Aggressive intervention with high-dose loperamide therapy should consist of 4 mg taken at the first sign of soft or watery stools, followed by 2 mg orally every 2 hours until symptom-free for 12 hours; this regimen can be modified to 4 mg taken orally every 4 hours during the night.

5 The severity of delayed diarrhea is correlated with the systemic exposure (ie, area under the concentration-vs-time curve) of irinotecan and SN-38 (irinotecan's active metabolite) and with genetic polymorphisms in the enzyme UGT1A1, which is responsible for the glucuronidation of SN-38 to inactive metabolites. Reduced or deficient levels of the UGT1A1 enzyme are observed in Gilbert syndrome, a familial hyperbilirubinemia disorder, and correlate with irinotecan-induced diarrhea and neutropenia.[66] FDA-approved testing to determine *UGT1A1* genotype is commercially available. Although some individuals advocate testing *UGT1A1* genotype prior to starting irinotecan, widespread testing has not been adopted.[44,67] The prescribing information recommends considering a reduced dose of irinotecan in patients with *UGT1A1*28* genotype.

Oxaliplatin, in combination with infusional fluorouracil plus leucovorin, is FDA-approved for use in first-line and salvage regimens for metastatic colorectal cancer. Oxaliplatin incorporation into fluorouracil-based regimens as first-line therapy for metastatic colorectal cancer is associated with higher response rates and prolonged progression-free survival, with variable effects on overall survival.[68] Oxaliplatin is not effective as a single agent in colorectal cancer and is therefore only used in combination regimens.

To further improve survival rates achieved with FOLFOX and FOLFIRI regimens, a four-drug regimen (FOLFOXIRI) was developed and has been compared with FOLFIRI. FOLFOXIRI improved progression-free survival and overall survival compared to FOLFIRI, and a higher proportion of patients receiving FOLFOXIRI were able to undergo radical resection of metastases.[44] As expected, FOLFOXIRI causes more neutropenia, neurotoxicity, diarrhea, and alopecia, but may be appropriate for medically fit individuals with diffuse aggressive disease to palliate symptoms and as potential conversion therapy.

Capecitabine is an oral, tumor-activated, and tumor-selective fluoropyrimidine carbamate. Capecitabine can be administered alone or in combination with oxaliplatin (CAPEOX, also known as XELOX). When administered alone, it has higher response rates but comparable time-to-progression and median survival to fluorouracil/leucovorin. CAPEOX has similar progression-free and overall survival when compared with FOLFOX.[69] Hand-foot syndrome is common with capecitabine, while grades 3 or 4 neutropenia and stomatitis are more common with fluorouracil plus leucovorin. The convenience of oral administration and different toxicity profile make capecitabine a useful alternative to infusional fluorouracil in regimens for metastatic disease.

Targeted Therapy

Guidelines and clinical practice recommend the addition of targeted therapy to one of the chemotherapy backbones mentioned earlier.[44]

8 Bevacizumab is a recombinant, humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). A modest increase in progression-free and overall survival benefit occurs when bevacizumab is combined with chemotherapy as compared with chemotherapy alone.[44] However, bevacizumab results in higher treatment-related mortality than chemotherapy alone (relative risk 1.33; 95% CI, 1.02-1.73) because of hemorrhage (24%), neutropenia (12%), and gastrointestinal perforation (7%).[70]

Hypertension is also common with bevacizumab.[44] The hypertension is easily managed with oral antihypertensive agents. Bleeding,

thromboembolism, and proteinuria can also occur with bevacizumab. Proteinuria is monitored with urine dipsticks regularly during therapy, and the therapy is withheld in patients with 2+ protein or more, confirmed with a 24-hour urine collection. The risk of gastrointestinal perforation is increased by the addition of bevacizumab and extensive prior intra-abdominal surgery. Patients complaining of abdominal pain associated with vomiting or constipation should be evaluated for this rare but potentially fatal complication. Bevacizumab is also associated with a twofold increased risk of arterial thrombotic events, with patients who are older than 65 years or who have a prior history of arterial thrombotic events at greatest risk. Since bevacizumab can also interfere with wound healing, there should be at least a 6- to 8-week interval between the last dose of bevacizumab and elective surgery and wait at least 6 to 8 weeks to reinitiate bevacizumab after surgery. Necrotizing fasciitis can occur following wound healing or gastrointestinal perforation.

9 Cetuximab and panitumumab are monoclonal antibodies directed against EGFR. EGFR inhibitors may be used in combination with first-line chemotherapy regimens FOLFOX or FOLFIRI, or administered as single agents, but should not be combined with bevacizumab because of increased toxicity and no efficacy benefit.[44] The benefit of EGFR inhibitors, however, is limited to patients with wild-type *RAS* and *BRAF* tumors and they should not be used in patients with tumor *RAS* or *BRAF* mutations. Furthermore, patients with left-sided primary tumors have improved overall survival when treated with EGFR inhibitors while those with right-sided tumors (cecum to hepatic flexure) do not. Because fewer than 60% of patients with wild-type *KRAS* tumors respond to cetuximab or panitumumab, additional factors downstream of *RAS* signaling have been explored for their ability to predict response to EGFR inhibitors, including *BRAF* V600E mutation, and mutation or loss of *PTEN* or *PIK3CA.* Tumors with wild-type *KRAS*/*NRAS* and *BRAF* V600E mutation do not respond to anti-EGFR antibodies. The only situation where this might be beneficial is if the EGFR is administered in combination with a BRAF inhibitor, but now this has only been recommended after failure of the first-line setting (see "Metastatic Disease: Second-Line and Subsequent Therapy" section).

Severe infusion reactions, including anaphylaxis, can occur with cetuximab (3%) and panitumumab (1%).[44] Administration of panitumumab seems feasible in those who experienced a reaction with cetuximab.[71] Skin toxicity is also a common adverse drug reaction with these drugs and is not part of the infusion reaction. The presence of papulopustular skin rash correlates with response and survival. It most commonly occurs within 2 to 4 weeks of therapy initiation and preventative therapy with topical corticosteroids with moisturizer, sunscreen, and oral doxycycline is recommended unless contraindications exist.[72] Both these agents have also been associated with diarrhea and hypomagnesemia, which can occur even after discontinuation of the drug.

Trastuzumab and pertuzumab are monoclonal antibodies directed against HER2. Fam-trastuzumab deruxtecan-nxki is, an antibody drug conjugate with a trastuzumab backbone, linked to cytotoxic chemotherapy. Lapatinib is an oral tyrosine kinase inhibitor of both HER2 and EGFR1 receptors. A two-drug combination, trastuzumab + pertuzumab or lapatinib, or fam-trastuzumab deruxtecan-nxki alone is recommended as an option for patients with HER2 amplification and wild-type *RAS* and *BRAF* tumors.[44,45] Typically, they are reserved for second-line or subsequent therapy unless the patients cannot tolerate intensive therapy in the first-line setting (see "Metastatic Disease: Second-Line and Subsequent Therapy" section).

Immunotherapy

10 Immunotherapy is effective in dMMR tumors because these tumors encode mutant proteins and have the potential to be recognized and targeted by the immune system. Because the immune system can become suppressed when programmed death-ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells bind to programmed cell death protein (PD-1) receptors on T cells, the use of PD-1 inhibitor drug therapy is reasonable in these tumors. The PD-1 inhibitor nivolumab has also been evaluated in combination with ipilimumab, a cytotoxic-T-lymphocyte-associated protein 4 (CTLA4) inhibitor; these drugs act synergistically to promote T-cell antitumor activity.[73] For more information about these therapies, see "Metastatic Disease: Second-Line and Subsequent Therapy" section.

Selection of an Initial Metastatic Regimen

Several factors should be considered when selecting first-line therapy for metastatic colorectal cancer when disease palliation is the primary treatment goal. The first consideration is whether intensive therapy is appropriate for the patient. Those with multiple comorbidities or low performance status would likely better tolerate less-intensive therapy. The second consideration is *RAS* and *BRAF* status and side of tumor involvement. Those with wild-type *RAS* and *BRAF* and left-sided tumors can receive an EGFR inhibitor therapy. Patients with dMMR or MSI-H tumors could receive immunotherapy as first-line therapy. Also, patients with wild-type *RAS* and *BRAF* tumors, HER2-amplification, and are not appropriate for intensive therapy can receive HER2 inhibitor therapy. Once these factors are known, the selection of the appropriate regimen is based on the toxicity profile and convenience of

administration for the patient. Based on the comparable results of FOLFIRI versus FOLFOX, either of these regimens is considered the reference standard in metastatic colorectal cancer. Most patients will receive first- and second-line regimens and patient preference for either sequence of treatments based on their different toxicity profiles is important. FOLFIRI may be chosen initially in patients with preexisting neuropathies, whereas FOLFOX may be chosen in patients with increased bilirubin or known UGT1A1 deficiency (known risk factors for delayed diarrhea). Alopecia occurs much more frequently with irinotecan compared to oxaliplatin combinations. Because FOLFOX can cause persistent neuropathy, a rationale for starting with FOLFIRI is that time-to-progression is longer with first-line treatment than in second line. Therefore, the time to death during which some patients will have to live with neuropathy may be shorter. Capecitabine is an appropriate substitute for IV fluorouracil in oxaliplatin combination regimens. Because of a higher response rate and modest survival benefit with FOLFOXIRI, this four-drug combination may be useful for patients with initially aggressive and symptomatic disease. Select patients who are candidates for FOLFOXIRI may benefit from the addition of bevacizumab, but the incidence of moderate or severe toxicities is increased.

Metastatic Disease: Second-Line and Subsequent Therapy

Systemic chemotherapy represents the mainstay of therapy for patients who have progressive disease following initial treatment for metastatic disease. Table 153-7 lists treatment options for relapsed/refractory metastatic disease.[44,45] Treatment options are based on the type of and response to prior treatments, the site and extent of disease, and patient factors and treatment preferences.

TABLE 153-7

Second-Line and Salvage Chemotherapy Regimens for Metastatic Colorectal Cancer

Disease Progression with First-Line Regimen	Comments
Second-line options	
FOLFIRI or irinotecan	After previous oxaliplatin-based regimen (without irinotecan) (ie, FOLFOX, CAPEOX); use with caution in patients with elevated bilirubin
FOLFIRI + bevacizumab or ziv-afilbercept or ramucirumab	After previous oxaliplatin-based regimen (without irinotecan) (ie, FOLFOX, CAPEOX); use with caution in patients with elevated bilirubin; bevacizumab is preferred antiangiogenic agent based on toxicity and cost
FOLFOX or CAPEOX ± bevacizumab	After previous irinotecan-based regimen (without oxaliplatin) (ie, FOLFIRI); bevacizumab FDA-approved to continue with second-line options
FOLFOX + cetuximab or panitumumab	After previous irinotecan-based regimen (without oxaliplatin) (ie, FOLFIRI); only if *RAS* wild-type and *BRAF* wild-type
Irinotecan + bevacizumab or ziv-afilbercept or ramucirumab	After previous oxaliplatin-based regimen (without irinotecan) (ie, FOLFOX, CAPEOX); use with caution in patients with elevated bilirubin; bevacizumab is preferred antiangiogenic agent based on toxicity and cost
FOLFIRI + cetuximab or panitumumab	After previous oxaliplatin-based regimen (without irinotecan) (ie, FOLFOX, CAPEOX); only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin
Irinotecan ± cetuximab or panitumumab	Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin
Encorafenib + (cetuximab or panitumumab)	Only if *BRAF V600E* mutation positive
Nivolumab ± ipilimumab	Only if dMMR/MSI-H
Dostarlimab	Only if dMMR/MSI-H
Pembrolizumab	Only if dMMR/MSI-H
Trastuzumab + (pertuzumab or lapatinib) or fam-trastuzumab deruxtecan-nxki	Only if *HER2*-amplified and *RAS* and *BRAF* wild-type
Therapy After Second Progression or Third Progression (can use any of the previous recommendations)	
Regorafenib	Used after progressed through all available regimens
Trifluridine/tipiracil ± bevacizumab	Used after progressed through all available regimens
Clinical trial	If available and only if patient eligible
Best supportive care	Appropriate for patients who do not want to pursue treatment, or not eligible for cancer-directed therapy, or if quality of life is expected to decrease

CAPEOX, capecitabine plus oxaliplatin; dMMR, DNA mismatch repair deficiency; FOLFIRI, fluorouracil plus leucovorin plus irinotecan; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin; MSI-H, high microsatellite instability.

Data from References 44,45.

Systemic Chemotherapy

On disease progression following standard initial therapy, appropriate treatment options depend primarily on the type of prior therapy received (see Table 153-7). Because most patients will have received a combination of a fluoropyrimidine with either irinotecan or oxaliplatin, second-line therapy with the alternate regimen should be considered. Patient survival can exceed 2 years with this approach and it is important for patients to receive all traditional chemotherapy options if possible. Targeted agents can either be added to the regimens or used as single agents.

Irinotecan

Irinotecan improves overall survival as compared to either best supportive care or continuous-infusion fluorouracil in patients who had progressed within 6 months of treatment with fluorouracil.[44] However, this approach is rarely used since single-agent fluorouracil is rarely given as first-line therapy.

The use of the FOLFIRI regimen after progression with first-line FOLFOX demonstrated an objective response rate of 4% with a median progression-free survival of 2.5 months.[44] These results are consistent with observations that demonstrate improved outcomes in those patients who are able to receive all active cytotoxic agents during the course of their disease.

Based on these results, irinotecan-based therapy should be considered standard second-line therapy for patients with disease progression with first-line treatment with oxaliplatin-containing regimens. Continuous-infusion fluorouracil with leucovorin and irinotecan (FOLFIRI), with or without targeted therapy, is most commonly given.

Oxaliplatin

Oxaliplatin plus fluorouracil and leucovorin should be considered for patients who received primary treatment with irinotecan plus fluorouracil.[44] The combination of oxaliplatin plus fluorouracil and leucovorin is also effective as salvage therapy after initial treatment with irinotecan plus fluorouracil and leucovorin, with a similar response rate. Although irinotecan can be used effectively as a single agent in colorectal cancer, it should be noted that oxaliplatin does not have substantial activity alone, and should only be given in combination regimens.

Trifluridine/Tipiracil

Trifluridine is a thymidine-based nucleoside analog that is incorporated into DNA and inhibits cell proliferation. The addition of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. This combination chemotherapy product has activity in both *RAS* mutant and wild-type tumors. Trifluridine/tipiracil is FDA-approved for treatment of metastatic colorectal cancer patients who have been previously treated with a fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens, an anti-VEGF targeted therapy, and an anti-EGFR monoclonal antibody if *RAS* wild-type.[74] Trifluridine/tipiracil improves overall survival by approximately 2 months. This chemotherapy product is administered 35 mg/m^2 orally twice daily within 1 hour of completing morning and evening meals on days 1 through 5 and days 8 through 12 of a 28-day cycle. Common adverse drug reactions include myelosuppression, fatigue, diarrhea, nausea/vomiting, abdominal pain, and pyrexia.

Targeted Therapy

The addition of targeted therapy to chemotherapy in second and subsequent therapies does improve outcomes, but typically also increases toxicity. EGFR inhibitors may be administered in combination with other regimens in second-line and subsequent therapies. Angiogenesis inhibitors can also be used in second-line and subsequent therapy in combination with other regimens, even when they were used in first-line therapy.

EGFR Inhibitors

9 Patients with wild-type *RAS* and wild-type *BRAF* tumors who experience progression on therapies that do not contain an EGFR inhibitor may benefit from the combination of cetuximab or panitumumab and irinotecan, FOLFOX, or FOLFIRI.[44] However, further treatment is not recommended in those who had progressed while receiving an EGFR inhibitor. The combination of cetuximab and irinotecan significantly improves response rates (16% vs 4%) and progression-free survival (4 vs 2.6 months), but not overall survival when compared with irinotecan alone.[75] Panitumumab in combination with FOLFIRI also improves response rates (35% vs 10%) and progression-free survival (5.9 vs 3.9 months), but did not improve overall survival.[76]

BRAF Inhibitors

In patients with *BRAF V600E* mutations, a two-drug regimen of encorafenib (a BRAF inhibitor) and an EGFR inhibitor (cetuximab or panitumumab) is recommended to improve overall outcomes in second- and subsequent-line therapies for metastatic disease. This regimen produces overall response rates of 20% and a median overall survival time of 9.3 months.[77] The most common adverse drug reactions with this doublet regimen are acneiform rashes and diarrhea.

Angiogenesis Inhibitors

Angiogenesis inhibitors including VEGF inhibitors bevacizumab, ramucirumab, and ziv-aflibercept and the multikinase inhibitor regorafenib may be used in patients who have progressed on other therapies (see Table 153-7). VEGF inhibitors may be used as second- or subsequent-line therapies, whereas regorafenib is indicated for to third- or subsequent-line use. The NCCN guidelines recommend bevacizumab over ramucirumab and ziv-aflibercept based on toxicity and cost. Continuation of bevacizumab as second-line therapy provides a modest improvement in overall survival based on several clinical trials.[44] Bevacizumab may also be added to another second-line therapy in patients who did not receive it as part of their initial therapy, also resulting in a modest improvement in overall survival (12.1 vs 10.8 months).[78] Single-agent bevacizumab is not recommended because it is inferior to combination therapy.[44]

Ziv-aflibercept is a soluble recombinant fusion protein designed to block the angiogenic process. The agent was developed by fusing sections of the VEGFR-1 and VEGFR-2 immunoglobulin domains to the F_c portion of human immunoglobulin G1 and blocks VEGF-A, VEGF-B, and placental growth factor (PIGF) by "trapping" the ligands before they get to the native transmembrane receptors. In a phase III randomized trial, FOLFIRI plus ziv-aflibercept modestly, but significantly improves overall survival (13.5 vs 12.1 months) compared to FOLFIRI after progression on an oxaliplatin-based regimen.[79] It is dosed at 4 mg/kg as an IV infusion over 1 hour every 2 weeks and is associated with similar adverse drug reactions as bevacizumab.

Ramucirumab is a human monoclonal antibody that binds directly to the ligand-binding pocket of VEGFR-2 to block binding of VEGF-A, VEGF-C, and VEGF-D. A phase III randomized placebo-controlled trial of patients who progressed on an oxaliplatin-based regimen and bevacizumab were randomized to receive FOLFIRI with or without ramucirumab.[80] A modest but significant improvement in overall survival (13.3 vs 11.7 months) and progression-free survival (5.7 vs 4.5 months) were observed. Ramucirumab is administered as 8 mg/kg IV over 1 hour every 2 weeks and is associated with similar adverse drug reactions as bevacizumab.

The addition of ziv-aflibercept or ramucirumab to oxaliplatin regimens has not been evaluated and therefore is not recommended.[44] Additionally, the use of either of these drugs following failure of a bevacizumab-containing regimen has not been evaluated. Therefore, ziv-aflibercept and ramucirumab should only be used in patients naïve to antiangiogenic regimens and only with irinotecan-containing regimens.

Regorafenib, a small-molecule inhibitor of tumor angiogenesis (VEGFR-1, VEGFR-2, and VEGFR-3) and other downstream targets (FGF receptors, PDGF receptors, BRAF, KIT, and RET), is approved for the third- or fourth-line treatment of metastatic colorectal cancer. This oral agent is dosed 160 mg once daily for the first 21 days of each 28-day cycle, although it is common to start at a lower dose (80 or 120 mg) and titrate as tolerated.[44] In a phase III trial of patients with metastatic colorectal cancer and progression during or within 3 months of last chemotherapy, regorafenib demonstrated a 1.4-month improvement in overall survival when compared to placebo.[81] Patients with mutant or wild-type *RAS* may receive this therapy. Because this is an oral-only regimen, patients must be counseled on its use and potential toxicity. Regorafenib should be taken with a low-fat breakfast and may interact with CYP450 3A4 inducers and inhibitors. Toxicities include hypertension, hand-foot syndrome, diarrhea, and hepatotoxicity.

HER2 Inhibitors

HER2, a member of the same kinase family as EGFR, is rarely overexpressed in colorectal cancer.[44] However, *HER2* overexpression/amplification is more common in *RAS* and *BRAF* wild-type tumors. MyPathway, a basket trial, showed that in patients with HER2 amplified metastatic colorectal cancer, the combination of trastuzumab and pertuzumab (HER2 monoclonal antibodies) produced response rates of 32%.[82] The most common adverse drug reactions are diarrhea, fatigue, and nausea. According to HERACLES study, trastuzumab and lapatinib (a *HER2* inhibitor) produced responses in patients with refractory *RAS* wild type colorectal cancer, who typically are refractory to therapy, producing a 30% response rate.[83] Adverse drug reactions of *HER2* inhibitors include fatigue, skin rash, and bilirubin increases.[82] *HER2* inhibitor therapy can be an option for those with tumor *HER2* overexpression when other options have failed.

Immunotherapy

10 Pembrolizumab, a humanized, IgG4 monoclonal antibody that binds to programmed cell death ligand-1, or PD-L1, with high affinity, is effective in metastatic colorectal cancer with dMMR or high tumor mutational burden. When used as first-line therapy in patients with metastatic colorectal cancer with dMMR, pembrolizumab has improved response rates and progression-free survival times compared with chemotherapy.[84] Nivolumab, another humanized IgG4 monoclonal antibody PD-1 inhibitor, has also been evaluated with or without ipilimumab in patients with metastatic colorectal cancer who have dMMR/MSI-H tumors. As first-line therapy, nivolumab and ipilimumab also improve response rates and progression-free survival times compared with chemotherapy alone.[85] Immunotherapy (dostarlimab, pembrolizumab, nivolumab +/− ipilimumab) may also be used as subsequent-line therapy if patients who have not previously received immunotherapy.

Immune checkpoint inhibitors are generally well tolerated. The adverse drug reactions are typically immune-mediated and commonly affect the skin, liver, kidneys, gastrointestinal tract, lung, and endocrine systems. Immune-mediated pneumonitis is an uncommon but serious adverse drug reaction. Close monitoring for these adverse drug reactions is important to allow for prompt identification and treatment to minimize morbidity and mortality. Treatment includes temporary treatment suspension and corticosteroid treatment. Refractory cases may require infliximab or immunotherapies.[86]

EVALUATION OF THERAPEUTIC OUTCOMES

The goal of monitoring is either to evaluate whether the patient is receiving any benefit from the management of the disease or to detect recurrence for those who have completed curative intent therapy. During treatment for active disease, patients should undergo monitoring for measurable tumor response, progression, or new metastases; these tests may include chest, abdominal or pelvic CT scans, or other imaging modalities, depending on known sites of disease and previous imaging results, and CEA measurements every 3 months if the CEA is or was previously elevated. These radiologic tests and other selected laboratories should also be evaluated with the development of any new symptoms or significant change in disease status. Patients should be evaluated during every treatment visit for the presence of anticipated adverse drug reactions, which generally include loose stools or diarrhea, nausea or vomiting, mouth sores, fatigue, and fever, as well as other adverse drug reactions such as neuropathy (oxaliplatin) and skin rash (EGFR inhibitors). In addition, a complete blood cell count should be obtained prior to each course of chemotherapy administration to ensure that hematologic indices are adequate. Baseline liver function tests and an assessment of renal function should be evaluated prior to and periodically during therapy. Hepatotoxicity may be seen with regorafenib, and in addition to neuropathy, oxaliplatin may cause renal injury. Serum electrolytes, including magnesium, should be monitored during treatment with EGFR inhibitors. Patients receiving bevacizumab, ziv-aflibercept, or regorafenib should be evaluated for hypertension and proteinuria.

Symptoms of recurrence such as pain syndromes, changes in bowel habits, rectal or vaginal bleeding, pelvic masses, anorexia, and weight loss develop in less than 50% of patients. Recurrences can be detected in asymptomatic patients because of increased serum CEA levels that lead to further examination. Although the value of CEA monitoring for disease recurrence is controversial because of its cost and emotional stress associated with false-positive elevations, CEA monitoring plays an important role in postoperative follow-up studies. A PET scan can identify sites of metastatic disease when a rising CEA level suggests metastatic disease but CT scans and other imaging studies are negative.

Patients who undergo curative surgical resection, with or without adjuvant therapy, require close follow-up based on the premise that early detection and treatment of recurrence could still render them cured. In addition, early treatment for asymptomatic metastatic colorectal cancer appears to be superior to delayed therapy. Specific practice guidelines for postoperative surveillance examinations following successful treatment for stage II or III disease were developed by NCCN and include history, physical examination, and CEA test every 3 to 6 months for the first 2 years, then every 6 months for a total of 5 years; chest and abdominal and pelvic CT scans every 6 to 12 months for up to 5 years following primary therapy; and colonoscopy at

about 1 year after surgery. If an obstructing lesion prevented preoperative colonoscopy, it should be done within 3 to 6 months. Repeat colonoscopies are recommended at 3 years, unless findings of polyps warrant closer follow-up. PET/CT is not routinely indicated. Less intensive surveillance is recommended for patients treated for stage I disease because of low risk of recurrence.[44]

Posttreatment surveillance should also include a survivorship care plan with immunizations for vaccine-preventable diseases, early detection of second primary cancers, and support systems that encourage smoking cessation, establish regular exercise and maintain a healthy BMI, and encourage healthy lifestyle and dietary choices.[44] In addition, if there is a strong family history of colorectal cancer or related malignancies or clinicopathologic findings in an individual consistent with a hereditary syndrome, a consultation with a genetic counselor is indicated. Advances in the treatment for colorectal cancer now offer the potential to improve patient survival, but for many patients, improved disease-free and progression-free survival represent equally important therapeutic outcomes. Although treatment approaches for metastatic colorectal cancer have been historically assessed by their ability to produce a measurable objective tumor response, which is generally believed necessary for any treatment to improve survival, the effects of therapies on survival are clinically more meaningful than their ability to induce a tumor response. However, with the availability of multiple active treatments for metastatic disease, and the likelihood that patients will receive more than one during the course of their treatment, improvements in overall survival with new therapies will be increasingly difficult to determine.

In the absence of the ability of a specific treatment to demonstrate improved overall survival, important outcome measures should include the effects of the treatment on patient symptoms, daily activities, performance status and other quality-of-life indicators, progression-free survival, and time-to-treatment failure. Because most metastatic colorectal cancers are incurable, a specific decision regarding an individual patient's care will ultimately be required. This decision should be based on a careful assessment of the balance between risks associated with treatment (or lack thereof) and benefits of treatment. Efforts should also be made to ensure that the costs of screening, diagnostic tests, treatments, and procedures for colorectal cancer are consistent with their value in improving patient outcomes.

CONCLUSION

Colorectal cancer is a common cancer diagnosed in adults, but can be detected early through routine screening starting at the age of 45 years. Early-stage cancers can be cured with surgery. The addition of chemotherapy with a fluoropyrmdine-based regimen in some individuals with stage II and all individuals with stage III colorectal cancer is recommended following surgery to improve outcomes. In patients with rectal cancer, neoadjuvant chemotherapy and chemosensitized XRT followed by surgery is recommended to decrease the likelihood of recurrence. In patients with advanced colorectal cancer, chemotherapy is palliative and all active cytotoxic agents are administered to improve survival. The addition of targeted therapy in subsequent-line treatments is beneficial and depends upon specific patient factors. Unlike some other solid tumors, immunotherapy is only beneficial in a small subset of patients, but the benefit can be substantial in eligible patients.

ABBREVIATIONS

APC	adenomatous polyposis coli (gene)
BMI	body mass index
CAPEOX	capecitabine plus oxaliplatin
CEA	carcinoembryonic antigen
CI	confidence interval
CIN	chromosomal instability
CIMP	CpG island methylator phenotype
COX-2	cyclooxygenase-2

CT	computed tomography
DPD	dihydropyrimidine dehydrogenase
EGFR	epidermal growth factor receptor
EpCAM	epithelial cell adhesion molecule
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
FIT	fecal immunochemical test
FOBT	fecal occult blood test
FOLFIRI	fluorouracil, leucovorin, and irinotecan
FOLFOX	fluorouracil, leucovorin, and oxaliplatin
FOLFOXIRI	fluorouracil and leucovorin, oxaliplatin, irinotecan
FSIG	flexible sigmoidoscopy
gFOBT	guaiac-based fecal occult blood test
HDI	human development index
HR	hazard ratio
LOH	loss of heterozygosity
MAPK	mitogen-activated protein kinase
MMR	mismatch-repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
mt-sDNA	multi-target stool DNA
NCCN	National Comprehensive Cancer Network
NSAID	non-steroidal anti-inflammatory drug
PD-1	programmed cell death protein
PD-L2	programmed cell death ligand-2
PET	positron emission tomography

PI3K	phosphatidylinositol 3-kinase
TGF-β	transforming growth factor-β
TS	thymidylate synthase
UGT1A1	uridine diphosphate-glucuronosyltransferase
USPSTF	United States Preventive Services Task Force
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
XELOX	capecitabine plus oxaliplatin
XRT	radiation therapy

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SELF-ASSESSMENT QUESTIONS

1. Which of the following factors is associated with an increased risk of developing colorectal cancer?

   A. High dietary caffeine intake

   B. Rectal hemorrhoids

   C. Gastroesophageal reflux disease

   D. Chronic ulcerative colitis

2. A 30-year-old healthy individual has a father and paternal grandfather who were diagnosed with colon cancer. The individual would like to know what to take to prevent colon cancer. Which of the following recommendations is *most* appropriate?

   A. No preventative therapy is recommended in colon cancer.

   B. Take calcium (1,000 mg) and vitamin D (400 international units) orally each day.

   C. Take a low dose of aspirin (81-160 mg) orally each day.

   D. Take celecoxib (100 mg) orally twice daily.

3. At what age should routine colorectal cancer screening begin for an individual with average risk?

   A. 40 years

   B. 45 years

   C. 50 years

   D. 55 years

4. A 58-year-old White individual is diagnosed with stage III rectal cancer. Which of the following is the most appropriate treatment?

   A. Surgery followed by adjuvant FOLFOX

B. Neoadjuvant chemoradiation followed by surgery followed by adjuvant chemotherapy with FOLFOX

C. Neoadjuvant chemoradiation therapy followed by surgery

D. FOLFOX × 6 months alone

5. Which of the following colorectal cancer screening methods is *most* appropriate for a 55-year-old individual that refuses to take a bowel prep as part of the procedure?

A. Virtual (CT) colonoscopy every 10 years

B. Annual digital rectal exam

C. Annual FIT

D. mt-sDNA every 5 years

6. A 53-year-old individual with stage II hypertension is diagnosed with Stage IIB colon cancer following a routine screening colonoscopy. A surgical resection of the mass and regional mesenteric lymph nodes was performed. The tumor was poorly differentiated and showed evidence of lymphatic invasion. Which of the following statements regarding adjuvant chemotherapy for this individual is true? Adjuvant chemotherapy:

A. does not benefit patients with stage II colon cancer; should not receive additional treatment.

B. should be offered because this cancer is associated with several poor prognostic factors.

C. is standard of care for stage II colon cancer; should receive treatment.

D. is contraindicated in patients with hypertension; should not receive additional treatment.

7. Which of the following adjuvant treatment regimens for stage III colon cancer is most appropriate? Postoperative:

A. XRT

B. FOLFOX (fluorouracil, leucovorin, oxaliplatin) chemotherapy

C. Regorafenib

D. Pembrolizumab

8. A 67-year-old individual is diagnosed with stage IV cancer of the colon with several liver and lung metastases. Capecitabine chemotherapy will be initiated. What is the goal of chemotherapy in this individual?

A. Shrink the disease so that surgery can be performed to remove the tumors

B. Eradicate potential micrometastases after surgical resection

C. Provide symptom control only

D. Reduce symptoms, avoid disease-related complications, and prolong survival

9. A 62-year-old individual with a history of type 2 diabetes mellitus and peripheral neuropathy is diagnosed with inoperable metastatic colon cancer. The oncologist has suggested the combination of infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as an initial regimen instead of an oxaliplatin-containing regimen based on the treatment toxicity profile. What adverse drug effect should be minimized with FOLFIRI?

A. Diarrhea

B. Myelosuppression

C. Neuropathy

D. Mucositis

10. A 68-year-old individual with a history of hypertension was diagnosed with stage IV colorectal cancer. The tumor was *KRAS* mutant and EGFR positive. His blood pressure is controlled with medications. Which of the following initial treatment regimens is *most* appropriate?

A. FOLFOX plus bevacizumab

B. FOLFOX plus cetuximab

C. Capecitabine plus oxaliplatin plus ziv-aflibercept

D. FOLFOXIRI plus cetuximab

11. A 61-year-old individual with *KRAS*-mutated and MSI-high metastatic colon cancer was initially treated with FOLFOX. After 6 months of chemotherapy, they experienced a partial response to treatment and therapy was continued. Four months later, worsening abdominal pain developed and an abdominal CT scan showed new sites of disease in the liver. The treatment regimen was changed to FOLFIRI. Two months later, imaging studies show an increase in the size and number of liver metastases. Which of the following modifications to the current treatment regimen is now *most* appropriate?

A. Discontinue current regimen; start pembrolizumab

B. Continue FOLFIRI and add bevacizumab

C. Continue FOLFIRI; discontinue bevacizumab; start ziv-aflibercept

D. Discontinue current regimen; start FOLFOXIRI plus panitumumab

12. An adult patient is diagnosed with metastatic right-sided colorectal cancer, *KRAS* wild-type and is suitable for intensive therapy. Which of the following would be an appropriate regimen?

A. FOLFOX plus bevacizumab

B. FOLFOX plus cetuximab

C. Cetuximab

D. Regorafenib

13. An adult individual with metastatic colorectal cancer is considered for initial systemic chemotherapy. Genoytping as part of the pretreatment evaluation shows a homozygous UGT1A1*28. Based on the results of this test, how might the treatment plan be adjusted?

A. Capecitabine might be preferred to fluorouracil in this therapy.

B. Paitent might not be a candidate for oxaliplatin.

C. The initial dose of irinotecan might need to be adjusted.

D. Bevacizumab might be indicated as part of this therapy.

14. A 60-year-old individual is to receive cetuximab plus irinotecan for metastatic colorectal cancer that progressed with irinotecan, fluorouracil, and leucovorin chemotherapy. Previous chemotherapy was well tolerated, with only minor nausea and occasional loose stools. Which of the following counseling points is *most* appropriate with regard to this new chemotherapy regimen?

A. Infusion-related reactions with cetuximab are common.

B. Dose-limiting diarrhea is the most frequent complication with this regimen.

C. Cetuximab is associated with a papulopustular skin rash.

D. Peripheral neuropathy associated with this regimen is often dose-limiting.

15. A 61-year-old adult underwent surgical resection 8 months ago for stage III colon cancer. Six months of postoperative treatment with weekly fluorouracil plus leucovorin was administered. Routine follow-up imaging and laboratory tests confirmed cancer recurrence in the liver and lungs. Otherwise patient is asymptomatic and healthy and is now about to start the FOLFOX regimen (oxaliplatin, fluorouracil, and leucovorin). Which of the following patient counseling points is *most* appropriate for this regimen?

A. Avoid cold drinks and use of ice and cover skin before exposure to cold or cold objects the day before, day of and up to 2 days after chemotherapy.

B. If diarrhea begins after chemotherapy, begin atropine 4 mg po then 2 mg every 2 hours until symptom-free for 12 hours.

C. Eat a low-fat diet throughout chemotherapy.

D. Contact your physician immediately if you experience abdominal pain with vomiting or constipation.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Inflammatory bowel disease such as ulcerative colitis has a twofold greater risk of developing colorectal cancer compared with average-risk individual. See "Etiology and Risk Factors" section for more information on this and other risk factors.

2. **A.** Physical inactivity and elevated BMI are associated with an elevated risk of colon adenoma, colon cancer, and rectal cancer. Although tobacco use is associated with an increased risk of colon cancer, supplementation with folic acid and vitamin D has not been proven to be beneficial. Daily aspirin is limited to individuals in whom the benefit outweighs the risk. Dairy products have not been associated with an increased risk of colorectal cancer. High consumption of red and processed meat is associated with an increased colon cancer risk and a diet high in fiber such as fruit, vegetables and grain is associated with a lower risk. See "Lifestyle Factors" section for more information on this and other factors.

3. **B.** The age to begin colorectal cancer screening for the average-risk individual is 45 years. This is a relatively new change in guidelines based on the increasing incidence of colorectal cancer in adults younger than 50 years. Recommended programs for regular screening include a colonoscopy every 10 years, annually with a high-sensitivity gFOBT or FIT, or an FSIG every 5 years or every 10 years along with FIT every 1-2 years. See "Screening" section for more information.

4. **B.** Combined-modality therapy consisting of chemoradiation and fluoropyrimidine-based chemotherapy perioperatively for a total of 6 months is the treatment for stage II and III rectal cancers. Most commonly, neoadjuvant (preoperative) chemoradiation followed by surgery and adjuvant (postoperative) chemotherapy or total neoadjuvant therapy (fluoropyrimidine-based chemotherapy followed by chemo XRT [or vice versa] followed by surgery) are used. FOLFOX or CAPEOX are the preferred fluoropyrimidine-based chemotherapy regimens used. FOLFOX × 6 months is the standard treatment for stage III colon cancer. See "Treatment; Adjuvant and Neoadjuvant Therapy for Rectal Cancer" section for more information.

5. **C.** An annual FIT is noninvasive and does not involve a bowel preparation. It is recommended as an option for colorectal cancer screening. Multi-targeted stool DNA is also an option that does not require a bowel preparation but the recommended interval for colorectal screening is every 1-3 years. Although a virtual colonoscopy is not invasive, it still requires a bowel preparation to clear out the colon for viewing and is recommended at an interval of every 5 years. Finally, a digital rectal examination is not recommended for CRC screening. See "Prevention and Screening" (Screening) section for more information.

6. **B.** Patients with stage II disease at high risk for relapse should be offered adjuvant chemotherapy. High-risk features include those patients with inadequate lymph node sampling, perforation of the bowel at presentation, poorly differentiated tumors, lymphovascular invasion, perineural invasion, inadequately sampled lymph nodes (<12 evaluated), T_4 lesions (stage IIB/IIC), and lesions with localized perforation or close or indeterminate margins. This patient has lymphatic invasion which is a risk factor and would benefit from adjuvant chemotherapy. See "Treatment"

(Operable Disease; Adjuvant Chemotherapy for Colon Cancer) section for more information.

7. **B.** FOLFOX (fluorouracil/leucovorin and oxaliplatin) is a preferred regimen for patients with stage III colon cancer who can tolerate combination therapy according to the NCCN guidelines. Alternatives are capecitabine + oxaliplatin, capecitabine alone, or fluorouracil/leucovorin. Neoadjuvant XRT may be used in a small group of patients (eg, those with T4 tumors adfixed to other structures), although it is most commonly given in combination with chemotherapy. Regorafenib and pembrolizumab are used in metastatic colon cancer. See "Treatment" (Operable Disease; Adjuvant Chemotherapy for Colon Cancer) section for more information.

8. **D.** In patients with metastatic (stage IV) colorectal cancer, the goal of therapy is to reduce symptoms, avoid disease-related complications, and prolong survival. Treatment goals for cancer of the colon or rectum are based on the stage of disease at presentation. Stages I, II, and III disease are considered potentially curable and the goal of management is to eradicate potential micrometastases after surgical resection. Most patients with stage IV disease are not curable, and treatments for metastatic disease are considered palliative to reduce symptoms, avoid disease-related complications, and prolong survival. However, special attention should be given to those with oligometastatic lesions in the liver or lung since potential cure is still possible for some of these patients. See "Treatment: Desired Outcomes" section for more information.

9. **C.** Neuropathy is associated with oxaliplatin and the FOLFIRI regimen does not contain oxaliplatin. Diarrhea (both acute and late) and mucositis can occur with irinotecan and also with fluorouracil. Myelosuppression tends to be more common/severe with FOLFIRI than with oxaliplatin-containing regimens. See "Treatment" (Operable Disease; Fluorouracil Plus Oxaliplatin Regimens; Metastatic Disease: Initial Therapy; Unresectable Metastatic Colorectal Cancer) section for more information.

10. **A.** First-line treatment of *RAS* mutated metastatic colorectal cancer includes a fluorouracil-based regimen +/- bevacizumab. Although this patient has EGFR positive disease, and EGFR inhibitor, such as cetuximab, is not indicated. EGFR inhibitors are only appropriate when *RAS* and *BRAF* wild-type disease is present. Ziv-aflibercept is only indicated for progression after other therapies. See Table 153-6 and "Treatment" (Metastatic Disease: Initial Therapy; Unresectable Metastatic Colorectal Cancer) section for more information.

11. **A.** When progression occurs during a regimen for metastatic colorectal cancer, the regimen is always discontinued and a new one is initiated. Patients with metastatic colorectal cancer and high microsatellite instability receive benefit from immunotherapy after disease progressions. Pembrolizumab, dostarlimab, nivolumab, and or the combination of nivolumab and ipilimumab may be used. See "Treatment" (Metastatic Disease: Initial Therapy; Unresectable Metastatic Colorectal Cancer; Immunotherapy) section and Table 153-6 for more information.

12. **A.** EGFR inhibitors (cetuximab, panitumumab) are appropriate when *RAS* and *BRAF* wild-type disease is present; however, those with right-sided tumors (cecum to hepatic flexure) do not have improved survival. Therefore, EGFR inhibitors are not recommended in patients with right-sided tumors and instead you would use same regimen as you might in those with mutations of *RAS* or *BRAF* (eg, FOLFOX + bevacizumab). Regorafenib is recommended as third- or fourth-line therapy. See "Treatment" (Metastatic Disease: Initial Therapy; Targeted Therapy) section for more information.

13. **C.** Patients with UGT1AI*28 genotype should be considered to receive a dose reduction of irinotecan because they are not able to glucuronidate irinotecan as effectively as those who do not have this genotype. The prolonged systemic exposure to irinotecan and its active metabolite SN-38 can result in severe delayed diarrhea. Therefore, dose adjustments are recommended to avoid this adverse drug reaction. See "Treatment" (Metastatic Disease: Initial Therapy; Unresectable Metastatic Colorectal Cancer; Chemotherapy) section for more information.

14. **C.** Cetuximab, an EGFR monoclonal antibody, is associated with a papulopustular skin rash that can be severe, requiring treatment, and in some cases dose reductions or interruptions. Infusion-related reactions can occur but are rare (3%). Neither dose-limiting diarrhea or neuropathy is common with cetuximab. See "Treatment" (Metastatic Disease: Initial Therapy; Targeted Therapy) section for more information.

15. **A.** Oxaliplatin can cause acute neuropathies, occur in about 90% of patients, and are precipitated or exacerbated by exposure to cold temperatures or cold objects. Thus, patients should be instructed to avoid cold drinks and use of ice, and to cover skin before exposure to cold or cold objects before, during, and for 2 days following chemotherapy. Irinotecan is associated with moderate-to-severe late diarrhea and high-dose loperamide is used to treat it. Regorafenib is taken with a low-fat breakfast. Because of the risk of gastrointestinal perforation with bevacizumab patients should be instructed to call immediately if signs such as abdominal pain with vomiting or constipation occur. See (Operable Disease; Adjuvant Chemotherapy for Colon Cancer; Metastatic Disease: Initial Therapy; Unresectable Metastatic Colorectal Cancer; Chemotherapy; and Targeted Therapy) sections for more information.