Colorectal Cancer

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- Complete the questions at the end of the course.
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Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure
The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with colorectal cancer.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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This activity has been designated for 15 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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NetCE designates this continuing education activity for 15 ANCC contact hours.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals with information regarding the screening, diagnosis, and treatment of colorectal cancer in order to improve adherence to established guidelines and, by extension, patient outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the epidemiology of colorectal cancer.
2. Identify modifiable colorectal cancer risk factors.
3. Describe nonmodifiable risk factors, including familial and genetic colorectal cancer syndromes.
4. Evaluate the role of colonoscopy in colorectal cancer screening, including strategies to improve effectiveness.
5. Identify available modalities used in colorectal cancer screening.
6. Apply the correct colorectal cancer screening interval for patients with specific findings.
7. Describe the pathways by which colorectal cancer develops.
8. Discuss the histologic features of colorectal cancer precursor lesions.
9. Relate the diagnostic and staging criteria for colon and rectal cancers.
10. Identify molecular and clinical factors used to determine prognosis in patients with colorectal cancer.
11. Select the appropriate treatment approach for early stage (I–III) colon cancer.
12. Choose the most effective treatment option for patients with rectal cancer.
13. Analyze the role of chemotherapy in the treatment of colorectal cancer, including the action of specific agents.
14. Discuss the treatment of metastatic and recurrent colorectal cancers.
15. Describe potential treatment-induced toxicities and adverse effects in patients with colorectal cancer.
16. Outline recommended follow-up for patients treated for colorectal cancer.

E B
EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in the United States, and roughly 35% of those who develop colorectal cancer die from the disease [1; 2; 3]. Improved therapies and widespread primary prevention through screening have resulted in the United States being the only developed country with declining colorectal cancer incidence and mortality [4]. However, there is substantial room for improvement, and primary care provider knowledge of colorectal cancer is essential to continue reducing cases through screening and early detection. While this course addresses important content domains related to colorectal cancer, a few related areas are not addressed: management of cancer-related pain and cancer of the anus. With 90% of anal cancer cases associated with the human papillomavirus (HPV), this malignancy is considered distinct from rectal cancer [5]. In contrast, rectal cancer bears such similarity to colon cancer that both cancers are frequently combined in epidemiologic and clinical reports.

EPIDEMIOLOGY

Worldwide, colorectal cancer is the second leading cause of cancer-related death among both sexes [6]. The incidence varies geographically, with the highest estimated rates per 100,000 population in Australia/New Zealand (34.9 in men, 27.7 in women) and lowest in Africa (9.1 in men, 7.5 in women). The highest estimated mortality rates per 100,000 population are in Europe (12.1 in both sexes) and the lowest are in Africa (5.6 in both sexes) [6].

In the United States, colorectal cancer is the third leading cause of cancer death, with 107,320 new diagnoses of colon cancer, 46,950 new diagnoses of rectal cancer, and 52,900 deaths projected for 2025 [7]. From 2011 to 2019, rates decreased by about 1% per year overall, although declining incidence was confined to individuals 65 years of age and older. Rates have increased by 1% to 2% per year since the mid-1990s in adults younger than 55 years of age and have stabilized in adults 55 to 64 years of age [8]. The death rate has decreased by 56%, from 29.2 per 100,000 in 1970 to 12.8 in 2021, primarily due to earlier detection and improvements in treatment [8].

During 2016 to 2020, the overall mortality rate from colorectal cancer in the United States was 13.1 per 100,000 population and was 43% higher in men (15.7) than in women (11.0). From 2015 to 2019, the incidence of colorectal cancer was highest in American Indian/Alaska Native individuals (48.6 per 100,000), followed by non-Hispanic Black individuals (41.7), and lowest in Asian American/Pacific Islander individuals (28.6) [9]. However, there are striking differences within these heterogeneous populations. For example, Japanese and Native Hawaiian people have a higher incidence of colorectal cancer than White people, and Alaska Native individuals have a two-fold higher incidence (88.5 per 100,000) and mortality (35.9 per 100,000) than American Indian individuals (46 and 17.5, respectively) [10].

The risk of colorectal cancer increases after 44 years of age. The incidence rates increase by about 80% to 100% with each five-year age group until 50 years of age and then by 20% to 30% from ages 55 to 59 years and older. From 2015 to 2019, the age-specific incidence of colorectal cancer in the United States ranged from 60.6 per 100,000 population in individuals 55 to 59 years of age to 234.7 in individuals 85 years of age and older [10]. Most cases (90%) of colorectal cancer are diagnosed after 50 years of age; only 6% are diagnosed in persons younger than 55 years of age [1; 11; 12]. Although colorectal cancer remains more common in older individuals, the incidence is increasing among younger adults. Between 2004 and 2013, the number of young-onset (before 50 years of age) cases increased 11.4% [13]. In that same period, the number of cases in adults 50 years of age or older decreased 2.5%.

Figures for rectal cancer alone are more difficult to ascertain because epidemiologic studies usually report colon and rectal cancer together as colorectal cancer. However, 2024 projections estimate 46,220 new rectal cancer diagnoses [8].

Approximately 4.2% of Americans will be diagnosed with colorectal cancer at some point in their lifetime. Of those diagnosed, 50% will die from the disease. The overall five-year survival rate is 65.7% [11]. Cancer stage at diagnosis strongly influences duration of survival. With colon and rectum cancer, the five-year survival is approximately 91% in patients diagnosed with localized cancer, 73% with limited regional extension, and 13% with distant metastases [14]. Despite advances in surgical techniques and adjuvant therapy, the modest survival improvements in patients with advanced neoplasm provide the rationale for implementing primary and secondary preventive approaches to reduce morbidity and mortality from colorectal cancer [1; 2; 3].

COLORECTAL CANCER RISK FACTORS

For most people, the dominant risk factor for colorectal cancer is increasing age. As noted, risk increases dramatically after 50 years of age. Other nonmodifiable factors, such as family history of colorectal cancer, personal history of colorectal cancer or high-risk adenomas, genetic predisposition, and inflammatory bowel disease, also elevate the risk of colorectal cancer [15]. There are also modifiable factors that increase (or decrease) an individual's risk of colorectal cancer, including alcohol use, cigarette smoking, diet, and physical activity.

MODIFIABLE FACTORS

Factors Associated with Increased Risk of Colorectal Cancer

Excessive Alcohol Use

Solid evidence indicates that excessive alcohol use is associated with increased risk of colorectal cancer. Analysis of pooled data found that alcohol consumption greater than 45 g/day was associated with a 41% increase in risk of colorectal cancer [15; 16; 17]. The more pronounced association between current alcohol intake and larger adenomas suggests that alcohol may act during the promotional phase of the adenoma-carcinoma sequence [16; 17].

Cigarette Smoking

Cigarette smoking is associated with an increased risk of colorectal cancer incidence and mortality, significantly increased risk of small and large adenomas, adenoma recurrence following polypectomy, and a long cancer induction period (35 years minimum). Rates of colorectal cancer mortality are highest in current smokers, intermediate in former smokers, and lowest in nonsmokers. Increased risk was observed after 20 years of smoking in men and women. Estimates from U.S. data attribute 11% of all colorectal cancer deaths to smoking [8]. Current smoking (vs. never smoking) increases the risk of developing colorectal cancer by 18% [18; 19].

Obesity

Obesity, defined as a body mass index (BMI) ≥30, has been consistently associated with increased incidence and mortality from colorectal cancer, particularly in men. Compared with BMI <22, the risk of colorectal cancer increases with a BMI >28.5 by 60% in men and 30% in women. A BMI ≥30 increases the overall risk of colorectal cancer by 45%. The mechanism of increased vulnerability to colorectal cancer in obese patients is not known but may involve the elevated release and bioavailability of growth factors, insulin, and insulin-like growth factor 1. Heightened risk in obese patients appears to be mitigated by high levels of physical activity [20; 21].

BMI is associated with risk of colorectal adenomas and colorectal cancer, but few studies have accrued large enough sample sizes to allow stratified analyses. Evaluation of pooled data from 8,213 participants in seven prospective studies found higher BMI was significantly associated with most histologic characteristics of metachronous adenomas in men, but not in women. The researchers concluded that body mass may affect colorectal carcinogenesis at comparatively early stages, particularly in men [22].

A study of 11,598 survivors of incident primary colorectal cancer examined the effect of obesity on risk of developing a second obesity-associated cancer (e.g., postmenopausal breast, kidney, pancreas, esophageal adenocarcinoma, endometrium). Compared with colorectal cancer survivors of normal prediagnostic BMI, the risk of developing a second obesity-associated cancer was increased 39% in overweight patients and 47% in obese patients [23]. This compares to the risk for developing a first primary obesity-associated cancer, which was increased by 18% in overweight persons and 61% in obese persons. The authors state that colorectal cancer survivors who were overweight or obese before diagnosis had an increased risk of second obesity-associated cancers relative to normal-weight survivors. Elevated risk of developing a second cancer in colorectal cancer survivors is more likely the result of the increased prevalence of overweight and obesity rather than increased susceptibility [23].

Researchers have associated a common mutation in colorectal cancer with elevated risk of metabolic disease. *APC* is a tumor-suppressor gene that indirectly regulates cell proliferation by encoding a protein called beta-catenin. *APC* inactivation by mutation leads to loss of beta-catenin function, which results in unchecked cellular replication and other processes that drive progression to malignant phenotype. Activation of the Wnt signaling pathway, normally mediated by beta-catenin, also occurs. Beta-catenin-Wnt signaling is involved in glucose metabolism and metabolic diseases such as obesity and type 2 diabetes. Using a molecular pathologic epidemiology database, researchers found that risk of beta-catenin-negative colorectal cancer was significantly higher with greater BMI and lower with increased physical activity level. Risk of beta-catenin-positive colorectal cancer was unrelated to BMI or physical activity level [24].

Factors Associated with a Decreased Risk of Colorectal Cancer

Polyp Removal

Removal of adenomatous polyps significantly reduces the risk of colorectal cancer. This will be discussed in detail later in this course.

Physical Activity

A sedentary lifestyle has been associated with an increased risk of colorectal cancer, although this finding has not been consistent [15]. More consistent is the association between regular physical activity and a decreased incidence of colon but not rectal cancer, with an estimated 22% to 27% risk reduction [25; 26; 27; 28].

Diet Low in Fat and Meat

Colon cancer rates are high in populations with high total fat intakes and are lower in those consuming less fat [29]. On average, fat comprises 40% to 45% of total caloric intake in high-incidence Western countries; in low-risk populations, fat accounts for only 10% of dietary calories [30]. Several case-control studies have explored the association of colon cancer risk with meat or fat consumption as well as protein and energy intake [31]. Positive associations with meat consumption or fat intake have been found frequently but have not always achieved statistical significance [32]. One hypothesis is that heterocyclic amines formed when meat or fish are cooked at high temperatures may contribute to the increased risk of colorectal cancers associated with meat consumption observed in epidemiologic studies [33; 34].

Diet High in Fiber

Despite evidence from case-control studies of a protective effect, results from a large prospective study found no difference in the risk of colorectal cancer between women in the highest quintile group compared with the lowest quintile group with respect to dietary fiber, after adjusting for age, known risk factors, and total energy intake [35]. One study evaluated the associations between dietary fiber, fat, and colorectal cancer risk in the Women's Health Initiative prospective cohort, which included 134,017 women [36]. During a mean 11.7 years follow-up (1993–2010), 1,952 incident cases of colorectal cancer were identified. When fiber and fat intake were assessed individually, the authors found a modest trend toward lower cancer risk with increased intakes of total fiber, suggesting a mild protective effect of higher fiber intake on risk of colorectal cancer, but not when combined with intake of dietary fats [36]. Results of a pooled analysis of 3,209 participants combined from two trials indicate that men may experience more benefit from dietary fiber than women [37].

Diet High in Fruits and Vegetables

Overall, results from more rigorously designed randomized controlled trials have washed out findings of significant correlation in earlier studies that linked higher fruit and vegetable consumption with lower rates of colorectal cancer. Diets low in fat and meat and high in fiber, fruits, and vegetables started as an adult do not appear to reduce the risk of colorectal cancer by a clinically important degree [36; 38].

Lifestyle and Diet Modification in Recurrence Risk Reduction

Cohort studies have demonstrated associations between specific diet or exercise regimens with improvements in disease-specific and/or overall survival in patients following treatment for colorectal cancer, but these results have not been replicated by prospective randomized trials. When verification by more rigorous studies is absent, cohort study data should be interpreted with caution, because numerous uncontrolled variables are present that may confound the observational findings [15].

Physical Activity

A meta-analysis of prospective cohort studies evaluating physical activity in patients found a 25% reduction in colorectal cancer-specific mortality associated with any amount of physical activity (vs. no activity) and a 30% reduction associated with a high amount of physical activity (vs. low amount). After colorectal cancer was diagnosed, a 26% reduction in colorectal cancer-specific mortality was associated with participation in any physical activity (vs. no activity), and a 35% reduction was associated with a high amount of physical activity (vs. a low amount) [39].

A 2022 analysis used data from the Global Burden of Disease 2019 study to analyze colorectal cancer deaths associated with low physical activity and high body mass index (BMI) *[40]*. The analysis included data from 1990 to 2019 at global, regional, and national levels. In 2019, colorectal cancer deaths attributed to low physical activity and high BMI were an estimated 58.7 and 85.9 per 100,000 population, respectively. Corresponding age-standardized mortality rates were 0.77 (low physical activity) and 1.07 (high BMI). Since 1990, age-adjusted mortality rates from colorectal cancer attributable to low physical activity and high BMI have increased in many geographic regions, particularly in low-middle and middle sociodemographic index regions. Countries with a higher baseline burden in 1990 and a higher sociodemographic index in 2019 had a faster decline in age-adjusted mortality rates of colorectal cancer attributed to high BMI and low physical activity [40].

Diet

Among the observational study findings, patients with stage III colon cancer who had the lowest Western dietary pattern post-treatment showed significantly greater rates of disease-free survival and overall survival versus patients with highest Western dietary pattern [41; 42]. Also, patients with the highest dietary glycemic load showed significantly greater overall survival rates compared with those with the lowest dietary glycemic load. Another uncontrolled cohort study of patients diagnosed with colorectal cancer found the extent of red and processed meat ingestion was associated with a 29% greater risk of death before colorectal cancer diagnosis, but red meat ingestion after diagnosis had no effect on overall mortality [43].

Plasma Vitamin D Level

There is evidence that vitamin D may be an important cofactor in immune protection against colorectal cancer risk. A large, population-based case-control study, derived from the Nurses' Health Study and Health Professionals Follow-Up Study, found a significant association between plasma vitamin D level and colorectal cancer risk according to the degree of local antitumor immune response. The study consisted of 318 colorectal cancer cases and 624 matched controls. Subjects were divided into three groups based on the median plasma vitamin D level (tertile I 19.0 ng/mL, tertile III 37.4 ng/mL) and analyzed according to the degree of lymphocytic immune reactivity within and surrounding the tumor. Subjects in the highest vitamin D tertile were seen to have a significantly lower risk of developing colorectal cancer subtype showing an intense intratumoral cellular immune reaction. This association was not found for tumor subtypes characterized by a poor intratumoral immune response. The authors discuss possible mechanisms and conclude that these observations support a role for vitamin D in cancer immunoprevention through tumor-host interaction [44].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Comprehensive Cancer Network does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with colorectal cancer.

(https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

Chemoprevention

Chemopreventive agents are often prescribed to healthy subjects at risk for colorectal cancer, who will take the agent for the rest of their lives to prevent a potential cancer. In addition to the preventive benefit, this raises the bar very high when defining acceptable safety and toxicity [45].

Practice guidelines and expert opinion have been hesitant to recommend chemoprevention of colorectal cancer. One reason is that very promising earlier findings have often washed out under rigorous evaluation. Epidemiologic and large cohort studies have found a number of agents with significant association to reduced colorectal cancer risk. Not infrequently, these findings were verified by other observational studies, followed by identification in pre-clinical research of plausible mechanisms for a cause-effect relationship. However, results from rigorous investigation using well-designed randomized controlled trials reveal new safety concerns or fail to confirm the significant relationships suggested by data from uncontrolled trials. Thus, guideline authors and experts are reluctant to suggest chemoprevention in the absence of large-scale, long-term, randomized controlled trials [46].

Use of surrogate endpoint markers in many chemoprevention trials may also dissuade recommendation. As the precursor of most colorectal cancers, adenomas have often been used as surrogate endpoints in efficacy evaluation of agents for prevention. Their use as surrogate markers of colorectal cancer in chemoprevention randomized controlled trials permits the reduction of the study observation period from roughly 10 years required for assessing colorectal cancer development to around 2 years. Despite the theoretical and pragmatic basis, preventive efficacy based on this surrogate endpoint may contribute to reluctance in recommending colorectal cancer chemoprevention [45].

The true benefit of chemoprevention is reliant on lifetime colorectal cancer risk in the patient population. Greatest potential benefit may come from use in patients diagnosed by colonoscopy with pre-malignant lesions, with family history of colorectal cancer, or genetically diagnosed and surgically resected for colorectal tumors. Chemoprevention will probably show modest benefit at best when used as prevention in average-risk patients [47; 48].

Cyclooxygenase Inhibitors

A 2015 prospective observational study published the first-ever results of cyclooxygenase-2 (COX-2) inhibitor and aspirin use as adjuvant therapy following resection in patients with stage III colon cancer. All patients received standard adjuvant chemotherapy with fluorouracil (5-FU) plus leucovorin with or without irinotecan. In the aspirin arm of 799 patients, 75 (9.4%) used aspirin during and after chemotherapy. In the COX-2 inhibitor arm of 843 patients, 59 (7.5%) used celecoxib or rofecoxib after completing chemotherapy. Both groups had a median follow-up of 6.5 years [49]. Among patients taking aspirin (vs. no aspirin), recurrence-free survival (i.e., time period until tumor recurrence, death with recurrence, or development of a new invasive colon cancer) was increased by 49%, disease-free survival (i.e., time period until tumor recurrence, occurrence of a new colon cancer, or death from any cause) was increased by 32%, and overall survival (i.e., time period until death from any cause) was increased by 37%. Adjusted hazard ratios were censored at five years to minimize misclassification from non-cancer death and showed increases in disease-free survival by 39% and overall survival by 52% (vs. no aspirin). Patients taking a COX-2 inhibitor (vs. no COX-2 inhibitor) found increases in recurrence-free survival by 47%, disease-free survival by 40%, and overall survival by 50%. Censor of survival data at five years found disease-free survival increased by 53% and overall survival by 74% [49].

Although this study was not designed to identify the optimal dose and duration of aspirin or COX-2 inhibitors for protection against colorectal cancer, the data suggest a dose-response relationship in aspirin with increased frequency, while any dose of COX-2 inhibitors was associated with benefit. The statistically significant associations between aspirin and COX-2 inhibitor use and reduced colon cancer recurrence and mortality found in this study will continue to be evaluated [49].

Celecoxib, rofecoxib, and aspirin share a similar mechanism of action in colon (and presumably rectal) cancer involving COX-2 inhibition. COX synthesizes the conversion of arachidonic acid to prostaglandins. Prostaglandins mediate tumor growth by altering stem cell gene expression, hypermethylating genes involved in proliferation and differentiation, promoting angiogenesis and Wnt/CTNNB1 signaling, and inhibiting apoptosis. Thus, suppression of prostaglandin synthesis through COX inhibition interferes with the processes involved in tumor promotion and growth [49; 50].

Long-term follow-up data from two large studies initiated in the 1980s found that ≥300 mg aspirin daily taken for five or more years was associated with a 37% overall reduction in colorectal cancer risk. In subjects who remained adherent to the protocol for 5 or more years, those randomized to aspirin were found to have a 40% risk reduction in colorectal cancer mortality after 20 years and absolute risk reduction from 3.1% to 1.9% relative to those receiving placebo. Mortality reduction was primarily from the effect of aspirin on proximal colon cancer. These findings were serendipitous, because the research was designed to examine the protective effects of aspirin against cardiovascular events [51; 52].

Prospective studies have demonstrated significant reduction in colorectal cancer among regular aspirin users [53]. In a randomized controlled trial of 861 persons with Lynch syndrome, primary colorectal cancer developed in 4.2% of patients taking daily aspirin 600 mg, compared with 6.9% in those receiving daily placebo (mean follow-up: 55.7 months). Time to first colorectal cancer was increased 37% with aspirin versus placebo; with regression analysis incorporating multiple primary events, aspirin led to a 44% reduction in colorectal cancer incidence. In subjects completing at least two years of intervention, time to first colorectal cancer was increased 59% and incidence of colorectal cancer was reduced 63%. Adverse events did not differ between aspirin and placebo groups during the intervention [54]. A planned 10-year follow-up to this trial (the double-blind, randomised CAPP2 trial) included 861 patients with Lynch syndrome from 43 international centers worldwide. The participants were randomly assigned to receive either 600-mg aspirin daily (427 participants) or placebo (434 participants). Cancer outcomes were monitored for at least 10 years from recruitment; some of the participants (i.e., English, Finnish, and Welsh participants) were monitored for up to 20 years. The primary endpoint was development of colorectal cancer *[55].* Forty (9%) of the aspirin group developed colorectal cancer compared with 58 (13%) of the placebo group. Noncolorectal Lynch syndrome cancers were reported in 36 participants who received aspirin and 36 participants who received placebo. Adverse events between the aspirin and placebo groups were similar [55]. Likewise, a randomized controlled trial of patients with a history of adenomas or colorectal cancer found a statistically significant 21% reduction in risk of adenoma recurrence in patients randomized to aspirin (versus placebo) [56].

A prospective cohort study examined the effects of aspirin in participants following a diagnosis of colorectal cancer. Regular use of aspirin after colorectal cancer diagnosis was associated with a 29% increase in colorectal cancer-specific survival and a 21% increase in overall survival [57]. In the long-term Nurses' Health Study and the Health Professional Follow-up Study, 964 patients diagnosed with rectal or colon cancers were evaluated. In those with *PI3K*-mutant colorectal cancer, regular use of aspirin was associated with a 46% increase in overall survival [58].

The benefit of aspirin in prevention of colorectal cancer is not apparent until 10 years after aspirin therapy is started and is most effective when started between 50 and 59 years of age. Because of the time required before a reduced incidence in colorectal cancer is realized, persons 70 years of age and older are less likely to realize a benefit and may be at risk of advanced cancer or of dying from cancer [59; 60; 61]. Additionally, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with potentially serious adverse effects that should be considered when determining the risk-benefit ratio [56]. Aspirin use increases risk of upper gastrointestinal complications by 60%. Risk increases with age [61].

While no studies have assessed adenoma or colorectal cancer risk reduction with use of NSAIDs in the general (and presumably average-risk) population, multiple lines of evidence from epidemiologic studies, observational cohort studies, and randomized controlled trials have consistently affirmed the association between NSAID use and a 30% to 50% reduction in adenomatous polyps, incident disease, and death from colorectal cancer [56; 62; 63; 64]. In one study, patients with familial adenomatous polyposis (FAP) who were followed over four years of treatment with NSAIDs showed a trend in reduction in adenoma incidence and statistically significant reductions in polyp number and size. A 34% reduction in adenoma recurrence risk and a 55% reduction in advanced adenoma incidence were found in patients with a history of adenomas [56].

The NSAIDs sulindac and celecoxib have been shown in randomized controlled trials to induce adenoma regression in patients with FAP, which, together with supportive preclinical data, led the U.S. Food and Drug Administration (FDA) to approve celecoxib for patients with FAP in 1999. However, in 2011, the FDA requested Pfizer voluntarily withdraw the FAP indication for celecoxib, because the company never fulfilled a condition for approval requiring postmarketing evaluation to verify clinical benefit, which Pfizer did [65]. Despite the change of celecoxib use in FAP to off-label status and withdrawal of regulatory approval, several health insurance companies have codified the use of celecoxib in FAP as an authorized indication [66].

The consistently positive findings of NSAID benefit in suppressing the development of adenomas and improving recurrence-free, disease-free, and overall survival in patients with histories of adenomas and colon cancer has posed a dilemma for researchers and clinicians, given the known toxicity profile. NSAID-related morbidity is fairly common and potentially serious and includes upper gastrointestinal bleeding, renal dysfunction, and serious cardiovascular events such as myocardial infarction, heart failure, and hemorrhagic stroke. Among other findings, use of NSAIDS increases the risk of serious cardiovascular events by 50% to 60% [62; 67].

Hormones (for Women Only)

The Women's Health Initiative (WHI) randomized participants to estrogen plus progestin or placebo. At a mean follow-up of 11.6 years, women receiving active hormone therapy had a 28% lower risk of colorectal cancers [68]. However, in the hormone therapy group, colorectal cancers that developed were significantly more likely to exhibit lymph node involvement and higher stages (regional and distant) compared with those in the placebo group. Deaths from colorectal cancers in the active group were somewhat higher, but the difference from placebo was not statistically significant [68]. A meta-analysis of cohort studies observed a 14% risk reduction for incidence of colorectal cancer associated with combined hormone therapy [69].

Conjugated equine estrogens do not improve incidence or survival in invasive colorectal cancer [68]. Definite harms have been established in using combined estrogen plus progestin hormone in postmenopausal women. The WHI trial found increased risks of invasive breast cancer, coronary heart disease events, and thromboembolic events [68; 70].

Vitamin Supplementation

Vitamin E

A prospective cohort study of 35,215 women found an inverse association between the risk of colon cancer and vitamin E intake [71]. However, a later cohort study found no relationship between every-other-day use of vitamin E 600 IU and colorectal cancer, and a meta-analysis of 14 randomized trials of supplemental antioxidant vitamins involving 170,025 individuals found no evidence for prevention of colorectal adenoma or colorectal cancer [72; 73].

Vitamin D

A systematic review of published cohort studies found that daily intake of 1,000 IU of vitamin D and 25-hydroxyvitamin D serum concentration of 33 ng/mL were each associated with a 50% risk reduction of colorectal cancer [74]. A population-based case-control study found an inverse relationship between vitamin D intake and colorectal cancer risk [75]. More recent research is focused on the role of vitamin D as an adjunct treatment after a diagnosis of colorectal cancer. For example, two randomized, placebo-controlled trials of vitamin D in patients with metastatic colorectal cancer are underway to assess patient survival as a primary endpoint. The first study is a phase II trial comparing high-dose vitamin D3 (8,000 IU/day for two weeks followed by 4,000 IU/day) versus a standard dose (400 IU/day). The second study is a phase I–II trial comparing customized oral doses of vitamin D3 titrated to raise serum 25(OH)D levels to 80–100 ng/mL versus 2,000 IU/day. The results of these and subsequent phase III trials may provide more definitive answers about the role of vitamin D in the treatment of colorectal cancer [76].

Folate

An observational study of women with a family history of colon cancer found use of folic acid supplements for more than 15 years was associated with a 75% lower risk of colorectal cancer [77]. One hypothesis is that folate is required for DNA synthesis, and suboptimal amounts may cause abnormalities in DNA synthesis or repair [78]. However, a trial that randomized 1,021 men and women with recent colorectal adenoma history to daily folic acid 1 mg or placebo found folic acid was associated with greater risks of developing ≥1 advanced adenoma, ≥3 adenomas, and extra-colonic malignancy compared with placebo [79]. General population studies have not found benefit of folic acid on colorectal cancer risk, but outcomes obtained over relatively short duration may have missed detection of benefit from longer exposure and/or follow-up [56].

Calcium

Researchers have suggested that calcium's action of binding bile acids and fatty acids may lower colon cancer risks through reducing exposure to toxic intraluminal compounds *[80]*. To study the effects of calcium on adenoma recurrence, persons with a recent history of colorectal adenomas were randomized to daily 3 g calcium carbonate (1,200 mg elemental calcium) or placebo. At four-year follow-up, those receiving calcium (compared with placebo) showed a 19% reduction in developing one or more recurrent adenoma and the average number of adenomas was 24% lower. This reduced risk was likely to extend up to five years following cessation of calcium supplementation [81; 82].

Calcium has not shown benefit in patients with FAP. In the general population, there was no significant effect of calcium on risk of colorectal cancer, although studies were of relatively short duration [56]. There is fair evidence that 1,000–1,200 mg/day oral calcium without vitamin D supplementation increases the risk of myocardial infarction. Calcium supplementation with vitamin D at doses less than 1,000 mg/day has few harmful effects [83; 84].

NONMODIFIABLE RISK FACTORS

While most cases of colorectal cancer result from complex interactions between inherited susceptibility and environmental or lifestyle factors, certain heritability factors place the individual at very high risk of colorectal cancer, while other patterns of familial colorectal cancer elevate individual risk. Furthermore, specific medical conditions are associated with colorectal cancer risk. The presence or absence of these nonmodifiable risk factors influences the probability that colorectal cancer will develop. Assessment and identification of these risk factors determines the timing, frequency, and modality of colorectal cancer screening and intervention [85; 86].

PERSONAL COLORECTAL CANCER RISK FACTORS
Age
Older than 50 years
Medical conditions
Inflammatory bowel disease
History of ≥1 adenomatous polyps (size ≥1 cm, with high-grade dysplasia or villous features that confer higher risk)
Cancer history
Personal history of colorectal cancer
Personal history of other Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)-associated cancers, including endometrial, ovarian, small bowel, gastric, ureteral/renal pelvis, hepatobiliary/pancreas, brain (particularly glioblastoma), or sebaceous adenoma/cancer
Early-onset colorectal cancer or Lynch syndrome-associated cancer
Genetic factors
Confirmed carrier of a mutation that causes a hereditary colorectal cancer syndrome
Lifestyle, behavioral, and dietary risk factors
Diet high in saturated fats and red and processed meats
Diet low in folate
Physical inactivity
Obesity
Smoking
≥2 alcoholic drinks/day
Source: [88; 89] — *Table 1*

Assessment of Nonmodifiable Colorectal Cancer Risk Factors

Clinicians should perform an individualized assessment of colorectal cancer risk in all adults in order to understand patient risk level for colorectal cancer. Patient risk is assessed by a thorough personal and family history to identify factors associated with increased vulnerability to colorectal cancer. The colorectal cancer risk factors of smoking, obesity, coronary artery disease, diabetes, acromegaly, renal transplantation, and cholecystectomy have no bearing on the timing, frequency, and modality of colorectal cancer screening or intervention (in the absence of adenomatous polyps or colorectal cancer) [87].

Familial Colorectal Cancer Risk Factors

A targeted colorectal cancer family history should include a detailed family history of cancer and polyps, especially in first-degree (e.g., parent, sibling, child) and second-degree (e.g., grandparent, uncle/aunt, half sibling) relatives on both sides of the family [88; 89]. Clinicians should ask about polyps in relatives, including [90]:

- Age at first colon exam
- How diagnosed (e.g., colonoscopy, flexible sigmoidoscopy, barium enema)
- How many (during each colonoscopy or lifetime total)
- Type (adenomas, hyperplastic, juvenile, serrated, hamartomas)
- Polyp surgery

- Diagnoses:
  - Colorectal cancer (and age at diagnosis)
  - Polyposis syndrome
  - Extracolonic conditions such as osteoma, sebaceous cysts, desmoid tumors, congenital hypertrophy of retinal pigment epithelium (CHRPE), or extra teeth
- Genetic testing for polyposis or hereditary cancer
- Is relative willing to sign release to share relevant medical records?

In addition to familial factors, patients' personal risk factors should also be assessed (***Table 1***).

Patients should be assessed for all cancer types. Cancer syndromes include risk for multiple types of malignancy; colorectal cancer is not always a presenting cancer. A three-generation pedigree is the gold standard. The minimum for colorectal cancer should include cancer and polyp history for the patient's generation and two previous generations. The patient's risk status can change over time with updated personal or family history.

Assessment Red Flags

Findings suggestive of heritable colorectal cancer risk are termed "red flags" and direct the healthcare provider to probe further. One red flag is a personal history of colon cancer diagnosed before 60 years of age or endometrial cancer diagnosed before 50 years of age [88; 89]. Early age at diagnosis suggests that genetic factors are playing a strong role in the development of disease.

A family history of colon or endometrial cancer diagnosed before 50 years of age is another red flag. Early age at diagnosis of cancer in a closely related family member suggests that genetic factors are playing a role in the development of disease, and these factors can be passed on to other relatives. If multiple family members have been diagnosed with colorectal cancer, or other Lynch/hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers, this strongly suggests genetic factors are increasing individual cancer risks, especially among first-degree relatives [88; 89].

One to two polyps in a lifetime is common, but more than 10 in a lifetime is unusual and suggests genetic contribution. Polyposis is associated with increased colorectal cancer risk. In addition, diagnosis of two or more Lynch/HNPCC-associated cancers suggests an inherited mutation, increasing the overall risk for cancer in different organs [88].

Past diagnosis of Lynch/HNPCC, FAP, or other inherited cancer syndrome in a family member is another risk factor. Many of these conditions are inherited in a dominant pattern, but not everyone who inherits gene mutations for these conditions develops cancer. Therefore, a diagnosis of HNPCC in a grandparent may be relevant to the patient. HNPCC carries a lifetime risk of developing colorectal cancer between 30% and 72% [88].

Patient Colorectal Cancer Risk Level

Of total colorectal cancer cases, 75% are due to sporadic disease without apparent inherited origin, 10% to 30% are due to familial risk factors, and 5% to 6% are due to heritable genetic mutations. The absolute risk of colorectal cancer by 79 years of age is [90; 91; 92]:

- 4% with no family history
- 9% with colorectal cancer in one first-degree relative
- 16% with colorectal cancer in two or more first-degree relatives
- 15% with colorectal cancer in one first-degree relative diagnosed before 45 years of age
- 8% with colorectal adenoma in one first-degree relative

COLORECTAL CANCER RISK LEVELS	
Risk Level	**Factors**
Average	Lack of specific risk factors
Increased (moderate)	Inflammatory bowel disease Previous colonoscopy polyp findings: • Small rectal hyperplastic polyps • 1–2 small tubular adenomas with low-grade dysplasia • 3–10 adenomas • 1 adenoma >1 cm • Any adenoma with villous features or high-grade dysplasia • >10 adenomas on a single examination • Sessile adenomas removed piecemeal Family history: • Colorectal cancer or adenomatous polyps in a first-degree relative • Two second-degree relatives with colorectal cancer
High	Diagnosis of Lynch/HNPCC or FAP Family or medical history highly suggestive of hereditary colorectal cancer syndrome
Source: [95]	*Table 2*

Family history of two or more relatives with colorectal cancer substantially increases the possibility of a genetic syndrome, and relative to older individuals, young patients reporting a positive colorectal cancer family history are more likely to represent a high-risk pedigree [93; 94]. Patient risk level is categorized as high, increased (moderate), or average based on the presence of specific factors (***Table 2***) [95].

Familial and Genetic Colorectal Cancer Syndromes

Heritable gene mutations that confer elevated risk of colorectal cancer broadly cluster into two groups: stability genes, including mutations in DNA mismatch repair (MMR) genes responsible for Lynch syndrome, and tumor suppressor genes, including *APC* gene mutations responsible for FAP. Lynch syndrome and FAP account for the vast majority of heritable colorectal cancer cases and 5% to 6% of all colorectal cancer cases [96]. The absolute risks for colorectal cancer in mutation carriers of hereditary colorectal cancer syndromes are [90]:

- Lynch syndrome: 10% to 56% by 75 years of age
- FAP: 90% by 45 years of age
- Attenuated FAP: 69% lifetime
- MYH-associated polyposis: 35% to 53% by 65 years of age
- Peutz-Jeghers syndrome: 39% by 70 years of age
- Juvenile polyposis syndrome: 17% to 68% by 60 years of age

Individuals with single-gene disorders are at increased risk of developing colorectal cancer, and single-gene disorders related to known syndromes account for 10% to 15% of colorectal cancer cases. The hereditary syndromes and involved genes include Lynch syndrome, FAP, familial colorectal cancer, and rare genetic syndromes [90].

Lynch Syndrome

Lynch syndrome is the most prevalent form of hereditary colorectal cancer, accounting for 3% to 5% of all cases [90]. It primarily involves defects in MMR genes, most commonly *MSH2*, *MLH1*, *PMS1*, *PMS2*, or *MSH6*. In affected families, 15% to 60% of family members possess *MSH2* or *MLH1* mutations [91; 96; 97].

Lynch syndrome is an autosomal dominant disorder in which families and patients possess a germline mutation in a DNA MMR gene or loss of expression of the *MSH2* gene due to deletion in the *EPCAM* gene. These genes function to maintain DNA fidelity during replication and are inactivated in Lynch syndrome [90; 98].

Genetic Testing. Genetic risk assessment of Lynch syndrome considers family cancer history and patient age if diagnosed with colorectal cancer or malignancies associated with Lynch syndrome. Mutation in MMR genes can be detected using immunohistochemistry techniques (IHCs) or DNA microsatellite instability (MSI) analysis. Several validated computer models predict MMR gene mutation probability (even when MSI or IHC information is absent) and also incorporate family history of endometrial cancer. Mutation detection rates are higher for patients with more striking family histories or informative tumor testing data [99; 100].

Clinical Features. Colorectal cancer and extracolonic malignancies are the primary consequences of Lynch syndrome. Colorectal cancer associated with Lynch syndrome is characterized by early age of onset, excess synchronous and metachronous colorectal neoplasm, right-sided dominance (roughly 67%), and extracolonic tumors. The average age of colorectal cancer diagnosis in patients with Lynch syndrome is 44 to 52 years, versus 71 years in sporadic colorectal cancer. *MLH1* and *MSH2* account for close to 90% of gene mutations, and the lifetime risk of colorectal cancer in *MLH1* and *MSH2* mutation carriers is 68.7% in men and 52% in women [98].

Risk of extracolonic malignancy is greatest for endometrial cancer. At least one female member in about half of all Lynch syndrome pedigrees is affected, and 50% of women with an MMR gene mutation present with endometrial cancer as first malignancy.

Patients with Lynch syndrome have an elevated risk of several other cancers. Risk of extracolonic tumor development by 70 years of age in Lynch syndrome is shown below, with prevalence rate ranges reflecting differences between specific MMR mutations [98]:

- Endometrial (*MLH1/MSH2*): 14% to 54%
- Ovarian: 4% to 20%
- Urinary tract: 0.2% to 25%
- Stomach: 0.2% to 13%
- Small bowel: 0.4% to 12%
- Brain/central nervous system: 1% to 4%
- Prostate: 9% to 30%
- Breast: 5% to 18%

The adenoma-carcinoma sequence of polyp-to-cancer dwell time is an estimated mean 35 months, considerably more rapid than the 10- to 15-year average in sporadic colorectal cancer. This accelerated rate is likely the result of MMR gene dysfunction that creates frequent DNA mismatches in multiple genes to disrupt their normal function [98]. Until recently, Lynch syndrome was termed hereditary nonpolyposis colorectal cancer, a misnomer because polyps are usually present [88; 101].

Diagnosis. Clinical criteria to identify patients with Lynch syndrome were published in 1990 and termed the Amsterdam criteria. These were revised and expanded with the 1999 Amsterdam II criteria, which included extracolonic cancers. The Amsterdam II defines minimum criteria for a clinical diagnosis of Lynch syndrome as at least three relatives with a Lynch-associated cancer (e.g., colorectal cancer, endometrial, small bowel, ureter, renal pelvis) and [88; 96; 102]:

- Two or more successive generations affected
- One or more relatives diagnosed before 50 years of age (at least one first-degree relative)

- FAP excluded
- Tumors verified by pathologic examination

The 2004 updated Bethesda Guidelines were developed to improve the false-negative rates with Amsterdam II and outline criteria to prompt MSI tumor testing to identify Lynch syndrome. Tumors meeting one or more of these criteria require testing for MSI [88; 96; 98; 103]:

- Colorectal cancer diagnosed at 50 years of age or younger
- Synchronous or metachronous Lynch-associated cancer present, regardless of age
- Colorectal cancer with Lynch-like histology (e.g., tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) in patients younger than 60 years of age
- Colorectal cancer in a patient with one or more first-degree relatives with Lynch-associated cancer diagnosed at or before 50 years of age
- Colorectal cancer in a patient with two or more first- or second-degree relatives with a Lynch-associated tumor, regardless of age

Although more sensitive than Amsterdam II in identifying families with Lynch syndrome, only 15% to 30% of families not meeting Amsterdam II but meeting Bethesda criteria exhibit MSI gene mutation. Thus, Amsterdam II or Bethesda criteria may be used to help identify patients who should receive genetic testing, but they should not be used as diagnostic instruments [96; 104]. With the advent of alternative approaches, including universal testing of all newly diagnosed cases of colorectal cancer for MSI (regardless of age at diagnosis or family history of cancer), clinical criteria for Lynch syndrome have been rendered obsolete [88]. Given the limited modalities available to assess unaffected individuals for Lynch syndrome, family history and the use of clinical criteria may be appropriate in identifying those who warrant further genetic evaluation and testing.

Surveillance. The differing surveillance approach in persons with Lynch syndrome relative to average-risk persons is dictated by the biologic behavior of Lynch syndrome [90]. Lynch syndrome develops earlier than sporadic colorectal cancer, which suggests screening should begin earlier in life. Most Lynch syndrome colorectal cancers occur in the right colon, making sigmoidoscopy alone insufficient. Annual colonoscopic surveillance is recommended [90; 96]. The accelerated progression from normal mucosa to adenoma to cancer suggests a shorter colonoscopy screening interval (i.e., every one to two years). The substantially higher lifetime incidence of colorectal cancer suggests that surveillance should use the most sensitive test available [90].

Patients with Lynch syndrome are at an elevated risk of extracolonic cancers, especially endometrial and ovarian [90]. While routine screening in women with Lynch syndrome is recommended due to substantially increased risk of endometrial cancer, routine transvaginal ultrasound screening for endometrial cancer is insensitive, nonspecific, and without benefit in the general population.

Interventions. A study randomized 861 Lynch mutation carriers to daily aspirin 600 mg or placebo. No difference was found at 24 months, but 56-month follow-up found somewhat lower adenoma rate and colorectal cancer risk in the aspirin group. Further analysis and a planned 10-year follow-up found decreased incidence of all Lynch-associated cancers in the aspirin group [54; 55].

Prophylactic surgery is an alternative to annual colorectal cancer and endometrial cancer screening. The high risk of developing metachronous lesions is the basis for prophylactic surgery [104]. The incidence of metachronous colorectal cancers has been reported to be 16% at 10 years, 41% at 20 years, and 63% at 30 years following segmental colectomy [105]. With the increased incidence of synchronous and metachronous neoplasms, the treatment of choice for a patient with Lynch syndrome with neoplastic lesions in the colon is generally an extended colectomy. The results of a follow-up study help in the selection of surgical approach. In this trial, 382

MMR mutation carriers were followed over time after surgery. During follow-up, metachronous colorectal cancer developed in no patient receiving total or subtotal colectomy compared with 22% of patients receiving segmental colectomy [106; 107]. An important factor in the decision to offer prophylactic surgery is the ability of the patient to comply with surveillance examinations.

Consideration of total or subtotal colectomy should be balanced with patient comorbidities, clinical stage of the disease, patient wishes, and surgical expertise. One retrospective study examined data collected on 242 patients with Lynch syndrome who underwent surgery for a first colon cancer between 1984 and 2009 [108]. Patients underwent either standard segmental colectomy or extended colectomy. Primary outcomes measured were risk of subsequent colorectal cancer, overall and disease-specific survival, and operative mortality. One patient died of postoperative septicemia within 30 days after segmental colectomy. Subtotal colectomy decreased the risk of subsequent colorectal cancer compared with segmental resection. The cumulative risk of subsequent colorectal cancer was 20% in 10 years and 47% within 25 years after standard resection, and 4% and 9% after extended surgery, respectively. However, disease-specific and overall survival within 25 years did not differ significantly between the standard and extended surgery groups (82.7% vs. 87.2%) [108]. Although no data have been published showing a survival advantage in extended versus segmental resection for patients with Lynch syndrome, clinicians might consider extensive colectomy to prevent subsequent colorectal cancer in patients with Lynch syndrome [109]. Also, subtotal or total colectomy does not eliminate rectal cancer risk, and the risk of developing rectal cancer following abdominal colectomy is estimated at 12% at 12 years post-surgery [105; 110].

Familial Adenomatous Polyposis

FAP accounts for 1% of all colorectal cancers and involves germline mutations in the tumor suppressor gene *APC* [91; 97]. Ashkenazi Jews have elevated risk of colorectal cancer due to *APC* gene mutation, which occurs in 6% to 7% of this population [111].

Other FAP disorder variants include [91; 97]:

- Attenuated FAP: *APC* gene
- Turcot syndrome: *APC* gene, MMR genes
- Serrated polyposis syndrome (previously hyperplastic polyposis syndrome): *BRAF* and *KRAS2* genes
- *MYH*-associated polyposis: *MYH* gene

Genetic diagnosis of FAP in pre-symptomatic patients is performed with linkage or direct detection of *APC* mutations by analyzing lymphocyte DNA in a blood sample. Linkage analysis tests blood samples from multiple persons to identify gene carriers in close and ancillary family members [91; 97; 104].

Clinical Features. FAP is caused by parental transmission of mutation in the *APC* gene, a tumor suppressor or gatekeeper gene that controls cell proliferation. The most common FAP phenotype is development of hundreds to thousands of colorectal polyps, with usual onset during adolescence or early adulthood. Malignancy develops in one or more polyps as early as 20 years of age, and colorectal cancer develops in almost 100% of patients by 40 years of age if the colon is not removed for primary prevention. Other characteristics of FAP can include polyps in the upper gastrointestinal tract; extracolonic manifestations, such as congenital hypertrophy of retinal pigment epithelium, osteomas and epidermoid cysts, supernumerary teeth, and desmoid formation; and other malignancies, such as thyroid tumors, small bowel cancer, hepatoblastoma, and brain tumors (particularly medulloblastoma) [91; 97; 104]. The lifetime risk of extracolonic tumor development in FAP is [90]:

- Desmoid: 15%
- Duodenum: 5% to 12%
- Thyroid: 2%
- Brain: 2%
- Ampullary: 1.7%
- Pancreas: 1.7%
- Hepatoblastoma: 1.6%
- Gastric: 0.6%

Diagnosis. The clinical diagnostic criteria of FAP is a patient with 10 to 99 adenomatous colon polyps diagnosed by 40 years of age, or more than 100 polyps diagnosed at an older age than expected [90].

Surveillance. The recommended age at which surveillance for polyposis should begin involves a trade-off. On one hand, a patient who waits until the late teens to begin surveillance faces a remote possibility that a cancer will have developed at an earlier age. Although it is rare, colorectal cancer can develop in a teenager who carries an *APC* mutation. On the other hand, it is preferable to allow people at risk to develop emotionally before they are faced with a major surgical decision regarding the timing of colectomy. Therefore, surveillance is usually begun in the early teenage years (10 to 15 years of age) [112]. Surveillance has consisted of either flexible sigmoidoscopy or colonoscopy (preferred) every year. If flexible sigmoidoscopy is utilized and polyps are found, colonoscopy should be performed. Historically, sigmoidoscopy may have been a reasonable approach at the time in identifying early adenomas in a majority of the patients [113]. However, colonoscopy should be considered the tool of choice in light of improved instrumentation for full colonoscopy, safer and deeper sedation (with propofol), recognition that malignancy is more common in the right colon with attenuated FAP, and the growing tendency to defer surgery for a number of years [90]. Individuals testing negative for an otherwise known family mutation do not need FAP-oriented surveillance and can undergo average-risk population screening. In the case of families where no family mutation has been identified in an affected person, clinical surveillance is warranted [90; 91; 97; 104].

Colon surveillance should not be stopped in carriers of an *APC* mutation who do not yet manifest polyps, because adenomas occasionally do not appear before the fourth and fifth decades of life. In some circumstances, full colonoscopy is preferred over the more limited sigmoidoscopy. Tolerability of endoscopic procedures among pediatric patients has improved with the use of deeper intravenous sedation [91; 97; 104].

Interventions. After an *APC* mutation is identified in a patient or member of their family, evaluation for polyposis by flexible sigmoidoscopy or colonoscopy begins promptly. In those showing polyps, the only effective management to prevent colorectal cancer is eventual colectomy. In patients with early-stage classic FAP, the surgeon, endoscopist, and patient/family may opt to delay surgery for several years in the interest of achieving social milestones [90]. Carefully selected patients with attenuated FAP who show minimal polyp burden and are of advanced age may also defer decision-making about colectomy [112].

The timing of risk-reducing surgery is based on symptomatology and the number, size, and histology of polyps. Surveillance colonoscopy is not useful after numerous polyps have developed, because it is no longer possible to remove and biopsy all of them. It is appropriate for patients at this time to consult with a surgeon experienced with available options, including total colectomy and postcolectomy reconstruction techniques. Rectum-sparing surgery followed by sigmoidoscopic surveillance of the remaining rectum is an option for patients who wish to avoid total colectomy, provided they are able to understand the risks and consequences and to follow through with surveillance recommendations [112].

Familial Colorectal Cancer

Many families exhibit aggregation of colorectal cancer and/or adenomas in the absence of known or identifiable genetic susceptibility factors; this is termed familial colorectal cancer [114]. The presence of colorectal cancer in more than one family member may be caused by hereditary factors, shared environmental risk factors, or even chance. Familial colorectal cancer accounts for 20% of all colorectal cancer cases [115].

In the general population, 7% to 10% of individuals have a first-degree relative with colorectal cancer and 14% to 20% have either a first-degree or a second-degree relative with colorectal cancer [91; 97; 104]. A simple family history of colorectal cancer (i.e., colorectal cancer in one or more close relatives, known hereditary colon cancer absent) confers a two- to six-fold increase in risk, with degree of risk influenced by family member's age of colorectal cancer onset, the number of affected relatives, closeness of the genetic relationship, and whether colorectal cancer has occurred across generations. A positive family history of colorectal cancer appears to increase the risk of colorectal cancer earlier in life such that at 45 years of age, the annual incidence is more than three times higher than in average-risk people; at age 70 years, the risk is similar to that in average-risk individuals [116]. The incidence in individuals 35 to 40 years of age is about the same as that of an average-risk person at 50 years of age. There is no evidence to suggest that colorectal cancer in people with one affected first-degree relative is more likely to be proximal or more rapidly progressive [91; 97; 104].

Although controlled comparisons have not been performed of genetic screening in persons with modest family history of colorectal cancer, expert opinion is fairly consistent that colorectal cancer screening should begin earlier in life (35 to 40 years of age, when risk magnitude approximates that of an individual 50 years of age) [116]. Screening in persons with average risk of colorectal cancer should begin at 50 years of age with repeat screening every 10 years. Increased risk with greater extent of family history warrants room for clinical judgment in favor of even earlier screening based on family history, and shortening the frequency of screening interval to every five years. There is no empirical or logical support to initiate colorectal cancer screening 10 years younger in age than the family member with youngest age of colorectal cancer detection [91; 117].

Other Genetic Factors

In addition to FAP and Lynch syndrome, several rare genetic syndromes confer an increased risk for colorectal cancer, including [91; 97]:

- Peutz-Jeghers syndrome: *STK11/LKB1* gene
- Juvenile polyposis syndrome: *SMAD4/DPC4* and *BMPR1A* genes
- Cowden syndrome: *PTEN* gene
- Ruvalcaba-Myhre-Smith syndrome: *PTEN* gene
- Hereditary mixed polyposis syndrome

Factors that Suggest Hereditary Colorectal Cancer Predisposition Syndrome

With the exception of autosomal recessive inheritance with *MYH*-associated polyposis, all gene mutations known to cause colorectal cancer predisposition are inherited in an autosomal dominant fashion [114]. Thus, family characteristics consistent with autosomal dominant inheritance of cancer predisposition are important to identify because they indicate high risk and possibly the presence of a cancer-predisposing mutation [90]. Factors that suggest a hereditary colorectal cancer predisposition syndrome include [112; 114]:

- Vertical transmission (i.e., presence of a genetic predisposition in sequential generations) of cancer predisposition in autosomal dominant conditions
- Inheritance risk of 50% for both men and women because when a parent carries an autosomal dominant genetic predisposition, each child has a 50% chance of inheriting the predisposition regardless of sex
- Other clinical characteristics:
  - Cancers with an earlier age of onset than sporadic (non-genetic) cases
  - Predisposition to other cancers, such as endometrial cancer

- Two or more primary cancers in a single individual, including multiple primary cancers of the same type (e.g., two separate primary colorectal cancers) or primary cancer of different types (e.g., colorectal and endometrial cancer)
- Presence of non-neoplastic extracolonic features, as with congenital retinal pigment epithelium hypertrophy and desmoids in FAP
- Uncommon tumors such as adrenocortical, sebaceous carcinoma, ampullary, and small bowel
- The presence of multiple polyps, even when family history appears negative

Oligopolyposis (i.e., polyp count greater than expected) can involve as few as 10 to 15 polyps, and the diverse pathology of polyps requires careful attention to polyp count and histology to determine whether genetic testing and/or further clinical evaluation is appropriate [112].

Genetic Testing

As discussed, many genes associated with inherited colorectal cancer syndromes have been identified, and genetic testing is available for diagnosis and is the accepted standard of clinical care. Genetic testing of asymptomatic persons without colorectal cancer symptoms or precursors (adenomatous polyps) is performed to identify increased probability of developing colorectal cancer. Positive findings should lead to diagnostic testing to investigate the presence of occult cancer, followed by treatment if cancer or precursors are found. The intent is to prevent the development of colorectal cancer or increase the likelihood of curative outcome afforded by early detection. Patients can also use this information for decisions related to family planning, work, or retirement.

Disease-causing mutations can be found in most families affected by one of the inherited syndromes, and once a mutation is found in an index case of the family, relatives can be tested for the presence or absence of that mutation with near-100% accuracy. Cancer screening and management is then based on the genetic testing results [118].

Clinical issues somewhat unique to genetic testing include genetic counseling and informed consent for genetic testing. Genetic screening for inherited colorectal cancer syndromes can be hampered by patient or proband resistance, but consent to testing is greatly improved with coordination between the pathologist, referring surgeon or oncologist, and a cancer genetics counselor [99; 118].

Clinical criteria used to identify candidates for genetic testing to determine the presence of an inherited susceptibility to colorectal cancer include [91; 97; 104]:

- A strong family history of colorectal cancer and/or polyps
- Multiple primary cancers in a patient with colorectal cancer
- Family history of other cancers consistent with known inherited syndromes causing a high risk of colorectal cancer
- Early age at colorectal cancer diagnosis

Screening/Surveillance Recommendations for Hereditary Colorectal Cancer

Patients diagnosed with a hereditary colorectal cancer syndrome or with a highly suggestive family or personal history require a more intensive and frequent screening and surveillance protocol than patients with average risk because of their high risk for colorectal and extracolonic malignancies. ***Table 3*** provides a summary of recommendations for patients with specific hereditary colorectal cancer syndromes [112]. For each hereditary colorectal cancer syndrome, the left column lists malignancies associated with the syndrome, and the corresponding right column describes screening or surveillance approach specific to the at-risk malignancy.

SCREENING AND SURVEILLANCE RECOMMENDATIONS FOR COLOREC TAL CANCER AND EXTRACOLONIC MALIGNANCIES IN PATIENTS WITH HEREDITARY COLORECTAL CANCER SYNDROMES	
Cancer Screening	**Recommendations**
Lynch syndrome/HNPCC	
Colorectal	Colonoscopy every one to two years starting at 20 to 25 years of age or two to five years before earliest colorectal cancer in the family if diagnosed before 25 years of age
Gastric and small bowel	Consider baseline EGD beginning at 30 to 40 years of age and surveillance EGD every two to four years in conjunction with colonoscopy
Urothelial	Annual urinalysis may begin at 30 to 35 years of age
CNS	Annual physical exam, no added screening
Pancreatic	Consider screening beginning at 50 years of age (or 10 years younger than earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of the family as the identified pathogenic/likely germline variant
Endometrial and ovarian (women)	Endometrial sampling every one to two years beginning at 30 to 35 years of age Transvaginal ultrasound is not recommended May consider prophylactic hysterectomy and bilateral salpingo-oophorectomy after childbearing is completed
Diagnosis of familial adenomatous polyposis (FAP)	
Colorectal: *APC* gene-positive	Flexible sigmoidoscopy or colonoscopy annually starting at 10 to 15 years of age, then every two to three years Consider colectomy
Colorectal: Suspected FAP, not tested	Flexible sigmoidoscopy or colonoscopy starting 10 to 15 years of age, then annually until 24 years of age, every two years until 34 years of age, and every three years until 44 years of age, then every three to five years thereafter
Personal history of FAP, post-colectomy	
Colorectal	Endoscopic evaluation every six months to three years, depending on proctocolectomy or colectomy status NSAID chemoprevention to reduce polyp burden as pharmacologic adjunct to endoscopy
Duodenal, gastric, or periampular	Baseline upper endoscopy (including side-viewing exam), beginning at 20 to 25 years of age, repeated every one to three years depending on severity of polyposis Examine stomach at time of duodenoscopy
Thyroid	Annual thyroid exam starting in late teens
CNS cancer	Annual physical exam, no added screening
Intra-abdominal desmoids	Annual abdominal palpation With a family history of desmoids, consider abdominal CT or MRI every 1 to 3 years post-colectomy and then at 5- and 10-year intervals
Small bowel polyps and cancer	Add small bowel visualization with CT or MRI for desmoids as outlined above, especially with advanced duodenal polyps
Hepatoblastoma (childhood cancer associated with FAP)	Liver palpation, abdominal ultrasound, and measurement of α-fetoprotein every three to six months until 5 years of age FAP genetic testing in untested children with hepatoblastoma
Pancreatic	No recommendations
Personal history of AFAP	
Colorectal: <21 years, small adenoma burden	Colonoscopy and polypectomy every one to two years; surgical evaluation and counseling

Table 3 continues on next page.

SCREENING AND SURVEILLANCE RECOMMENDATIONS FOR COLORECTAL CANCER AND EXTRACOLONIC MALIGNANCIES IN PATIENTS WITH HEREDITARY COLORECTAL CANCER SYNDROMES (*Continued*)	
Cancer Screening	**Recommendations**
Colorectal: 21–40 years, small adenoma burden	Colectomy with IRA or colonoscopy and polypectomy every one to two years; surgical evaluation and counseling
Colorectal: >40 years, small adenoma burden	Colectomy with IRA; surgical evaluation and counseling
Colorectal: Significant polyposis not manageable with polypectomy	Colectomy with IRA (preferred) or proctocolectomy with ileal J-pouch anal anastomosis
Colorectal	If patient had colectomy with IRS, endoscopic exam of rectum every 6 to 12 months depending on polyp burden Annual physical exam; annual thyroid exam NSAID chemoprevention Baseline upper endoscopy every six months to four years starting at 25 to 30 years of age
Family history of AFAP	
Colorectal: *APC* positive or not tested	Colonoscopy starting in late teens, then every two to three years
Colorectal: *APC* negative	Average risk screening
Diagnosis of *MYH*-associated polyposis or family history of sibling with *MYH* polyposis	
Colorectal: Sibling with *MYH* polyposis and patient is asymptomatic	Colonoscopy starting at 25 to 30 years of age and every three to five years if negative (shorter intervals with advancing age)
Colorectal: *MYH* mutation positive or untested	Upper endoscopy and side viewing duodenoscopy starting at 30 to 35 years of age and every three to five years Patients with duodenal adenomas are treated as in FAP Genetic counseling and testing for the familial *MYH* polyposis mutation(s)
Personal history of *MYH*-associated polyposis	
Colorectal: Personal history of positive *MYH* mutation, polyposis, and negative *APC* testing	Genetic counseling and testing for *MYH* polyposis mutation(s); if negative, refer to increased risk colorectal cancer screening guidelines for multiple adenomatous polyps
Colorectal: History of adenomatous polyposis and negative *APC* testing (>10 at one time or >15 in 10 years)	If adenomas are manageable with colonoscopy and polypectomy: • Colonoscopy and polypectomy every one to two years • Upper endoscopy and side viewing duodenoscopy starting at 30 to 35 years of age every three to five years • Patients with duodenal adenomas treated as in FAP
	If dense or large polyps are not manageable with colonoscopy and polypectomy: • Subtotal colectomy or proctocolectomy depending on adenoma density and distribution; counseling regarding surgical options • Upper endoscopy and side viewing duodenoscopy starting at 30 to 35 years of age every three to five years • Patients with duodenal adenomas treated as in FAP • Counseling regarding surgical options
AFAP = attenuated familial adenomatous polyposis, CNS = central nervous system, CT = computed tomography, EGD = esophagogastroduodenoscopy, FAP = familial adenomatous polyposis, HNPCC = hereditary nonpolyposis colorectal cancer, IRA = ileorectal anastomosis, MRI = magnetic resonance imaging, NSAID = nonsteroidal anti-inflammatory drug.	
Source: [112]	*Table 3*

Inflammatory Bowel Disease as Colorectal Cancer Risk Factor

Patients with inflammatory bowel disease, which includes ulcerative colitis and Crohn disease, have an elevated risk of developing colorectal cancer. The extent that colorectal cancer risk is elevated depends on the extent and duration of disease, but earlier age at onset is not associated with greater risk. Older estimates of colorectal cancer risk in patients with ulcerative colitis indicated a 2% greater risk after 10 years, 7.7% to 8% after 20 years, and 15.8% to 18% after 30 years of disease [119]. More recent estimates are somewhat lower, the result of more widespread prescribing of chemoprotective aminosalicylates, earlier and more liberal use of colectomy for medically refractory disease, and higher rates of surveillance colonoscopy. Studies involving patients with either ulcerative colitis or Crohn disease have shown comparable risk in both diseases [119].

The extent of inflammatory bowel syndrome is defined as the point in time when histologically identified disease is most extensive. Most colorectal cancers develop in patients with pancolitis, and disease extent is a major risk factor for colorectal cancer in patients with inflammatory bowel syndrome [119]. Patients with left-sided disease (up to the splenic flexure) have an intermediate risk level, while proctitis, ulcerative proctosigmoiditis, and backwash ileitis have little to no influence on risk level. A family history of sporadic colorectal cancer in a first-degree relative doubles the risk of colorectal cancer, and risk increases nine-fold if the first-degree relative was younger than 50 years of age when first diagnosed with colorectal cancer.

The extent of macroscopic and histologic inflammation is associated with increased risk of colorectal cancer, which can develop in areas of endoscopically normal but histologically active colitis. Colorectal cancer can occur in areas where colitis has remitted or where histologic findings show inactive colitis such as crypt distortion in the absence of active inflammation. Lack of endoscopic inflammation at the time of neoplastic detection does not mean absence of inflammation in the area before neoplastic development, and risk of neoplasia is not increased in mucosa that has never been inflamed. Thus, histologic instead of macroscopic evidence of tissue changes from inflammatory bowel syndrome serves as a more accurate determinant for assessing colorectal cancer risk. In the context of surveillance, extent of disease should be defined histologically [119].

Practice recommendations for the diagnosis and treatment of colorectal cancer in inflammatory bowel syndrome patients were developed and published by the American Gastroenterology Association [119]. The guideline format presents a series of clinically relevant questions raised by an expert panel, followed by the response based on analysis of the published research.

Natural History of Dysplasia

Colorectal cancer in inflammatory bowel syndrome develops from dysplasia in most cases, and although imperfect, dysplasia is considered the best marker of colorectal cancer risk in inflammatory bowel syndrome. Predicting the natural history of dysplasia is more difficult, because dysplasia is present in 75% to 90% of patients with inflammatory bowel syndrome and colorectal cancer, but colorectal cancer can develop in the absence of previous history of dysplasia. Not all patients with low-grade dysplasia progress through a phase of detectable high-grade dysplasia before developing cancer. Importantly, interpretation of dysplasia in mucosal biopsy specimens is highly subject to observer subjectivity. Therefore, pathologists with particular expertise in gastrointestinal disorders should review all cases diagnosed as indefinite, low-grade dysplasia, or high-grade dysplasia.

Colectomy

Strong evidence indicates that patients with inflammatory bowel syndrome and a non-adenoma-like dysplasia-associated lesion or mass should receive a colectomy. Patients with inflammatory bowel syndrome and an adenoma-like dysplasia-associated lesion or mass, without evidence of flat dysplasia elsewhere in the colon, can be managed safely by polypectomy and continued surveillance.

There is also strong evidence that colectomy for flat high-grade dysplasia treats undiagnosed synchronous cancer and prevents metachronous cancer. However, current evidence is insufficient to assess the balance of benefits and harms.

Surveillance Colonoscopy

Surveillance colonoscopy is at least moderately effective in reducing colorectal cancer risk in patients with inflammatory bowel syndrome. It is recommended for patients with inflammatory bowel disease who are at an increased risk of colorectal cancer. Patients most likely to benefit are those with extensive ulcerative colitis or Crohn disease.

Surveillance colonoscopy in patients with inflammatory bowel syndrome should include extensive biopsies of all anatomic segments of colorectal mucosa. Definitive data are lacking to inform the optimal surveillance intervals, but one- to three-year intervals are suggested. Careful mucosa inspection and sufficient number of biopsy specimens should be obtained from all anatomic segments of the colon.

Newer Imaging Techniques

Chromoendoscopy is more sensitive in dysplasia detection than white-light endoscopy when used by endoscopists with expertise. However, the natural history of chromoendoscopically detected dysplasia is unknown. In addition, more research is needed to determine the utility of narrow band imaging and confocal endomicroscopy in detecting dysplasia.

Chemopreventive Agents

Ursodeoxycholic acid has demonstrated significant reductions in colorectal cancer in patients with ulcerative colitis who also have primary sclerosing cholangitis. Aminosalicylates are also considered chemopreventive against colorectal cancer. Oral or topical corticosteroids, while demonstrating antineoplastic effects in clinical trials, are associated with too many side effects for routine chemopreventive use. There is insufficient evidence to inform a recommendation for or against the use of azathioprine, 6-mercaptopurine, folic acid, calcium or multivitamin supplements, or statins.

COLORECTAL CANCER SCREENING

As noted, the United States is the only developed country experiencing declining incidence rates of colorectal cancer, despite the increase in colorectal cancer risk factors such as obesity [4]. Increasingly widespread colorectal cancer screening is believed to be the root of this seeming paradox.

Colorectal cancer is a serious disease but in many cases is preventable, and its incidence, mortality, and financial burden to society make it an important healthcare concern. The usually long and often asymptomatic premalignant natural history and the clinical features of colorectal cancer make the malignancy amenable to prevention by screening. Colonoscopy has become the dominant screening approach, and optical (versus computed tomography [CT] or "virtual") colonoscopy has the advantage of providing cure via polypectomy during the session [120].

Evidence supports screening for colorectal cancer as part of routine care for all adults 45 to 50 years of age or older, especially those with first-degree relatives with colorectal cancer, for the following reasons [121; 122]:

- Increased incidence in those 50 years and older
- Ability to identify high-risk groups
- Slow growth of primary lesions
- Better survival of patients with early-stage lesions
- Relative simplicity and accuracy of screening tests

Consistent evidence supports population-level colorectal cancer screening, which has become the foundation for primary colorectal cancer prevention. In a 2012 study involving 2,602 patients initially referred to colonoscopy for adenomas and nonadenomatous polyps from 1980 to 1990, participants were followed up to 23 years (median: 15.8 years). Their mortality from colorectal cancer was compared against the expected colorectal cancer

mortality in the general population. Colonoscopy was associated with a 53% reduction in mortality (12 colorectal cancer deaths versus 25.4 expected). During the first 10 years post-polypectomy, colorectal cancer mortality was comparable between patients with adenomas or nonadenomatous polyps [123].

In another study, 46,551 healthy subjects between 50 and 80 years of age were randomized to annual or biennial fecal occult blood testing (FOBT) or no screening from 1976 to 1992. Those with positive FOBT screens received colonoscopy and treatment for malignant findings. At 30-year follow-up, 33,020 had died, 732 from colorectal cancer, including 200/11,072 (1.8%) with annual, 237/11,004 (2.2%) with biennial, and 295/10,944 (2.7%) with no screening. At 30 years, colorectal cancer mortality was reduced by 32% with annual screening and 22% with biennial screening compared with no colorectal cancer screening [124].

Researchers compared 3,148 patients with first diagnosis of colorectal cancer with 3,274 non-colorectal cancer subjects to assess associations between colonoscopy for specific indications and the risk of colorectal cancer over a 10-year period. History of screening colonoscopy was associated with a reduction of colorectal cancer risk of 89% and of malignancy in the right colon of 78%. History of diagnostic colonoscopy (and indication) was associated with colorectal cancer risk reduction of 67% with assessment of positive FOBT; 67% with surveillance after a preceding colonoscopy; 72% with assessment of rectal bleeding; and 85% with assessment of abdominal symptoms [125].

Another large study followed 40,826 patients for a median 7.7 years to study the impact of adenoma removal during screening colonoscopy on colorectal cancer mortality. Using data from the Norway national cancer and cause-of-death registries, researchers found that, relative to expected colorectal cancer mortality (the general Norwegian population), adenoma removal during screening was associated with a 25% reduction in mortality rate [126].

Unfortunately, despite sophisticated nationwide efforts to elevate screening awareness, routine screening of eligible individuals remains low [127]. Currently, about one in three Americans 50 years of age or older, for whom screening is recommended, have never been screened consistent with current guidelines [128].

To better understand potential provider and systemic obstacles to achieving higher utilization rates of colorectal cancer screening, a national survey of colorectal cancer screening education, prioritization, and self-perceived preparedness was performed of 835 primary care residents. In regards to advising patients about colorectal cancer screening, current colorectal cancer screening guidelines, and criteria for familial colorectal cancer syndromes, a significant proportion of respondents felt they lacked sufficient knowledge in these areas. These data suggest opportunities to improve the colorectal cancer screening curriculum in primary care residency programs [129].

As colonoscopy has increasingly become widespread and preferred as a colorectal cancer screening approach, questions concerning its optimal use have emerged. Research has now established that the ability of colonoscopy to detect precancerous polyps and malignant tissue critically depends on examination quality. Patient adherence to pre-colonoscopy preparation is also essential. Practice guidelines addressing these important issues have been published to bridge the knowledge gaps between the latest research, primary care, and specialist providers. Practice guidelines for colorectal cancer screening are updated as new information becomes available. For example, in 2014 (and reiterated in 2024) the National Comprehensive Cancer Network (NCCN) expanded its recommendation for screening for Lynch syndrome to all patients diagnosed with colorectal cancer [130; 131].

EFFICACY OF COLORECTAL CANCER SCREENING TESTS	
Screening Approach	**Magnitude of Effect**
Effect on colorectal cancer mortality reduction	
Fecal occult blood test (FOBT)	15% to 33%
Fecal occult blood test (fecal immunochemical-based, FIT)	Fair
Sigmoidoscopy	About 22% to 31%; 13% to 50% for distal colon
Digital rectal examination	No effect
Colonoscopy	About 60% to 70% for left colon, uncertain for right colon
Effect on incidence	
Sigmoidoscopy	20% to 25%
FOBT	Likely small to none
Colonoscopy	About 60% to 70% for left colon; uncertain for right colon
Immunochemical FOBT	Fair
Source: [1]	*Table 4*

The National Comprehensive Cancer Network recommends universal screening for Lynch syndrome in all patients with colorectal cancer, in order to maximize sensitivity for Lynch syndrome detection and simplify care processes.

(https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

COMMON COLORECTAL CANCER SCREENING TESTS

There are several screening tests available for colorectal cancer, with varying levels of efficacy and clinical utility (***Table 4***). Of these, the criterion standard is colonoscopy.

Colonoscopy

With screening colonoscopy, a colonoscope (a thin tube with a light and video camera on one end connected to a display monitor) is inserted through the rectum and guided through the length of the colon for observation on the monitor screen. Instruments to remove polyps and obtain biopsy are inserted through the rectum as needed [132]. Colonoscopy allows direct visualization of the colonic mucosa, lesion biopsy, and polyp removal over the entire colon. The sensitivity and specificity for colorectal cancer and advanced adenomas are very high, and colonoscopy is the confirmatory test used with all other screening approaches when positive findings occur [121].

Potential Complications and Harms

Colonoscopy may fail to detect as many as 6% of colorectal malignancies, and the miss rate for adenomas smaller than 1 cm has ranged from 12% to 17% [133]. This is largely the result of high inter-operator variability in adenoma detection rate. Greater awareness of this hazard from inadequate colonoscopy performance has led to heightened emphasis on training and continuous quality assurance of endoscopists [121]. In addition, colonoscopy is an invasive procedure, requires an invasive bowel cleansing, is time-consuming and uncomfortable, and thus possesses several characteristics that negatively affect patient acceptance as a first-line screening test [121].

Clinically significant complications that require medical intervention are rare and include perforation, bleeding, and cardiovascular events. Complication rates may increase in older patients [134; 135]. More than 85% of serious colonoscopy complications occur during polypectomy, and a study of 97,000 colonoscopies found polypectomy associated with a seven-fold increase in risk of bleeding or perforation [136]. Up to 33% of patients report one or more minor, transient gastrointestinal symptoms after colonoscopy, and a review of 12 studies involving 57,742 colorectal cancer screening colonoscopies in average-risk patients found the aggregate rate of serious complications was 2.8 per 1,000 procedures [135; 137].

Recommendations to Optimize the Adequacy of Colonoscopy Bowel Preparation

The U.S. Multi-Society Task Force on Colorectal Cancer has published guidelines for adequate pre-colonoscopy bowel cleansing [138]. The goals of this consensus document are to provide expert, evidence-based recommendations for clinicians to optimize colonoscopy preparation quality and patient safety.

The adequacy of pre-procedure bowel cleansing merits special attention because this patient factor is strongly associated with colonoscopy success. Up to 20% to 25% of colonoscopies are attempted in patients with inadequate bowel preparation, leading to diminished adenoma detection rates, longer procedural time, lower cecal intubation rates, and increased electrocautery risk [139; 140; 141].

Patient risk factors for inadequate preparation include older age, male sex, higher BMI, history of inadequate preparation, history of constipation, and use of opioids or other constipating medications. Patients with complex past medical histories or current conditions, including previous gastric or colonic resection, spinal cord injury, Parkinson disease, and stroke, are generally more difficult to prepare adequately. Diabetes is associated with the highest prevalence of inadequate bowel preparation [138].

A preliminary assessment of preparation quality should be done in the recto-sigmoid colon. If the indication is screening or surveillance and the preparation is clearly inadequate for polyp detection greater than 5 mm, terminate and reschedule the procedure or attempt an additional bowel cleansing approach without canceling the procedure that day. If the colonoscopy is complete to cecum, and the preparation ultimately is deemed inadequate, the examination should be repeated, generally within one year; intervals shorter than one year are indicated when advanced neoplasia is detected and there is inadequate preparation.

Adequacy of bowel preparation should be assessed after completing appropriate efforts to clear residual bowel debris. The rate of adequate preparation should be routinely recorded, and adequate patient preparation should be achieved in at least 85% of all examinations per physician [138].

Split-dose bowel-cleansing regimens are strongly recommended for screening colonoscopy. A same-day regimen is an acceptable alternative to split dosing, especially for patients undergoing afternoon examination. The second dose of split preparation should ideally begin four to six hours before the time of colonoscopy, with completion of the last dose at least two hours before the procedure time. With split-dose bowel-cleansing regimens, diet recommendations include low-residue or full liquids until evening on the day before colonoscopy.

Healthcare professionals should give oral and written patient instructions for all components of colonoscopy preparation and emphasize the importance of compliance. The physician performing the colonoscopy should ensure that appropriate support and process measures are in place for patients to achieve adequate colonoscopy preparation quality.

Selection of a bowel-cleansing regimen should consider patient's medical history, medications, and, when available, previously reported bowel preparation adequacy. A split-dose regimen of a 4-L polyethylene glycol electrolyte lavage solution (PEG-ELS)-based cleansing agent provides high-

quality bowel cleansing. In healthy, non-constipated individuals, a 4-L PEG-ELS formulation produces a bowel-cleansing quality comparable to lower-volume PEG formulations.

Over-the-counter bowel cleansing agents have variable efficacy depending on the agent, dose, timing of administration, and whether used alone or in combination. Regardless of the agent, efficacy and tolerability are enhanced with a split-dose regimen. Although over-the-counter purgatives are generally safe, caution is required in certain populations, such as strictly avoiding magnesium-based preparations in patients with chronic kidney disease. Routine use of adjunctive agents for bowel cleansing before colonoscopy is not recommended.

Split-dose bowel cleansing is associated with greater willingness to repeat the regimen compared with day-before regimens. In addition, low-volume bowel cleansing agents are associated with greater compliance in repeat colonoscopies.

There is insufficient evidence to recommend specific bowel preparation regimens for children, adolescents, and elderly persons, but sodium phosphate preparations should be avoided in the elderly, in children younger than 12 years of age, and in those with risk factors for complications from this medication, including known or suspected inflammatory bowel disease.

Additional bowel purgatives should be considered in patients with risk factors for inadequate preparation. Low-volume preparations or extended time delivery for high-volume preparations are recommended for patients after bariatric surgery. Tap water enemas should be used to prepare the colon for sigmoidoscopy in pregnant women. There is insufficient evidence to recommend specific regimens for persons with a history of spinal cord injury; additional bowel purgatives should be considered.

There is also insufficient evidence to recommend a single salvage strategy for patients whose poor preparation precludes effective colonoscopy completion. In these cases, large-volume enemas may be attempted in patients who present for colonoscopy and report brown effluent despite compliance with the colon-cleansing regimen. Through-the-scope enema with completion of colonoscopy the same day may also be considered, especially for patients receiving propofol sedation. Waking the patient from sedation and continuing with further oral ingestion of cathartic with same-day or next-day colonoscopy is associated with better outcomes than delayed colonoscopy.

Quality Indicators for Colonoscopy Performance

In 2019, an estimated 13.8 million outpatient colonoscopies were performed in the United States [142]. In addition to patient bowel preparation, optimal colonoscopy efficacy depends on operator performance. Inadequate colonoscopy performance demonstrably worsens the ability to prevent colorectal cancer diagnoses and deaths, and practice recommendations have been developed to better ensure quality colonoscopy performance [143].

Cecal Intubation. Cecal intubation involves advancing the colonoscope beyond the ileocecal valve, allowing the colonoscopist to visualize the medial wall of the cecum between the ileocecal valve and the appendiceal orifice. Cecal intubation is essential for optimal colonoscopy because many colorectal neoplasms are harbored in the proximal colon, including the cecum, and low cecal intubation rates are linked to higher rates of interval proximal colon cancer [144]. Colonoscopists should be able to intubate the cecum in ≥95% of screening colonoscopies in healthy adults. Photography of the cecum is mandated to verify intubation [143].

Adenoma Detection. Missed adenoma detection is strongly associated with failure to prevent colorectal cancer during multi-year follow-up colonoscopy trials, and most interval colorectal cancers are due to missed lesions and incomplete polypectomy. The marked variation in colonoscopist adenoma detection rates within practice groups, and the essential role of adenoma detection in colorectal cancer prevention led to adenoma detection as a performance target [145; 146; 147]. The examination is considered adequate if detection of polyps >5 mm is unimpeded.

In screening colonoscopies of asymptomatic, average-risk persons, a minimum adenoma detection target rate of 25% is recommended. Adenoma detection rates of less than 25% indicate that performance improvement steps should be initiated. Adenoma detection rate is considered the primary measure of mucosal inspection quality and is the single most important quality measure in colonoscopy. Colonoscopists with high adenoma detection rates clear colons better, and patients with precancerous lesions are brought back earlier for their next colonoscopy. Colonoscopists with low adenoma detection rates fail to identify patients with precancerous lesions and multiple lesions, placing these patients at elevated risk for cancer from inappropriately long intervals between colonoscopy [143].

Withdrawal Time. The time taken to remove the colonoscope after cecum intubation (excluding time for biopsies or polypectomy) is termed withdrawal time, and colonic mucosa should be carefully examined for polyps during scope withdrawal. The recommended colonoscope withdrawal time should be at least six minutes in colorectal cancer screening of patients without previous bowel surgery (when no biopsies or polypectomies are performed) [143]. Numerous studies have demonstrated increased detection of significant neoplastic lesions in colonoscopic examinations with an average withdrawal time of at least six minutes, and longer withdrawal time is associated with higher detection rates [148; 149; 150].

Correction of Poor Performance. The objective for measuring quality indicators is to improve patient care by identifying poor performers for retraining or removal of their privileges to perform colonoscopy if performance cannot be improved. Most quality indicators are amenable to improvement. An exception may be withdrawal time; despite overwhelming evidence that withdrawal time is positively associated with detection, imposing longer withdrawal times on colonoscopists has not been found effective [143].

Computed Tomographic Colonography

CT colonography, also termed virtual colonoscopy, involves examination of computer-generated colorectal images constructed from abdominal CT imaging that simulate a conventional colonoscopy. Pre-procedure laxatives are required to clean the colon, and the colon is insufflated with air just prior to the CT examination, which may be uncomfortable [151]. The risk of complications is extremely low because the test is non-invasive. CT colonography is now in use to perform screening and diagnostic imaging in patients with incomplete colonoscopy or for whom colonoscopy is contraindicated. Randomized trials are in progress comparing CT colonography with immunochemical FOBT (iFOBT) and colonoscopy, and should produce valuable information concerning patient acceptance, diagnostic yield, and costs [121; 152]. One systematic review that compared iFOBT with colonoscopy found no significant differences in bowel preparation discomfort, screening procedure discomfort, screening preference, and patient willingness to repeat screening [153]. A meta-analysis that included more than 15,000 participants found that the screening populations seemed more likely to participate in CT colonography, especially with reduced and/or no cathartic preparation [154].

Potential Complications and Harms

Specificity for polyp detection is consistently high with CT colonography, but the broadly variable sensitivity requires confirmatory colonoscopy for findings suggestive of colorectal cancer. Another disadvantage with CT colonography is the inability to remove polyps [155]. Extracolonic abnormalities are common in CT colonography, most commonly renal, splenic, uterine, hepatic, ovarian, pancreatic, and gallbladder abnormalities. Very little information is available on the clinical value of their detection or the impact on patient anxiety and psychologic function [156; 157]. One study found CT colonography to be a useful diagnostic tool in patients who previously underwent incomplete optical colonoscopy [158].

Flexible Sigmoidoscopy

Flexible sigmoidoscopy involves anal insertion of a sigmoidoscope (similar to the colonoscope) to visualize the rectum and sigmoid colon—the lower one-third of the colon. The scope inflates the large bowel with air to improve imaging, and polyp removal or biopsy may be performed during the procedure [159]. A 60-cm flexible sigmoidoscope was introduced decades ago that is more tolerable to patients than the older, rigid sigmoidoscope. It allows a more complete distal colon examination and can discover up to 65% of polyps, compared with 25% using the older instrument [160].

Potential Complications and Harms

Sigmoidoscopy can be an uncomfortable or painful procedure. Women may have more pain during the procedure, which may discourage them from returning for future screening sigmoidoscopies. Sigmoidoscopy can also cause perforation of the colon, bleeding, severe abdominal pain, and death, although this is rare [85; 159]. Bleeding and perforation are the most common complications. Most cases of bleeding occur in patients who have polyps removed [159].

Double-Contrast Barium Enema

Double-contrast barium enema (DCBE) consists of the patient receiving an enema with a barium solution. Air is then pumped into the colon, and a series of x-rays are performed to image the entire colon and rectum [161].

Potential Complications and Harms

DCBE is no longer recommended as an alternative test for colorectal cancer screening, and its use has declined dramatically. DCBE effectiveness for polyp detection is substantially lower than that of colonoscopy and CT colonography [116].

Fecal Occult Blood Tests

In FOBT testing, the patient collects stool samples that are analyzed for presence of blood. Different FOBT tests involve different collection approaches but commonly require collection of consecutive stool specimens for up to three days. The first FOBTs to enter clinical use were guaiac-based (gFOBT); more recent versions employ immunochemical tests (iFOBT) or markers of DNA mutation (stool DNA tests or sDNA) [1].

Colorectal lesions and adenomatous polyps tend to bleed, and the resulting presence of hemoglobin in stool that is detectable even with intermittent or minimal bleeding formed the basis for gFOBT use in colorectal cancer screening. Hemoglobin is used as a biomarker for detecting blood in stool with guaiac, which identifies peroxidase-like activity that characterizes hemoglobin. However, gFOBT cannot discriminate human from nonhuman or intact from partially digested hemoglobin and is being phased out of clinical use. This results in detection of blood from ingested meat and upper airway and gastrointestinal bleeding as well as colorectal lesions. The low specificity of gFOBT requires confirmatory colonoscopy to validate positive findings [162].

iFOBT was developed to detect intact human hemoglobin originating from colorectal tissue. Unlike gFOBT, it does not detect hemoglobin from nonhuman dietary sources or partly digested human hemoglobin originating from the upper respiratory or gastrointestinal tract [163]. The sDNA variation of FOBT incorporates markers of DNA mutation that detect molecular genetic changes associated with colorectal cancer gene mutations shed into the stool [164].

Potential Complications and Harms

The very low sensitivity of gFOBT leads to a high proportion of false-positive results when confirmed by colonoscopy or DCBE plus flexible sigmoidoscopy, which a systematic review of published clinical trials estimated at greater than 80% [165]. iFOBT is increasingly recognized as superior to gFOBT for sensitivity, accuracy, and compliance, and it shows greater ability in detecting advanced neoplasia.

While iFOBT requires colonoscopy confirmation of positive results and cannot detect many precancerous polyps, higher participation in iFOBT than in colonoscopy screening may offset some of its comparative limitations [121].

DNA fecal testing is emerging as a potentially important addition to the stool-based tests for colorectal cancer screening. More research is needed to understand the role of sDNA testing in organized colorectal cancer screening and unaddressed factors, such as screening interval, patient adherence, and costs [121].

PRACTICE GUIDELINE RECOMMENDATIONS FOR COLORECTAL CANCER SCREENING

American College of Physicians

The American College of Physicians (ACP) published their practice recommendations for colorectal cancer screening based on the review and synthesis of guidelines for screening colorectal cancer produced by several other professional organizations. Several tests to detect adenomatous polyps and cancer were evaluated for colorectal cancer screening efficacy, including flexible sigmoidoscopy, colonoscopy, DCBE, and CT colonography. Tests to primarily detect cancer (e.g., gFOBT, iFOBT, and sDNA) were also assessed [85].

Screening Initiation

The ACP recommends that individualized assessment of colorectal cancer risk should be performed in all adults [85].

Screening of asymptomatic, average-risk patients should begin at 50 years of age with a stool-based test, flexible sigmoidoscopy, or optical colonoscopy [85]. The ACS supports a qualified recommendation for colorectal cancer screening in average-risk adults 45 to 49 years of age. This recommendation is based on the increasing incidence of colorectal cancer in this age group, the availability of accurate screening tests, and modeling results from other organizations [85]. . Screening is not recommended in adults older than 75 years of age or with a life expectancy of less than 10 years [85].

Note: The National Cancer Institute states that history of colorectal cancer in a first-degree relative, especially before 55 years of age, approximately doubles the risk [1]. The Institute suggests that the benefit of screening might be improved by tailoring the recommended screening test to the patient's degree of risk [1].

In response to rising rates of colorectal cancer among persons younger than 50 years of age, the U.S. Preventive Services Task Force (USPSTF) lowered its recommended age of initiation of screening to all adults 45 years of age, though the strength of recommendation is slightly lower than for those 50 years of age and older [122].

Clinical Considerations and Best Practice Advice for Colorectal Cancer Screening

Based on limited evidence, the USPSTF does not make a separate, specific recommendation on colorectal cancer screening in Black adults, and modeling results also do not support different screening strategies by race [122]. Other organizations, such as the U.S. Multi-Society Task Force, recommend starting screening in Black adults at 45 years of age while starting screening at age 50 years for persons of other races [166]. The USPSTF recognizes the higher colorectal cancer incidence and mortality in Black adults and strongly encourages clinicians to ensure their Black patients receive recommended colorectal cancer screening, follow-up, and treatment [122].

Recommended Colorectal Cancer Screening Intervals

Clinicians should select the screening test with the patient on the basis of a discussion of benefits, harms, costs, availability, frequency, and patient preferences. The ACP recommends that patients between 50 and 75 years of age with average risk should be screened [85]:

- Every 10 years for colonoscopy
- Every 10 years for flexible sigmoidoscopy, plus iFOBT every 2 years
- Every 2 years for high-sensitivity gFOBT or iFOBT

These recommended intervals, especially for colonoscopy, are based on the assumption of optimal patient preparation and operator performance in the initial screen, allowing removal and biopsy of all polyps and detection of any precancerous lesion. Inadequate colonoscopy performance and resultant failure to detect adenomas or precancerous lesions places the patient at much greater risk of developing colorectal cancer (referred to as interval colorectal cancer) and renders the recommended interval unsafe [133].

The National Comprehensive Cancer Network recommends screening for persons at average risk for colorectal cancer begin at 45 years of age after available options have been discussed. Currently, recommended options include: colonoscopy every 10 years; annual high-sensitivity guaiac-based testing or fecal immunochemical test; multitarget-stool DNA-based testing (every 3 years); flexible sigmoidoscopy every 5 to 10 years; or CT colonography every 5 years.

(https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

Recommended Colonoscopy Surveillance after Screening and Polypectomy

The timing of follow-up surveillance colonoscopy after initial colorectal cancer screening colonoscopy is an essential component of colorectal cancer prevention (***Table 5***). Adenomatous polyps are cancer precursor lesions and the most common neoplasm found during colorectal cancer screening. Their detection and removal reduces colorectal cancer incidence and mortality, but patients with adenomas have heightened risk of developing interval cancers (metachronous adenomas or colorectal cancer) within three to five years of colonoscopy and polypectomy [167].

RECOMMENDED SURVEILLANCE INTERVALS FOR AVERAGE-RISK PATIENTS[a]

Baseline Colonoscopy Findings	Surveillance Interval
No polyps (normal)	10 years
1–2 tubular adenomas <10 mm	7 to 10 years
3–10 tubular adenomas <10 mm	3 to 5 years
5-10 tubular adenomas <10 mm	3 years
One or more tubular adenomas ≥10 mm	3 years
One or more villous adenomas	3 years
Adenoma with high-grade dysplasia	3 years
<10 adenomas on single examination	1 year
Piecemeal resection of adenoma ≥20 mm	6 months
Serrated lesions	
Sessile serrated polyp(s) <10 mm with no dysplasia ≤20 hyperplastic polyps in rectum or sigmoid colon <10 mm	10 years
Piecemeal resection of sessile serrated polyp(s) ≥20 mm	6 months
[a]Strong recommendation	
Source: [167]	*Table 5*

The basis for recommended time intervals between screening and surveillance colonoscopy should involve evidence that examinations prevent interval cancers and cancer-related mortality. Interval diagnosis of advanced adenomas has been used as a surrogate marker for colorectal cancer incidence or mortality. The U.S. Multi-Society Task Force guidelines for post-polypectomy surveillance in average-risk patients emphasize use of baseline colonoscopy findings for risk stratification, which is clustered into two groups [168]:

- Low-risk adenomas: One to two tubular adenomas <10 mm
- High-risk adenomas: Adenoma with villous histology, high-grade dysplasia, size ≥10 mm, or numbering three or more

The British Society of Gastroenterology surveillance guidelines categorizes patients into three risk groups [169]:

- Low risk: One to two adenomas <10 mm
- Intermediate risk: Three or four small adenomas, or one adenoma ≥10 mm
- High risk: More than five small adenomas, or three or more adenomas with at least one ≥10 mm

Surveillance at one year was recommended for high-risk patients over concerns of missed lesions at baseline, differing from U.S. guideline emphasis (and assumption) of high-quality baseline examination [167]. This update of surveillance recommendations was developed to address emerging issues in post-colonoscopy surveillance [167].

Limitations of Colonoscopic Surveillance

As discussed, interval colorectal cancers are advanced adenomas that develop after polypectomy or negative baseline colonoscopy and before the next screening colonoscopy, a 10-year period for most patients. Within five years of negative screening colonoscopy, the risk of developing advanced adenomas is 1.3% to 2.4%. The greatest risk of interval colorectal cancer is within five years of screening colonoscopy, usually resulting from missed lesions progressing to diagnosable colorectal cancer [170].

Studies suggest that most interval colorectal cancers result from missed lesions during baseline colonoscopy. Failure to detect lesions is directly associated with colonoscopy examination quality [147; 171]. Residual neoplastic tissue from incomplete adenoma removal can also progress to malignancy. Interval colorectal cancers may differ from prevalent colorectal cancers by more frequent location in the proximal colon and by molecular/genetic properties that confer more aggressive growth. The relationship is established between inadequate colonoscopy quality and risk of interval cancer following colonoscopy.

Halting Surveillance

Colonoscopy risks increase with advancing age and at some point outweigh the benefits of surveillance and screening. The USPSTF recommends clinicians selectively offer screening for colorectal cancer in adults 76 to 85 years of age [122]. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences. Patients with high-risk adenoma may especially benefit from continued surveillance.

PATHOPHYSIOLOGY

The pathogenesis and pathophysiology of colorectal cancer is very complex, and the following section is intended to be a brief overview.

There are three broad pathways by which colorectal carcinoma develops [172]:

- The chromosome instability (CIN) pathway
- The microsatellite instability (MSI) pathway
- Inflammatory bowel disease dysplasia

Colorectal tumors first develop through one of these pathways, but once established as malignancy, the final common pathway to metastases is identical and involves the spread of cancer cells to locoregional lymph nodes and dissemination to and colonization of the liver (through enteric venous drainage) and the lungs (via hematogenous transport) [173].

Importantly, sporadic (i.e., in the absence of an apparent inherited disorder) colorectal cancers originating from polyps and hereditary colorectal cancers (i.e., originating from inherited colorectal cancer predisposition syndromes) share in common the sequences of gene-level altered function and mutation that transform benign tissue to precancerous lesion to malignancy. The distinction is that germline mutations underlie the well-described inherited colorectal cancer syndromes, while sporadic cancers arise from a stepwise accumulation of somatic genetic mutations [174].

With very few exceptions, the pathogenesis and pathophysiology of colon and rectal cancer is identical. Unless otherwise stated, the following information pertains to both.

HISTOLOGIC CHARACTERISTICS OF COLORECTAL CANCER

Cellular Classification

Data from more than 180,000 patients with colorectal cancer were entered into the Surveillance, Epidemiology, and End Results (SEER) cancer database from 1975–2015 and analyzed [11]. Histologic subtypes in the population were overwhelmingly adenocarcinoma (92.1%); others included neuroendocrine carcinoid (4.4%), unspecified carcinoma (0.8%), and squamous cell (0.7%). The relative five-year survival rates were highest for carcinoid tumors (90.1%) and lowest for neuroendocrine tumors (14.4%) [11]. The SEER cancer database for 1975–2021 does not include information on histologic subtypes of colorectal cancer [11].

Colorectal Cancer Precursor Lesions

Colorectal lesions present as a broad spectrum of neoplasms that range from benign growths to invasive tumors. Most colorectal cancers develop slowly over years, typically beginning as non-cancerous polyps on the inner lining of the colon or rectum. Some, but not all, polyps develop into cancer, and the risk of malignant progression is influenced by polyp type. Colorectal lesions are classed into three groups [175]:

- Adenomatous polyps (adenomas): These polyps have the greatest malignant potential and are termed pre-cancerous.
- Non-neoplastic and inflammatory polyps: These are generally not pre-cancerous, but when located in the ascending colon, the risk of pre-cancerous status or development into adenomas and cancer is increased. Includes hyperplastic, juvenile, hamartomatous, inflammatory, and lymphoid polyps.
- Dysplasia: A non-polyp pre-cancerous condition of the colorectal lining, usually associated with inflammatory bowel disease.

Adenomas are the primary precursor lesion of colorectal cancer. These polyps are benign tumors that may transform into malignancy. Of all patients with adenomatous polyps discovered by screening colonoscopy, one-year follow-up colonoscopy reveals additional polyps in 29%. The risk of colorectal malignancy in patients with history of polyp removal is 2.7 to 7.7 times that of the general population [176; 177].

Epithelial-derived adenoma or adenocarcinoma tumors represent the predominant colorectal cancer tumor type. More than 95% of colorectal cancers are carcinomas, and more than 95% of these adenocarcinomas. Other histologic types account for the remaining 2% to 5%. Adenomas are histologically classified, by order of increasing malignant potential, as tubular, tubulovillous, or villous adenomas. Characteristics of adenomas that highly predict malignant transformation include [1; 178]:

- Larger size
- Villous pathology
- Degree of dysplasia within the adenoma

Adenomas may reflect an innate or acquired tendency of the colon to form tumors. Benign and malignant tissue occurs within colorectal tumors, and 20-year follow-up of patients with adenomas has found a 25% malignancy rate in adenoma sites. Removal of adenomatous polyps is linked with reduced colorectal cancer incidence and represents the foundation of primary colorectal cancer prevention [173].

The transition from normal epithelium to adenoma to carcinoma is associated with acquired molecular events. The mucosa in the large intestine regenerates roughly every six days. Crypt cells migrate from the base of the crypt to the surface, where they undergo differentiation and maturation and ultimately lose the ability to replicate. As noted, most colorectal carcinomas are adenocarcinomas. Adenomas precede adenocarcinomas, with roughly 10% of adenomas

eventually developing into adenocarcinomas during a process that occurs over up to 8 to 10 years with sporadic colorectal cancers. Dysplastic adenomas progress to colorectal malignancies through a multistep process involving inactivation of a variety of tumor-suppressor and DNA-repair genes and simultaneous activation of oncogenes. Colonic epithelial cells are selectively vulnerable to the transformation from normal colonic epithelium to adenomatous polyp to invasive carcinoma [174; 179; 180].

POLYP-TO-CARCINOMA PATHWAYS OF COLORECTAL CARCINOGENESIS

The accumulation of acquired genetic and epigenetic changes transforms normal epithelial cells into benign neoplasms (adenomas and sessile serrated polyps), invasive adenocarcinomas, and ultimately, metastatic colorectal cancer. The polyp-to-carcinoma progression sequence of colorectal carcinogenesis occurs through at least two well-recognized pathways: the CIN pathway and the MSI pathway [172].

The CIN Pathway

CIN is the most common form of genomic instability and is found in as many as 85% of colorectal cancers. The hallmark of the CIN phenotype is mutations that inactivate the *APC* gene, found in up to 70% of sporadic colorectal cancers, and that cause FAP. *APC* mutations occur during the earliest stages of neoplasia and are predominantly associated with the classic tubular adenoma pathway and CIN tumor [172]. Increasing size, increasing number, and worsening histology of polyps reflect the linear process of carcinogenesis along the CIN pathway [181].

As discussed, the *APC* gene is a tumor-suppressor gene that indirectly regulates the transcription of several critical cell proliferation genes by encoding transcription factor beta-catenin, a protein involved in cell adhesion, signal transduction, transcription regulation, cell cycle control, apoptosis, and maintenance of chromosomal segregation fidelity. *APC* inactivation produces loss of beta-catenin function, allowing unchecked cellular replication at the crypt surface, and activation of oncogenes *c-myc* and cyclin D1 that drive the progression to malignant phenotype [104; 174; 182].

The MSI Pathway

MSI tumors are characterized by MMR system defects. DNA MMR genes correct nucleotide base miss-pairs and small insertions or deletions that occur during DNA replication. The MMR defect promotes adenoma development and accelerates the progression from adenoma to carcinoma. These colorectal malignancies are distinguished at the molecular level by alterations in repeating units of DNA that occur normally throughout the genome, termed DNA microsatellites. Microsatellite unstable tumors are generally considered mutually exclusive of CIN tumors [172; 183].

The mechanisms that underlie MSI involve MMR gene inactivation by aberrant methylation or somatic mutation. Roughly 20% to 30% of colorectal cancers display a characteristic pattern of gene hypermethylation, termed the CpG island methylator phenotype (CIMP). Some CIMPs display MSI, and these account for roughly 90% of Lynch syndrome cases and 15% to 20% of sporadic colon and rectal cancers [107; 174; 184].

THE INFLAMMATORY BOWEL DISEASE DYSPLASIA PATHWAY

A separate carcinogenic pathway is described for inflammatory bowel syndrome that does not involve an adenoma-carcinoma sequence. Chronic inflammation, such as ulcerative colitis, can result in genetic alterations that promote dysplasia and carcinoma formation [181]. The elevated risk of colorectal cancer in ulcerative colitis and Crohn disease is mediated through an intermediate step of intraepithelial dysplasia [174].

Chronic colorectal inflammatory disease is a risk factor for colorectal cancer, and such tumors may result from longstanding, continuous damage, inflammation, and repair (LOCDIR). LOCDIR changes cellular features of the epithelium, causing loss of cellular differentiation (loss of cellular mucus) and development of cellular atypia and mutations at multiple sites. DNA damage, with MSI and genomic instability, may arise within one year [185]. LOCDIR may play a role in the commonly observed inactivation of Kruppel-like factor 6 (KLF-6), a tumor-suppressor gene [186].

As cellular atypia increase, there may be progression from low- to high-grade dysplasia. After 10 or more years, carcinomas may develop without an exophytic feature. After 10 years of ulcerative colitis, the risk of colorectal cancer is 20 to 30 times that for a matched population. As an effective preventive measure, most patients with ulcerative colitis undergo total colectomy with ileostomy. A more controversial but also effective procedure is proctocolectomy with distal rectal mucosectomy. Although Crohn disease had long been thought to lack association with the development of colorectal cancers, it is now known that there is an 8% risk of developing colorectal cancer over a 20-year period. The problem of chronic inflammation with healing and epithelial changes at the cellular and molecular levels may be involved, as most of these cancers occur in strictured areas of the large bowel [181; 185].

SIGNALING PATHWAY DEREGULATION

Important contributions to the pathogenesis of colorectal cancer come from accumulated mutations in specific genes and resultant deregulation in signaling pathways that mediate cell proliferation, differentiation, apoptosis, immortalization, angiogenesis, and invasion [172].

Transforming Growth Factor-Beta Pathway

Transforming growth factor-beta signaling is a tumor-suppressor pathway in the colon. Deregulation in this pathway occurs by inactivating mutations in receptor genes, post-receptor signaling pathway genes, and transforming growth factor-beta superfamily members [172; 183].

Functionally significant mutations in *TGFBR2*, a signaling receptor gene, are detected in up to 30% of all colorectal cancers. They are most common in MSI tumors but also occur in 15% of CIN tumors and are associated with transformation of late adenomas to malignancy.

Mediators of Epidermal Growth Factor Receptor Signaling

Mutations of *PI3K* pathway genes occur in up to 40% of colorectal cancer cases and may promote the transition from adenoma to carcinoma. *PTEN*, a tumor suppressor gene that negatively regulates *PI3K* signaling, is mutated in up to 30% of MSI tumors and 9% of CIN tumors. The *PI3K* pathway is modulated by epidermal growth factor receptor (EGFR) signaling in part via *KRAS* activation [172; 183].

The most clinically important oncogene in colorectal cancer, *KRAS* is a downstream effector of EGFR that signals (through *BRAF)* the activation of mitogen activated kinase (MAPK) pathways and promotion of cell growth and survival. *KRAS* mutations occur in roughly 40% of colorectal cancers, primarily in CIN tumors secondary to inactivating *APC* mutations [172; 183].

Mutated in roughly 10% to 15% of colorectal cancers, *BRAF* encodes a protein kinase that acts as the downstream effector of *KRAS* in the *RAS/RAF/* MAPK signaling pathway. *KRAS* and *BRAF* mutations are mutually exclusive; activating mutation in either gene is sufficient to promote tumorigenesis via increased MAPK signaling. *BRAF* mutations are more frequent in MSI tumors (35%) than CIN tumors (5%) [172; 183].

PATIENT AND TUMOR CHARACTERISTICS ASSOCIATED WITH *KRAS* AND *BRAF*^{V600E} MUTATIONS IN COLON CANCER

KRAS and *BRAF*^{V600E} mutations are important predictive and prognostic markers, respectively, in colon cancer, but until recently little has been known about the associated patient and clinical characteristics. Analysis of 2,326 patients with stage III colon cancer found that 35% showed *KRAS* mutations and 14% *BRAF* mutations, which were near-100% mutually exclusive [187].

KRAS mutations were more frequent in patients with negative family history of colon cancer and never smokers. Tumors with *KRAS* mutations were significantly less likely to have defective MMR (dMMR) and high-grade histology and were more often right-sided [187].

Tumors with *BRAF*^{V600E} mutations were more frequent in patients 70 years of age or older and current or former smokers, and less frequent in non-Whites and men. Tumors with *BRAF*^{V600E} mutations were more frequently right-sided, with four or more positive lymph nodes, high-grade histology, and dMMR [187].

PROGNOSTIC/PREDICTIVE RELATIONSHIP TO GENETIC/ MOLECULAR PATHOLOGY

Advances in the understanding of genetic and molecular alterations in the pathogenesis of colorectal cancer have been used to link specific gene mutations in colorectal cancer with treatment response and prognosis in colorectal cancer [172; 183; 188]:

- MSI vs. CIN: Numerous studies have established a better prognosis, independent of colorectal cancer stage, in patients with MSI tumors and unfavorable prognosis with CIN tumor.
- *KRAS* codon 12/13 mutations: Present in roughly 40% of colorectal cancers, strong evidence demonstrates this mutation predicts resistance to anti-EGFR therapy.
- *BRAF*^{V600E} mutations: Occurring in 10% of colorectal cancers, moderate evidence suggests this mutation is likely to predict resistance to anti-EGFR therapy.
- MSI: Present in 15% of colorectal cancers, moderate evidence suggests this mutation may predict response to 5-FU and irinotecan.
- 18qLOH/*SMAD4* loss: Present in 50% of colorectal cancers, moderate evidence suggests this mutation may predict resistance to 5-FU.
- COX-2 overexpression: Emerging data show that colorectal cancer tumors with COX-2 overexpression are significantly associated with worse outcomes. This is consistent with the body of research associating long-term COX-2 inhibitor use with decreased rates of adenoma and colorectal cancer development and/or recurrence.

DIAGNOSIS AND STAGING OF COLON AND RECTAL CANCER

DIAGNOSTIC WORKUP

Patients with colorectal cancer typically present in one of three ways:

- Outpatients with suspicious symptoms and signs
- Asymptomatic persons discovered by routine screening
- Emergency admission with intestinal obstruction, peritonitis, or bleeding

A diagnosis of colorectal cancer is confirmed and other conditions ruled out by conducting a thorough patient history and physical examination and using appropriate testing. During the workup, the clinician should be mindful that, unless otherwise indicated, surgical resection is the first-line treatment for localized malignancy and is the only curative option for colorectal cancer. Thus, the diagnostic workup involves characterization of the malignancy and preoperative assessment.

History

Patient history and physical examination are the foundations of assessment. A thorough disease history should be obtained by eliciting disease-specific symptoms, associated symptoms, and family history. A cancer-specific history helps direct the exploration of associated pathology or metastatic disease and any further workup. When possible, all patients should undergo a full colonic evaluation with histologic assessment of the colorectal lesion before treatment.

Patients should also be assessed for their fitness to undergo surgery, including assessment of cardiac risk, and preoperative radiologic staging should be routinely performed [189; 190].

The incidence of colorectal cancer increases with age. Patients younger than 44 years of age account for fewer than 5% of cases, and the mean age at diagnosis is 71 years. Men and women older than 50 years of age have similar rates of colorectal cancer. However, the colorectal cancer prevalence in men increases in tandem with age beyond 50 years [98].

Physical Examination

With increasingly widespread and effective screening, colorectal cancer is frequently detected at an earlier, asymptomatic phase. Physical examination findings early in the disease course can be normal or nonspecific (e.g., fatigue, weight loss) [115; 189]. With more advanced colon cancer, common clinical presentations include iron-deficiency anemia, rectal bleeding, abdominal pain and tenderness, change in bowel habits, intestinal obstruction or perforation, hepatomegaly, and ascites. Right-sided lesions are more likely to bleed and cause diarrhea, while left-sided tumors are usually detected later and may present as bowel obstruction [115; 189].

In addition to these signs and symptoms in colon cancer, physical examination of patients with rectal cancer may reveal a palpable mass and bright red blood in the rectum. Adenopathy, hepatomegaly, or pulmonary signs may be present with metastatic rectal cancer. Proctosigmoidoscopy and digital rectal examination should be performed to determine tumor distance from the anal verge, mobility, and position relative to the sphincter complex.

Signs and Symptoms

Healthcare professionals should be attentive to both common and uncommon signs and symptoms during the history and physical exam that suggest colorectal cancer. More common diagnostic factors include increasing age, rectal bleeding, rectal mass, change in bowel habits, family history, abdominal mass or distension, and anemia [174; 191; 192; 193].

Rectal Bleeding

Although patients presenting with rectal bleeding may have a benign condition, this is a common symptom in patients with colon and rectal cancer. A primary care study found a positive correlation between each new episode of rectal bleeding in patients older than 45 years of age and colorectal cancer [193].

Change in Bowel Habit

Especially with rectal bleeding present, an increased frequency or looser stools is common in left-sided colorectal cancer. Bowel habit changes with reduced frequency and hard stools have low predictive value for colorectal cancer.

Rectal Mass

Palpable rectal mass is present in 40% to 80% of patients with rectal cancer [194]. Assessment using digital rectal examination is useful to estimate tumor proximity to the sphincter but unreliable to determine tumor involvement of the pelvic wall and suitability for surgery. These latter investigations are more accurately assessed by magnetic resonance imaging (MRI) and transrectal endoscopic ultrasound.

Positive Family History

Although only 10% to 20% of patients with colorectal cancer have a positive family history of colorectal cancer, persons with one affected first-degree relative are more than twice as likely to develop colorectal cancer, while those with two affected first-degree relatives are four times more likely to develop colorectal cancer [88; 89].

Abdominal Changes

The abdominal examination is typically unremarkable in patients with colorectal cancer, but the presence of a palpable tumor mass is common in advanced disease. Presence of abdominal distension indicates ascites or intestinal obstruction secondary to advanced disease. Patients are unlikely to have colorectal cancer when abdominal pain is present in the absence of other gastrointestinal symptoms, but those with colorectal cancer often have abdominal pain in addition to other symptoms.

Anemia

Anemia is present in close to 90% of patients with right-sided colon cancer at the time of diagnosis [192].

Other Signs and Symptoms

Weight loss and anorexia are more associated with advanced disease, as are palpable lymph nodes.

Endoscopic Evaluation

Patients with suspected colorectal cancer require a complete colon examination, and this is best performed with colonoscopy [195; 196]. Flexible sigmoidoscopy may be appropriate for low-risk patients, such as those with isolated rectal bleeding or who are younger than 50 years of age. However, positive findings with flexible sigmoidoscopy require pre- or postoperative confirmation and additional visualization of the entire colon, because roughly 5% of patients also harbor synchronous tumors [174; 197].

In the absence of intestinal obstruction contraindicating the administration of bowel preparation, colonoscopy is the first-line investigational choice because it demonstrates the highest sensitivity for colorectal cancer of any diagnostic modality, lacks the radiation exposure of CT, and enables the removal of incidental polyps and biopsy of suspicious lesions. The disadvantages of colonoscopy include a false-negative rate of 2% to 6% and accuracy that is highly operator-dependent and strongly influenced by patient adherence to proper preparatory bowel cleansing. Tumor localization is improved with administration of intraluminal ink or tattooing of the suspected cancer site [133; 197].

Diagnostic Imaging

CT colonography sensitivity in colorectal cancer detection is comparable to optical colonoscopy and has been used following incomplete colonoscopy assessment. DCBE has also been used in cases of poor colonoscopy visualization of the sigmoid colon (e.g., with severe diverticular disease), usually combined with flexible sigmoidoscopy. However, the superior sensitivity and specificity of CT colonography have led to the phasing out of DCBE for these indications [195; 196].

Elderly or frail patients may have difficulties with immobility or an inability to tolerate bowel preparation, which can impede conventional colonoscopy. One alternative is colorectal imaging using plain CT scan. Plain abdominal CT scan with oral contrast (but without bowel preparation) of symptomatic patients has shown an 88% to 94% sensitivity for colon cancer detection at 12- to 30-month follow-up [198; 199].

Laboratory Tests

Serum concentrations of carcinoembryonic antigen (CEA) are elevated in about 80% of patients with colorectal cancer, but CEA lacks sufficient sensitivity or specificity for use in screening or diagnosis. Instead, its greatest value comes from detecting colorectal cancer recurrence in patients who have undergone surgical resection. Patients should have baseline CEA values measured for comparison during the surveillance period to monitor for signs of recurrence [190].

Routine complete blood count, liver biochemistry, bone mineral density profile, and renal function are recommended before treatment to establish patient baseline values, to assess for hepatic and renal metastases, and to identify anemia [190].

Differential Diagnosis

During the diagnostic workup, other conditions with similarity to colon or rectal cancer should be considered and ruled out. These include [115; 174]:

- Irritable bowel syndrome
- Crohn disease
- Ulcerative colitis
- Ileus
- Diverticular disease
- Ischemic bowel
- Arteriovenous malformation
- Hemorrhoids and anal fissure in suspected rectal cancer

Rare gastrointestinal tumors should also be ruled out, such as:

- Carcinoid/neuroendocrine tumors
- Small-intestine carcinomas
- Gastrointestinal lymphoma

STAGING OF COLON AND RECTAL CANCER

Accurate staging provides crucial information about the location and size of the primary tumor, and if present, the size, number, and location of metastases. Accurate initial staging influences therapy by guiding the selection of surgical intervention and choice of neoadjuvant therapy to maximize an outcome of resection with clear margins.

Imaging Modality

After colorectal cancer is diagnosed, additional imaging is required for disease staging. Liver and chest imaging, preferably using CT, is necessary to detect metastases. Rectal cancers should be staged using endorectal ultrasonography or MRI. Positron emission tomography (PET) imaging is increasingly used in colorectal cancer to detect extrahepatic metastases in patients considered for hepatic resection of presumed liver-only metastatic disease. PET is also used to localize disease in patients thought to have a recurrence, as reflected by emergent symptoms or rising CEA [174; 200; 201]. PET is generally not recommended for routine colon cancer staging [190].

Practice guideline recommendations for imaging to stage colorectal cancer have been published by the American Society of Colon and Rectal Surgeons (ASCRS) and by Cancer Care Ontario [190; 202]. They recommend contrast-enhanced CT of the chest, abdomen, and pelvis should be performed in all patients with colon cancer (unless contraindicated) to estimate disease stage and identify metastases. If local excision is considered for low rectal cancer (0–5 cm from the anal verge), transrectal ultrasonography is preferred over MRI to improve discrimination between T1 and T2 lesions. For upper rectal cancers (10–15 cm above the anal verge), whereby the mesorectal fascia is not threatened, MRI is not considered superior to pelvic CT. MRI can stage the local rectum but is not adequate to assess regional disease at the level of the inferior mesenteric artery or distant disease. CT of the abdomen and pelvis should be used to assess for distant metastases and regional disease, including lymph node involvement along the inferior mesenteric artery. Pelvic CT and/or transrectal ultrasonography are recommended with contraindications to MRI. All patients with rectal cancer should have preoperative radiologic staging with contrast-enhanced CT to assess for metastatic disease [190; 202].

Histologic Assessment

Histologic confirmation of colon cancer is ideal, and for rectal cancer, it is essential [174]. Research has demonstrated an association between the number of lymph nodes examined in colon and rectal cancer surgery and oncologic outcomes [203]. In patients with colon or rectal cancer, the American Joint Committee on Cancer (AJCC) and National Cancer Institute jointly recommend examination of a minimum of 12 lymph nodes to rule out regional lymphatic node involvement [204].

The TNM Classification System

The AJCC has developed the TNM classification system, and this approach is the universal standard in clinical cancer care [204]. The AJCC TNM classification system is identical for colon and rectal cancer. The 2023 update to the AJCC system uses the pathologic stage (also called the surgical stage), as this is likely to be more accurate than the clinical stage, which takes into account the results of the physical exam, biopsies, and imaging tests done prior to surgery (***Table 6***) [204; 205]. The system was initially developed as a prognostic tool. While numerous studies have evaluated other clinical, pathologic, and molecular parameters for validity in outcome prediction, none have been validated in multi-institutional prospective trials, and the TNM system remains the only prognostic tool validated in multi-institutional prospective studies. With TNM [205]:

AMERICAN JOINT COMMISSION ON CANCER TNM CLASSIFICATION FOR COLON AND RECTAL CANCER	
Code	**Description**
Primary Tumor (T)	
TX	Primary tumor cannot be evaluated
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor extends through the mucosa and into the submucosa
T2	Tumor extends through the submucosa and into muscularis propria
T3	Tumor extends through the muscularis propria and into the subserosa but not to any neighboring organs or tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to adjacent organs or structures
Regional Lymph Node Involvement (N)	
NX	Regional lymph nodes cannot be evaluated
N0	No regional nodal involvement
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolorectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site
M1b	Metastasis in more than one organ/site or the peritoneum
Source: [204]	*Table 6*

- T describes the extent of primary tumor growth into the intestinal wall or adjacent areas. This grade reflects the extent of tumor spread in the colon and rectum wall, from the inner to the outermost layers.
- N describes the extent of primary tumor spread to nearby (regional) lymph nodes.
- M indicates whether the tumor has metastasized to other organs (most commonly, the liver or lungs).

When the T, N, and M categories have been determined (usually after surgery), the information is combined for stage grouping, with stage I the least advanced and stage IV the most advanced (***Table 7***) [189; 190].

In rectal cancer, AJCC staging does not apply to the following malignant histologies [206]:

- Sarcoma
- Lymphoma
- Carcinoid tumors
- Melanoma

STAGES OF COLORECTAL CANCER		
Stage	**TNM Classification**	**Description**
Stage 0	Tis, N0, M0	Tumor is in the earliest stage and has not grown beyond the colon or rectum mucosa. Also termed carcinoma in situ.
Stage I	T1–2, N0, M0	Tumor extends through the muscularis mucosa into the submucosa (T1) or into the muscularis propria (T2).
Stage IIA	T3, N0, M0	Tumor extends into the outermost layers of the colon or rectum but not beyond (T3).
Stage IIB	T4a, N0, M0	Tumor extends through the wall of the colon or rectum but not into adjacent tissues or organs (T4a).
Stage IIC	T4b, N0, M0	Tumor extends through the wall of the colon or rectum and is attached to or has grown into adjacent tissues or organs (T4b).
Stage IIIA	T1–2, N1/N1c, M0	Tumor extends through the mucosa into the submucosa (T1) or into the muscularis propria (T2). It has spread to 1–3 regional lymph nodes (N1) or into areas of fat near regional lymph nodes but not into the nodes (N1c).
	T1, N2a, M0	Tumor extends through the mucosa into the submucosa (T1) and has spread to 4–6 regional lymph nodes (N2a).
Stage IIIB	T3–4a, N1/N1c, M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1–3 regional lymph nodes (N1a/N1b) or into areas of fat near regional lymph nodes but not the nodes themselves (N1c).
	T2–3, N2a, M0	The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4–6 regional lymph nodes (N2a).
	T1–2, N2b, M0	The cancer has grown through the mucosa into the submucosa (T1) or it may also have grown into the muscularis propria (T2). It has spread to 7 or more regional lymph nodes (N2b).
Stage IIIC	T4a, N2a, M0	The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4–6 regional lymph nodes (N2a).
	T3–4a, N2b, M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more regional lymph nodes (N2b).
	T4b, N1–2, M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one (up to three) regional lymph node or into areas of fat near the lymph nodes (N1 or N2).
Stage IVA	Any T, Any N, M1a	The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to regional lymph nodes. It has spread to one distant organ or set of lymph nodes (M1a).
Stage IVB	Any T, Any N, M1b	The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to regional lymph nodes. It has spread to more than one distant organ or set of lymph nodes, or it has spread to distant parts of the peritoneum (M1b).
Stage IVC	Any T, Any N, M1c	The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to regional lymph nodes. It has spread to more than one distant organ or set of lymph nodes, or it has spread to one or more distant organs distant parts of the peritoneum (M1c).
Source: [206]		*Table 7*

PROGNOSTIC FACTORS

PROGNOSTIC FACTORS ASSOCIATED WITH STAGING

As discussed, *KRAS* mutations are present in 40% of colon adenocarcinomas and affect sensitivity to treatment with biologic agents directed against EGFR. The FDA has approved a qualitative real-time polymerase chain reaction assay, the therascreen *KRAS* RGQ PCR Kit, for detection of specific mutations in the *KRAS* oncogene [207].

dMMR is associated with high-frequency MSI (H-MSI), a predictor of better clinical outcomes for resectable colon cancer based on analysis of several large trials. In addition, patients with stage II dMMR (H-MSI) do not appear to benefit from 5-FU-based adjuvant therapy. Among patients with stage III disease, the predictive impact of dMMR status for adjuvant chemotherapy remains controversial [208; 209; 210].

Testing for dMMR with H-MSI has become an integral part of the routine diagnostic workup for colorectal cancer and has gained interest as a biomarker for patients with advanced cancer to determine their eligibility for immune checkpoint inhibitors [211; 212]. Some research also emphasizes the role of immune regulation in the natural course and prognosis of patients with colorectal cancers [213]. Amino acid metabolism is a verified part of the progression of cancer and is an area of interest for its potential role in colorectal cancer [214; 215].

MOLECULAR AND CLINICAL PROGNOSTIC FACTORS

There are a variety of molecular/genetic and clinical factors that impact the disease course and prognosis. Molecular prognostic factors include [216]:

- *p53*
- Loss of heterozygosity for *18q*
- Mutations of deleted in colon cancer (*DCC*) gene
- *EGFR* gene amplification

Specific clinical features associated with worse prognosis are [216]:

- Bowel obstruction at diagnosis
- Ulcerative growth pattern
- Perforation
- Elevated preoperative CEA level

HISTOLOGIC SUBTYPES AS PREDICTORS OF METASTASES

A study of autopsy results from 1,675 patients with metastasized colorectal cancer and from 88 patients with synchronous metastases observed that histologic subtype and localization of the primary colorectal cancer tumor strongly influenced metastatic pattern [217]. Metastatic disease was more prevalent, and more frequent in multiple sites, in patients with mucinous adenocarcinoma (33.9% and 58.6%, respectively) or signet-ring cell carcinoma (61.2% and 70.7%) than with adenocarcinoma (27.6% and 49.9%) [217]. Liver metastases were more frequent in patients with adenocarcinoma (73.0%) or mucinous adenocarcinoma (52.2%) than in those with signet-ring cell carcinoma (31.7%). Peritoneal metastases were more common in patients with signet-ring cell carcinoma (51.2%) or mucinous adenocarcinoma (48.2%) than in those with adenocarcinoma (20.1%) [217]. Metastases to distant lymph nodes occurred in more signet-ring cell carcinoma patients (43.9%) than patients with either mucinous adenocarcinoma (22.3%) or adenocarcinoma (19.9%). Abdominal metastases were more frequent with colon cancer, and extra-abdominal metastases more common with rectal cancer [217].

PROGNOSTIC FACTORS FOLLOWING RESECTION OF LIVER METASTASES

Approximately one in three patients who undergo resection for colorectal liver metastases become actual five-year survivors. Of those, approximately half survive 10 years and are considered "cured" of colorectal liver metastases [218]. Surgical resection of colorectal cancer with liver metastases continues to be the most important modality for long-term survival [219]. A multivariate analysis of 1,001 patients who underwent potentially curative resection of liver

metastases identified five factors as independent predictors of worse outcome [220]:

- Tumor size >5 cm
- Disease-free interval less than one year
- More than one tumor
- Primary lymph-node positivity
- CEA level >200 ng/mL

Other potential prognostic indicators being investigated include the value of circulating tumor DNA and the level of KRAS mutated circulating cell-free tumor DNA in patients with colorectal liver metastases [221; 222; 223].

SURVIVAL

Prognostic Factors of Survival by TNM Stage

Patient prognosis is most powerfully associated with clinical and histopathologic stage of colorectal cancer at diagnosis as reflected by the TNM classification and staging. The National Cancer Institute SEER database tracks five-year relative survival rates for colon and rectal cancer, based on how far the cancer has spread; it does not group cancers by AJCC TNM stages. Instead, it groups cancers into localized, regional, and distant stages (***Table 8***) [14].

Other Prognostic Factors of Survival

Several other factors have shown prognostic significance, including the number of harvested and processed lymph nodes, histologic grade, and evidence of lymphovascular and perineural invasion. In patients with metastatic colorectal cancer, the level of circulating tumor cells measured at baseline after the initiation of new therapy was an independent predictor of survival. In patients with baseline CEA values ≥25 ng/mL, those with low baseline levels of circulating tumor cells (fewer than three) had longer survival, and measurements of both circulating tumor cell number and CEA level at 6 to 12 weeks independently predicted survival [224]. Additionally, an emerging focus in research and literature is the role of host immune-centered factors (e.g., antitumor cells in the liver) in the clinical outcomes of colorectal liver metastases [225; 226].

COLORECTAL CANCER FIVE-YEAR SURVIVAL RATES BY STAGE

SEER Stage	Five-Year Relative Survival Rate
Colon cancer	
Localized	91%
Regional	73%
Distant	13%
All SEER stages combined	63%
Rectal cancer	
Distant	13%

Source: [14] *Table 8*

TREATMENT OF COLON AND RECTAL CANCER

MECHANISM OF CHEMOTHERAPY AND TARGETED THERAPIES

The chemotherapy agent 5-FU entered clinical use for patients with colorectal cancer more than 40 years ago and remains a mainstay of colorectal cancer treatment today. In the mid-1990s, the drugs irinotecan hydrochloride and oxaliplatin became available for colorectal cancer, and standard chemotherapy regimens were refined through extensive trials. Patients with metastatic colorectal cancer unsuitable for surgery represent more than 50% of those diagnosed with disseminated disease, and while they did benefit, the modest increases in life expectancy came with substantial toxicities. These patients, and their overall prognoses, remained poor. The therapeutic outlook improved with introduction of bevacizumab, the first FDA-approved antiangiogenic agent for metastatic colorectal cancer. Several additional targeted biologic agents have received FDA approval for metastatic colorectal cancer. As of 2025, these include cetuximab, capecitabine, panitumumab, ziv-aflibercept, regorafenib, and ramucirumab. Subsequent-line treatment options include pembrolizumab, nivolumab, nivolumab plus ipilimumab, and trifluridine/tipiracil (TAS-102) [227; 228; 229; 230; 231; 232]. In 2020, pembrolizumab was approved as a first-line treatment for

patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer [233]. In 2023, fruquintinib received FDA approval as treatment for patients with refractory metastatic colorectal cancer [234]. Also in 2023, tucatinib (in combination with trastuzumab) received accelerated FDA approval as second-line treatment of RAS wild-type HER2-positive unresectable or metastatic colorectal cancer [235]. In 2024, the FDA granted accelerated approval to encorafenib (in combination with cetuximab and mFOLFOX6) for patients with metastatic colorectal cancer with a *BRAF* ^{V600E} mutation [236].

EGFR is a glycoprotein with three primary components: an extracellular ligand binding domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain. EGFR is activated by ligand binding from EGF or transforming growth factor-alpha, which triggers downstream activation in signaling pathways that facilitate development and progression of colorectal cancer. This critical role of EGFR in oncogenesis has made it an attractive target for colorectal cancer therapy, and the targeted biologic agents cetuximab and panitumumab primarily act through binding EGFR to inhibit downstream signaling [172; 237; 238].

Colorectal tumors that grow beyond 1–2 mm^3 require increased access to oxygen and nutrients and develop neoangiogenesis to enable tumor growth and metastases. Neoangiogenesis originates from complex interactions between pro- and anti-angiogenic factors. Vascular endothelial growth factor (VEGF), the most potent pro-angiogenic factor known to date, is overexpressed in gastrointestinal tumors and is essential for the proliferation and metastases of colorectal cancer [238; 239]. VEGF overexpression is associated with increased tumor vascularity, proliferation, progression, invasion, and metastasis. VEGF binds to and activates one of the three VEGF receptors located on the vascular endothelium. Among the VEGF receptor types, VEGFR-2 is the primary mediator of the mitogenic and angiogenic effects of VEGF, while VEGFR-3 is involved in lymphangiogenesis [227].

Following VEGF binding, VEGF receptors activate several downstream intracellular signal transduction pathways that promote inhibition of apoptosis, degradation of the extracellular matrix to facilitate endothelial cell proliferation and migration to form new blood vessels, and stimulation of mitosis and cytoskeletal changes associated with motility. Colorectal tumors also express VEGF and other proangiogenic factors on their cell surface; their presence is associated with increased vascularity, advanced disease, and poor prognosis [239].

Findings of elevated VEGF levels in patients with metastatic colorectal cancer led to the development and FDA approval of several anti-VEGF agents (i.e., bevacizumab, ramucirumab, regorafenib, ziv-aflibercept, and fruquintinib) [231; 232; 238]. In addition to the therapeutic targeting of VEGF, VEGF antagonists have also shown the ability to increase intratumoral delivery of chemotherapeutic agents to improve their antitumor efficacy [226; 227].

Secondary Drug Resistance

Patients with chemotherapy-refractory colorectal cancer who initially respond and then become resistant to cetuximab or other monoclonal antibodies have essentially run out of therapeutic options. This emergence of secondary drug resistance within 9 to 18 months of initiation is a major limitation of anti-EGFR therapies. A substantial proportion of patients with colorectal cancer who initially respond to anti-EGFR therapies have, at the time of disease progression, tumors with focal amplification or somatic mutations in *KRAS* that were undetectable before initiation of anti-EGFR therapy. Drug-resistant *KRAS* alteration results from pre-existent *KRAS* mutant and amplified clones and from new mutations arising from ongoing mutagenesis [240]. A mechanism by which *KRAS* mutation nullifies anti-EGFR therapy involves bypassing the need for upstream EGFR signals to activate downstream oncogenic processes [172; 183]. It is now established that patients with any *KRAS* or *NRAS* mutation should not be treated with cetuximab or panitumumab, as these mutations strongly predict resistance to EGFR inhibitor agents. In contrast, non-mutational *KRAS*, termed wild-type *KRAS*, responds to targeted therapy [112; 203; 226; 231; 241; 242].

GENERAL APPROACH TO TREATMENT

Overall, there is a substantial overlap between treatment approaches for colon and rectal cancer, especially in stage IV and metastasized cancer. Treatment approaches for stage I–III cancer (earlier stage) differs the most. In this section, treatment of earlier-stage colon and rectal cancer are discussed separately, and discussion of metastatic colon and rectal cancer is combined. For both cancers, the foundation of care is surgical resection for patients with local or locally advanced tumor, and chemotherapy for stage IV, metastatic, and recurrent tumor. Unlike rectal cancer, radiotherapy has limited use in colon cancer.

The timing of chemotherapy and/or radiotherapy is sequenced in relation to surgery as follows:

- Neoadjuvant chemotherapy and/or radiation therapy: Delivered before surgery, to downsize the tumor. Most often used in rectal cancer.
- Adjuvant chemotherapy and/or radiation therapy: Delivered following surgery with the intent to destroy remaining local or micro-metastasized malignant cells and colonies.
- Palliative chemotherapy or radiotherapy: Delivered to downsize or eradicate colorectal cancer tumors that have metastasized to other organs. The objective is to relieve symptoms and pain, instead of cure or prolonging survival.
- Liver metastases: The liver is the most common site of metastatic colon and rectal cancer. Treatment of hepatic metastases of primary colorectal cancer can involve surgery with neoadjuvant or adjuvant chemotherapy, local ablation, or intra-arterial chemotherapy.

The use of chemotherapy in stage IV, metastatic, or recurrent disease involves the combination of agents. A number of chemotherapy regimens have been evaluated and represent the core of therapy. Newer biologically targeted agents are added to the established chemotherapy regimens to gain the advantage of synergistic drug action, and NCCN guidelines recommend the use of as many chemotherapy drugs as possible to maximize the effect of adjuvant therapies for colon and rectal cancer [229; 243].

Several practice guidelines for the treatment of colon and rectal cancer are available and are updated and revised on a regular basis. The importance of guideline-adherent treatment was underscored by a 2015 study of all patients receiving primary treatment for colorectal cancer in a major academic medical center between 2003 and 2010. The results showed that treatment non-adherent to NCCN guidelines was associated with 3.6 times the risk of death in the first year after diagnosis and an 80% increased risk of death after two to five years. The authors state that while medically justifiable reasons for guideline deviation do occur, the overall impact on patients is a markedly greater risk of death, especially in the first year following diagnosis [244].

TREATMENT OF COLON CANCER, STAGES I–III

The standard treatment options for colon cancer are [203]:

- Stage 0: Surgery
- Stage I: Surgery
- Stage II: Surgery, adjuvant chemotherapy
- Stage III: Surgery, adjuvant chemotherapy
- Stage IV and recurrent: Surgery, chemotherapy, and immunotherapy

Surgical Resection

Treatment of localized and locally advanced colon cancer primarily involves surgical resection, and roughly 80% of patients with colon cancer exhibit localized disease amenable to resection with curative intent [190]. Aside from palliative resection (e.g., alleviating obstruction), the objective of surgery is curative resection based on clear macroscopic and histologic resection margins. Practice recommendations from the ASCRS were published to optimize surgical care of these patients (***Table 9***) [190].

ASCRS GUIDELINES FOR SURGICAL MANAGEMENT OF COLON CANCER
Surgical Treatment of the Primary Tumor
A thorough surgical exploration should be performed and documented. The extent of colon resection should correspond to the lymphovascular drainage of the colon cancer site. The lymphadenectomy should be complete and en bloc with (i.e., at the same time as) the bowel segment. Clinically positive lymph nodes located outside the standard field of resection identified at the time of resection and suspected to contain metastatic disease should be biopsied or removed at the time of primary resection. Resection of involved adjacent organs should be en bloc. Synchronous colon cancers can be treated by two separate resections or subtotal colectomy. Sentinel lymph node (SLN) mapping for colon cancer does not replace standard lymphadenectomy. Laparoscopic and open colectomy achieve equivalent oncologic outcomes for localized colon cancer. The use of the laparoscopic approach should be based on the surgeon's documented experience in laparoscopic surgery as well as on patient- and tumor-specific factors. Treatment of the malignant polyp is determined by the morphology and histology of the polyp.
Prophylactic Oncologic Resection of Extraintestinal Organs
Oophorectomy is advised for grossly abnormal ovaries or contiguous extension of the colon cancer, but routine prophylactic oophorectomy is not necessary
Management of Synchronous Stage IV Disease
Resectable stage IV disease: The treatment of patients with resectable stage IV colon cancer should be individualized based on comprehensive multidisciplinary evaluation. Unresectable stage IV disease: Palliative intervention or resection of the symptomatic primary tumor should be considered, but routine resection of the asymptomatic primary tumor is not recommended.
Tumor-Related Emergencies
Bleeding: Surgical resection to stop severe blood loss from localized colon cancer should follow the same oncologic principles as in elective resection. Perforation: Perforation is a life-threatening complication. After resuscitation of the patient, surgical resection to address both the perforation and the tumor should be performed, if at all possible. Obstruction: Initial colectomy or endoscopic stent decompression and interval colectomy may be performed. The management of patients with an obstructing cancer should be individualized but may include a definitive surgical resection with primary anastomosis.
Management of Locoregional Recurrence
The treatment of patients with locoregionally recurrent colon cancer should be multidisciplinary, and curative resection should adhere to the principles of primary resection and should be performed when indicated to improve overall survival.
Management of Peritoneal Carcinomatosis
The treatment of patients with peritoneal carcinomatosis should be multidisciplinary and individualized and may include surgical cytoreduction (debulking). The role of intraperitoneal chemotherapy remains insufficiently defined.
Palliative Procedures
In patients with extensive incurable extent of tumor burden, palliative surgical interventions should be individualized based on the presence of symptoms.
Adjuvant Therapy
Adjuvant chemotherapy may be considered for patients with high-risk stage II colon cancer. Adjuvant chemotherapy should be recommended for patients with stage III colon cancer.
Source: [190] *Table 9*

The primary treatment for localized resectable colon cancer is colectomy with en bloc removal of all associated regional lymph nodes and involved adjacent structures. The extent of a curative resection for colon cancer depends on the site of the primary lesion and lymphovascular drainage of the cancer site. The length of bowel resected is governed by the blood supply to that segment. In the absence of synchronous pathology, an anatomic colon resection for cancer should achieve at least a 5-cm to 7-cm negative margin on either side of the tumor. Colectomy with local excision is not adequate for curative resection, because it increases risks of tumor spillage into the peritoneal cavity and tumor progression from lack of lymphadenectomy [190; 229].

For resectable non-metastatic colon cancer, the National Comprehensive Cancer Network preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes.

(https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

Surgery is curative in 25% to 40% of highly selected patients who develop resectable metastases in the liver and lung. Refinements in surgical technique and preoperative imaging have improved patient selection and resection outcomes [203; 245; 246; 247].

Before surgery, all patients should be given information about the likelihood of having a stoma, why it might be necessary, and how long it might be needed. The psychologic and emotional impacts of having a stoma should not be overlooked. Between 16% and 26% of patients with a stoma will experience negative psychologic symptoms immediately postoperatively, including anxiety, depression, and suicidal ideation [229; 248; 249]. Having a stoma also can potentially decrease patients' quality of life as they experience changes to body image, sexual function, social isolation, stigma, embarrassment, and decreased mood [250]. A trained stoma professional should provide specific information on the care and management of stomas to all patients considering surgery that might result in a stoma [229; 251].

Post-Resection Staging

Given that tumor depth, nodal metastasis, and distant metastasis strongly predict post-surgical prognosis in colon cancer, staging should be performed following surgical resection using TNM staging, histologic grade of the tumor, and resection completeness [190].

Adjuvant Chemotherapy

Stage II

The value of adjuvant chemotherapy for stage II colon cancer is controversial. In one study, adjuvant 5-FU-based chemotherapy was evaluated in patients with high-risk stage II colon cancer following curative resection. Compared with surgery alone, adjuvant 5-FU showed inconsistent benefit; these and other results led to guidelines issued by the American Society of Clinical Oncology (ASCO) stating that evidence does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer who are not in a high-risk subgroup [252; 253].

The NCCN guideline also states there is no survival advantage by adding oxaliplatin to 5-FU/leucovorin, including in patients 70 years of age or older [229]. The combination of folic acid, 5-FU, and oxaliplatin (FOLFOX) is considered reasonable in high-risk cases, but it is not indicated in good-to-average-risk stage II cancers.

Stage III

Stage III colon cancer denotes lymph node involvement. Studies have shown that prognosis is related to the number of involved lymph nodes; patients with one to three involved nodes have a significantly better survival than those with four or more involved nodes. Before 2000, 5-FU was the only adjuvant chemotherapy with activity in stage III colon cancer. With patients in many earlier trials of adjuvant 5-FU

not showing a survival benefit, modifications and additions to the core 5-FU therapy were investigated in stage III colon cancer. More recently, capecitabine was established as comparable to 5-FU/leucovorin. The addition of oxaliplatin to 5-FU/leucovorin (FLOX) improved overall survival compared with 5-FU/leucovorin alone and has become the reference standard for the future generation of clinical trials for stage III colon cancer [203; 229; 254].

For stage II/III colon cancer, the NCCN asserts that adjuvant bevacizumab, cetuximab, panitumumab, or irinotecan should not be used outside of clinical trials [229]. In stage III colon cancer, FOLFOX is superior to 5-FU/leucovorin, and capecitabine/oxaliplatin (CAPEOX) is superior to bolus 5-FU/leucovorin. FLOX is an alternative to FOLFOX or CAPEOX, but FOLFOX or CAPEOX are preferred [229].

Adjuvant Radiation Therapy

Unlike in rectal cancer, the role of adjuvant radiation therapy is poorly defined in colon cancer treatment. Radiation therapy has no current adjuvant role following curative resection but may have a potential role in patients with residual disease [229]. If used, radiation fields should include the tumor bed, as defined by preoperative radioimaging or surgical clips. Radiation should be given in doses of 45–50 Gy in 25 to 28 fractions; the dose in the small bowel should be no greater than 45 Gy [229]. Neoadjuvant chemoradiotherapy that includes 5-FU should be delivered concurrently to aid resectability. Conformal external beam radiation is preferred; intensity-modulated radiation therapy should be limited to unique clinical situations. Intraoperative radiation therapy should be considered in T4 or recurrent cancer [229].

TREATMENT OF RECTAL CANCER, STAGES 0–III

The standard treatment options for rectal cancer are [206]:

- Stage 0: Polypectomy or surgery
- Stage I: Surgery with or without chemoradiation therapy
- Stage II and III: Surgery, neoadjuvant chemoradiotherapy, short-course neoadjuvant radiotherapy, adjuvant chemoradiotherapy, immunotherapy
- Stage IV, metastatic, and recurrent: Surgery with or without chemotherapy or radiotherapy, chemotherapy, and targeted therapy

Approximately 30% of colorectal malignancies are attributable to rectal carcinoma. Although surgical resection is the only curative option for rectal cancer, complete resection is rendered technically difficult by the lack of serosa covering the rectum and proximity of the rectum to the bony pelvis and other pelvic organs. Local tumor invasion is promoted by this extra-colorectal proximity to other organs, which, along with surgical difficulty, contributes to high local recurrence rates [189; 206].

Compared with colon cancer, the increased risk of local recurrence and poorer overall prognosis in rectal cancer has led to differences in the management of localized or locally advanced disease, including greater emphasis on multimodal treatment to minimize morbidity, decrease recurrence risk, and prolong survival [255]. Other differences in rectal cancer treatment include surgical techniques, use of radiation therapy, and chemotherapy protocol. In stage II or III rectal cancer, neoadjuvant therapy is now favored over adjuvant therapy based on evidence of improved local control and increased rates of sphincter preservation [243; 256; 257; 258].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Comprehensive Cancer Network recommends combined-modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis, and chemotherapy for the majority of patients with stage II or stage III rectal cancer.

(https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

ASCRS GUIDELINES FOR SURGICAL MANAGEMENT OF RECTAL CANCER
Surgical Techniques and Operative Considerations, Local Excision
Local excision is appropriate for carefully selected T1 rectal cancers without high-risk features.
Surgical Techniques and Operative Considerations, Radical Excision
A thorough surgical exploration should be performed and the findings documented in the operative report. Total mesorectal excision should be used for curative resection of tumors of the middle and lower thirds of the rectum, either as part of low anterior or abdominoperineal resection. For tumors of the upper third of the rectum, a tumor-specific mesorectal excision should be used with the mesorectum divided ideally no less than 5 cm below the lower margin of the tumor. A 2-cm distal mural margin is adequate for most rectal cancers when combined with a total mesorectal excision. For cancers located at or below the mesorectal margin, a 1-cm distal mural margin is acceptable. Proximal vascular ligation at the origin of the superior rectal artery with resection of all associated lymphatic drainage is appropriate for most rectal cancer resections. In the absence of clinical involvement, extended lateral lymph node dissection is not necessary in addition to total mesorectal excision. Patients with an apparent complete clinical response to neoadjuvant therapy should still be offered definitive resection. After low anterior resection and total mesorectal excision, the formation of a colonic reservoir may be considered. Intraoperative anastomotic leak testing should be performed to help identify an anastomosis at increased risk of a subsequent clinical leak. A diverting ostomy should be considered for patients undergoing a total mesorectal excision for rectal cancer. In patients undergoing a total mesorectal excision, an intraoperative rectal washout may be considered. In patients with T4 rectal cancers, resection of involved adjacent organs should be performed with an en bloc technique. Current evidence indicates that laparoscopic total mesorectal excision can be performed with equivalent oncologic outcomes in comparison with open total mesorectal excision when performed by experienced laparoscopic surgeons possessing the necessary technical expertise. Oophorectomy is advised for grossly abnormal ovaries or contiguous extension of a rectal cancer, but routine prophylactic oophorectomy is not necessary.
Tumor-Related Emergencies
In patients with large-bowel obstruction, an expanding stent is an acceptable treatment option in the palliative setting or as a bridge to definitive resection.
Multimodality Neoadjuvant Therapy
Neoadjuvant therapy should be used for locally advanced cancers of the mid or distal rectum.
Multimodality Adjuvant Therapy
Adjuvant chemoradiotherapy should be recommended for select patients with stage III or high-risk stage II rectal cancer who have not received neoadjuvant therapy. Adjuvant chemotherapy should be recommended for patients with high-risk stage II and all stage III disease previously treated with neoadjuvant therapy.
Source: [189] *Table 10*

An important consideration is the impact of rectal cancer surgery on the structure and function of adjacent sensitive tissues, and the therapeutic issues related to the maintenance or restoration of normal anal sphincter, genitourinary, and sexual function [255; 259; 260]. Practice recommendations for the surgical treatment of localized rectal cancer have been published by the ASCRS (***Table 10***) [189].

Treatment of rectal cancer is determined by clinical disease stage and the risk of local recurrence. Low-risk, early-stage disease is generally treated with primary surgical therapy, while locally advanced or high-risk disease requires multimodality therapy that includes neoadjuvant radiation or chemoradiation [189]. The risk of local recurrence is estimated using MRI imaging before surgical intervention. Risk level is defined as low, moderate, or high based on the following criteria [189; 251]:

Low Risk

- Clinical stage T1, T2 or T3a, AND
- No lymph node involvement

Moderate Risk

- T3b or greater, in which the potential surgical margin is not threatened, OR
- Any suspicious lymph node not threatening surgical resection margins, OR
- The presence of extramural vascular invasion

High Risk

- A threatened (<1 mm) or breached resection margin, OR
- Low tumors encroaching onto the intersphincteric plane or with levator involvement

Primary Surgical Therapy

Rectal cancer surgery involves surgical resection of the primary tumor. Surgical approach is guided by tumor location, disease stage, and presence of high-risk features (e.g., positive margins, lymphovascular invasion, perineural invasion, poorly differentiated histology) [206].

Polypectomy alone may be sufficient when polyps with invasive cancer can be completely resected with clear margins and show favorable histologic features, generally select T1 cancers [206; 261]. Approaches with minimal morbidity and mortality include transanal excision and transanal endoscopic microsurgery. Local excision is appropriate in selected T1 tumors, with mesorectal excision preferred for all other T1–T2/N0 tumors. Endoscopic microsurgery cannot perform excision and staging of mesorectal lymph nodes, a limitation because T1 lesions have a 6% to 11% risk of harboring nodal metastasis [262]. Local recurrence rates range from 7% to 21% for T1 lesions and 26% to 47% for T2 lesions [262; 263; 264].

Total mesorectal excision with autonomic nerve preservation via low-anterior resection is preferred, followed by colorectal anastomosis in advanced mid- to upper-rectal tumor. Low anterior rectal resection is associated with bowel urgency, increased bowel frequency, clustering, and fecal incontinence from loss of rectum reservoir function. The colonic J-pouch is the superior approach for improving postoperative bowel function [58; 265]. In patients unsuitable for sphincter-preservation, total mesorectal excision via abdominoperineal resection is preferred, although this leaves patients with a permanent colostomy [266; 267; 268]. Total mesorectal excision has demonstrated reproducible reductions in local recurrence and improvement in disease-free and overall survival [269].

The low incidence of local relapse after meticulous mesorectal excision has led some investigators to question the routine use of adjuvant radiation therapy. Because of an increased tendency for first failure in locoregional sites only, the impact of perioperative radiation therapy is greater in rectal cancer than in colon cancer [206].

Multimodality Therapy

Multimodality therapy has been the standard of care for patients with locally advanced rectal cancer since 1990, when the National Cancer Institute recommended adjuvant therapy for stage II and III disease [206]. This was based on findings of 33% to 55% reduction in local recurrence and significant prolongation in disease-free survival. Although the National Cancer Institute recommended adjuvant therapy, subsequent findings have shown superior efficacy, lower toxicity, and better long-term outcomes with neoadjuvant therapy. The Institute now recommends neoadjuvant therapy as the preferred treatment option for patients with stages II or III disease [206; 270; 271; 272].

Preoperative radiation therapy is more effective because well-oxygenated tissue responds better to irradiation; postoperative tissue is relatively hypoxic from surgery and may be more resistant to radiation therapy. Also, postoperative complications may delay initiating adjuvant therapy [273].

Neoadjuvant Chemoradiation Therapy

As stated, neoadjuvant chemoradiation therapy is the preferred treatment option for patients with stage II or III disease, although adjuvant chemoradiation therapy remains an acceptable option [206]. Preoperative chemoradiation therapy is the standard of care for patients with clinically staged T3–T4 or node-positive disease (stages II/III) with benefits found in multiple trials, including [206]:

- Tumor regression and downstaging
- Improved tumor resectability
- Higher rates of local control
- Improved toxicity profile of chemoradiation therapy
- Higher rates of sphincter preservation

The most common neoadjuvant regimens for locally advanced tumors of the mid and lower third of the rectum are [206; 273; 274; 275]:

- Short-course radiation therapy with 5 Gy daily for five days, followed by surgery within one week. This approach results in a lower rate of grade 3/4 acute toxicity and better compliance. It is more commonly used when tumor regression and downsizing would not improve resection or sphincter preservation.
- Long-course chemoradiation therapy using 45 to 50.4 Gy over 5 to 6 weeks with concurrent administration of 5-FU, followed by surgery 8 to 12 weeks later. Tumor regression and downsizing is more likely, making sphincter-preserving surgical procedures more feasible.

When followed by proper surgical approach and execution, both regimens provide excellent local control for locally advanced tumors. Combined neoadjuvant radiation therapy and surgery may result in substantial long-term morbidity, including chronic bowel, sphincter, and sexual dysfunction, making careful selection of patients with greatest potential benefit from radiation therapy essential [276; 277].

Neoadjuvant radiation therapy or chemoradiation therapy should not be used in low-risk operable rectal cancer [251].

Adjuvant Therapy

Compared with adjuvant chemoradiation therapy, preoperative chemoradiation therapy is preferred because it decreases local recurrence and adverse effects. However, the evidence demonstrates that compared to observation alone or radiation therapy alone following surgery, adjuvant chemoradiation therapy improves survival and reduces local recurrence rates in patients with resected stage II or III rectal cancer who have not received preoperative radiation therapy [243; 270].

Many patients do not benefit from conventional 5-FU therapy, and introduction of newer chemotherapy regimens and biologic agents in colon cancer have prompted efforts to enhance survival benefits by optimizing radiation sensitization and chemotherapeutic selection and delivery. The NCCN now recommends m(modified)FOLFOX, CAPEOX, FOLFIRINOX, or mFOLFIRINOX as adjuvant chemotherapy in stage II/III rectal cancer. This comes with the caveat that conclusive data in rectal cancer are lacking, with recommendation for use in rectal cancer based solely on extrapolation of colon cancer data [243]. The merit of adding oxaliplatin to adjuvant 5-FU/leucovorin in stage II/III rectal cancer is the subject of ongoing debate due to issues with acute toxicity [206].

Radiotherapy Toxicity

The greater toxicity concerns with pelvic irradiation of rectal cancer involve potential late-onset morbidity. Relative to patients receiving surgical resection alone, those with additional radiation therapy treatment have shown increased risks of chronic bowel problems, sphincter dysfunction, sexual dysfunction, and elevated risk of surgical morbidity [206; 270].

The improved local tumor control with neoadjuvant radiation therapy should be weighed against greater risks for acute toxicity (e.g., pelvic or perineal wound infection) and chronic/late-onset toxicity (e.g., stool frequency and incontinence problems, pelvic fractures, worsening sexual function) [206]. The frequency of these adverse effects found in patients receiving radiation therapy plus surgery versus surgery-only includes fecal incontinence in 62% vs. 38%, and urinary incontinence requiring pad wearing in 56% vs. 33%, respectively [206].

CHEMOTHERAPY AGENTS AND REGIMENS USED IN ADVANCED COLON AND RECTAL CANCER

Chemotherapy is the primary therapeutic modality for stage IV, metastatic, and recurrent colorectal cancer and the first treatment option for unresectable or metastatic tumors. Metastases develop in at least 50% of patients with colorectal cancer, and most metastatic tumors are unresectable. Management of metastatic colorectal cancer involves a continuum of care with sequential use of a variety of active agents in combination or as single agents. The choice of therapy is based on treatment goals, the type and timing of previous therapy, specific efficacy and toxicity profiles, tumor mutational status, and patient preference [243; 278].

The specific chemotherapy agents and combinations used in colon cancer and rectal cancer overlap substantially. The following agents have received FDA approval for use in colorectal cancer [279; 280].

5-Fluorouracil (5-FU)

As discussed, 5-FU has been the foundation of chemotherapy for colorectal cancer for more than four decades. As a single agent, it inhibits tumor cell growth through at least three different mechanisms that ultimately disrupt cellular viability or DNA synthesis, transcription, and replication.

Capecitabine

Capecitabine is an oral fluoropyrimidine that undergoes a three-step enzymatic conversion to 5-FU, with the last step occurring in the tumor cell.

Leucovorin Calcium

Leucovorin is a reduced form of folic acid that does not require enzymatic reduction reaction for activation. This agent allows for purine and pyrimidine synthesis, both of which are needed for normal erythropoiesis. Leucovorin counteracts the toxic effects of current standard combination chemotherapy for colorectal cancer and potentiates the effects of 5-FU and its derivatives by stabilizing the binding of the drug's metabolite to its target enzyme to prolong drug activity.

Irinotecan Hydrochloride

Irinotecan is inactive in its parent form and is converted by the carboxylesterase enzyme to its active metabolite form SN-38, which is 1,000 times more potent than its parent compound. SN-38 binds to and stabilizes the topoisomerase I-DNA complex and prevents the relegation of DNA after it has been cleaved by topoisomerase I, inhibiting DNA replication. Irinotecan is a current standard therapy for metastatic colon cancer as the combination 5-FU/leucovorin/irinotecan.

Oxaliplatin

A third-generation platinum-based antineoplastic agent, oxaliplatin is used in combination with 5-FU/leucovorin for metastatic colorectal cancer. As with other platinum compounds, oxaliplatin destroys tumor cells through interaction with DNA to form intra-strand/inter-strand DNA cross-linking that interferes with DNA base pairing, replication, and gene transcription, resulting in cell death [281].

Cetuximab

Cetuximab is a partially humanized monoclonal antibody against EGFR that specifically binds to the extracellular domain of EGFRs. The cetuximab-bound EGFR inhibits activation of receptor-associated kinases, which inhibit cell growth, induce apoptosis, and decrease production of matrix metalloproteinase and VEGF. Cetuximab is indicated for the treatment of *KRAS* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer. Importantly, patients with mutant *KRAS*

tumors may experience worse outcome when cetuximab is added to multiagent chemotherapy regimens containing bevacizumab.

Bevacizumab

Bevacizumab is a partially humanized monoclonal antibody that binds to VEGF to inhibit angiogenesis. The inhibition of new blood vessel formation denies blood, oxygen, and other nutrients needed for tumor growth.

Panitumumab

Panitumumab is a fully humanized antibody that binds to EGFR. It is approved by the FDA for use in chemotherapy-refractory metastatic colorectal cancer and is indicated for wild-type *KRAS* metastatic colorectal cancer.

Ziv-Aflibercept

Ziv-aflibercept is a novel anti-VEGF molecule that acts as a decoy receptor for VEGF-A, VEGF-B, and placental growth factor. The antiangiogenic mechanism of ziv-aflibercept involves competition with VEGF in the blood and extravascular space to prevent VEGF from interacting with its receptors on endothelial cells. It is indicated for metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin regimen [282].

Ramucirumab

Ramucirumab is a monoclonal antibody with a high affinity for VEGF receptor 2. It binds to and blocks VEGFR ligands, which inhibits ligand-induced proliferation and migration of endothelial cells. VEGFR2 inhibition results in reduced tumor vascularity and growth.

Regorafenib

Regorafenib inhibits multiple tyrosine kinase pathways, including VEGF, and was approved in 2012 for the treatment of metastatic colorectal cancer in patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy (e.g., bevacizumab, ziv-aflibercept); and, if *KRAS* wild type, an anti-EGFR therapy (e.g., cetuximab, panitumumab).

Encorafenib

Encorafenib is a *BRAS* kinase inhibitor that targets *BRAF* V600 and inhibits tumor cell growth. It received accelerated FDA approval in 2024 (in combination with cetuximab and mFOLFOX6) for patients with metastatic colorectal cancer with a *BRAF* V600E mutation.

Fruquintinib

Fruquintinib is a small molecule kinase inhibitor of VEGFRs. It inhibits cell proliferation, tubular formation, and tumor growth. It was approved in 2023 as treatment for patients with refractory metastatic colorectal cancer.

Trifluridine-tipiracil

Trifluridine-tipiracil is used to treat metastatic colorectal cancer, either as a single agent or in combination with bevacizumab. The triphosphate form of trifluridine is incorporated into DNA, which interferes with DNA synthesis and inhibits cell proliferation. Tipiracil hydrochloride is a potent inhibitor of thymidine phosphorylase, which actively degrades trifluridine. The combination of trifluridine and tipiracil allows for adequate plasma levels of trifluridine.

Combination Regimens

The basis of chemotherapy for the treatment of colon and rectal cancer is combination therapy, with agents identified to work synergistically to manage unresectable lesions and minimize drug resistance. These combinations are generally known by their acronyms (***Table 11***).

RESECTABLE STAGE IV METASTATIC AND RECURRENT COLON AND RECTAL CANCER

With recurrent or advanced colon and rectal cancer, treatment is determined by disease location. For patients with locally recurrent or liver- and/or lung-only metastatic disease, surgical resection, if feasible, is the only potentially curative treatment [203]. Improved surgical techniques and advances in preoperative imaging have improved patient selection for resection. In addition, multiple studies with multiagent chemotherapy have demonstrated that

COMBINATION CHEMOTHERAPY REGIMENS USED IN THE TREATMENT OF COLON AND RECTAL CANCER		
Name	**Agents**	**Regimen**
Arbeitsgemeinschaft Internistische Onkologie (AIO) or German AIO	Folic acid (leucovorin), 5-FU, and irinotecan	Irinotecan (100 mg/m^2) and leucovorin (500 mg/m^2) administered as two-hour infusions on day 1, followed by 5-FU (2,000 mg/m^2) IV bolus administered via ambulatory pump weekly over 24 hours, four times per year (52 weeks)
CAPOX	Capecitabine and oxaliplatin	Capecitabine (1,000 mg/m^2) twice daily on days 1 through 14, plus oxaliplatin (130 mg/m^2) on day 1 every three weeks
FOLFIRI	Leucovorin, 5-FU, and irinotecan	Irinotecan (180 mg/m^2) and leucovorin (400 mg/m^2) administered as two-hour infusions on day 1, followed by a loading dose of 5-FU (400 mg/m^2) IV bolus administered on day 1, then 5-FU (1,200 mg/m^2) for two days (total 2,400 mg/m^2 over 46 to 48 hours) every two weeks
mFOLFOX6	Oxaliplatin, leucovorin, and 5-FU	Oxaliplatin (85–100 mg/m^2) and leucovorin (400 mg/m^2) administered as two-hour infusions on day 1, followed by a loading dose of 5-FU (400 mg/m^2) IV bolus on day 1, then 5-FU (2,400–3,000 mg/m^2) administered via ambulatory pump over 46 hours every two weeks
FOLFOX7	Oxaliplatin, leucovorin, and 5-FU	Oxaliplatin (130 mg/m^2) and leucovorin (400 mg/m^2) administered as two-hour infusions on day 1, followed by a loading dose of 5-FU (400 mg/m^2) IV bolus administered over 46 hours on day 1, then 5-FU (2,400 mg/m^2) administered via ambulatory pump over 46 hours beginning on day 1, every two weeks, for a total of eight cycles
FOLFOXIRI	Irinotecan, oxaliplatin, leucovorin, and 5-FU	Irinotecan (165 mg/m^2) administered as a 60-minute infusion, then concomitant infusion of oxaliplatin (85 mg/m^2) and leucovorin (200 mg/m^2) over 120 minutes, followed by 5-FU (3,200 mg/m^2) administered as a 48-hour continuous infusion.
FU-LV (Roswell Regimen)	5-FU and leucovorin	Leucovorin (200 mg/m^2) administered as a 2-hour infusion on days 1 and 2, followed by a loading dose of 5-FU (600 mg/m^2) IV bolus over 22 hours on days 1 and 2 every two weeks
BRAFTOVI	Encorafenib and cetuximab	Oral encorafenib (300 mg) days 1 to 28 and cetuximab IV (400 mg/m^2) on day 1 followed by 250 mg/m^2 days 8, 15, and 22.
XELOX	Oxaliplatin and capecitabine	Oral capecitabine (1,000 mg/m^2) administered twice daily for 14 days plus oxaliplatin (130 mg/m^2) IV infusion administered over 2 hours on day 1 every 3 weeks
Source: [229; 230; 231; 283]		*Table 11*

patients with metastatic disease isolated to the liver, which historically would be considered unresectable, can occasionally be made resectable after the administration of chemotherapy [203].

Stage IV colon cancer denotes distant metastatic disease, and therapeutic options for stage IV and recurrent disease include [203]:

- Surgical resection of locally recurrent cancer
- Surgical resection and anastomosis or bypass of obstructing or bleeding primary lesions in selected metastatic cases
- Resection of liver metastases in selected metastatic patients (i.e., those for whom the five-year cure rate for resection of solitary or combination metastases exceeds 20%) or ablation in selected patients
- Resection of isolated pulmonary or ovarian metastases in selected patients
- Palliative radiation therapy
- Palliative chemotherapy
- Targeted therapy
- Clinical trial enrollment

As with colon cancer, surgical resection is the only potentially curative treatment for patients with locally recurrent, liver-only, or lung-only metastatic rectal cancer [203]. Patients with limited pulmonary metastasis and patients with both pulmonary and hepatic metastasis may also be considered for surgical resection, with five-year survival possible in highly selected patients [284; 285]. The presence of hydronephrosis associated with recurrence appears to be a contraindication to surgery with curative intent as it indicates a lower chance for complete surgical resection of the recurrence [286; 287]. However, target drugs in combination with chemotherapy may improve the treatment efficacy and prognosis of patients [288].

Locally recurrent rectal cancer may be resectable, particularly after an inadequate prior operation. For patients with local recurrence alone after an initial attempted curative resection, aggressive local therapy with repeat low anterior resection and coloanal anastomosis, abdominoperineal resection, or posterior or total pelvic exenteration can lead to long-term disease-free survival [206].

The use of induction chemoradiation therapy for previously nonirradiated patients with locally advanced pelvic recurrence (i.e., pelvic side-wall, sacral, and/or adjacent organ involvement) may increase resectability and allow for sphincter preservation [206]. Intraoperative radiation therapy in patients who previously received external-beam radiation therapy may improve local control in patients with locally recurrent disease, with acceptable morbidity [206].

STAGE IV COLORECTAL CANCER WITH UNRESECTABLE OR MEDICALLY INOPERABLE METASTASES

Pivotal studies have established the clinical use and/or FDA approval of chemotherapy and targeted therapy agents and regimens in metastatic colorectal cancer treatment. Unless stated otherwise, all outcomes are median values and all studies were randomized double-blinded with active or placebo control group. Outcomes are time-to-progression, progression-free survival, disease-free survival, and overall survival. Data from several studies suggest that there is little difference in clinical outcomes when intensive therapy is given first-line versus when less intensive therapy is given first followed by more intensive combinations. Additionally, first-line combination therapy can be more toxic but not more effective [229; 289].

5-FU

When 5-FU was the only available chemotherapeutic option with colorectal cancer activity, trials in patients with locally advanced, unresectable, or metastatic disease showed partial response, prolonged time-to-progression of disease, and improved survival and quality of life compared with best supportive care only. Several trials analyzing the activity and toxicity of various 5-FU/leucovorin regimens found comparable results and median survival of roughly 12 months [290; 291; 292].

Capecitabine

Randomized studies found capecitabine equivalent in efficacy to the 5-FU/leucovorin regimen [293; 294]. Other studies in metastatic colorectal cancer found non-inferiority between capecitabine/oxaliplatin (CAPOX) and 5-FU/oxaliplatin regimens as first-line therapy [295; 296].

Irinotecan and Oxaliplatin

In patients with previously untreated metastatic colorectal cancer, adding irinotecan or oxaliplatin to 5-FU/leucovorin has led to improved treatment response, progression-free survival, and overall survival [297; 298; 299].

A comparison of FOLFOX4 against irinotecan, 5-FU, and leucovorin (IFL) showed progression-free survival of 8.7 vs. 6.9 months and overall survival of 19.5 vs. 15.0 months [300]. Comparisons of FOLFOX and FOLFIRI found identical progression-free survival and overall survival, although patients were allowed to cross over after progression. The toxicity profiles of the regimens differed [301; 302].

Patients randomized to FOLFIRI, modified IFL (mIFL), or capecitabine/irinotecan (CAPIRI) showed progression-free survival of 7.6 vs. 5.9 months with FOLFIRI vs. mIFL, and 7.6 vs. 5.8 months with FOLFIRI vs. CAPIRI. CAPIRI also led to the highest rates of grade 3 or greater nausea, vomiting, diarrhea, dehydration, and hand-foot syndrome [303].

FOLFOX and FOLFIRI are first-line treatments for patients with metastatic colorectal cancer, with FOLFIRI preferred when using irinotecan [303].

Oxaliplatin

CAPOX was found comparable to 5-FU and oxaliplatin as an oxaliplatin-based regimen for first-line treatment of metastatic colorectal cancer [295; 296]. As second-line treatment following progression on irinotecan and 5-FU/leucovorin, patients randomized to FOLFOX4 or infusional 5-FU/leucovorin showed a median time-to-progression of 4.6 versus 2.7 months [304].

Bevacizumab

Bevacizumab is effective when added to FOLFIRI or FOLFOX as first-line treatment of metastatic colorectal cancer. In a 2009 study of patients with metastatic colorectal cancer, patients randomized to FOLFIRI/bevacizumab showed an overall survival of 28.0 months compared with 19.2 months with mIFL/bevacizumab *[305]*. In a separate study, patients randomized to IFL/bevacizumab or IFL/placebo showed progression-free survival of 10.6 vs. 6.2 months and overall survival of 20.3 vs. 15.6 months [306].

A trial randomized 1,401 patients with stage IV colorectal cancer to CAPOX or FOLFOX4, and then to bevacizumab or placebo. Patients receiving bevacizumab versus placebo showed progression-free survival of 9.4 vs. 8.0 months and overall survival of 21.3 vs. 19.9 months. Patients in the pooled CAPOX versus FOLFOX4 arms had a progression-free survival of 8.0 vs. 8.5 months. Overall survival had less benefit from bevacizumab than previously reported [307].

In another study, patients who progressed on FOLFIRI were randomized to FOLFOX plus bevacizumab or placebo, and showed a progression-free survival of 7.43 vs. 4.7 months, and overall survival of 12.9 vs. 10.8 months *[308]*. Based on these studies, bevacizumab was deemed a reasonable addition to FOLFIRI or FOLFOX as first-line treatment of metastatic colorectal cancer.

In a 2012 study, patients progressing on a first-line regimen that included bevacizumab were randomized to a different chemotherapy regimen plus continued bevacizumab or placebo. Participants who continued bevacizumab showed an overall survival of 11.2 months and progression-free survival of 5.7 months, compared with 9.8 months and 4.1 months, respectively, with placebo *[309]*. These results led to FDA approval of bevacizumab continuation in patients with progression during first-line chemotherapy, allowing patients to continue bevacizumab after switching to a different regimen containing irinotecan or oxaliplatin that may improve the synergistic activity [310].

FOLFOXIRI plus bevacizumab was compared to FOLFIRI plus bevacizumab in patients with untreated metastatic colorectal cancer, who showed a progression-free survival of 12.1 vs. 9.7 months and overall survival of 31.0 vs. 25.8 months. FOLFOXIRI led to significantly more grade 3/4 toxicities, including neutropenia, stomatitis, and peripheral neuropathy [311].

Ziv-Aflibercept

As second-line therapy, 1,226 patients with metastatic colorectal cancer randomized to FOLFIRI plus ziv-aflibercept or placebo showed overall survival of 13.50 vs. 12.06 months and progression-free survival of 6.90 vs. 4.67 months. Both statistically significant outcomes favored ziv-aflibercept, and FOLFIRI plus ziv-aflibercept is an accepted second-line regimen for patients previously treated with FOLFOX [312].

Cetuximab

Tumors with *KRAS* mutations are cetuximab-insensitive, but adding cetuximab to multiagent chemotherapy improves survival in patients with colorectal cancers lacking *KRAS* mutation (i.e., *KRAS* wild type). As discussed, patients with mutant *KRAS* tumors may experience worse outcomes when cetuximab is combined with bevacizumab. These differences are evident in the clinical trial data.

Patients who progressed on irinotecan regimens randomized to cetuximab plus irinotecan or placebo showed a time-to-progression of 4.2 vs. 1.5 months [313]. A trial of 1,198 patients with stage IV colorectal cancer randomized to FOLFIRI plus cetuximab or placebo found improved progression-free survival but not overall survival with cetuximab. With emerging evidence that cetuximab response is limited to patients with wild-type *KRAS* tumors, the results were re-analyzed by *KRAS* status. A significant interactive effect was found for *KRAS* mutation status and cetuximab treatment response but not progression-free survival, with *KRAS* wild-type outcomes favoring FOLFIRI and cetuximab [314].

In a 2009 study, patients were randomized to capecitabine/oxaliplatin/bevacizumab plus cetuximab or placebo for metastatic colorectal cancer. The median progression-free survival was 9.4 vs. 10.7 months, and patients with *KRAS* gene mutation (versus wild-type) receiving cetuximab had progression-free survival of 8.1 vs. 10.5 months. Patients with *KRAS* tumor mutation receiving cetuximab (as opposed to placebo) showed progression-free survival of 8.1 vs. 12.5 months and overall survival of 17.2 vs. 24.9 months [305].

The benefit of adding cetuximab to first-line combination chemotherapy was studied in patients with *KRAS* wild-type tumors. The 1,630 patients were randomized into three treatment groups and cetuximab or placebo:

- Arm A: Fluoropyrimidine/oxaliplatin
- Arm B: Fluoropyrimidine/oxaliplatin/cetuximab
- Arm C: Intermittent fluoropyrimidine/oxaliplatin

In patients receiving chemotherapy plus placebo versus cetuximab, the overall survival was 17.9 vs. 17.0 months and progression-free survival was 8.6 vs. 8.6 months. In patients treated continuously (arm A) versus intermittently (arm C), median survival was 15.8 vs. 14.4 months [315; 316]. None of these findings were statistically significant.

In a separate study, patients with EGFR-expressing metastatic colorectal cancer were randomized to first-line FOLFOX-4 plus cetuximab or placebo. The participants did not differ in response rate or progression-free survival. However, in patients with *KRAS* wild-type tumors, the response rate was 61% vs. 37% and progression-free survival was 7.7 vs. 7.2 months. In contrast, patients with *KRAS* mutant tumors showed progression-free survival of 5.5 vs. 8.6 months [317].

Panitumumab

Panitumumab is approved for use in patients with chemotherapy-refractory metastatic colorectal cancer. In clinical trials, panitumumab as single agent or combination therapy demonstrated improvements in progression-free survival and overall survival comparable to cetuximab [318; 319; 320].

Regorafenib

The safety and efficacy of regorafenib was evaluated by a single clinical trial of 760 patients with previously treated metastatic colorectal cancer. Participants were randomized to regorafenib or placebo plus best supportive care and showed a median overall survival of 6.4 vs. 5.0 months [321].

Second-Line Chemotherapy

Second-line chemotherapy with irinotecan in patients treated with 5-FU/leucovorin as first-line therapy led to improved overall survival versus infusional 5-FU or supportive care [322]. Conversely, patients who progressed on irinotecan and 5-FU/leucovorin and then received FOLFOX4 or 5-FU/leucovorin showed a median time-to-progression of 4.6 vs. 2.7 months [304]. Tucatinib plus trastuzumab had clinically meaningful anti-tumor activity and favorable tolerability. This combination is the first FDA-approved anti-HER2-positive regimen for metastatic colorectal cancer [235].

TREATMENT OF LIVER METASTASES

Approximately 15% to 25% of patients with colorectal cancer will present with liver metastases at diagnosis, and another 25% to 50% will develop metachronous hepatic metastasis after resection of the primary tumor. Only a small proportion of patients with hepatic metastases are candidates for surgical resection, but advances in tumor ablation techniques and regional and systemic chemotherapy administration have now expanded the treatment options [203].

Diagnosis

In general, the imaging appearances of liver metastases are nonspecific, requiring biopsy specimens for histologic diagnosis. CT is the imaging modality of choice for evaluating hepatic metastases. CT permits better evaluation of the involvement of extrahepatic tissues, including the bones, bowel, lymph nodes, and mesentery. MRI may be superior to CT and PET scan for detection and characterization of small lesions [323].

Surgery

Advances in chemotherapy have steadily improved survival in patients with colorectal cancer liver metastases, with trials now reporting a median survival of 20 months. However, with chemotherapy alone, five-year survival has been poor historically—less than 1%. This has been modestly improved in trials using FOLFOX and/or FOLFOXIRI, with five-year survival rates of 5% to 10% [300; 324]. Despite advances in chemotherapy, liver resection is the best option for achieving long-term survival and may be curative in stage IV disease confined to the liver [325; 326]. Resection of liver metastases with clear margins is associated with a 5-year survival rate of 45% and 10-year overall survival rate of 25% [285; 327; 328; 329].

According to the National Comprehensive Cancer Network, hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer. Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.

(https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

Hepatic metastases are considered suitable for resection based on the following criteria [203]:

- Limited number of lesions
- Intrahepatic location of lesions
- Lack of major vascular involvement
- Absent or limited extra-hepatic metastases
- Sufficient functional hepatic reserve

Cancer Care Ontario recommends that patients with extra-hepatic metastases limited to the lungs may be suitable for liver resection if all pulmonary metastases are eradicated [327]. Studies of patients with combined liver and lung resection found three-year survival of 36% to 59%, and five-year survival of 9% to 74% [330]. The study showing 74% survival at five years calculated survival from the first metastasectomy instead of the more common second metastasectomy (usually the lungs). Median survival was 42 months when calculated from last metastasectomy [331]. Pooled data from all studies showed five-year survival of 30% [330]. Routine liver resection is not recommended in patients with portal nodal disease or non-pulmonary extra-hepatic metastases [327].

Liver resection is recommended in patients with initially unresectable liver metastases sufficiently downstaged by neoadjuvant chemotherapy [203]. If complete resection has been achieved, adjuvant chemotherapy should be used; neoadjuvant chemotherapy in patients without extra-hepatic metastases led to complete resection in 15% to 36%, and the five-year survival in these patients (33% to 42%) is similar to survival in patients with liver metastases considered resectable without chemotherapy [203; 330]. Consensus is lacking on the best regimen to convert isolated liver metastases from unresectable to resectable [203].

Resection of all lesions, including those with radiographic complete response, is recommended when technically feasible and an adequate functional liver remnant can remain. When a lesion with radiographic complete response is present in an unresectable portion of the liver, surgery may still be an option if all other visible disease can be resected. Adjuvant chemotherapy should also be considered. Closely follow the lesion to allow localized treatment or further resection for in-situ recurrence [327].

Perioperative Chemotherapy

Cancer Care Ontario recommends perioperative chemotherapy for patients with resectable liver metastases and extra-hepatic metastases amenable to resection with clear margins [327]. However, the role of adjuvant chemotherapy in potentially curative liver metastases resection is uncertain [203]. Before FOLFOX and FOLFIRI were introduced, two trials randomized patients after resection of liver metastases to 5-FU/leucovorin or observation. Both studies closed early due to poor accrual, but some data were obtained. Patients randomized to 5-FU/leucovorin or observation had five-year disease-free survival of 33.5% vs. 26.7% and overall survival of 51.1% vs. 41.1% [332]. In patients randomized to post-surgery 5-FU/leucovorin, the progression-free survival was 27.9 months compared with 18.8 months in the observation group [333].

Since the introduction of FOLFOX and FOLFIRI, multiagent chemotherapy has been evaluated as adjuvant therapy following resection of colorectal cancer liver metastases. In one study, patients randomized to 5-FU/leucovorin or FOLFIRI showed disease-free survival of 21.6 vs. 24.7 months; disease-free survival and overall survival were statistically comparable [334].

In another study, patients with up to four resectable liver metastases received perioperative FOLFOX (six cycles before and after surgery) or surgery alone. The progression-free survival was 42.4% vs. 36.2%. Reversible postoperative complications were more frequent after chemotherapy than surgery alone (25% vs. 16%), and there was one fatality after chemotherapy versus two fatalities after surgery [335].

Based on these findings, some physicians feel perioperative therapy is reasonable [203]. However, improved overall survival from resection plus chemotherapy has not been found.

Intra-Arterial Chemotherapy after Liver Resection

Hepatic intra-arterial chemotherapy with floxuridine for liver metastases has shown higher overall response rates but no consistent improvement in survival compared with systemic chemotherapy [203]. In one trial, patients receiving curative liver resection were randomized to combined hepatic intra-arterial floxuridine and dexamethasone plus systemic 5-FU/leucovorin or to systemic 5-FU/leucovorin alone. Combined therapy improved two-year progression-free survival (57% vs. 42%) and overall survival (86% vs. 72%) but not median survival (72.2 vs. 59.3 months) [336].

A meta-analysis of randomized trials of fluoropyrimidine systemic therapy found no survival advantage. Furthermore, hepatic intra-arterial therapy is associated with increased local toxic effects, including liver function abnormalities and fatal biliary sclerosis [337].

Radiofrequency Ablation

Radiofrequency ablation (RFA) has emerged as a safe technique (2% major morbidity and less than 1% mortality rate) that may provide for long-term tumor control [203; 338]. With RFA, high-frequency alternating current is delivered through needle electrodes inserted into the hepatic tumor area. The generated heat induces localized coagulative necrosis and tissue destruction. RFA is performed under imaging guidance, and the patient receives local or general anesthesia [339].

With hepatic colorectal cancer metastases, RFA is indicated as primary treatment in patients medically unfit for surgery; when the number, location, and size of metastases contraindicate resection; for treatment of post-resection recurrence; and as resection adjunct to ablate small-volume colonies in the future remnant liver. The National Institute for Health and Clinical Excellence (NICE) concluded in 2009 that RFA safety and efficacy evidence was sufficient to support its use in patients unfit or unsuitable for hepatic resection and in patients with previous hepatic resection [339].

Other Local Ablation

Cryosurgical ablation is an option for patients with tumors that cannot be resected and for patients who are not candidates for liver resection [340; 341]. Other local ablative techniques include embolization and interstitial radiation therapy [203; 342]. Patients with limited pulmonary metastases, or with both pulmonary and hepatic metastases, may also be considered for surgical resection, with five-year survival possible in select patients [343].

TREATMENT-INDUCED TOXICITY AND COMPLICATIONS

According to the results of one systematic review and meta-analysis of chemotoxicity in patients with colorectal cancer, 45.7% experienced overall moderate-to-severe toxicities, with gastrointestinal toxicity (22.9%) and neuropathy or neutropenia (17.9%) being the most common [344]. Risk factors for toxicity included malnutrition, frailty, impaired immune or hepatorenal functions, low gut lactobacillus levels, age, female sex, aggressive chemotherapy, and low quality of life [344].

Chemotherapy-Induced Bone Marrow Suppression

Neutropenia, thrombocytopenia, and anemia may develop with the chemotherapeutic agents used in colorectal cancer treatment. Management of these short-term complications is temporary drug cessation and supportive treatment until recovery of bone marrow function [174].

Oxaliplatin-Associated Hepatotoxicity

Elevations in serum liver enzymes are common during treatment with oxaliplatin. Oxaliplatin-induced sinusoidal obstruction syndrome (SOS) (formerly known as hepatic veno-occlusive disease) has become a key concern for patients receiving the agent for colorectal cancer [345].

Chemotherapy-Associated Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, and/or abdominal pain commonly occur with chemotherapeutic agents. Management is symptomatic, with loperamide for diarrhea, antiemetics for nausea and vomiting, and analgesia for pain [174].

Chemotherapy-Associated Alopecia

Alopecia is a short-term adverse effect of certain chemotherapies. This effect will resolve with cessation of treatment, but in the interim, management is largely cosmetic.

Cetuximab-Associated Rash

Acneiform rash is very common in patients being treated with cetuximab. It primarily occurs on the face and upper torso, often improves with continued treatment, and is reversible. This complication is associated with improved chance of treatment response independent of *KRAS* status [174].

Radiation Therapy-Associated Fecal Incontinence

Loose stool, urgency, and fecal incontinence are common after radiation therapy for rectal cancer [174]. Patients should be prepared for this long-term complication.

Bladder Dysfunction after Rectal Excision

Bladder dysfunction can result from damage to the pelvic nerves during rectal cancer surgery. Symptoms can include urinary urgency, incontinence, and retention. Urinary catheterization may be required to relieve retention [174].

Erectile Dysfunction after Rectal Excision

Erectile dysfunction can also occur due to pelvic nerve damage. In one study of 28 men treated for colorectal cancer, 24 reported experiencing erectile dysfunction after treatment (i.e., chemotherapy, radiation, and/or surgery) [346]. Almost none of the men in the study received adequate care and education related to this complication.

Oxaliplatin-Associated Pulmonary Fibrosis

Pulmonary fibrosis occurs in less than 1% of patients being treated for colorectal cancer [174]. This generally presents as dry cough, dyspnea, basal crepitations, and pulmonary infiltrates on chest x-ray or CT.

Oxaliplatin-Associated Neuropathy

Neurotoxicity is a common adverse effect of oxaliplatin, usually presenting as acute or chronic peripheral neuropathy. The acute form develops in more than 90% of patients, with usual onset during or shortly after the first few infusions. Symptoms include paresthesias and dysesthesias in the hands, feet, and perioral region, and may be exacerbated by cold. It is self-limiting [174].

The chronic form is a cumulative axonal sensory neuropathy and may be dose limiting. The neuropathy is reversible in most patients after halting treatment. No intervention has shown definitive prevention of neurotoxicity.

Adverse Effects of Anti-EGFR Agents

Anti-EGFR agents have a specific adverse effect profile primarily involving skin toxicities. Electrolyte abnormalities also occur with these agents, especially magnesium-wasting syndrome. Cetuximab is associated with an infusion reaction caused by the immunogenicity of the chimeric antibody. The most prominent adverse effects of anti-EGFR agents are skin lesions (e.g., acneiform eruption, paronychial inflammation) and hair abnormalities (including a marked increase in the length of eyelashes). These are sometimes dose-limiting complications that, while not fatal, can greatly interfere with patients' quality of life. The development of skin toxicities (particularly more intense reactions) has actually been associated with better outcomes of cetuximab and panitumumab. Preliminary evidence shows benefit with use of a pre-emptive prophylactic skin treatment regimen of skin moisturizers, sunscreen, topical steroids, and doxycycline [237; 347]. The risk of high-grade skin toxicity tends to be elevated for patients in which treatment duration is longer [348].

POST-TREATMENT FOLLOW-UP

After patients with colorectal cancer finish their treatment, they are often discharged from specialist care, with follow-up performed by community-based family physicians or institution-based, nurse-coordinated care. As there is a transfer of responsibilities, it is important to have guidelines for the follow-up of these patients. A treatment plan from the specialist should be sent to the patient's other providers, particularly primary care providers, and it should include clear directions on appropriate follow-up [349].

Postoperative surveillance of colorectal cancer is essential, and the objectives are to assess initial treatment efficacy, detect synchronous or metachronous malignancies, and identify potentially curable recurrent or metastatic cancers [350]. The benefits from routine, periodic assessments following colorectal cancer treatment include earlier identification and management of recurrent disease. Clinical trials have shown a significant survival advantage with more intensive follow-up protocols [350; 351].

Several guidelines for surveillance of patients following resection of stage II/III colorectal cancer have been published. Due to minimal available and current data, few surveillance guidelines have been published for patients with stage I or resected metastatic disease [349].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Comprehensive Cancer Network recommends survivors of colorectal cancer be encouraged to maintain a healthy body weight throughout life; adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week); consume a healthy diet with emphasis on plant sources; eliminate or limit alcohol consumption; and quit smoking.

(https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Last accessed March 21, 2025.)

Level of Evidence: 2a (Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

Post-Resection Colon Cancer

Outcomes from several large clinical trials were pooled and analyzed and demonstrated that following resection of the primary tumor, 85% of colon cancer recurrences occur within three years and 95% occur within five years. These results underscored the importance of regular surveillance for a minimum of five years following the resection of stage II and III colon cancer [349]. Accordingly, several professional organizations have published updated practice recommendations for surveillance of patients with resected stage II and III colon cancer. The recommendations by the ASCO, the NCCN, and the joint European Society of Medical Oncology and Japanese Society of Medical Oncology (ESMO/JSMO) are broadly similar but differ on some parameters (***Table 12***) [349; 352].

Post-Resection Rectal Cancer

Guidelines for surveillance of patients following resection of stage II/III colon and rectal cancer have been produced by Cancer Care Ontario and endorsed by the ASCO. Many recommendations for patients with stage II/III rectal cancer are the same as those described for patients with colon cancer [353]. A medical history, physical examination, and CEA testing should be performed every six months for five years. In addition to abdominal and chest CT imaging, pelvic CT should be performed every 6 to 12 months for two to three years, then annually until five years from surgery.

Rectosigmoidoscopy should be performed every six months for two to five years in patients who did not receive pelvic radiation [353]. In the absence of complete pre-diagnosis colonoscopy, a colonoscopy should be done as soon as is reasonable after completing adjuvant therapy and within six months of completing primary treatment. New and persistent or worsening symptoms, such as pelvic pain, sciatica, and difficulty urinating or defecating, may indicate rectal cancer recurrence.

Carcinoembryonic Antigen

Measurement of the serum glycoprotein CEA as a tumor marker for colorectal cancer has been used to help guide patient management and follow-up. Serum CEA testing is not valuable in screening for colorectal cancer because of its low sensitivity and specificity [354]. Use of postoperative CEA testing is usually limited to patients who may benefit from further intervention, including [353]:

- Patients with stage II or III colorectal cancer
- Patients who would be candidates for resection of liver metastases

PRACTICE RECOMMENDATIONS FOR RESECTED STAGE II/III COLON CANCER SURVEILLANCE			
Parameter	**Organization**		
	ASCO	**NCCN**	**ESMO/JSMO**
History and physical exam	Every 3 to 6 months for 3 years, then every 6 months until 5 years	Every 3 to 6 months for 2 years, then every 6 months until 5 years	Every 3 to 6 months for 3 years, then every 6 to 12 months in years 4 and 5
Carcinoembryonic antigen (CEA)	Every 3 months for 3 years[a]	Every 3 to 6 months for 2 years, then every 6 months until 5 years	Every 3 to 6 months for 3 years, then every 6 to 12 months in years 4 and 5
Chest CT[a]	Annually for 3 years	Annually for 5 years	Every 6 to 12 months for first 3 years
Colonoscopy[b]	At 1 year, then every 5 years, based on previous colonoscopy findings	At 1, 3, and 5 years if negative	At 1 year after surgery, then every 3 to 5 years thereafter
Abdominal CT[a]	Annually for 3 years	Annually for 5 years, including pelvic scan	Every 6 to 12 months for first 3 years
[a]For patients at high risk for recurrence (e.g., lymphatic/venous invasion, poorly differentiated tumor) [b]Colonoscopy is indicated 3 to 6 months postoperatively if preoperative colonoscopy was not performed due to obstructing lesion. Otherwise, colonoscopy should be done after 1 year. If abnormal, repeat in 1 year; if no advanced adenoma (e.g., villous polyp, polyp >1 cm, high-grade dysplasia), repeat in 3 years, then every 5 years.			
Source: [349; 352]			*Table 12*

Patient Support after Apparently Curative Resection

The NICE recommends offering follow-up for the first three years to all patients with primary colorectal cancer undergoing treatment with curative intent [251]. Follow-up should begin at an outpatient clinic visit four to six weeks after potentially curative treatment. Regular surveillance with colonoscopy, CEA testing, and CT of the chest, abdomen, and pelvis, should be provided as indicated by the treating oncology team. Any clinical, radiologic, or biochemical finding suspicious of recurrent disease should initiate further testing [251]. Regular follow-up may be halted when the patient and healthcare professional have discussed and agreed that likely benefits no longer outweigh risks of further tests or when the patient can no longer tolerate further treatments.

Information about Bowel Function

After any treatment, patients should receive specific information on managing the effects of treatment on their bowel function. This could include information on incontinence, diarrhea, difficulty emptying bowels, bloating, excess flatus, diet, and where to go for help in the event of symptoms. Verbal and written information should be clearly understood by the patient and free from jargon. Information about support organizations or Internet resources may be included [251].

Culturally and Linguistically Competent Patient Education

As a result of the evolving demographics in the United States, interaction with patients for whom English is not a native language is inevitable. It is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures is being provided, the use of an interpreter should be considered.

CONCLUSION

Several critical needs regarding the care of patients with colorectal cancer have been identified. The high volume of new emerging information on colorectal cancer therapies can overwhelm clinicians who lack the time to adequately review the new information in this rapidly expanding field. However, improved clinician knowledge of the most recent research on new diagnostic and therapy modalities is required in order to improve patient outcomes and reduce side effects.

GLOSSARY

Colostomy: Surgery in which the end of the colon is passed through the abdominal wall to make the stoma [355].

Ileostomy: Surgery whereby the end of the ileum is passed through the abdominal wall to make the stoma [355].

Metachronous colorectal tumors: Primary tumors diagnosed more than six months apart [356].

Oncogene: Mutated form of a gene involved in normal cell growth, which can facilitate cancer cell growth. Gene mutations that become oncogenes arise through an inherited trait or environmental exposure to carcinogens [356].

Ostomy pouch: A removable external collection pouch attached to the stoma and worn outside the body for collection of intestinal contents or stool [355].

Ostomy surgery: Surgery of the bowel (also termed bowel diversion) involving removal of a bowel segment with the need to reroute passage of stool from the anus to and through the abdominal wall [355]. The ostomy brings the end of the intestines through an abdominal incision and attaches it to the skin, creating an opening outside the body.

Stoma: Refers to the end of the intestines that exits through the abdominal incision. Stomas range in width from 0.75–2 inches [355].

Synchronous colorectal tumors: Primary tumors diagnosed within six months of each other [356].

Tumor suppressor gene: Gene that produces a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may promote cancer [356].

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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