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86 Colorectal Cancer

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Colorectal Cancer ■ ■INCIDENCE Colorectal cancer is the most common cancer of the gastrointestinal system in the United States. In 2024, 153,000 cases are expected, with ~106,000 cases in the colon and 46,000 cases in the rectum. It is the second most common cause of death from cancer (lung cancer is first) with 53,000 expected deaths. There is a slight male predominance in the incidence of colorectal cancer, and it is more common in black Americans than white Americans. Since 1985, there has been a steady decline in the incidence of colorectal cancer in both men and women likely due to the adoption of widespread screening guidelines for colonoscopy. This decline is seen in adults older than 50. However, a steady increase in the incidence of colorectal cancer has been seen in patients under the age of 50. While in older adults a gradual shift into predominantly right-sided cancer has been noted, a gradual increase in left-sided colon and rectal cancers has been seen in patients under the age of 50. This increase in incidence has resulted in an increase in mortality rates from colorectal cancer among young adults. Colon cancer is now the leading cause of cancer death for young men age 20–49 and the second leading cause of cancer death after breast cancer for women age 40–49. ■ ■ADENOMATOUS POLYPS Most colorectal cancers arise from adenomatous polyps as opposed to a hyperplastic polyp, hamartomatous polyp, or a serrated polyp. While adenomatous polyps are clearly premalignant, only a minority of adenomatous polyps will ever develop into an adenocarcinoma. Adenomatous polyps are common in the United States and western societies, with approximately 25% of people having adenomatous

polyps by age 50. The rate steadily rises as people age, and as many as 50% of 70-year-old people will have adenomatous polyps. Less than 5% of adenomatous polyps are expected to progress to an adenocarcinoma. The vast majority of adenomatous polyps are asymptomatic and do not bleed. The risk of progression to cancer is associated with size of the polyp and the histology. Villous adenomas develop into cancer three fold more often than tubular adenomas.

■ ■MOLECULAR PATHOGENESIS The majority of colon cancers arise from a series of genetic and epi genetic events involving tumor suppressor genes and oncogenes. Three major types of molecular pathways are involved in sporadic colorectal cancer: the chromosomal instability (CIN) pathway, the mismatch repair (MMR) pathway, and the CpG island methylation pathway (CIMP). The CIN pathway is the most common molecular pathway associated with colon cancer and is characterized by early loss of the adenomatous polyposis coli (APC) gene, which is a tumor suppressor gene. Subsequent mutations in important oncogenes involving the MAP kinase pathway, such as KRAS and BRAF, are acquired sequen tially. Finally, loss of p53 tumor suppressor gene is a common final step. The defects in the MMR pathway in sporadic colon cancer are often caused by hypermethylation of the promoters for mismatch repair genes. This results in a phenotype known as microsatellite instability high (MSI-high), which is characterized by altered sizes of various mono- and di-nucleotide repeat sequences. A defect in the MMR pathway is the etiology of Lynch syndrome, which involves a germline mutation in one of the genes encoding for the proteins involved in the MMR pathway. It is critical to test for MSI-high because these tumors are dramatically sensitive to immune checkpoint inhibition and less sensitive to chemotherapy. The third major molecular pathway is the CIMP phenotype. These tumors are often right sided and associated with methylation of MLH1. They can be either MSI-high or microsat ellite stable (MSS). The three major pathways are not mutually exclu sive, and often overlapping changes can be seen in individual cancers. CHAPTER 86 Colorectal Cancer ■ ■ETIOLOGY AND RISK FACTORS Risk factors for the development of colorectal cancer are listed in Table 86-1. ■ ■HEREDITARY FACTORS AND SYNDROMES Advances in germline genotyping have made this technology more widely available to the population of patients getting colon cancer. Approximately 10% of all patients with colorectal cancer will have an inherited, germline predisposition to colorectal cancer, and this rises to ~15% of young adults with colorectal cancer (Table 86-2). The germline mutations can be divided into high penetrance and moderate penetrance based on their risk of colon cancer development. Familial Adenomatous Polyposis (FAP) FAP and its variants are due to a mutation in the APC gene located on chromosome 5q2122. It is inherited in an autosomal dominant pattern, although a sig nificant minority of cases are due to de novo mutations. FAP accounts for <1% of all colon cancer and is characterized by the development of hundreds to thousands of colonic polyps. It is diagnosed in childhood in the classical form of FAP, and colorectal cancer develops in virtually 100% of individuals if left untreated. An attenuated form of FAP is char acterized by tens of polyps and cancers developing at a later age. FAP TABLE 86-1 Risk Factors for the Development of Colorectal Cancer Diet: Animal fat, obesity Hereditary syndromes Polyposis coli MYH-associated polyposis Nonpolyposis syndrome (Lynch’s syndrome) Inflammatory bowel disease Streptococcus bovis bacteremia Tobacco use

TABLE 86-2 Heritable (Autosomal Dominant) Gastrointestinal Neoplasia Syndromes DISTRIBUTION OF POLYPS HISTOLOGIC TYPE SYNDROME Familial adenomatous polyposis Large intestine Adenoma Common — Gardner’s syndrome Large and small intestines Adenoma Common Osteomas, fibromas, lipomas, epidermoid cysts, ampullary cancers, congenital hypertrophy of retinal pigment

epithelium Turcot’s syndrome Large intestine Adenoma Common Brain tumors MYH-associated polyposis Large intestine Adenoma Common None Lynch syndrome (nonpolyposis syndrome) Large intestine (often proximal) Adenoma Common Endometrial and ovarian tumors (most frequently), gastric, genitourinary, pancreatic, biliary cancers (less frequently) Peutz-Jeghers syndrome Small and large intestines, stomach Hamartoma Rare Mucocutaneous pigmentation; tumors of the ovary, breast, pancreas, endometrium Juvenile polyposis Large and small intestines, stomach Hamartoma, rarely progressing to adenoma can be associated with extracolonic manifestations such as desmoid tumors (Gardner’s syndrome) or brain tumors (Turcot’s syndrome). Patients with classic FAP should undergo colectomy, as well as those patients with attenuated FAP that is too difficult to screen endoscopi cally. Colectomy patients with FAP should be followed for extracolonic tumors and manifestations. Chemoprevention with nonsteroidal antiinflammatory drugs (NSAIDs) can be tried because it has been asso ciated with polyp regression and delayed progression, but its overall effect on cancer prevention has not been established. PART 4 Oncology and Hematology MUTYH-Associated Polyposis (MAP) MAP is an autosomal recessive polyposis syndrome caused by a biallelic mutation in the MUTYH gene. The MUTYH gene is a base excision repair gene, and failure of base excision repair leads to somatic CG-AT transversions in multiple genes. MAP accounts for <1% of colorectal cancers. The clini cal presentation of MAP overlaps with attenuated FAP in that individu als may have tens of polyps that develop by the fifth or sixth decade of life. Individuals with MAP are at increased risk of duodenal cancers and thyroid cancer. Screening and colectomy guidelines for this syndrome are less clear than for polyposis coli, but annual to biennial colonoscopic surveillance is generally recommended starting at age 25–30 years. Lynch Syndrome Lynch syndrome, previously known as heredi tary nonpolyposis colon cancer, is the most common inherited pre disposition to colorectal cancer, accounting for ~3% of all colorectal cancers, and confers an up to 17-fold risk of colorectal cancer. Lynch syndrome is due to a mutation in one of the MMR genes. The MMR genes are MLH1 (Chr 3p22), MSH2 (2p21-16), MSH6 (2p16), and PMS2 (7p22). Lynch syndrome can also occur due to deletion of the EPCAM gene, which causes loss of expression of MSH2. These muta tions are inherited in an autosomal dominant fashion. The MMR system maintains genomic integrity by correcting base substitution mismatches, and failure of the MMR system results in the accumula tion of a thousand-fold more mutations in genes that drive carcino genesis compared with MMR-proficient tumors. Lynch syndrome has multiple extracolonic manifestations including increased risk of cancers of the ovary, endometrium, stomach, small bowel, pancreati cobiliary system, genitourinary system, brain, and skin. Lynch syndrome may not be associated with multiple polyps and therefore is often unrecognized. Universal testing of colorectal tumors for defects in the MMR system is recommended and accomplished by either immunohistochemistry for MMR proteins in the tumor sample or evaluation for microsatellite instability on the tumor sample. For patients without a Lynch syndrome–associated cancer, family history is the most reliable way to recognize Lynch syndrome, and several family history criteria (Amsterdam Criteria and Revised Bethesda Criteria) have been developed. Germline testing is recommended for all patients with defects in the MMR system noted on the tumor sample or for those non-cancer-affected patients with an appropriate family history. Germline testing should be done in the context of appropriate pre- and posttest genetic counseling.

MALIGNANT POTENTIAL ASSOCIATED LESIONS Rare Various congenital abnormalities BRCA1/2 Mutation The hereditary breast and ovarian cancer syndromes due to mutations in the tumor suppressor genes BRCA1 and BRCA2 may carry an increased risk of colorectal cancer. In particular, BRCA1 mutation may confer a 1.5-fold increased risk of colorectal can cer. Currently, the evidence

is inconsistent, and therefore, guidelines do not recommend increased screening. Nevertheless, BRCA carriers may have an increased risk of young adult–onset colorectal cancer, and clinicians should be aware of these data. Diet The etiology for most cases of large-bowel cancer appears to be related to environmental factors. The disease occurs more often in upper socioeconomic populations who live in urban areas. Mortality from colorectal cancer is directly correlated with per capita con sumption of calories, meat protein, and dietary fat and oil as well as elevations in the serum cholesterol concentration and mortality from coronary artery disease. Geographic variations in incidence largely are unrelated to genetic differences because migrant groups tend to assume the large-bowel cancer incidence rates of their adopted countries. Furthermore, population groups such as Mormons and Seventh Day Adventists, whose lifestyle and dietary habits differ somewhat from those of their neighbors, have significantly lowerthan-expected incidence and mortality rates for colorectal cancer. The incidence of colorectal cancer has increased in Japan since that nation has adopted a more “Western” diet. At least three hypotheses have been proposed to explain the relationship to diet, none of which is fully satisfactory. ANIMAL FATS One hypothesis is that the ingestion of animal fats found in red meats and processed meat leads to an increased propor tion of anaerobes in the gut microflora (the “microbiome”), resulting in the conversion of normal bile acids into carcinogens. This provoca tive hypothesis is supported by several reports of increased amounts of fecal anaerobes (Fusobacterium nucleatum, Bacteroides fragilis) in the stools of patients with colorectal cancer. Diets high in animal (but not vegetable) fats are also associated with high serum cholesterol, which is also associated with enhanced risk for the development of colorectal adenomas and carcinomas. INSULIN RESISTANCE The large number of calories in Western diets coupled with physical inactivity has been associated with a higher prevalence of obesity. Obese persons develop insulin resistance with increased circulating levels of insulin, leading to higher circulating concentrations of insulin-like growth factor type I (IGF-I). This growth factor appears to stimulate proliferation of the intestinal mucosa. FIBER Contrary to prior beliefs, the results of randomized trials and case-controlled studies have failed to show any value for dietary fiber or diets high in fruits and vegetables in preventing the recurrence of colorectal adenomas or the development of colorectal cancer. The weight of epidemiologic evidence, however, implicates diet as being the major etiologic factor for colorectal cancer, particularly diets high in animal fat and in calories.

■ ■INFLAMMATORY BOWEL DISEASE (CHAP. 337) Colon and rectal cancers (but not anal cancers) are more common in patients with inflammatory bowel disease (IBD). Most of the data supporting this come from patients with ulcerative colitis. The risk of colorectal cancer in a patient with IBD is relatively small during the first 10 years of the disease but then appears to increase at a rate of ~0.5–1% per year. Cancer may develop in 8–30% of patients. The risk is higher in patients with more extensive, more severe, and longer-lasting colitis. The data are less consistent with Crohn’s disease, but this may be due to the difficulty in distinguishing the two entities and also the different amount of pancolitis in the two diseases. The molecular pathogenesis of colorectal cancer arising from IBD appears to be distinctly different from sporadic cancers. For instance, K-ras and APC mutations appear to be less common in colon cancers arising in IBD patients. Cancer surveillance strategies in patients with IBD are unsatisfac tory due to the lack of the classic polyp-to-cancer sequence. Symptoms such as bloody diarrhea, abdominal cramping, and obstruction, which may signal the appearance of a tumor, are similar to the complaints caused by a flare-up of the underlying inflammatory disease. Surveil lance for colorectal cancer in patients with IBD is highly technical and requires management by physicians specializing in this area. In patients with

longstanding ulcerative colitis, surgical removal of the colon (sub total or total) eliminates or significantly reduces the risk of colorectal cancer depending on the extent of the operation. In patients undergo ing subtotal colectomy with preservation of the rectum, continued surveillance of the remaining rectum is required. ■ ■OTHER HIGH-RISK CONDITIONS Tobacco Use Cigarette smoking is linked to the development of colorectal adenomas, particularly after >35 years of tobacco use. No biologic explanation for this association has yet been proposed. Alcohol Use Moderate to excessive alcohol consumption has been associated with an increased risk of colorectal cancer. It is difficult to tease out the effect compared with other lifestyle risk factors. Obesity, Insulin Resistance, and Diabetes Mellitus Mul tiple studies demonstrate an increased risk of colorectal cancer in obese individuals. Additionally, diabetes is associated with an increased risk of colorectal cancer. This has led to a theory that metabolic syndrome and hyperinsulinemia are risk factors for the development of colorectal cancer. Vitamin D Deficiency Multiple studies have demonstrated an association between low levels of vitamin D and colon cancer. Never theless, no evidence suggests that vitamin D supplementation results in fewer colon cancers. ■ ■PRIMARY PREVENTION Several orally administered compounds have been assessed as possible inhibitors of colon cancer. The most effective class of chemopreventive agents is aspirin and other NSAIDs, which are thought to suppress cell proliferation by inhibiting prostaglandin synthesis. Regular aspirin use as demonstrated in randomized studies reduces the risk of colon adenomas. Regular aspirin use in cohort studies has demonstrated reduced incidence of colon cancer. However, prospective trials using aspirin to prevent colon cancer have had conflicting results in part due to the delayed effects of aspirin on colon carcinogenesis; prevention may increase with the duration and dosage of aspirin, and the effects may take years to manifest. Meta-analyses have suggested that regular aspirin use prevents colon cancer. However, given the potential side effects of aspirin, regular use of aspirin is an individualized decision. Antioxidant vitamins such as ascorbic acid, tocopherols, and β-carotene are ineffective at reducing the incidence of subsequent adenomas in patients who have undergone the removal of a colon adenoma. Estrogen replacement therapy has been associated with a reduction in the incidence of colorectal cancer in women but not mor tality from colorectal cancer. ■ ■SCREENING The rationale for colorectal cancer screening programs is that the removal of adenomatous polyps will prevent colorectal cancer and that

TABLE 86-3 Screening Strategies for Colorectal Cancer Digital rectal examination Stool testing • Occult blood • Fecal DNA Imaging • Contrast barium enema • Virtual (i.e., computed tomography colonography) Endoscopy • Flexible sigmoidoscopy • Colonoscopy earlier detection of localized, superficial cancers in asymptomatic indi viduals will increase the surgical cure rate. It is important to note that screening studies did not take into account the presence of inherited predisposition and germline genetics. Due to the rise in incidence of colorectal cancer in younger adults, the U.S. Preventative Services Task Force updated their screening recommendations in 2021 and lowered the age for recommended screening to 45. Screening strategies for colorectal cancer that have been examined during the past several decades are listed in Table 86-3. CHAPTER 86 The rationale for screening asymptomatic individuals has under gone change over many decades, and it is important to understand how that change influences our current approach. Initially, patients were screened for the presence of occult blood in the stool, which would then lead to colonoscopy. Unfortunately, even when performed opti mally, the fecal occult blood test has major limitations as a screening technique. About 50% of patients with documented colorectal cancers have a negative fecal occult blood test, consistent with the intermittent bleeding pattern of these tumors. When random cohorts of asymptom atic persons have been tested, 2–4% have fecal occult blood–positive

stools. Colorectal cancers have been found in <10% of these “test-posi tive” cases, with benign polyps being detected in an additional 20–30%. Thus, a colorectal neoplasm will not be found in most asymptomatic individuals with occult blood in their stool. Nevertheless, prospec tively controlled trials have shown a statistically significant reduction in mortality rate from colorectal cancer for individuals undergoing annual stool guaiac screening. However, this benefit only emerged after many years of follow-up and was due to colonoscopic intervention, which likely provided the opportunity for cancer prevention through the removal of potentially premalignant adenomatous polyps because the eventual development of cancer was reduced by 20% in the cohort undergoing annual screening. Colorectal Cancer Due to the importance of endoscopic screening in preventing death from colon cancer, many societies shifted from testing stool for the presence of occult blood to offering endoscopic screening for the asymptomatic population. Colonoscopy evaluates the entire colon but is associated with more complications, the need for cathartics to remove stool from the colon, the need for sedation in most cases, and more overall expense. Sigmoidoscopy does not require an enema, is associated with less perforations and morbidity, does not require sedation, and can identify patients at high risk of needing a full colo noscopy if polyps or cancer is found in the rectum or sigmoid colon. The recommendation for the inclusion of flexible sigmoidoscopy is strongly supported by randomized studies evaluating a one-time sig moidoscopy as opposed to usual standard of care. A reduction in both colorectal cancer incidence and colorectal cancer mortality is obtained for patients undergoing screening, and this effect persists for >15 years. One of the downsides of using screening sigmoidoscopy alone is that in the presence of a normal sigmoidoscopy, ~1.5% of individuals will have either a high-risk polyp or adenocarcinoma in the proximal colon. The issue of missing advanced neoplasms in the proximal colon when using only sigmoidoscopy was addressed by increased frequency of sig moidoscopy (every 5 years instead of every 10 years for colonoscopy) and the use of annual fecal immunohistochemical test (FIT) for occult blood. While randomized studies evaluating the combination are

lacking, most professional societies offer this approach as an alternative to colonoscopy screening.

With the appreciation that the carcinogenic process leading to the progression of the normal bowel mucosa to an adenomatous polyp and then to a cancer is the result of a series of molecular changes, investi gators have examined fecal DNA for evidence of mutations associated with such molecular changes as evidence of the occult presence of precancerous lesions or actual malignancies. A multitarget stool DNA test evaluates stool that is collected at home for DNA changes including methylation combined with a FIT test. This multitarget stool DNA test, when done in patients undergoing colonoscopy, has a >90% specificity and sensitivity for detecting a colorectal adenocarcinoma but a <50% sensitivity for detecting an advanced precancerous lesion. The use of imaging studies to screen for colorectal cancers has also been explored. Air contrast barium enemas had been used to identify sources of occult blood in the stool prior to the advent of fiberoptic endoscopy; the cumbersome nature of the procedure and inconve nience to patients limited its widespread adoption. The introduction of computed tomography (CT) scanning led to the development of virtual (i.e., CT) colonography as an alternative to the growing use of endoscopic screening techniques. Virtual colonography requires use of colon cathartic bowel preparations and appears to have good accu racy at detecting large lesions (>10 mm) but has not been compared in a randomized study with colonoscopy. Two other disadvantages of virtual colonoscopy are that it may have interuser variability and any findings need to be followed up with a colonoscopy

requiring a second bowel cathartic preparation. PART 4 Oncology and Hematology Most professional societies agree that screening for colon cancer should begin at age 45 for patients at average risk. In the United States, there is ~60% compliance with screening and the emphasis is on get ting patients screened initially with either direct observation using sig moidoscopy or colonoscopy or indirect tests such as FIT or multitarget stool DNA. The best combination approach and frequency of screening likely will involve risk stratification factors in the future. ■ ■CLINICAL FEATURES Presenting Symptoms Symptoms vary with the anatomic loca tion of the tumor. Because stool is relatively liquid as it passes through the ileocecal valve into the right colon, cancers arising in the cecum and ascending colon may become quite large without resulting in any obstructive symptoms or noticeable alterations in bowel habits. Lesions of the right colon commonly ulcerate, leading to chronic, insidious blood loss without a change in the appearance of the stool. Consequently, patients with tumors of the ascending colon often pres ent with symptoms associated with hypochromic, microcytic anemia, indicative of iron deficiency. As a result, the unexplained presence of iron-deficiency anemia in any adult (with the possible exception of a premenopausal, multiparous woman) mandates a thorough endoscopic and/or radiographic visualization of the entire large bowel (Fig. 86-1). Because stool becomes more formed as it passes into the transverse and descending colon, tumors arising there tend to impede the pas sage of stool, resulting in the development of abdominal cramping, occasional obstruction, and even perforation. Radiographs and CTs of the abdomen often reveal characteristic annular, constricting lesions (“apple-core”) (Fig. 86-2). Cancers arising in the rectosigmoid are often associated with hematochezia, tenesmus, and narrowing of the caliber of stool. While these symptoms may lead patients and their physicians to suspect the presence of hemorrhoids, the development of rectal bleeding and/or altered bowel habits demands a prompt digital rectal examination and sigmoidoscopy. Staging, Prognostic Factors, and Patterns of Spread The prognosis for individuals having colorectal cancer is related to the depth of tumor penetration into the bowel wall and the presence of both regional lymph node involvement and distant metastases. These variables are incorporated into a TNM classification method, in which T represents the depth of tumor penetration, N the presence of lymph node involvement, and M the presence or absence of distant

FIGURE 86-1 Double-contrast air-barium enema revealing a sessile tumor of the cecum in a patient with iron-deficiency anemia and guaiac-positive stool. The lesion at surgery was a stage II adenocarcinoma. metastases (Fig. 86-3). Superficial lesions that do not involve regional lymph nodes and do not penetrate through the submucosa (T1) or the muscularis (T2) are designated as stage I (T1–2N0M0) disease; tumors that penetrate through the muscularis but have not spread to lymph nodes are stage II disease (T3–4N0M0); regional lymph node involve ment defines stage III (TXN1–2M0) disease; and metastatic spread to sites such as liver, lung, or bone indicates stage IV (TXNXM1) disease. Unless gross evidence of metastatic disease is present, disease stage cannot be determined accurately before surgical resection and patho logic analysis of the operative specimens. The majority of recurrences occur within the initial 5 years after resection. Occasionally tumors can recur between 5 and 10 years after resection, and this appears to be more common with rectal cancer FIGURE 86-2 Annular, constricting adenocarcinoma of the descending colon. This radiographic appearance is referred to as an “apple-core” lesion and is always highly suggestive of malignancy.

Stage I II T1 T2 No deeper than submucosa Not through muscularis Extent of tumor

90% 5-year survival 95% 23% Colon Stage at presentation Rectal 34% Mucosa Muscularis mucosa Submucosa Muscularis propria Serosa Fat Lymph nodes FIGURE 86-3 Staging and prognosis for patients with colorectal cancer. than colon cancer. The likelihood for 5-year survival in patients with colorectal cancer is stage-related (Fig. 86-3), and the survival rates per stage have been improving in the past several decades. The most plau sible explanation for improved survival is the more thorough evalua tion for metastatic disease and the positive effects of chemotherapy for treatment of adjuvant and systemic disease. A minimum of 12 sampled lymph nodes is thought necessary to accurately define tumor stage, and the more nodes examined, the better reliability that a patient is either node negative or node positive. Other predictors of a poor prog nosis after a total surgical resection include tumor penetration through the bowel wall into pericolic fat, poorly differentiated histology, per foration and/or tumor adherence to adjacent organs (increasing the risk for an anatomically adjacent recurrence), and venous invasion by tumor (Table 86-4). Tumors with microsatellite instability or defects in MMR have improved prognosis presumably due to an enhanced immune response against the tumor. Tumors arising in the left colon are associated with a better prognosis than those appearing in the right colon, likely due to differences in molecular patterns. In contrast to most other cancers, the prognosis in colorectal cancer is not influenced by the size of the primary lesion when adjusted for nodal involvement and histologic differentiation. Colorectal cancer generally spreads to the liver, lungs, and peritoneal cavity. The liver represents the most frequent visceral site of metastasis; it is the initial site of distant spread in one-third of recurring colorectal TABLE 86-4 Predictors of Poorer Outcomes Following Total Surgical Resection of Colorectal Cancer Tumor spread to regional lymph nodes Number of regional lymph nodes involved Tumor penetration through the bowel wall Poorly differentiated histology Perforation Tumor adherence to adjacent organs Venous invasion Preoperative elevation of CEA titer (>5 ng/mL) Specific chromosomal deletion (e.g., mutation in the b-raf gene) Right-sided location of primary tumor Abbreviation: CEA, carcinoembryonic antigen.

Staging of colorectal cancer III IV N1 N2 M T3 ≥4 lymph node metastases 1–3 lymph node metastases Distant metastases Through muscularis 50–70% 25–60% <5% 70–85% 26% 20% 31% 26% 15% 25% CHAPTER 86 Colorectal Cancer cancers and is involved in more than two-thirds of such patients at the time of death. It can spread to the brain and bones but not typically as an initial site of metastatic disease, but rather after years of having systemic metastases. Nevertheless, prompt evaluation of signs and symptoms of bone and brain involvement should be efficiently done because lack of prompt treatment can have devastating consequences (e.g., cord compression, brain hemorrhage). TREATMENT Colorectal Cancer Staging should consist of a complete blood count, comprehensive metabolic panel, serum carcinoembryonic antigen (CEA), and a chest, abdomen, and pelvic CT scan. Additional imaging such as magnetic resonance imaging (MRI) and positron emission tomog raphy (PET) scan can be dependent on the findings of the CT scan. When possible, a colonoscopy of the entire large bowel should be performed to

identify synchronous neoplasms and/or polyps. While surgical resection is the standard of care for cure in patients with localized disease, initial treatment of colorectal cancer when possible should be delayed until MMR status or microsatellite sta bility status is known. MSI-high rectal cancers can be treated for cure with checkpoint inhibitors (PD-1 antibodies) without the need for surgery, radiation, and chemotherapy. Studies are underway involving management of MSI-high colon cancers with checkpoint inhibition. LOCALIZED COLON CANCER For the vast majority of patients with MSS colon adenocarcinoma, initial surgical resection is the standard of care. Surgery with minimally invasive techniques such as laparoscopy and robotic approaches has largely replaced open approaches. Following com plete surgical resection, patients with stage I disease are considered cured. Patients with high-risk stage II and stage III colon cancer are considered for the appropriateness of adjuvant chemotherapy. The standard adjuvant approaches generally improve overall survival and cure rates by ~30%. Adjuvant chemotherapy for 3–6 months either with single-agent fluoropyrimidine (IV or oral) or in combination with oxaliplatin is considered the standard adjuvant treatment for MSS colon cancer.

Following recovery from a complete resection, patients should be observed carefully for 5 years using physical examinations and blood chemistry measurements at regular intervals. Some authorities favor measuring plasma CEA levels at 3-month inter vals because of the sensitivity of this test as a marker for otherwise undetectable tumor recurrence. The value of periodically assessing plasma for the presence of circulating tumor DNA as a biomarker for residual or recurrent disease is under study. Subsequent endo scopic surveillance of the large bowel 1 year after resection and then usually every 3 years is indicated because patients who have been cured of one colorectal cancer have a 3–5% probability of develop ing an additional bowel cancer during their lifetime and a >15% risk for the development of adenomatous polyps. Anastomotic (“sutureline”) recurrences are infrequent in colorectal cancer patients, provided the surgical resection margins were adequate and free of tumor. The value of periodic CT scans of the abdomen, assess ing for an early, asymptomatic indication of tumor recurrence, is uncertain; however, CT has been recommended semi-annually to annually for the first 3 postoperative years.

LOCALIZED RECTAL CANCER For the vast majority of patients with MSS rectal adenocarcinoma, surgical resection is considered the standard curative therapy. In addition to the staging above, pelvic MRI should be standard in staging for all patents with rectal cancer to assess mesorectal mar gin and nodal status. Surgical resection can either be a low anterior resection (LAR) or an abdominal-perineal resection (APR). An APR requires a permanent colostomy due to resection of the anal sphincter. Unlike colon cancer, rectal cancers (defined as tumor at or below the peritoneal reflection) have an increased risk of local recurrence after surgery. The risk of local recurrence increases with stage and closeness to the mesorectal border and decreases with distance from the anus. Thus, tumors requiring an APR have a high risk of local recurrence. The risk of local recurrence can be reduced with preoperative chemotherapy and radiation. Patients with stage II and III rectal cancer are deemed to have a risk high enough to warrant consideration of preoperative therapy. PART 4 Oncology and Hematology Two new treatment paradigms have emerged for patients with rectal cancer in specific circumstances. The first situation involves patients in whom the consequences of radiation therapy are deemed unacceptable. Radiation is associated with the potential long-term side effects of radiation proctitis (increased risk in patients with IBD), small-bowel obstruction to adhesions, and malignancy (~1% risk after 10 years). Notably, radiation therapy in women causes infertility due to the effects of radiation on the uterus

even when the ovaries are not included in the radiation field. Preoperative therapy with a fluo ropyrimidine and oxaliplatin followed by surgical resection produces similar rates of local control to preoperative chemoradiation and can be considered for average-risk stage II and III rectal cancer patients. The second circumstance involves patients with stage II and III rectal cancer treated with total preoperative therapy who experience a complete clinical response. Nonoperative management can be considered in these patients because 60–70% will be cured without an LAR or APR. It is important to note that 30–40% of patients will experience a recurrence so patients need to be followed intensively in the years following chemotherapy and radiation. The majority of patients who experience a local recurrence during nonoperative management can be cured with surgery. METASTATIC COLORECTAL CANCER The first principle to note is that complete resection of metastatic disease is considered curative for patients with colorectal cancer, particularly in the setting of metastases isolated to one site (liver, lungs, peritoneum). Consultation with the appropriate surgical spe cialists is preferred before starting systemic chemotherapy. The detection of metastases should not preclude surgery to remove the primary tumor in patients with tumor-related symp toms such as gastrointestinal bleeding or obstruction but usually prompts the initiation of chemotherapy unless those symptoms are

viewed to be life-threatening. Studies have demonstrated that resec tion of the primary tumor in the setting of unresectable metastatic disease does not improve overall survival and should be done only on an ad hoc basis. Patients with MSI-high colon cancer should be treated with a checkpoint inhibitor as initial treatment. Long-term survival is pos sible in these patients, and some will have a complete response and may not ever have recurrence of their cancer. For the vast majority of patients with MSS colorectal adenocarcinoma who are not can didates for complete resection of metastatic disease, treatment with systemic chemotherapy is associated with marked improvement in overall survival compared with palliative care alone. A patient with metastatic disease lives on average for 2–3 years with systemic che motherapy, and as many as 25% of patients will live for at least 5 years on and off chemotherapy. The mainstays of therapy for patients with metastatic colon cancer are the following medications: 5-fluorouracil (5-FU; or capecitabine), irinotecan, oxaliplatin, and bevacizumab. These medications are used in combination all together (e.g., FOLIR INOX-bevacizumab or FOLFOXIRI-bevacizumab) or in partial combination (e.g., FOLFOX-bevacizumab, FOFIRI-bevacizumab). 5-FU is an inhibitor of thymidylate synthase and is used in con junction with folinic acid (leucovorin). It is metabolized by dihy dropyrimidine dehydrogenase (DPD), which is deficient in ~1% of adults. Individuals with DPD deficiency can experience increased side effects from 5-FU, especially myelosuppression and mucositis. Testing for DPD gene mutations may identify patients at high risk of DPD deficiency and toxicity from 5-FU. Irinotecan is a topoi somerase I inhibitor and is metabolized by glucuronidation in the liver. Thus, patients with UGT mutations can experience decreased clearance and enhanced toxicity, principally myelosuppression. Oxaliplatin is a platinum analogue that is metabolized generally and can cause permanent peripheral neuropathy. Bevacizumab is a monoclonal antibody against vascular endothelial growth fac tor (VEGF). Side effects of bevacizumab include hypertension, nephrotic syndrome, and impaired wound healing. Untreated hypertension from bevacizumab has been associated with posterior reversible leukoencephalopathy syndrome. Other agents with proven disease-altering effects in the meta static setting include trifluridine-tipiracil, regorafenib, and fruquin tinib. Trifluridine is a nucleoside analogue that is used with tipiracil, a thymidine phosphorylase inhibitor. Regorafenib is an oral multi targeted tyrosine kinase inhibitor, including VEGF. Fruquintinib is an oral VEFG tyrosine kinase inhibitor. Molecular genotyping of the primary tumor should be done in all patients with metastatic colon cancer if possible. Patients

without mutations of the RAS/RAF pathway can have excellent responses and prolonged survival with the addition of antibodies against epi dermal growth factor (EGF), such as cetuximab and panitumumab. These agents are often given in combination with either FOLFOX or FOLFIRI. The effect of cetuximab and panitumumab appears to be limited to left-sided colon cancers because right-sided colon cancers have upregulation of receptor tyrosine kinases that create resistance to these antibodies. The main side effects of these two antibodies are the class effects of diarrhea and acneiform rash. Cetuximab, which is partially murine, is also associated with aller gic reactions. Patients who harbor BRAF V600E mutations may have a particu larly virulent form of colon cancer that does not respond as well to standard chemotherapy. These mutations tend to occur more com monly in right-sided tumors and women. They often involve meth ylation of MLH1 and can be MMR deficient. The BRAF inhibitor encorafenib is approved for use with cetuximab in patients with BRAF-mutant colorectal cancer. HER2 overexpression can be seen in colorectal cancer, and con sideration of anti-HER2–targeted therapy is warranted. Tucatinib (HER2 tyrosine kinase inhibitor) and trastuzumab (anti-HER2 monoclonal antibody) are approved in the United States for patients with HER2-positive colorectal cancers that lack a RAS mutation.

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