**KEY POINT**

HVC
- Surveillance imaging and laboratory studies for cervical cancer survivors are recommended only if there are signs or symptoms suggestive of recurrence.

# Gastroenterological Malignancies

## Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer death in North America, yet it is largely preventable through screening. CRC screening of average-risk patients is discussed in MKSAP 18 General Internal Medicine. Most colon cancers are adenocarcinomas that begin in the inner lining and progress to involve or spread beyond the full thickness of the bowel wall, then to regional lymph nodes, and subsequently to distant organ metastases. Epidemiology, pathophysiology, risk factors (and screening high-risk patients), and clinical manifestations will be discussed in MKSAP 18 Gastroenterology and Hepatology.

Recent evidence suggests tumors on the right side of the large intestine (cecum, ascending colon, and proximal two thirds of transverse colon) have a completely different biology, likely related to embryologic origin, and a substantially worse prognosis than tumors on the left side (distal one third of transverse colon, descending colon, sigmoid colon, and rectum). Symptoms may also differ based on tumor location, with left-side tumors more likely to cause a change in bowel habits. Cancer in the cecum, with a larger lumen and less formed stool, does not generally cause a change in bowel habits until the tumor is advanced in size, but may present with iron-deficiency anemia with occult, chronic blood loss. Colon cancer at any location may also present with hematochezia, pain, or acute clinical signs from perforation or obstruction.

Approximately 15% of CRCs lack one or more mismatch repair enzymes and are known as mismatch repair deficient (dMMR)-CRC. This manifests itself as increased microsatellite instability (MSI) in the cancer cell's DNA; the terms *dMMR* and *MSI* are essentially synonymous. Most guidelines now recommend that all CRCs should be screened for dMMR or MSI. Approximately 25% of patients with dMMR tumors will have Lynch syndrome, which is associated with a high lifetime risk of CRC as well as endometrial and other cancers. Patients and family members with Lynch syndrome require formal genetic counseling and more intense cancer surveillance. Mismatch repair status or the tumor can affect treatment choices in patients with stage II or stage IV cancer as discussed below.

**KEY POINTS**

- Recent evidence suggests tumors on the right side of the large intestine have a different biology and substantially worse prognosis than tumors on the left side.

*(Continued)*

**KEY POINTS *(continued)***

- Tumors in all colorectal cancer patients should be screened for mismatch repair enzyme deficiency or microsatellite instability, which increases the risk of Lynch syndrome and other cancers.

### Staging

Staging with the TNM cancer staging system is the first step in treatment planning (**Table 45**). Evaluation includes serum carcinoembryonic antigen (CEA) in addition to routine laboratory studies; a full colonoscopy (if possible); and contrast-enhanced CT scans of the chest, abdomen, and pelvis. Rectal cancers also require a rectal MRI or endorectal ultrasonography, both of which offer more precision in assessing tumor penetration and lymph node involvement. PET scans have not been demonstrated to provide greater accuracy in staging and should not be routinely used for preoperative staging or postoperative surveillance.

### Treatment

#### Rectal Cancer

Rectal cancers without full thickness penetration of the bowel wall or enlarged lymph nodes are stage I and are treated with surgical resection. Small tumors may be resected by a transanal approach, decreasing postoperative morbidity. Unless more extensive disease is found at operation, no further treatment is warranted.

Full-thickness tumors (stage II) and involved lymph nodes (stage III) require radiation, chemotherapy, and surgery. The optimal sequencing and combining of the three treatment modalities is being studied. Attempts are made to preserve anal sphincter function, but distal rectal lesions may require an abdominal-perineal resection and permanent colostomy.

Intravenous 5-fluorouracil (5-FU) or oral capecitabine, a prodrug that is converted into 5-FU, is given concurrently with radiation therapy. The chemotherapy may be associated

**TABLE 45. Staging of Colorectal Cancer**

| Stage | Description | Approximate 5-Year Disease-Free Survival |
|---|---|---|
| I | Tumor does not invade the full thickness of bowel wall (T1, T2); lymph nodes not involved (N0) | 90%-95% |
| II | Tumor invades full thickness of the bowel and may invade into pericolonic or perirectal fat (T3, T4); lymph nodes not involved (N0) | 70%-85% |
| III | One or more lymph nodes involved with cancer (N1, N2); any T stage | 25%-70% |
| IV | Metastatic tumor spread to distant site (M1); any T stage; any N stage | 0%-10% |

with edema and erythema of the palms and soles that may progress to blistering and necrosis (hand-foot syndrome), mucositis, diarrhea, and neutropenia. Leucovorin, 5-FU, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) regimens are typically used for the chemotherapy-only portion of the treatment. Oxaliplatin often causes a peripheral neuropathy that does not resolve fully in some patients.

Following therapy, patients with rectal cancer should be evaluated at approximately 6-month intervals for up to 5 years with a history, physical examination, and serum CEA level assessment. Contrast-enhanced CT scans of the chest, abdomen, and pelvis are typically obtained annually for 5 years.

### Colon Cancer

Nonmetastatic colon cancers are managed with initial surgery. Pathologic evaluation determines further treatment.

Patients with stage II cancer lacking high-risk features, such as poorly differentiated histology, T4 primary tumor, lymphovascular invasion, inadequate lymph node sampling, poorly differentiated histology, elevated postoperative CEA, or perforation or obstruction, are unlikely to benefit from adjuvant treatment. Patients with one or more of these risk factors may be considered for adjuvant 5-FU or capecitabine. All stage II colon tumors should be assessed for MSI or dMMR, because such tumors, when stage II, are at low risk for recurrence, do not benefit from adjuvant chemotherapy, and should not be treated regardless of the presence of other potential risk factors.

FOLFOX and CAPOX, given for approximately 6 months, are equally acceptable adjuvant chemotherapy regimens and reduce the risk of cancer recurrence and death in patients with stage III cancer.

As with rectal cancer, routine evaluation and serum CEA assessment should be done at approximately 6-month intervals, with annual CT scans for up to 5 years after therapy.

Postoperative surveillance following curative resection is used to identify oligometastatic disease in the liver or lung that may be resectable. Patients with metastatic foci confined to liver or lung should be referred for surgical evaluation. Complete resection of metastatic foci may lead to cure in 25% of these patients. Contrast-enhanced CT scans of the chest, abdomen, and pelvis are recommended annually for up to 5 years postoperatively. PET scanning should not be used for routine surveillance. Colonoscopy is recommended one year after resection (or 3 to 6 months after resection if a complete colonoscopy was not done preoperatively), and then in 3 years, followed by every 5 years, unless abnormalities are found. In 2016, the United States Multi-Society Task Force on Colorectal Cancer recommended that flexible sigmoidoscopy or endoscopic ultrasound be performed every 3 to 6 months for the first 2 to 3 years after surgery in patients with rectal cancer who are at increased risk for local recurrence.

**KEY POINTS**

- Pretreatment evaluation of rectal cancer requires a rectal MRI or endorectal ultrasonography.
- PET scans should not be used for preoperative staging or postoperative surveillance in colorectal cancer. **HVC**
- Standard treatment of stages II and III rectal cancer is either chemoradiotherapy (with 5-fluorouracil or capecitabine), followed by surgery and adjuvant chemotherapy, or neoadjuvant chemotherapy followed by chemoradiotherapy, followed by surgery.
- Patients with stage II colon cancer that lacks high-risk features are unlikely to benefit from adjuvant chemotherapy. **HVC**
- Posttreatment surveillance for patients with colon cancer includes periodic history; physical examination; serum carcinoembryonic antigen level testing; and CT of the chest, abdomen, and pelvis, as early detection and resection of isolated metastatic disease can still result in cure; repeat colonoscopy should be done at 1 year, then in 3 years, followed by every 5 years.

### Metastatic Disease

All metastatic CRC requires molecular analysis for *KRAS*, *NRAS*, and *BRAF* gene mutation status as well as dMMR determination. This rarely affects the choice of first-line therapy but will define subsequent treatment options, discussed later. These tests can be done on either the primary tumor or a metastasis; rebiopsy of metastases for the purpose of these studies is rarely needed.

Patients with metastatic disease limited to the liver should be evaluated for surgical resection with curative intent. Unresectable metastatic CRC is treatable but not curable. Although chemotherapy may be palliative and even extend survival, patients who have a poor performance status may not benefit or may have unacceptable toxicity. A careful discussion should be undertaken with the patient to establish goals of care and expectations.

5-FU is at the center of most treatment regimens, with longer infusions preferable to bolus administration. Newer drugs have failed to replace 5-FU, but leucovorin is often combined with 5-FU, or capecitabine can be an alternative to 5-FU. Other cytotoxic agents used in metastatic CRC include irinotecan and oxaliplatin. The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab is often given concurrently with first-line cytotoxic chemotherapy regimens. This agent has essentially no antitumor activity in CRC on its own, but it does potentiate other chemotherapies, resulting in a modestly increased duration of progression-free survival, and in some studies, in increased duration of overall survival. Studies have shown that continuing an anti-VEGF agent with second-line chemotherapy also modestly improves overall survival. Bevacizumab commonly causes hypertension,

sometimes requiring antihypertensive medication. It also interferes with wound healing and needs to be discontinued 6 to 8 weeks before elective surgery and withheld for at least a month after surgery. Very rare but potentially life-threatening side effects include arterial thrombotic events such as myocardial infarction, cerebrovascular accidents, and gastrointestinal perforations.

Panitumumab and cetuximab are monoclonal antibodies that bind to and block activation of the epidermal growth factor receptor (EGFR). They are potentially active only in tumors that are nonmutated (wild-type) *KRAS, NRAS,* and *BRAF* genes. In addition, more recent data suggest that these agents may only have activity in tumors derived from the left side of the large intestine. The major side effect of these agents is an acneiform rash, which can be painful, pruritic, and socially debilitating. There is a tight correlation between rash and antitumor activity, and patients who have only a mild skin rash are unlikely to benefit from these agents. Anti-EGFR agents should not be used concurrently with anti-VEGF agents; two large randomized trials found an unexpected detriment with concurrent use.

Thus far, immune checkpoint inhibitors have been inactive in metastatic CRC, with the exception of those rare tumors that are metastatic and dMMR. The programmed death 1 (PD-1) receptor inhibitors pembrolizumab and nivolumab have both shown activity in such patients; however, dMMR tumors make up only 1% or 2% of metastatic CRC.

Multigene sequencing may open some experimental options, but it does not yield actionable information in terms of standard management options at this time. Thus the expense is not warranted outside of a potential research setting.

**KEY POINTS**

- All metastatic colorectal cancers require molecular analysis for *KRAS, NRAS,* and *BRAF* gene mutation status as well as mismatch repair gene deficiency, which will determine treatment after first-line therapy.
- The anti–vascular endothelial growth factor antibody bevacizumab potentiates the efficacy of 5-fluorouracil combined with either leucovorin or capecitabine in treating metastatic colon cancer, but is associated with worsening hypertension, arterial thrombosis, poor wound healing, and gastrointestinal perforation and fistula formation.

## Anal Cancer

Anal cancer is a human papillomavirus (HPV)–associated malignancy. Unlike rectal cancer, which is an adenocarcinoma, anal cancer is a squamous cell carcinoma. Anal cancer is often curable with combined radiation and chemotherapy; surgery is typically not indicated. Mitomycin plus 5-FU or capecitabine is the standard chemotherapy regimen. Although complete regression may be observed as soon as 8 weeks after radiation, responding tumors may continue to regress for up to 6 months after radiation. If tumor growth is seen after radiation, then salvage surgery with a permanent colostomy is indicated. Distant metastases are rare. When they do develop, chemotherapy with oxaliplatin, cisplatin, or carboplatin is often active.

Although HPV vaccination would be expected to be as effective at cancer prevention as it is with other HPV-related malignancies, there is no evidence that HPV vaccination plays a role in treatment or post-treatment management of patients with anal cancer. See MKSAP 18 General Internal Medicine for further discussion of HPV vaccination.

**KEY POINT**

- Anal cancer, a squamous cell carcinoma linked to human papillomavirus, is often cured by combination radiation and chemotherapy, sparing the need for surgical resection and subsequent colostomy.

## Pancreatic Cancer

There are approximately 53,000 patients diagnosed with exocrine pancreatic cancer per year in the United States. Mortality is high, with 42,000 deaths expected annually. Only patients who can undergo a complete resection have a chance of cure. When disease is unresectable because of invasion into critical vascular structures, median survival is approximately 1 year. For those with metastatic disease, median survival is typically less than half that.

Most pancreatic cancers lack a genetic predisposition, although 5% to 10% of patients have either a strong family history of pancreatic cancer, an identifiable mutation that confers increased risk, or both. Some rare familial pancreatic cancer syndromes have been recognized, including patients with *BRCA* gene mutations, but *BRCA* screening is not recommended for those without a strong family history. Chronic pancreatitis, obesity, type 2 diabetes mellitus, high red meat consumption, alcohol abuse, and tobacco use are implicated risk factors.

Painless jaundice, abdominal pain, weight loss, persistent fevers, or protracted nausea and vomiting may be presenting symptoms. Manifestations of hypercoagulability, including Trousseau syndrome (a migratory superficial thrombophlebitis of the lower extremities), chronic disseminated intravascular coagulation, deep venous thrombosis, or pulmonary embolism, may be the initial manifestations of underlying pancreatic cancer. H

A contrast-enhanced CT of the chest and abdomen (or noncontrast chest CT and abdominal MRI) are appropriate for staging and treatment planning. PET scans have not been shown to add value in pancreatic cancer and are not part of standard management. For patients whose disease is confined to the pancreas with or without involved local regional lymph nodes, resectability is the most important question. Endoscopic ultrasonography may help in staging and is used to more precisely guide diagnostic needle biopsy. Some patients with clinical features that strongly suggest malignancy may not require such preoperative biopsy, as false-negative results