Despite the existence of excellent screening and preventive strategies, colorectal carcinoma (CRC) remains a major public health problem in Western countries. ACS estimated that in 2010, 142,570 people will be diagnosed with CRC, and 51,370 will die of the disease. CRC is the third most common type of cancer in both sexes (after prostate and lung cancers in men and lung and breast cancers in women) and the second most common cause of cancer death in the United States.

About 72% of new CRCs arise in the colon, and the remaining 28% arise in the rectum. Rectal cancer is defined as cancer arising below the peritoneal reflection, up to approximately 12 to 15 cm from the anal verge.

The lifetime risk of being diagnosed with CRC in the United States is estimated to be 5.9% for men and 5.5% for women.

**Epidemiology**

**Gender** Overall, the incidence of CRC and mortality rates are higher in men than in women; tumors of the colon are slightly more frequent in women than in men (1.2:1), whereas rectal carcinomas are more common in men than in women (1.7:1).

**Age** The vast majority, 90%, of all new CRC cases occur in individuals older than age 50. In the United States, the median age at presentation is 72 years.

**Race** The incidence and mortality rates of CRC are highest among African-American men and women compared with white men and women (15% higher and 40% higher, respectively). The incidence rates among Asian Americans, Hispanics/Latinos, and American Indians/Alaskan natives are lower than those among whites.
**Geography** The incidence of CRC is higher in industrialized regions (the United States, Canada, the Scandinavian countries, northern and western Europe, New Zealand, Australia) and lower in Asia, Africa (among blacks), and South America (except Argentina and Uruguay).

**TABLE 1**

<table>
<thead>
<tr>
<th>Survival</th>
<th>Five-year relative survival rates in colorectal cancer by stage at diagnosis (1995–2005)</th>
</tr>
</thead>
</table>

**Survival** Five-year survival rates (Table 1) for patients with CRC have improved in recent years. This fact may be due to wider surgical resections, modern anesthetic techniques, and improved supportive care. In addition, better preoperative staging and abdominal exploration reveal clinically occult disease and allow treatment to be delivered more accurately. Survival also has improved through the use of adjuvant chemotherapy for colon cancer and adjuvant chemoradiation therapy for rectal cancer. Mortality from CRC is decreasing, likely from earlier diagnosis and screening as well as improvements in treatment modalities.

**Etiology and risk factors**

**TABLE 2**

<table>
<thead>
<tr>
<th>Environment</th>
<th>Summary of selected risk factors for colorectal cancer</th>
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</table>

The specific causes of CRC are unknown, but environmental, nutritional, genetic, and familial factors, as well as preexisting diseases, have been found to be associated with this cancer. A summary of selected risk factors for CRC is shown in Table 2.

**Environment** Asians, Africans, and South Americans who emigrate from low-risk areas assume the colon cancer risk for their adopted country, suggesting the importance of environmental factors in CRC. Smoking and alcohol intake (four or more drinks per week) increase the risk of CRC.

**Diet** Diets rich in fat and cholesterol have been linked to an increased risk of colorectal tumors. Dietary fat causes endogenous production of secondary bile acids and neutral steroids and increases bacterial degradation and excretion of these acids and steroids, thereby promoting colonic carcinogenesis. Historically, diets rich in cereal fiber or bran and yellow and green vegetables are said to have protective effects, although studies have failed to prove a risk reduction with increasing dietary fiber intake. A protective role also has been ascribed to calcium salts and calcium-rich foods, because they decrease colon-cell turnover and reduce the cancer-promoting effects of bile acid and fatty acids.

**Physical activity** Several studies have reported a lower risk of CRC in individuals who participate in regular physical activity. High levels of physical activity may decrease the risk by as much as 50%. Being overweight or obese has been consistently associated with a higher risk of CRC.
**Inflammatory bowel disease** Patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) have a higher incidence of CRC. The risk of CRC in patients with ulcerative colitis is associated with the duration of active disease, extent of colitis, development of mucosal dysplasia, and duration of symptoms.

The risk of CRC increases exponentially with the duration of colitis, from approximately 3% in the first decade to 20% in the second decade to > 30% in the third decade. CRC risk also is increased in patients with Crohn's disease, although to a lesser extent.

**Adenomatous polyps** Colorectal tumors develop more often in patients with adenomatous polyps than in those without polyps. There is approximately a 5% probability that carcinoma will be present in an adenoma; the risk correlates with the histology and size of the polyp. The potential for malignant transformation is higher for villous and tubulovillous adenomas than for tubular adenomas. Adenomatous polyps < 1 cm have a slightly greater than 1% chance of being malignant, in comparison with adenomas > 2 cm, which have up to a 40% likelihood of malignant transformation.

**Cancer history** Patients with a history of CRC are at increased risk of a second primary colon cancer or other malignancy. The risk of a second CRC is higher if the first diagnosis was made prior to age 60.

**Prior surgery** Following ureterosigmoidostomy, an increased incidence of colon cancer at or near the suture line has been reported. Cholecystectomy also has been associated with colon cancer in some studies but not in others.

**Prior radiation** to the prostate has been associated with a 1.7 relative risk of rectal cancer compared with nonirradiated tissues. In this study, the effect was limited to the irradiated tissues only, not to the rest of the bowel.

**TABLE 3** Hereditary polyposis syndromes

**Family history** and genetic factors Individuals with a first-degree relative with the disease have an increased risk of developing CRC. Those with two or more relatives with the disease make up about 20% of all people with CRC. The risk of developing CRC is significantly increased in several forms of inherited susceptibility (Table 3). About 5% to 10% of all patients with CRC have an inherited susceptibility to the disease. The risks of developing CRC in the subgroups of familial or hereditary CRC vary from 15% in relatives of patients with CRC diagnosed before 45 years of age, through 20% for family members with two first-degree relatives with CRC, to approximately 70% to 95% in patients with familial adenomatous polyposis and hereditary nonpolyposis CRC (HNPCC).
Familial adenomatous polyposis (FAP) is inherited as an autosomal-dominant trait with variable penetrance. Patients characteristically develop pancolonic and rectal adenomatous polyps. Approximately 50% of patients with FAP will develop adenomas by 15 years of age, and 95% by age 35. Left untreated, 100% of patients with FAP will develop CRC, with an average age at diagnosis ranging from 34 to 43 years. Prophylactic surgery, either total colectomy with ileorectal anastomosis or restorative proctocolectomy with an ileal anal pouch anastomosis, performed in the mid to late teens, is the prophylactic procedure of choice in this group of patients. The familial adenomatous polyposis coli (APC) gene has been localized to chromosome 5q21. Currently, it is possible to detect mutations in the APC gene in up to 82% of families with FAP. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac (Clinoril, nonspecific COX-1 [cyclo-oxygenase-1] and COX-2 inhibitor) and celecoxib (Celebrex, COX-2 inhibitor) has been shown to decrease the size and number of adenomas in FAP patients. However, these agents should not be a substitute for surgery. A small study also revealed that sulindac does not prevent adenomas in mutation carriers who had not yet developed adenomas.

HNPCC is transmitted as an autosomal-dominant trait. It is associated with germline mutations in DNA mismatch repair genes (MSH2, MLH1, PMS2, and MSH6). The incidence of a mutated mismatch repair (MMR) gene is approximately 1 in 1,000 people. In 1990 and 1991, the Amsterdam criteria were proposed and published, respectively. These criteria were proposed to identify high-risk families suspected of having Lynch syndrome to further study and delineate the syndrome. In 1999, they were revised (Amsterdam II) to recognize extracolonic manifestations as part of the family history. The criteria include the following factors:

- three or more relatives with a histologically verified HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two (FAP should be excluded)
- CRC involving at least two generations
- one or more CRCs diagnosed before the age of 50.

The majority of CRC tumors from HNPCC patients have microsatellite instability (MSI-H). The Bethesda guidelines were developed to test tumors from high-risk individuals for MSI-H to identify individuals at risk of HNPCC. These criteria are much less restrictive than the Amsterdam criteria and serve to help identify patients at risk of HNPCC who might benefit from further evaluation. They have been modified and include the following:

- CRC diagnosed in a patient who is younger than 50 years of age
- The presence of synchronous, metachronous CRC or other HNPCC-associated tumors regardless of age
- CRC with MSI-H histology diagnosed in a patient who is younger than 60 years of age
- CRC diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed younger than age 50 years
- CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors regardless of age.
With newer molecular techniques, mutations in the DNA MMR genes, namely \textit{MLH-1}, \textit{MSH-2}, \textit{MSH-6}, and on rare occasions \textit{PMS-2}, have been found in as many as 90\% of individuals meeting the original Amsterdam criteria, whereas detection of mutations has been lower using the other criteria or guidelines. Because MSI occurs in more than 90\% of cases of CRC with Lynch syndrome compared with sporadic cases (in which it occurs in about 15\% of colorectal tumors), MSI testing has been used to screen tumors prior to genetic testing. Immunohistochemistry (IHC) for DNA (MMR) has also been advocated for screening tumors prior to genetic testing. Both of these methods will not detect all tumors, but they are complementary. In addition to having MSI-H, \textit{MSH-6} colorectal tumors may be MSI-L (microsatellite instability low) or MSS (stable).

\textbf{Chemoprevention}

Chemoprevention aims to block the action of carcinogens on cells before the development of cancer.

Controlled trials of vitamins C and E and calcium have produced mixed results. Clinical trials have shown that calcium supplementation modestly decreases the risk of colorectal adenomas.

NSAIDs inhibit colorectal carcinogenesis, possibly by reducing endogenous prostaglandin production through COX inhibition. Sulindac has induced regression of large bowel polyps in patients with FAP. Controlled studies have shown a reduction in the incidence of colorectal polyps with regular, long-term use of aspirin. HMG-CoA (hydroxymethyl glutaryl coenzyme A) reductase inhibitors may reduce the risk of CRC after extended treatment.

Women who use postmenopausal hormones appear to have a lower rate of CRC than do those who do not. Postmenopausal hormones may increase the risk of other types of cancer, however.

\textbf{Signs and symptoms}

During the early stages of CRC, patients may be asymptomatic or complain of vague abdominal pain and flatulence, which may be attributed to gallbladder or peptic ulcer disease. Minor changes in bowel movements, with or without rectal bleeding, are also seen; they are frequently ignored and/or attributed to hemorrhoids or other benign disorders.

Cancers occurring in the left side of the colon generally cause constipation alternating with diarrhea; abdominal pain; and obstructive symptoms, such as nausea and vomiting.

Right-sided colon lesions produce vague, abdominal aching, unlike the colicky pain seen with obstructive left-sided lesions. Anemia resulting from chronic blood loss, weakness, weight loss, and/or an abdominal mass may also accompany carcinoma of the right side of the colon.

Patients with cancer of the rectum may present with a change in bowel movements; rectal fullness, urgency, or bleeding; and tenesmus.

\textbf{Screening and diagnosis}

\textbf{Fecal occult blood testing (FOBT)} consists of guiac-based testing (gFOBT), which can be performed in the doctor's office, or a fecal immunohistochemical test (FIT), which is usually processed in clinical
laboratories. The difference between these tests is based on the detected analyte. Blood in the stool detected by gFOBT depends on the reaction of a pseudoperoxidase with heme or hemoglobin, whereas FIT depends on the reaction with globin. These tests should collect two samples from three consecutive bowel movements. The majority of the adenomas and CRCs go undetected because they usually are not bleeding at the time of the test. Newer gFOBT and FIT appear to have a better sensitivity than older tests without sacrificing specificity.

Three large prospective randomized controlled clinical trials have demonstrated a 15% to 33% decrease in CRC mortality over an 8- to 13-year period of follow-up in those individuals randomized to undergo FOBT. A positive FOBT result should be followed by colonoscopy.

**Stool DNA (sDNA) testing** takes advantage of molecular changes or mutations that occur in the carcinogenesis of CRC. DNA shed in the stool is analyzed for molecular changes. Multiple targets, including mutations in KRAS, p53, APC, and BAT 26 (which can be a surrogate marker for MSI), are analyzed. There are no data on the performance of sDNA for screening; however, the test has been shown to be able to detect both significant adenomas and CRCs.

**Digital rectal examination** should be an integral part of the physical examination. It can detect lesions up to 7 cm from the anal verge.

**Sigmoidoscopy** Flexible proctosigmoidoscopy is safe and more comfortable than examination using a rigid proctoscope. Almost 50% of all colorectal neoplasms are within the reach of a 60-cm sigmoidoscope. Even though flexible sigmoidoscopy visualizes only the distal portion of the colorectum, the identification of adenomas can lead to colonoscopy. When we add the percentage of colorectal neoplasms in the distal 60 cm of the colorectum to the percentage of patients with distal polyps leading to complete colonoscopy, 80% of those individuals with a significant neoplasm anywhere in the colorectum can be identified. Four prospective randomized controlled trials evaluating flexible sigmoidoscopy for screening have been conducted in the United States and Europe, but results are not yet available.

**Colonoscopy (optical)** provides information on the mucosa of the entire colon, and its sensitivity in detecting tumors is extremely high. Most physicians consider colonoscopy to be the best screening modality for CRC. Colonoscopy can be used to obtain biopsy specimens of adenomas and carcinomas and permits the excision of adenomatous polyps. For this reason, colonoscopy is the only screening modality ever shown to reduce the incidence of cancer in screened individuals. Colonoscopy is the best follow-up strategy for evaluating patients with a positive gFOBT and the best screening modality for high-risk patients.

Limitations of colonoscopy include its inability to detect some polyps and small lesions because of blind corners and mucosal folds and the fact that sometimes the cecum cannot be reached. A supplementary double-contrast barium enema may be needed if a colonoscopic exam fails to reach the cecum.

**Colonoscopy (CT virtual)** utilizes CT images that are reconstructed to visualize the colon. It requires a bowel preparation and adequate distention of the colon for success. There is no prospective randomized study demonstrating that colonoscopic CT reduces CRC mortality. However, a trial comparing optical colonoscopy with colonoscopic CT resulted in similar detection rates for advanced neoplasia.
Barium enemas can accurately detect CRC; however, the false-negative rate associated with double-contrast barium enemas ranges from 2% to 61% because of misinterpretation, poor preparation, and difficulties in detecting smaller lesions. A supplementary colonoscopy may be needed if a double-contrast barium enema does not adequately visualize the entire colon or to obtain histopathology or perform polypectomy in the event of abnormal findings. There is no role for single-contrast barium enema. If this modality is to be used, a well-conducted double-contrast barium enema needs to be performed.

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**TABLE 4**

American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Average risk

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**TABLE 5**

Joint guideline from the American Cancer Society, the US Multi-Society Task Force on CRC, and the American College of Radiology for screening and surveillance in high-risk individuals

**Recommendations for average-risk individuals** Adults at average risk should begin CRC screening at age 50. The ACS guidelines on screening and surveillance for the early detection of colorectal adenomatous polyps and cancer provide several options for screening average-risk individuals (Table 4).

The recommendations for screening and surveillance for high-risk individuals are illustrated in Table 5.

**Treatment of endoscopically removed polyps** Adenomatous colon polyps should be completely removed endoscopically to prevent progression to malignancy. Colon polyps with severe dysplasia or carcinoma in situ can also be managed with colonoscopic polypectomy as long as the entire polyp is removed. A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (pT1).

Management of malignant polyps removed by colonoscopy is somewhat controversial. In general, malignant polyps can be removed colonoscopically as long as they can be removed with a confirmed negative margin and do not invade the submucosa beneath the polyp stalk, do not have lymphovascular invasion, or are poorly differentiated. These characteristics increase the risk of nodal metastases.
Studies from Japan and the United States have correlated the incidence of lymph node metastases with the level of submucosal involvement. Individuals with cancer in polyps invading the upper third of the submucosa have a low risk of nodal metastases, whereas those invading the lower third have up to a 25% incidence of nodal metastases. Sessile polyps with submucosal invasion should probably be removed by colon resection. Each situation should be individualized according to the histology, prognostic factors, extent of submucosal invasion, and completeness of excision. The comorbidities and general health of the patient are also factors to consider.

Initial workup An initial diagnostic workup for patients suspected of having colorectal tumors should include a complete history and physical examination including a three-generation family history. It should also include:

- digital rectal examination and FOBT
- colonoscopy
- biopsy of any detected lesions.

Adequate staging prior to surgical intervention requires:

- chest x-ray
- CT scan of the abdomen and pelvis
- endorectal ultrasonography or MRI to evaluate and appropriately stage a rectal cancer for potential neoadjuvant therapy
- CBC with platelet count
- liver and renal function tests
- urinalysis
- measurement of carcinoembryonic antigen (CEA) level. If CEA levels are elevated preoperatively, postoperative CEA levels should be monitored every 3 months for 3 years in patients with stage II or III CRC and every 6 to 12 months thereafter
- endoscopic ultrasonography (EUS) or MRI of the pelvis for rectal cancers.

In monitoring response to therapy for metastatic cancer, CEA levels should be measured every 1 to 8 months during active treatment.

FDG-PET scanning FDG (\(^{18}\)F-fluorodeoxyglucose)-PET scanning has emerged as a highly sensitive study for the evaluation of patients who have metastatic disease. Although not usually recommended in the evaluation of early-stage primary disease, this modality can aid in the staging of recurrence.

Pathology
Adenocarcinomas constitute 90% to 95% of all large bowel neoplasms. These tumors consist of cuboidal or columnar epithelium with multiple degrees of differentiation and variable amounts of mucin.

Mucinous adenocarcinoma is a histologic variant characterized by huge amounts of extracellular mucus in the tumor and the tendency to spread within the peritoneum. Approximately 10% of colorectal adenocarcinomas are mucinous. It is more commonly seen in younger patients.

Signet-ring-cell carcinoma is an uncommon variant, comprising 1% of colorectal adenocarcinomas. These tumors contain large quantities of intracellular mucinous elements (causing the cytoplasm to displace the nucleus) and tend to involve the submucosa, making their detection difficult with conventional imaging techniques.

Other tumor types Squamous cell carcinomas, small-cell carcinomas, carcinoid tumors, and adenosquamous and undifferentiated carcinomas also have been found in the colon and rectum. Nonepithelial tumors, such as sarcomas and lymphomas, are exceedingly rare.

Metastatic spread CRC has a tendency toward local invasion by circumferential growth and for lymphatic, hematogeneous, transperitoneal, and perineural spread. Longitudinal spread is usually not extensive, with microscopic spread averaging only 1 to 2 cm from gross disease, but radial spread is common and depends on anatomic location.

The most common site of extralymphatic involvement is the liver, with the lungs the most frequently affected extra-abdominal organ. Other sites of hematogeneous spread include the bones, kidneys, adrenal glands, and brain, although metastases can spread to any organ.

Staging and prognosis

The TNM staging classification, which is based on the depth of tumor invasion in the intestinal wall, the number of regional lymph nodes involved, and the presence or absence of distant metastases, has largely replaced the older Dukes' classification scheme (Table 6).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No evidence of invasion to muscular coat</td>
</tr>
<tr>
<td>II</td>
<td>Invasion to muscular coat but no invasion to serosal plane</td>
</tr>
<tr>
<td>III</td>
<td>Invasion to serosal plane but no invasion to adjacent organs</td>
</tr>
<tr>
<td>IV</td>
<td>Invasion to adjacent organs or distant metastases</td>
</tr>
</tbody>
</table>

Pathologic stage is the single most important prognostic factor following surgical resection of colorectal tumors. The prognosis for early stages (I and II) is favorable overall, in contrast to the prognosis for advanced stages.
Colorectal Cancer Treatment

Primary treatment of localized disease

Management of CRC relies primarily on resection of the bowel with the adjacent draining lymph nodes. The need for neoadjuvant or adjuvant chemotherapy, with or without concurrent irradiation, depends on tumor location (colon vs rectum) and stage of disease. In surgery for both colon and rectal cancers, if the tumor is attached to other organs, an en bloc resection of the primary tumor and adjacent organ(s) is indicated. If the adhesions are violated, there is an increase in local recurrence and a decrease in survival; thus, the potential cure for that patient will be compromised. Occasionally, neoadjuvant chemoradiation therapy will be indicated in colon tumors prior to surgical resection. In rectal cancer, preoperative (preferred) or postoperative chemoradiation is indicated for stages II and III disease.

Surgery

Colon The primary therapy for adenocarcinoma of the colon is surgical extirpation of the bowel segment containing the tumor, the adjacent mesentery, and draining lymph nodes. Based on studies that correlated the number of lymph nodes removed and survival, it is recommended that at least 12 lymph nodes be available for examination by a pathologist to confirm. Surgical resection can be performed by open or laparoscopic approach.

The type of resection depends on the anatomic location of the tumor. Right, left, or transverse colectomy is the surgical treatment of choice in patients with right, left, or transverse colonic tumors, respectively. Tumors in the sigmoid colon may be treated with wide sigmoid resection. The length of colon resected depends largely on the requirement for wide mesenteric nodal clearance.

Other prognostic factors (such as age at diagnosis, presurgical CEA level, gender, presence and duration of symptoms, site of disease, histologic features, obstruction or perforation, perineural invasion, venous or lymphatic invasion, ploidy status, and S-phase fraction) have not consistently been correlated with overall disease recurrence and survival. Furthermore, the size of the primary lesion has had no influence on survival. Elevated expression of thymidylate synthase (TS) and allelic loss of chromosome 18 have been correlated with a poor prognosis. MSI status has been correlated as an independent prognostic factor for survival, favoring patients with unstable tumors (MSI-H).

Histologic grade may be correlated with survival. Five-year survival rates of 56% to 100%, 33% to 80%, and 11% to 58% have been reported for grades 1, 2, and 3 colorectal tumors, respectively.

(III and IV). However, there appears to be superior survival for patients with stage III disease whose disease is confined to the bowel wall (ie, T2, N+).
**Rectum** For rectal carcinoma, the distal surgical margin should be at least 2 cm, although some investigators have suggested that a smaller but still negative margin may be adequate. The resection should include the node-bearing mesorectum surrounding the rectum. This procedure, which is termed total mesorectal excision (TME), is accomplished using a sharp dissection technique (see Figure 1). Posteriorly, the mesorectal dissection is carried out along the presacral fascia. Anteriorly, the dissection follows the posterior vaginal wall in females or Denonvilliers’ fascia in males, either of which may be resected in the presence of an anterior wall rectal cancer. The use of TME has been associated with a significant reduction in local recurrence rates for patients with rectal cancer.

Reported rates of local recurrence following TME for rectal cancer have generally been < 10%, compared with rates of recurrence up to 30% prior to the advent of TME. Selective use of radiation therapy can improve upon the results of TME alone.

Circumferential resection margin is an important predictor of local failure in patients with rectal cancer. A population-based review of 3,196 patients with rectal cancer found that local recurrence at 5 years was 23.7% with margins of 0-2 mm vs 8.9% with margins greater than 2 mm. Distant metastases and survival were also poorer for the group with smaller margins. Because only 10% of patients in this study received neoadjuvant therapy and patients who received postoperative radiation therapy were excluded, it is not clear whether these data can be extrapolated to patients treated with radiation therapy.

**Sphincter-sparing approaches** Technologies (eg, circular stapling devices) and the application of surgical techniques, such as coloanal anastomosis and creation of intestinal pouches, are employed to maintain anal sphincter function for tumors in the lower one-third of the rectum. If the tumor is located proximally between 6 and 15 cm from the anal verge, a low anterior resection with end-to-end anastomosis may be performed.

**Abdominoperineal resection**, removing the anus and sphincter muscle with permanent colostomy, may be necessary if the tumor is located in the distal rectum and other characteristics of the tumor (eg, bulky size, proximity to the sphincter musculature) preclude an oncologically adequate sphincter-sparing approach. An alternative procedure for distant rectal tumors is to resect the entire rectum, sparing the anoderm and anal sphincter musculature, and to perform a coloanal anastomosis. Either procedure, sphincter-sparing resection or abdominoperineal resection, can be performed with autonomic nerve preservation, minimizing bladder and sexual function morbidity.

**Local excision alone** may be indicated for selected patients who have small (< 3 to 4 cm), T1, well to moderately differentiated rectal cancers without histologic evidence of lymphovascular involvement, provided that a full-thickness negative margin can be achieved. In some series, transanal excision for these good histology T1 lesions results in excellent long-term control. However, some large studies with long-term follow-up demonstrated significant local recurrence rates, even with T1 lesions. For T2 or T3 tumors, the standard therapy remains a transabdominal resection because of the risk of mesorectal nodal spread. Preoperative transrectal ultrasonography is useful in defining lesions that can be resected by local excision alone. A trial sponsored by the CALGB demonstrated reasonable results for patients with
T2 rectal cancer undergoing negative margin local excision followed by fluorouracil (5–FU) and external-beam radiation therapy (EBRT). The locoregional recurrence rate at 6 years was only 14%. A similar study conducted by ACOSOG but with neoadjuvant chemoradiation followed by local excision has been completed, but results are not yet available.

**Laparoscopic colonic resection** Multiple large randomized trials have established laparoscopic colonic resection as an oncologically acceptable method of treating cancer of the colon. Resection of rectal cancer using laparoscopic approaches has also been and is being evaluated in a number of randomized trials. Laparoscopy for rectal resection still requires confirmation as an oncologically equivalent procedure to open surgery. The potential advantages include a shorter hospital stay, reduced postoperative ileus, decreased time away from work, fewer adhesive complications, and a lower risk of hernia formation. The potential disadvantages compared with open transabdominal resection include longer operative time, higher operative costs, and technical considerations related to operative skill. Large randomized trials with long-term follow-up are still needed. Robotic surgery is also being evaluated in rectal cancer.

**Patterns of failure**
The natural history and patterns of failure following "curative" resection are different for colon and rectal carcinomas. Locoregional failure as the only or major site of recurrence is common in rectal cancer, whereas colon cancer tends to recur in the peritoneum, liver, and other distant sites, with a lower rate of local failure. As a result, local therapy, such as irradiation, may play a significant role in the treatment of rectal tumors but is not used routinely for colon cancers.

**Adjuvant therapy for colon cancer**
Approximately 75% of all patients with CRC will present at a stage when all gross carcinoma can be surgically resected. Nevertheless, despite the high resectability rate, almost half of all patients with colorectal adenocarcinoma die of metastatic disease, primarily because of residual disease that is not apparent at the time of surgery. These individuals are candidates for adjuvant local or systemic therapies.

**Systemic chemotherapy**
The use of chemotherapy for resected stage II colon cancer is of uncertain survival benefit. When determining the benefit of adjuvant therapy for this group of patients, several factors should be taken into consideration, including the number of lymph nodes analyzed after surgery, the prognostic features (T4 lesion, perforation, peritumoral lymphovascular invasion, poorly differentiated histology, MSI), anticipated life expectancy, and comorbid conditions.

Two recent phase III trials of adjuvant therapy for resected colon cancer assessed the potential added benefit of targeted therapy to mFOLFOX6. NSABP C-08 randomized patients with resected stage II or III colon cancer to 12 cycles of mFOLFOX6 alone or with bevacizumab. Bevacizumab was given for 6 months beyond mFOLFOX6. NCCTG N0147 randomized patients with resected stage III colon cancer to 12 cycles of mFOLFOX6 alone or with cetuximab. The final design of this trial only randomized patients with wild-type KRAS to one of the two treatment arms. Both trials failed to show benefit to the addition of a targeted therapy to mFOLFOX6 (Wolmark N et al: J Clin Oncol 27:18s, abstract LBA4, 2009; Alberts SR et al: J Clin Oncol 28:18s, abstract CRA3507, 2010).
**FOLFOX, FLOX** Oxaliplatin has been approved by the FDA for adjuvant therapy for resected stage III CRC. In a phase III trial for resected stages II and III colon cancer from Europe (MOSAIC), the use of FOLFOX4 compared with the same infusional regimen without oxaliplatin led to a higher 3-year disease-free survival rate (78% vs 73%) in those receiving FOLFOX. More recently, FOLFOX6 or a modified version of it (Table 8) has been used in clinical trials as well as in clinical practice. In a subgroup analysis, a significant disease-free survival benefit was seen for patients with stage III colon cancer and for patients with high-risk stage II colon cancer. A significant overall survival advantage was also seen for patients with stage III disease.

In a separate randomized phase III trial, conducted by the NSABP, for patients with resected stage II or III colon cancer, FLOX was compared with a weekly bolus of 5–FU and leucovorin. The 3-year disease-free survival benefit from FLOX was similar to that seen with FOLFOX4. Stages II and III disease were not evaluated separately.

A phase III randomized trial of neoadjuvant radiation for T3-4, M0 rectal cancer compared outcomes when either capecitabine (Xeloda) or capecitabine and oxaliplatin (Eloxatin) was added to radiation therapy. With 598 patients randomized, this trial showed no significant benefit to the addition of oxaliplatin. The investigators concluded that oxaliplatin does not add meaningful benefit when added to capecitabine and radiation therapy (Gérard JP et al: J Clin Oncol 28:1638-1644, 2010).

**Capecitabine** is an oral fluorinated pyrimidine approved by the FDA for adjuvant therapy for patients with stage III colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. Capecitabine was not inferior to bolus 5–FU and low-dose leucovorin for disease-free survival, with a hazard ratio in the capecitabine group of 0.87 (95% CI = 0.75–1.00). Capecitabine is an alternative for patients who are unlikely to tolerate 5–FU, leucovorin, and oxaliplatin.

**5–FU plus leucovorin** Studies have demonstrated the benefits of 5–FU plus leucovorin in the adjuvant treatment of colon carcinomas. Acceptable adjuvant regimens of 5–FU plus leucovorin for colon cancer include both low-dose leucovorin and high-dose leucovorin regimens (Table 7).

![Table 7](image)

**TABLE 7** Adjuvant chemotherapy regimens for colorectal adenocarcinoma (nonmetastatic)

Irinotecan Two phase III trials of FOLFIRI (5–FU, irinotecan, leucovorin) compared the same infusional regimen without irinotecan in either patients with resected stages II and III colon cancer (PETACC3) or high-risk stage III disease (ACCORD-2). They did not show a benefit to the use of irinotecan in the adjuvant setting. Given the results of these two studies, the use of irinotecan currently is not considered a primary option for patients with resected stage II or III colon cancer.

**Radiation therapy** Postoperative irradiation to the tumor bed can be considered in patients with T4 (B3 or C3) tumors located in retroperitoneal portions of the colon, because more than 30% of these patients develop local...
recurrence. Retrospective studies suggest improved local tumor control with irradiation, particularly in patients with positive resection margins. If available, intraoperative radiotherapy may be considered for patients with T4 or recurrent cancers as an additional boost.

**Adjuvant therapy FOR rectal cancer**

Local recurrence alone or in combination with distant metastases occurs in up to 50% of patients with rectal carcinoma. Nodal metastases and deep bowel wall penetration are significant risk factors for locoregional failure.

In the absence of nodal metastases, the rate of local recurrence may be as low as 5% to 10% for stage I rectal cancer and 15% to 30% for stage II tumors. In stage III disease, the incidence of pelvic failure increases to 50% or more. The use of TME significantly reduces this risk of local recurrence; however, local recurrence remains a concern in patients with stages II and III disease.

Local recurrence in the pelvis is complicated by involvement of contiguous organs, soft and bony tissues, and deep nodal disease. Presenting symptoms vary from vague pelvic fullness to sciatica related to mass effect in the fixed space of the bony pelvis and invasion of the sciatic nerve.

Because local recurrence in the absence of metastatic disease is more common in rectal cancer than in colon cancer, aggressive resections, such as pelvic exenteration (anterior and posterior), sacral resection, and wide soft-tissue and pelvic floor resection, have been employed to treat these recurrences. Modern techniques of pelvic floor reconstruction, creation of continent urinary diversion, and vaginal reconstruction may be required for functional recovery.

The findings of the NSABP R-02 trial indicated postoperative adjuvant chemotherapy resulted in survival rates similar to those of postoperative chemoradiation therapy but was associated with a significantly higher rate of locoregional failure.

**Pre- or postoperative radiation therapy**

Radiation therapy has been used to reduce the locoregional recurrence rate of rectal tumors. Preoperative radiation therapy has been demonstrated to reduce local tumor recurrence, even in patients undergoing TME surgery. However, with the exception of one study, preoperative therapy has not affected overall survival in patients with stage II or III rectal cancer. An improvement in local tumor control also has been observed with postoperative irradiation, but again with no benefit with regard to disease-free or overall survival. Preoperative radiation therapy reduced local recurrence rates when combined with TME (11.4% vs 5.8%; \( P < .001 \)) in a Dutch phase III trial at a median follow-up of 4.8 years. In a French study of 762 patients, preoperative chemoradiation therapy compared with preoperative radiotherapy reduced local failure rates in patients with T3-T4 rectal cancers from 17% to 8%.

**Chemoradiation therapy**

Postoperative chemoradiation therapy Clinical trials of surgical adjuvant treatment indicate that postoperative radiation therapy with concurrent chemotherapy (chemoradiation therapy) is superior to postoperative radiation therapy alone or surgery alone. Postoperative chemoradiation therapy is a standard of care for patients with stage II or III rectal cancer based largely on the findings of the NCCTG and GITSG trials. A summary of the 5-year survival results of the Patterns of Care Study (PCS) of the American College of Radiology and the results of the National Cancer Data Base (NCDB), both of which are representative of American national averages, is shown in Table 9.
The most effective combination of drugs, optimal mode of administration, and sequence of irradiation and chemotherapy still need to be determined. Radiation doses of 45 to 55 Gy are recommended in combination with 5-FU-based chemotherapy. Postoperative bolus 5-FU administration with irradiation is inferior to protracted venous infusion, resulting in lower 3-year rates of both overall survival (68% vs 76%) and disease-free survival (56% vs 67%).

An adjuvant treatment combining chemotherapy and pelvic irradiation in patients with stage II or III rectal cancer used the following regimen: 5-FU, 500 mg/m²/day administered as a rapid IV infusion on days 1 to 5 and 450 mg/m²/day on days 134 to 138 and days 169 to 173. Patients received a protracted IV infusion of 5-FU, 225 mg/m²/day, by portable ambulatory infusion pump during the entire period of pelvic irradiation. Pelvic radiation therapy began on day 64 with a multiple-field technique to the tumor bed and nodal groups. A total of 4,500 cGy in 180-cGy fractions was administered over a 5-week period. Patients received a minimal boost dose of 540 cGy to the entire tumor bed, adjacent nodes, and 2 cm of adjacent tissue. A second boost dose of 360 cGy was allowed in selected patients with excellent displacement of the small bowel.

**Neoadjuvant therapy** For rectal cancers approaching the anal sphincter, preoperative (neoadjuvant) irradiation or the combination of chemotherapy and irradiation will significantly reduce the size of the majority of tumors. This approach allows for sphincter-preserving surgery in many patients. In addition, the long-term morbidity of radiation therapy for rectal cancer may be reduced if it is administered prior to surgery. The use of preoperative chemotherapy and radiation therapy is particularly important for patients presenting with locally advanced, unresectable rectal cancer, as the disease of the majority will be rendered resectable following neoadjuvant therapy. One additional role of neoadjuvant therapy may be in facilitating transanal excision of T2 and T3 rectal cancers in poor-surgical-risk patients. A number of investigators have reported good results with transanal excision of T2 and T3 tumors following a complete response to neoadjuvant therapy. However, this approach cannot be considered the current standard of care.

**Preoperative vs postoperative chemoradiation therapy** Preoperative chemoradiation therapy is now preferred in most cases to postoperative adjuvant treatment, particularly in patients with T3 or T4 lesions. Such treatment may enhance resectability and may be associated with a lower frequency of complications compared with postoperative treatment. In a report of a randomized trial conducted by the GRCSG, Sauer et al found that compared with postoperative chemoradiotherapy, preoperative chemoradiotherapy significantly decreased local failure (6% vs 13%; \( P = .006 \)) and sphincter preservation in low-lying tumors (39% vs 19%; \( P < .004 \)). In addition, the incidence of chronic anastomotic stricture was also lowest in the preoperative chemoradiotherapy group (4% vs 12%; \( P = .003 \)). These findings are consistent with those from another large multi-institutional phase III trial, which found that short-course preoperative radiation therapy improved local tumor control and disease-free survival compared with postoperative chemoradiation therapy. In the NSABP R-03 study that compared preoperative and postoperative chemoradiotherapy, patients treated with preoperative chemoradiotherapy had an improved 5-year disease-free survival (64.7% vs 53.4%). No patient with a
pathologic complete response had a recurrence. Collectively, these trials suggest that for patients with indications for chemoradiotherapy, preoperative therapy is preferred.

In patients with metastatic colorectal cancer responding to FOLFOX, a break from chemotherapy was compared with maintenance chemotherapy (5–FU, leucovorin) in the randomized trial OPTIMOX2. Control of disease was significantly longer with maintenance chemotherapy than with a break from chemotherapy (13.1 vs 9.2 months; Chibaudel B et al: J Clin Oncol 27:5757-5733, 2009).

**Choice of chemotherapy during radiation therapy** The optimal chemotherapy to use in combination with radiation remains an area of active research. Although most large randomized trials have used bolus or infusional 5–FU in combination with radiation, the availability of oral agents, such as capecitabine, has raised interest in combining capecitabine and radiation alone and with other chemotherapeutic agents. The NSABP R-04 is comparing capecitabine-containing regimens combined with radiation to infusional 5–FU regimens. A number of retrospective and phase II studies have suggested that the combination of capecitabine and radiation provides pathologic response rates similar to those observed with 5–FU and radiation.

A recent phase III trial of chemotherapy regimens during radiation suggested no benefit from a capecitabine and oxaliplatin regimen compared with capecitabine alone (see sidebar). Many studies are ongoing with combinations of capecitabine, oxaliplatin, and irinotecan during radiation therapy.

**Treatment of advanced colon cancer**

Local recurrences from colon cancers usually occur at the site of anastomosis, in the resection bed, or in the contiguous and retroperitoneal (para-aortic, paracaval) lymph nodes. Anastomotic recurrences diagnosed during surveillance in asymptomatic patients are the most curable, followed by local soft-tissue recurrences. Regional and retroperitoneal lymph node recurrences portend a poor prognosis and systemic disease.

**Chemotherapy**

The development of chemotherapy for advanced CRC has become an active field (Table 8). After decades of 5–FU-based treatment, and of little clinical gains, the arrival of new, effective agents has significantly changed the way this cancer is treated. Although 5–FU remains the backbone of most regimens, the new agents irinotecan and oxaliplatin have become an important part of front-line treatment of this disease in the United States and abroad. The recent development of molecular targeted agents has provided additional improvements in both response and survival for patients with CRC.
Chemotherapy for advanced disease

5–FU remains an important agent in the treatment of advanced CRC. Mainly in the past, 5–FU was administered as a bolus injection either weekly or daily for 5 days, every 4 to 5 weeks (Table 8). With these regimens, response rates have been approximately 10% to 15%. The development of permanent venous access devices and portable infusion pumps has permitted the prolonged infusion of 5–FU on an outpatient basis.

The pattern of 5–FU toxicity differs depending on whether it is administered as a bolus or a prolonged infusion than by other methods. Bolus administration has pronounced myelotoxic effects, whereas the dose-limiting toxic effects of prolonged-infusion 5–FU are mucositis and diarrhea. Palmar-plantar erythrodysthesia (hand-foot syndrome) has been reported with prolonged infusions. Infusional 5–FU is now an important component of therapy when combined with either irinotecan or oxaliplatin.

Biochemical modulation of 5–FU Interest in the biochemical modulation of 5–FU by leucovorin is based on preclinical studies demonstrating that leucovorin raises the level of \( N_5,N_{10} \)-methylene tetrahydrofolate and, thus, forms a stable tertiary complex of TS, the folate coenzyme, and 5–FU (in the form of 5-fluorodeoxyuridine). The use of 5–FU with leucovorin results in higher response rates than 5–FU alone and may prolong survival.

Although there is no agreement as to the optimal dose of leucovorin, historically two dosing schedules (as shown in Table 7) have been used with either low-dose or high-dose leucovorin.

FOLFOX was approved by the FDA in 2004 as first-line therapy. Initial evidence of activity was demonstrated in patients with pretreated, 5–FU-resistant CRC (45% response rate). In subsequent trials, patients with untreated metastatic CRC receiving FOLFOX had response rates of over 50%. In addition, patients receiving oxaliplatin, infusional 5–FU, and leucovorin have achieved overall survival rates > 20 months in several reported trials. However, many of these patients have received second- and even third-line therapies at the time of disease progression, reducing the validity of survival evaluation. Currently, there are several accepted FOLFOX regimens in use, including FOLFOX4, FOLFOX6, modified FOLFOX6, and FOLFOX 7.

Oxaliplatin's toxicity profile includes nausea/vomiting and cumulative, reversible peripheral neuropathy. Patients may also develop a reversible, cold-induced, acute pharyngolaryngeal neuropathy. The OPTIMOX trials demonstrated that patients with either stable or responding metastatic CRC may benefit from an oxaliplatin-free interval with either no therapy or maintenance 5–FU and leucovorin followed by reintroduction of FOLFOX at the time of disease progression. The use of maintenance therapy compared with continued FOLFOX provided a comparable overall period of disease control. Maintenance therapy lessened the amount of oxaliplatin-induced neuropathy.
**Irinotecan** has significant clinical activity in patients with metastatic CRC whose disease has recurred or spread after standard chemotherapy. Its FDA approval was based on two phase III trials showing that irinotecan (350 mg/m² once every 3 weeks) significantly increased survival, compared with best supportive care and infusional 5–FU, respectively, in patients with recurrent or progressive cancer following first-line 5–FU therapy. Irinotecan increased the median survival by 27% and 41%, respectively, in the two trials. Irinotecan is active in patients whose disease progressed while receiving 5–FU. Reproducible 15% to 20% response rates in this patient population led to the approval of irinotecan for use in patients with 5–FU-refractory disease. The dosage schedules most commonly used are 125 mg/m² weekly for 4 weeks, followed by a 2-week rest period (United States) and 350 mg/m² every 3 weeks (Europe). The primary toxicities of irinotecan are diarrhea and neutropenia. Intensive loperamide is important in the management of the former complication. An initial 4-mg loading dose is given at the first sign of diarrhea, followed by 2-mg doses every 2 hours until diarrhea abates for at least a 12-hour period.

The need for surgery, radiation, or intraluminal stenting of the primary tumor in patients presenting with synchronous metastatic colorectal cancer was assessed in patients from a prospective institutional database. All of the patients had received standard chemotherapy with or without bevacizumab (Avastin). Of 233 patients identified in the database, 217 (93%) never required any intervention for their primary tumor (Poultsides GA et al: J Clin Oncol 27:3379-3384, 2009).

Studies have shown that variation in the metabolism of irinotecan is associated with the pattern of allelic inheritance with the gene **UGT 1A1**. Although it is recommended that **UGT 1A1** testing be performed prior to the use of irinotecan, dose-modification recommendations, based on the pattern of alleles inherited, are not currently available. However, it is recommended that patients with the **UGT 1A1*28** pattern of inheritance should receive a reduced dose of irinotecan.

**FOLFIRI** Several randomized trials have shown improved response rates and overall survival when irinotecan is added to an infusional regimen of 5–FU and leucovorin compared with 5–FU and leucovorin alone. A bolus combination of irinotecan, 5–FU, and leucovorin (IFL) had also shown better response rates and overall survival but proved to be much more toxic. The use of IFL is no longer recommended.

In a phase III trial comparing the sequence of FOLFIRI followed by FOLFOX or the reverse sequence for patients with metastatic CRC, no difference in median survival was seen. Grade 3 or 4 mucositis, nausea, and vomiting occurred more frequently with FOLFIRI, whereas grade 3 or 4 neutropenia and neurosensory toxicity were more frequent with FOLFOX. Response rates were similar between the two groups. The results of this clinical trial and others stress the importance of using all available agents in the treatment of metastatic CRC, and the sequence of their use appears to be less important.

**Capecitabine** In a phase III trial of previously untreated patients with metastatic colon cancer, capecitabine produced higher response rates than did 5–FU and leucovorin. Overall survival and time to disease progression were similar (noninferior) to those with 5–FU and leucovorin. As established in European trials, the recommended dose of capecitabine is 2,500 mg/m² each day, given as a twice-daily dose, for 14 days followed by a 1-week rest period. However, most North American patients will not tolerate this dose of capecitabine and should instead receive 2,000 mg/m² each day, given as a twice-daily dose, for 14 days followed by a 1-week rest period. The side effects of capecitabine tend to be similar to those seen with prolonged infusion of 5–FU, with hand-foot syndrome being the most common.
Capecitabine and oxaliplatin may also provide significant benefit. Results of completed clinical trials with capecitabine and oxaliplatin are similar to those obtained with FOLFOX. This combination avoids the need for a central venous catheter.

Capecitabine and irinotecan may also be of benefit. This combination should be used with caution. Although some clinical trials have shown this combination to be tolerable and active, other trials of capecitabine and irinotecan have shown significant toxicity.

Molecular targeted agents
A variety of monoclonal antibodies and small molecules are being evaluated in clinical trials and preclinical studies. Three of these agents (bevacizumab [Avastin], cetuximab [Erbitux], and panitumumab [Vectibix]) have been approved by the FDA for use in CRC.

Bevacizumab is a humanized monoclonal antibody that binds circulating vascular endothelial growth factor (VEGF). When given with a 5–FU containing regimen in several different trials as first-line therapy in patients with metastatic CRC, bevacizumab led to an improved outcome. The addition of bevacizumab to 5–FU and leucovorin resulted in significant improvement in progression-free survival. Even better results were seen with IFL, when the addition of bevacizumab to IFL resulted in significant improvement in overall survival and response rates. These studies led to approval by the FDA of bevacizumab. It is indicated for use in first-line therapy for metastatic CRC when combined with 5–FU–based chemotherapy, such as FOLFOX.

The genes KRAS and to some degree BRAF have been associated with a lack of response to the EGF receptor inhibitors cetuximab (Erbitux) and panitumumab (Vectibix). There is increasing retrospective evidence to show that mutations in KRAS or BRAF may significantly shorten overall survival. However, these mutations do not preclude a potential benefit from chemotherapy (Laurent-Puig P et al: J Clin Oncol 27:5924-5930, 2009; Richman SD et al: J Clin Oncol 27:5931-5937, 2009).

Cetuximab is a human/mouse chimeric antibody directed against the epithelial growth factor receptor (EGFR). In a randomized trial of patients with CRC refractory to irinotecan, patients were randomized to receive either cetuximab and irinotecan or cetuximab alone. The addition of cetuximab to irinotecan led to a significantly higher response rate compared with cetuximab alone. The median survival for those receiving cetuximab and irinotecan was also longer, though not significantly. Based on the results of this study, cetuximab was approved by the FDA for use in patients whose disease is refractory to irinotecan with tumors expressing EGFR. Data from a phase III trial in which cetuximab was evaluated in addition to FOLFIRI compared with FOLFIRI alone suggest that patients with tumors harboring mutant KRAS derived no benefit from the addition of cetuximab. A benefit in progression-free survival and response rates was seen with the addition of cetuximab in patients with wild-type KRAS.

Panitumumab is a monoclonal antibody that targets EGFR. In a pivotal phase III trial, 463 patients with metastatic CRC who had failed to respond to previous standard therapy were randomized between panitumumab (6 mg/kg every 2 weeks) plus best supportive care vs best supportive care alone. Patients in the panitumumab arm achieved a significantly improved time to disease progression (96 days vs 60 days) and objective response rate (8% vs 0%). On the basis of the results of this trial, the FDA approved panitumumab for the treatment of patients with CRC that has metastasized following standard chemotherapy.

Combination of targeted agents The successes observed with cetuximab and bevacizumab in combination with 5–FU–based chemotherapy have led to studies combining these agents with 5–FU–based chemotherapy in patients with metastatic CRC. Combined antibody therapy with
bevacizumab and cetuximab, when added to chemotherapy, surprisingly has shown no benefit and in some cases resulted in significantly shorter progression-free survival and an inferior quality of life. Similarly, the addition of panitumumab and bevacizumab to chemotherapy results in increased toxicity and decreased progression-free survival when compared with chemotherapy and bevacizumab alone. Therefore, the combination of chemotherapy and bevacizumab with either cetuximab or panitumumab should not be used outside of a clinical trial.

**Chemotherapy and surgery for stage IV CRC**
For previously untreated patients with stage IV disease and limited organ involvement, such as liver-only metastases, in whom surgery is thought possible, consideration should be given to neoadjuvant chemotherapy followed by synchronous or staged partial colectomy and metastasectomy. The appropriate chemotherapy in this setting is uncertain. However, the use of FOLFOX or FOLFIRI is reasonable. The addition of bevacizumab may enhance the response. However, because of the potential risk for bleeding or other surgical complications, bevacizumab should be discontinued 6 to 8 weeks before surgery. In addition, because of liver-associated changes with oxaliplatin or irinotecan, after approximately 2 to 3 months of chemotherapy, it is preferable to proceed with surgery after about 3 months of chemotherapy. Additional chemotherapy can be given after recovery from surgery. Patients with the development of limited metastatic disease after surgery and adjuvant therapy for stages II to III disease may also obtain long-term benefit from further chemotherapy and surgery.

**Metastasectomy**
Metastases to the liver and lungs account for most cases of non-nodal systemic disease in CRC. Resection of metastases, or metastasectomy, has gained recognition as a viable treatment. Resection of liver metastases results in cure rates of 5% to 60%, depending on the number of metastases and the stage of disease. Resection of solitary metastases in patients with stage I or II disease results in a 5-year survival rate of ~40% to 60%.

Metastasectomy for liver metastases should only be considered when complete resection is feasible on the basis of anatomic grounds and when adequate hepatic function can be maintained. Debulking resections are generally not recommended. Patients who are initially unresectable can be considered for resection after neoadjuvant chemotherapy as long as all disease, including the primary tumor, can be resected. Hepatic resection is the treatment of choice for resectable liver metastases from CRC. Ablative techniques can be considered in amenable lesions where surgical resection is not feasible.

Metastasectomy for lung metastases can be considered for highly selected patients in whom complete resection is feasible with maintenance of adequate pulmonary function. Resectable extrapulmonary metastases, particularly liver metastases, do not preclude resection.

**Treatment of advanced rectal cancer**

**Radiation therapy**
Radiation therapy is moderately effective in palliating the symptoms of advanced rectal cancer. Pain is decreased in 80% of irradiated patients, although only 20% report complete relief. Bleeding can be controlled in more than 70% of patients. Obstruction cannot be reliably relieved by irradiation, and diverting colostomy is recommended. Only 15% of patients with recurrent rectal cancers achieve local disease control with irradiation, and median survival is <2 years.

**Chemoradiation therapy** may be useful to convert fixed unresectable lesions into resectable lesions. These regimens have generally used protracted infusions of 5–FU (200 to 250 mg/m²/day) delivered via a portable infusion pump during pelvic radiation therapy (450 cGy over 5 weeks).
Intraoperative radiotherapy (localized irradiation given to the tumor or tumor bed at the time of resection) is under active investigation in advanced and locoregionally recurrent rectal cancers.

**Laser photoablation**
Laser photoablation is occasionally employed for temporary relief of obstructive rectal cancer in patients who are not surgical candidates because of the presence of distant metastases, surgical comorbidity, or extensive intra-abdominal disease.

**Endoscopic stent placement**
Endoscopic stents may have a place in patients with obstructing neoplasms. In this situation, the stent can serve as a bridge to relieve the obstruction before surgery and/or to allow for the administration of systemic therapy. The stent can migrate; thus, if there is response to therapy, the stent may dislodge and cause acute problems, such as perforation or pain. In some instances, the stent can also erode into adjacent structures, such as when radiation is utilized.

**Follow-up of long-term survivors**
Patients who have completed therapy for CRC require monitoring for potential treatment-related complications, recurrent disease, and new metachronous cancers. Specific follow-up recommendations for these patients are controversial. Guidelines for post-treatment surveillance/monitoring adopted by the NCCN are shown in **Table 10**.

**Anal Canal Carcinoma**

**Epidemiology, etiology, and risk factors**

In the United States, about 4,650 new cases of anal canal carcinoma are diagnosed each year. Overall, it is slightly more common in women than in men. More than 80% of anal canal tumors occur in individuals > 60 years of age. Epidemiologic studies suggest that receptive anal intercourse is strongly related to anal cancer.

The incidence rate of anal cancer for single men is reported to be six times that for married men. In people < 35 years old, anal carcinoma is more common in men than in women. A history of genital warts has been observed, suggesting that papillomavirus may be an etiologic factor.

**Diagnosis**

The diagnosis of anal canal carcinoma is usually delayed because the symptoms (bleeding, pain, and sensation of mass) are so often attributed to benign anorectal disorders, such as hemorrhoids or anal fissures.
Evaluation should include a careful rectal examination, endoscopic examination with description of lesion size, and assessment of whether there is invasion of disease into adjacent organs (vagina, urethra, or bladder). Reexamination with the patient under general anesthesia may be necessary. A diagnostic incisional biopsy is required.

Pelvic CT is suggested to evaluate pelvic nodes. Although distant metastases are uncommon at diagnosis, a chest x-ray and liver function tests are recommended. Suspicious inguinal nodes discovered on physical examination must be assessed pathologically. The incidence of inguinal nodal metastases at diagnosis varies from 13% to 25%. The presence of perirectal, inguinal, and pelvic lymph node involvement correlates with tumor size and is unusual for tumors < 2 cm in diameter. Formal groin dissection is not advised; needle aspiration should be performed, with limited surgical biopsy if results of aspiration are inconclusive.

**Pathology**

Pathologic complete response to neoadjuvant therapy is known to predict improved disease control in patients with rectal cancer. A recently reported phase II trial evaluated concurrent infusional 5–FU and radiation prior to surgery vs the same regimen with two cycles of FOLFOX6 prior to surgery. Patients who received FOLFOX6 after 5–FU and radiotherapy had a pathologic complete response rate of 28%, compared with 21% in patients treated with 5–FU and radiotherapy. There was a 5% rate of grade 3 or higher toxicity during the FOLFOX6 treatment (Garcia-Aguilar J et al: 2010 Gastrointestinal Cancers Symposium: abstract 421, 2010). Other studies, such as the Lyon R90-01 trial, have suggested that longer durations between radiotherapy and surgery may increase pathologic downstaging without a detrimental effect or morbidity of surgery.

**Squamous cell carcinomas** Most anal canal malignancies are squamous cell carcinomas. They have been classified as cloacogenic carcinomas, basaloid carcinomas, transitional cell carcinomas, or mucoepidermoid carcinomas. However, there is little difference in the natural history of these various types.

**Unusual tumors** arising in the anal canal include small-cell carcinomas, anal melanomas, and adenocarcinomas.

Small-cell carcinomas of the anal canal are aggressive neoplasms similar in natural history to bronchogenic small-cell carcinomas. If such a histology is identified, the clinician should be alerted to the possibility of early distant metastases, and treatment should include chemotherapeutic regimens used in bronchogenic small-cell carcinomas.
Although advanced anal melanomas generally are associated with a dismal survival, prognosis may be related to the depth of disease penetration. Early anal melanomas < 2.0 mm in depth can be cured with wide excision. More advanced disease can be treated with local excision and EBRT, with excellent local tumor control. Abdominoperineal resection is indicated only rarely in the management of anal melanoma, because lesions large enough to require radical surgery are almost always associated with distant spread of disease.

Adenocarcinomas are uncommon cancers associated with a poor prognosis. Treatment should be aggressive and based on a multimodality approach. The rarity of this tumor precludes the development of specific clinical trials.

### Staging

The size of the primary tumor is the most important clinical predictor of survival for patients with anal carcinomas. Both the UICC and the AJCC have agreed on a unified staging system (Table 11). The TNM classification distinguishes between anal canal carcinoma and anal margin tumors, because the latter exhibit biologic behavior similar to that of other skin cancers and are staged as skin cancers.

### Treatment

#### Surgery

In selected individuals with small superficial T1 tumors, local excision has achieved adequate local tumor control and survival. However, most studies of local excision have been retrospective, with small numbers of patients. Prior to the advent of primary radiotherapy and combined-modality treatment (see later in this chapter), abdominoperineal resection was considered to be the conventional treatment for patients with invasive anal canal cancer. Unfortunately, even with radical surgical procedures, local recurrences are frequent. Currently, radical extirpative surgery is indicated only after the failure of combined-modality treatment. Salvage abdominoperineal resection for persistent or recurrent disease has resulted in a 5-year survival of up to 60%. In one series, patients presenting with lymphadenopathy at primary diagnosis and those who received less than 55 Gy at initial chemoradiation treatment had a worse prognosis.

#### Radiation therapy

Trials of primary EBRT in patients with anal canal carcinomas have used doses varying between 4,500
and 7,550 cGy. Local tumor control rates of 60% to 90%, with 5-year survival rates of 32% to 90%, are similar to the results of surgical series when the trials are controlled for tumor size.

Interstitial radiation therapy alone has been used primarily in Europe for early-stage lesions. A relatively high radiation dose is delivered to a small volume. This modality carries a high potential for radiation necrosis and fails to incorporate the treatment of the inguinal nodes.

**Combined-modality treatment**
Chemotherapy given concurrently with irradiation is the preferred therapy for most patients with anal canal cancer (Table 12). Investigators from Wayne State University pioneered the use of simultaneous pelvic irradiation and chemotherapy in the treatment of patients with anal canal carcinomas. They demonstrated that the majority of such patients could be treated with this combination, obviating the need for an abdominoperineal resection. The original study design used 3,000 cGy over 3 weeks with 5–FU (1,000 mg/m²/day) as a continuous infusion on days 1 to 4 and then repeated on days 29 to 32. Mitomycin, 15 mg/m², was administered as an IV bolus on day 1. A total of 4 to 6 weeks after the completion of therapy, patients had a deep muscle biopsy of the anal canal scar.

<table>
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<th>TABLE 12</th>
<th>Chemotherapy regimen for anal canal cancer</th>
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An updated analysis of this experience demonstrated that 38 of 45 patients (84%) were rendered disease-free after chemotherapy and irradiation. Individuals who had positive results on biopsy underwent an abdominoperineal resection.

Because of the success of this experience, other investigators have attempted to implement infusional 5–FU and mitomycin with irradiation as definitive therapy. Most studies have used similar schedules of 5–FU and mitomycin but have used higher doses of pelvic irradiation (4,500 to 5,700 cGy). Five-year survival rates > 70% have been reported.

A randomized trial from the RTOG showed that the use of mitomycin with irradiation and 5–FU increased complete tumor regression and improved colostomy-free survival over irradiation and 5–FU alone. At 4 years, the colostomy-free survival rate was higher in the mitomycin arm than in the 5–FU-alone arm (71% vs 59%), as was the disease-free survival rate (73% vs 51%).

Several investigators have compared the results of irradiation alone vs irradiation plus chemotherapy. The current standard chemotherapy regimen for concurrent radiation is concurrent 5–FU and mitomycin. Intergroup RTOG 98-11 compared concurrent mitomycin and 5–FU with induction 5–FU and cisplatin, with concurrent cisplatin, 5–FU, and mitomycin. The mitomycin-containing regimen resulted in a lower colostomy rate but greater hematologic toxicity. Cummings et al found that with identical irradiation doses and techniques, the local tumor control rate for cancers > 2 cm rose from 49% with radiation therapy alone to 85% when 5–FU and mitomycin were combined with irradiation. Papillon and Montbarbon found an increase in the rate of local tumor control with a combined-modality approach compared with pelvic irradiation alone (81% vs 66%). Two randomized studies have shown improved local tumor control with chemoradiation therapy over irradiation.

RTOG 0529 was a phase II trial that evaluated dose-painted IMRT with 5–FU and mitomycin in patients with T2-4N0-3M0 anal cancer. The dose of radiation was dependent on tumor and nodal stage. There was a reduction of grade 3 or higher gastrointestinal or genitourinary toxicities with IMRT compared with that observed on RTOG 9811, which utilized conventional radiation approaches. Real-time quality assurance resulted in modification of contours in 79%. Early clinical response rates
were similar to those observed with conventional regimens (Kachnic LA et al: 2010 Gastrointestinal Cancers Symposium: abstract 405, 2010). These data suggest IMRT with chemotherapy may be a suitable treatment for patients with anal carcinoma, but contouring is complicated for this indication, even when clearly defined in a clinical trial.

A complete response to combined chemotherapy and radiation therapy is expected in 80% to 90% of patients with anal cancer. It is important to evaluate the response of therapy with a careful examination of the anal canal after treatment. Anal canal cancers can continue to regress for up to 3 or more months after completion of treatment. For this reason, it is recommended that a biopsy be performed no sooner than 3 months after the completion of treatment, unless there is evidence of disease progression or other evidence to suggest early recurrence. If pathologic evidence of recurrence is diagnosed, abdominoperineal resection is expected to yield long-term disease control and survival in 40% to 60% of patients.

Toxicity from combined radiotherapy and chemotherapy for anal carcinoma is significant, with high rates of dermatitis (often requiring treatment breaks) and gastrointestinal toxicity. Treatment breaks may decrease the efficacy of radiation. Intensity-modulated radiotherapy (IMRT) can help reduce the radiation dose to normal structures, such as the bowel, skin, genitalia, and femurs.

Two recent trials have addressed the use of IMRT with concurrent chemotherapy to reduce these toxicities. These studies have suggested that local tumor control and survival may be improved with IMRT. Toxicity was markedly reduced with the IMRT approach. The RTOG has completed a trial of IMRT for anal cancer and has recently published contouring guidelines for radiation oncologists who use IMRT.

**Chemotherapy**

Reports of other chemotherapeutic agents in anal cancer have been relatively anecdotal, with limited phase II studies. Because of the activity of cisplatin in other squamous cell carcinomas, this agent has been employed as a single agent or combined with infusional 5-FU in advanced disease.

Novel chemoradiation regimens have been evaluated in the hope of providing improved tumor control rates in patients receiving combined chemotherapy and radiation. Recent studies have evaluated chemotherapy combinations including cetuximab with radiation. These early studies are promising in regard to tolerability and response rates. The combination of cetuximab, cisplatin, and 5-FU with radiation therapy is being tested by the AAMCTC and the ECOG.

**Considerations for immunocompromised patients**

Immunocompromised patients are at higher risk of developing anal carcinoma. Because these patients may also have increased toxicity with combined chemotherapy and radiation, careful delivery of combined therapy should include a consideration of chemotherapy dose modification. Several series have evaluated the ability of immunocompromised patients to tolerate definitive chemoradiotherapy for anal cancer. Some series suggest that a CD4+ cell count lower than 200 cells/L in HIV-positive patients is associated with higher rates of toxicity. Recent studies have shown that the vast majority of immunocompromised patients can tolerate concurrent chemoradiotherapy, although dose adjustments may be required. The use of IMRT may benefit this patient subset.

**SUGGESTED reading**

On colorectal carcinoma

http://www.cancernetwork.com/cancer-management/colorectal/article/10165/1802621


On ANAL CANAL carcinoma


Abbreviations in this chapter
AAMCTC = AIDS Associated Malignancies Clinical Trials Consortium; ACOSOG = American College of Surgeons Oncology Group; ACS = American Cancer Society; AJCC = American Joint Committee on Cancer; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; GITSG = Gastrointestinal Tumor Study Group; GRCSG = German Rectal Cancer Study Group; NCCN = National Comprehensive Cancer Network; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; RTOG = Radiation Therapy Oncology Group; UICC = International Union Against Cancer