Colorectal cancer is a leading cause of death in the United States. A family history of colon cancer is a strong risk factor for development of the disease. Dietary factors have also been associated with the development of colorectal cancer. This article reviews the epidemiology, pathogenesis, genetics, clinical presentation, staging, and treatment of colorectal cancer. Surgical and adjuvant therapies for both colonic and rectal cancers are discussed. The management of the adenomatous polyps that often precede carcinoma is also reviewed, including the histologic progression of adenomatous polyps to frank carcinoma.

**Epidemiology**

Adenocarcinoma of the large bowel is the second-leading cause of cancer death in the United States and affects about 1 in 17 people. The world-wide incidence of colorectal cancer varies dramatically, from 3.4 cases per 100,000 population in Nigeria to 35.8 cases per 100,000 population in Connecticut. The overall incidence of colorectal cancer in the United States is nearly identical in men and women, with the mean age of presentation between 60 to 65 years of age. Recent data show a decline in the mortality from colorectal cancer. Possible explanations include improvements in diet and lifestyle, screening and early diagnosis, preoperative staging, surgical technique, and adjuvant therapies.

During the past 30 to 40 years, an unexplained shift has occurred in the natural history of colorectal cancer, with an increase in more proximally occurring tumors. This may represent a change in genetic susceptibility, an increase in proximally active carcinogens, or a reduction in distal lesions through endoscopic screening and polyp eradication programs.

Colorectal cancer is not uniformly fatal, but substantial differences in outcome exist depending upon the site of disease and the stage at presentation. Most patients (approximately 55%) who have colorectal cancer present with localized disease (ie, stage I or II), whereas 25% have more advanced disease with regional lymph node metastasis. Distant metastasis is present in 20% of patients upon initial presentation.

**Pathogenesis**

Regardless of etiology, most colorectal cancers arise from adenomatous polyps (Figure 1). Adenomatous polyps are visible gland-forming projections of the mucosa and are classified according to their attachment—those with a stalk (pedunculated) versus those that are flat (sessile); and histologic appearance—tubular (75%-87%), villous (5%-10%), or mixed tubulovillous (8%-15%). The overall incidence of polyps in the United States is 12% and prevalence, 35%. These figures increase with age, reaching a 40% incidence and 63% prevalence by age 70 years.

Considerable evidence has accumulated to substantiate the polyp to cancer (adenoma to carcinoma) sequence. When stratified by age and geographic location, the frequency of polyps varies proportionally with the incidence of colorectal cancer. Many early cancers originate in polyps, although more advanced tumors completely replace the polyp of origin. More than 33% of patients who undergo resection for treatment of colon cancer have 1 or more colon polyps. Furthermore, 75% of patients with synchronous colon cancers have polyps. The presence of polyps doubles the risk of subsequent (metachronous) colon cancer.

**Progression from Adenoma to Carcinoma**

Colonic mucosa undergoes an orderly progression from the initial development of a polyp to the development of frank carcinoma. The evolution of normal...
colonic mucosa from a benign adenoma to invasive carcinoma has been associated with a series of genetic events, in which sporadic point mutations cause activation of proto-oncogenes and loss of tumor suppressor genes (Figure 2).17–21 Proliferation of colonocytes from stem cells in the glandular crypts is normally restricted to the lower one third of the crypt. In polyps, this proliferative activity migrates upward, first forming microadenomas, which then progress to grossly visible adenomas. These aberrant cell lines fail to undergo normal maturation and apoptosis. Eventually, this leads to focal growth of dysplastic mucosa in aberrant crypt foci. These progressive molecular genetic changes and resultant deregulation of cell growth and proliferation eventually lead to the development of invasive carcinoma. This is a very slow process—the doubling time of a typical adenomatous polyp is ten years.

Management of Adenomatous Polyps

The great majority of polyps are non-neoplastic (ie, hamartomas or hyperplastic polyps); therefore, histologic diagnosis is essential to distinguish these “innocent” lesions from their premalignant (neoplastic) counterparts. The risk of any single polyp harboring an invasive carcinoma is directly related to its size. Polyps smaller than 1 cm in diameter are associated with an incidence of carcinoma of less than 1%, whereas polyps greater than 2 cm in diameter are associated with a 50% incidence of carcinoma.22 The degree of villous architecture, grade of dysplasia, and multiplicity are also incremental risk factors.8,16,22,23

The incidence and mortality of colorectal cancer in patients with adenomatous polyps can be reduced by careful endoscopic surveillance and polypectomy.24 Polyps with high grade dysplasia, but without invasion, can be treated with endoscopic polypectomy with little or no risk of recurrence or metastasis.

Development of invasive cancer in a polyp is more ominous, but treatment depends on the level of invasion of the cancer (Figure 3).25 Level 1 lesions invade through the muscularis mucosa but are confined to the head of the polyp. Level 2 lesions invade the adenoma-stalk junction; level 3 lesions, the stalk itself. Level 4 lesions invade into the submucosa of the underlying colonic wall. All sessile polyps with invasive carcinoma (not carcinoma in situ, which is level 0) are level 4 lesions. Only level 4 involvement is associated with an appreciable (6%) risk of nodal metastasis and requires surgical resection.26

Although most patients with polyps can be treated with endoscopic fulguration or snare polypectomy, 30% will develop recurrent adenomas. Hence, close endoscopic surveillance is necessary every 3 to 5 years.27 The presence of polyps with invasive carcinoma and 1 or more of the following features places a patient at high risk for local residual or nodal metastatic disease: polyp size greater than 1.5 cm in diameter, more than 50% of the polyp volume replaced by tumor, poorly differentiated tumor grade, lymphatic vessel invasion, tumor invasion to level 3 or 4, and a positive margin.28,29

Dietary Risk Factors for Colorectal Cancer

Epidemiologic studies have revealed a direct correlation between the incidence of colorectal cancer and per capita consumption of calories, dietary fat, and meat protein.30 The finding that immigrants from low-risk regions of the world assume the incidence rate of their adopted country31 implies that geographic variations are not related to genetic differences. Burkitt observed that South African Bantus ingested a diet high in roughage and fiber and low in animal fat and meat products. He believed this diet was responsible for a very low incidence of primary colorectal cancer.32 According to this theory, dietary fiber accelerates intestinal transit time and reduces the exposure of the colonic mucosa to potential carcinogens. Recent studies have refuted this hypothesis, however.33

The proposed mechanism for the association between a diet high in meat protein and colorectal cancer is that the increase in saturated animal fats results in an increase in anaerobic bacteria in the gut microflora. This results in an excessive production of deconjugated bile acids, which are known to be carcinogenic.34
Further, prospective studies have demonstrated that patients with elevated cholesterol levels have a higher risk of developing colon cancer. Despite the plethora of positive studies regarding the relation between the intake of animal fat and colorectal cancer, other epidemiological studies do not support this association. Conflicting results probably reflect the lack of control of other dietary components.

GENETICS OF COLORECTAL CANCER

Family history undeniably influences risk of developing colon cancer, and is present in approximately 25% of patients with colorectal carcinoma. The relative risk of developing colon cancer increases for each first-degree family member with a history of colon cancer. Other epidemiological studies do not support this association. Conflicting results probably reflect the lack of control of other dietary components.

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FAP Syndrome

The rarest hereditary colon cancer syndrome is FAP syndrome, accounting for approximately 0.5% of colorectal carcinomas. FAP syndrome is caused by a heritable autosomal dominant mutation of the adenomatous polyposis coli (APC) tumor suppressor gene on chromosome 5q21, with incomplete penetrance (50%). The incidence is 1 in 7,000 to 1 in 10,000. Spontaneous mutations account for approximately 20% of cases in which no prior family history is present. Persons with FAP develop hundreds to thousands of colon polyps in adolescence and, if untreated, invariably develop colon cancer by age 40.

In addition to classic FAP, 3 other important related syndromes occur. Persons with Gardner's syndrome develop desmoid tumors, osteoma, gastroduodenal polyps, congenital hypertrophy of the retinal pigment epithelium, and periamillary tumors, as well as polyposis. Turcot's syndrome is associated with polyposis and central nervous system malignancies, including neuroepithelial tumors such as medulloblastoma and glioblastoma. Persons with attenuated adenomatous polyposis coli (AAPC) have fewer polyps that are distributed more proximally. Patients with AAPC are prone to develop cancer at an increased rate relative to the normal population, and usually by age 54 years.

Testing for the APC genetic abnormality is commercially available. Identification of the abnormality in kindred of affected individuals can lead to earlier diagnosis through colonoscopic screening in childhood before frank carcinoma develops.

HNPCC Syndrome

HNPCC, which includes both Lynch I and Lynch II syndromes, accounts for 5% to 10% of all colorectal cancers. This heritable syndrome involves an autosomal dominant mutation in the mismatch repair gene, with nearly complete penetrance (70% to 80%). Persons with Lynch I syndrome develop a small number of proximal polyps at a young age, which often progress rapidly to the
development of multiple colon cancers. Persons with Lynch II syndrome (hereditary site-specific nonpolyposis colon cancer) develop the characteristics of Lynch I syndrome together with an excessive number of adenocarcinomas involving the breast, stomach, small bowel, urinary tract, endometrium, and ovary, as well as. The presence of HNPCC in a family is based on the following criteria (Amsterdam criteria): (1) colorectal cancer in at least 3 relatives, one of whom is a first-degree relative of the other two; (2) colorectal cancer in at least 2 successive generations; and (3) at least 1 case of colorectal cancer occurring before age 50 years.

**CLINICAL PRESENTATION**

The presenting symptoms of patients with colorectal cancer are a function of the anatomic location and nature of the lesion and are quite variable. Tumors may be asymptomatic for long periods. Symptoms, which may result from obstruction, perforation, and bleeding, include abdominal pain, hematochezia (bloody stools), weight loss, anemia, diarrhea, constipation or a change in bowel habit, an abdominal mass, and, occasionally, nausea and vomiting.

Right-sided colonic lesions (ie, of the ascending colon and cecum) often cause vague epigastric pain and chronic blood loss leading to fatigue. Angina pectoris and microcytic hypochromic anemia are occasionally associated with these lesions. Because of the smaller lumen in the left, or descending colon, stool becomes more concentrated as it passes, and patients with tumors in this region of the colon often present with symptoms of obstruction, constipation, or a change in the caliber of the stool. If the ileocecal valve is incompetent, the disease can be insidious, with progressive constipation and episodes of obstipation lasting days to weeks. Cancer arising in the rectosigmoid region is associated with tenesmus (crampy rectal pain from tonic rectal muscle contraction), narrowing of the stool, and hematochezia. Pelvic pain is often a late manifestation of colon cancer and indicates extension into the pelvic nerve plexus.
Except for patients with obstructive or perforative cancers, the duration of symptoms does not correlate with prognosis. Prognosis of colorectal cancer is, however, strongly associated with stage at presentation. In any individual, the development of altered bowel habits and rectal bleeding, together with a microcytic anemia, mandate that a digital rectal examination and colonoscopy or flexible sigmoidoscopy and barium enema be performed. Rectal bleeding alone may also be an indication for further evaluation of the colon, even in the presence of anorectal pathology that explains the bleeding, such as hemorrhoids or anal fissure.

### STAGING AND PROGNOSIS

In 1932, Dukes first proposed a classification of staging for colorectal cancer that still has clinical value in predicting prognosis. To more accurately predict prognosis, many variations in Dukes' original classification have been proposed. In 1987, the American Joint Committee on Cancer and the Union Internationale Contre le Cancer agreed to standardized staging to evaluate results with uniformly comparable data. In the current TNM classification method, T represents the depth of tumor penetration; N, the presence or absence of lymph node involvement; and M, the presence of distant metastasis (Tables 1 and 2).

### Table 1. TNM Classification of Colorectal Cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 No evidence of tumor</td>
<td>N0 No lymph node involvement</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N1 1–3 perirectal or pericolic nodes involved</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>T1 Tumor invades submucosa</td>
<td>N2 4 or more perirectal or pericolic nodes involved</td>
<td></td>
</tr>
<tr>
<td>T2 Tumor invades muscularis propria</td>
<td>N3 Lymph node involvement along major vascular trunk</td>
<td></td>
</tr>
<tr>
<td>T3 Tumor invades subserosal, pericolic, or perirectal tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumor directly invades other organs or structures</td>
<td></td>
<td></td>
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</tbody>
</table>

### Table 2. Staging Systems for Colorectal Cancer

<table>
<thead>
<tr>
<th>Staging System</th>
<th>AJCC*</th>
<th>Modified Aster-Coller†</th>
<th>Dukes‡</th>
<th>TNM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Tis</td>
<td>A</td>
<td>A T1 N0 M0</td>
<td></td>
<td>Tis</td>
</tr>
<tr>
<td>I A</td>
<td>B1</td>
<td>T2 N0 M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II B2</td>
<td>B3</td>
<td>T3 N0 M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III C (C1 = T2, C2 = T3, C3 = T4)</td>
<td>C</td>
<td>Any T, N1, M0</td>
<td>Any T, N2, M0</td>
<td></td>
</tr>
<tr>
<td>IV D</td>
<td>Any T, any N, M1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer.


†Based on Gunderson LL, Sosin H: Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum. Clinicopathologic correlation and implications for adjuvant therapy. Cancer 1974;34:1278-1292.


Several factors in addition to disease stage affect prognosis and overall patient survival (Table 3). In 1958, Hoerner et al were the first to observe the poor prognosis for colorectal cancer in very young patients (younger than 20 years). Some authors have even suggested that colorectal carcinoma in the very young may represent a completely separate and distinct clinical, epidemiologic, etiologic, and prognostic entity. Survival in patients younger than 40 years is lower than overall survival due to features indicating aggressivity of the cancer, such as high histologic grade, mucinous histology, and higher stage at presentation.

Obstruction and perforation have also been shown to reduce survival. In aggregate, those patients presenting with obstruction or perforation have a worse overall 5-year survival rate—30% versus 40% in patients without obstruction or perforation (all stages combined). Surprisingly, rectal bleeding has been associated with a more favorable prognosis. Rectal bleeding, which indicates mucosal erosion, leads to earlier diagnosis and surgical intervention.
Several large studies have revealed an improved survival rate in women with colorectal cancer.\textsuperscript{3} Recent data further confirm a greater decline in mortality in women than in men over the past 50 years; however, the reasons for this difference are unknown.\textsuperscript{63}

Location and configuration of a tumor also affect prognosis. Tumors located below the peritoneal reflection (ie, the rectosigmoid junction) carry a poorer 5-year survival than those located more proximally.\textsuperscript{64} Ulcerating or infiltrating tumors tend to be more aggressive than exophytic tumors.\textsuperscript{65} Poor prognosis has also been associated with lymphatic or vascular invasion and poorly differentiated tumors, especially signet-ring cell or mucin-producing subtypes.

Finally, the preoperative level of the tumor marker carcinoembryonic antigen (CEA) is related to the stage of disease and is reflective of tumor burden in CEA-producing tumors. CEA values greater than 5.0 ng/mL have been associated with a poorer prognosis, independent of pathologic stage of the cancer. The CEA level also plays a role in predicting tumor recurrence and as a monitor of response to treatment. Increasing CEA values may predate clinical or radiographic evidence of recurrence.\textsuperscript{66}

**SURGICAL TREATMENT**

**Considerations in Planning Surgery**

Curative management of colorectal cancer requires surgical resection, often accompanied by perioperative adjuvant therapy (chemotherapy and/or radiation therapy). Considerations in planning appropriate surgical intervention involve accurate staging of the tumor; the technical feasibility of resection; anatomic site of the tumor; the chance of recurrence or complications; and the probability of cure.

Local considerations include the depth of invasion, histologic grade, extent of lymphovascular invasion, distance from the anal verge, and presence of fixation to surrounding structures. Regional factors include the presence of metastatic lymph nodes, distance of the lesion from the bony pelvis and from the anal sphincter, origination of the arterial blood supply, length of available bowel for anastomosis, and the risk of synchronous or metachronous lesions. Systemic considerations include the presence of distant metastases, underlying medical conditions, anticipated longevity, presence of peritoneal tumor implants/malignant ascites, overall activity level and functional status of the patient, and degree of fecal continence.\textsuperscript{67}

The timing of surgery (eg, urgent versus elective) depends on whether the tumor produces obstruction, hemorrhage, or perforation, or whether these urgent complications are impending. Patients are sometimes better served if temporizing measures can be undertaken so that a safer elective procedure may be performed at a later time.

Clinical preoperative staging is important to developing the best individualized treatment plan based on the nature and extent of the tumor and the patient's best chances for quality survival. A chest radiograph, contrast-enhanced abdominopelvic computed tomographic scan, complete blood count, liver and renal function tests, imaging evaluation of the entire colon (colonoscopy or barium enema), and measurement of CEA level should be performed in most instances before surgery. Preoperative staging is particularly important in cases of rectal cancer. Endorectal ultrasound is a valuable adjunct in the clinical preoperative staging of early rectal cancer. Preoperative staging for colon cancer is more controversial, and some believe computed tomography is unnecessary in these cases.

**Surgical Treatment of Colon Cancer**

Colon cancers are usually resected with their regional blood supply and lymphatic drainage (ie, right hemicolec tomy, transverse colectomy, left hemicolec tomy, or sigmoid colectomy). At least a 4-cm margin of grossly uninvolved proximal and distal tissue is also resected.\textsuperscript{68} Subtotal colectomy is performed for synchronous lesions or when the risk of metachronous lesions is present. Preoperative adjuvant therapy is usually unnecessary. If technically feasible, palliative resection is performed for patients with incurable disease to prevent bleeding, obstruction, or intractable pain.
Surgical Treatment of Rectal Cancer

The unique anatomy and function of the rectum and anal sphincters require special considerations in planning surgical treatment of rectal cancer. Radial margins are important in rectal lesions because these distances are more often limited by anatomic restrictions imposed by the bony pelvis and close proximity of vital local structures.

Rectal tumors are usually classified as upper third, middle third, or lower third, corresponding to distance from the anal verge (11–15 cm, 7–11 cm, and 3–7 cm, respectively). Lesions of the upper two thirds of the rectum are generally treated by low anterior resection (abdominal approach), with primary anastomosis (stapled or hand-sewn), and at least a 2-cm margin distally.

If the lesion is detected early (Stage I) or the patient is an unsatisfactory operative risk or refuses surgery, lesions of the lower third of the rectum may be amenable to local treatment by transanal excision. This preserves the anal sphincter and continence mechanisms, but may necessitate adjuvant therapy. More advanced lesions in this region may require perioperative adjuvant therapy and either attempted sphinctersaving colonoscopic procedures or abdominoperineal resection with permanent colostomy.

Locally invasive lesions (T4) of the rectum should be resected en bloc with adjacent involved structures. These lesions may be curable if completely resected with an adequate margin of normal tissue. Complete lymphadenectomy for rectal cancer (total mesorectal excision) has recently gained attention and has been promoted to decrease local recurrence and improve long-term survival.

ADJUVANT THERAPY

Colon Cancer

Systemic 5-fluorouracil (5-FU) forms the cornerstone of postoperative adjuvant therapy. The pathologic stage of disease is critical in determining which colon cancer patients receive adjuvant treatment. The excellent survival rate for stage I patients treated with surgery alone has excluded this group. Until recently, recommendations included treatment with 5-FU and levamisole for all patients with stage III colon cancer. These recommendations were based on 2 large-scale, randomized studies comparing fully resected stage III patients who received postsurgical observation only versus those who received 1 year of adjuvant treatment with 5-FU and levamisole. (Levamisole is an antihelmintic agent whose mechanism of action is thought to include immunostimulation.) The studies revealed a 15% absolute reduction in risk of recurrence and a 33% relative reduction in the overall death rate with the 5-FU/levamisole combination. The 3-year overall survival rate in the 5-FU/levamisole group was estimated at 71% versus 55% for the observation group.

However, these recommendations are now being challenged based on evolving data utilizing a less intensive regimen of 5-FU plus leucovorin for 6 months. In the past 2 years, 3 randomized phase III studies have compared 5-FU/levamisole as the control arm against 5-FU/leucovorin, with variables including the dose of leucovorin and the duration of the 5-FU/leucovorin treatment. These studies included more than 6000 patients and the end points analyzed, including survival, did not reveal any significant difference between the 5-FU/levamisole and the 5-FU/leucovorin arms. These studies confirm that the shorter duration leucovorin arms were as effective as the 12-month 5-FU/levamisole protocol with less cumulative toxicity. Taken together, these studies now provide the basis for the current recommendation of adjuvant therapy for stage III colon cancer, which is a 6 to 8 month course of 5-FU and leucovorin.

In contrast to stage III colon cancer, adjuvant treatment of patients with stage II disease remains an enigma. Surgery alone results in 5-year survival rates of 75%–80%. To date, no single study has demonstrated an overall benefit of adjuvant treatment, with improved overall survival as the endpoint. The inability to demonstrate a survival advantage in stage II patients is thought to represent flaws in the methodology and the low event rate observed in the small studies that have been performed. A recent meta-analysis of 4 National Surgical Adjuvant Breast and Bowel Project trials using 5-FU–based chemotherapy was performed to help clarify the role of chemotherapy in this setting. Relative reductions in recurrence and mortality comparable to those for stage III disease were observed in patients with stage II colon cancer. Although controversial, offering stage II patients with certain adverse factors adjuvant chemotherapy in a nonprotocol setting appears reasonable. These factors include complete bowel obstruction or perforation of the bowel wall and poorly differentiated histologic characteristics.

Rectal Cancer

The natural history and recurrence pattern of rectal cancer is unusual in its high frequency of locoregional failure (25%–30% recurrence rate). This unusual recurrence rate is the result of (1) the loss of the serosa in the rectum that acts as a barrier to transmural tumor penetration; and (2) the rich lymphatic supply of the
pelvic side wall adjacent to the rectum, which facilitates spread of tumor cells into surgically inaccessible tissue. Consequently, radiation therapy is integrated into the management of rectal cancer as an adjuvant therapy.

The results of 2 studies serve as the basis for recommending that patients with stage II or III rectal cancer receive postoperative combined-modality therapy consisting of approximately 4,500 to 5,000 rad of radiation therapy and 6 months of 5-FU therapy. These and other studies confirm that the addition of combined-modality adjuvant therapy is superior to surgery alone. However, the most effective combination of drugs, mode of administration, and sequence of radiation and chemotherapy has yet to be determined. Preoperative combined-modality therapy is gaining acceptance in the treatment of rectal tumors. The potential advantages of this approach, as compared to postoperative adjuvant therapy, include decreased tumor seeding at the time of surgery, increased radiosensitivity, and enhanced sphincter preservation. When adjuvant therapy is administered preoperatively, the surgery may be changed from an abdominoperineal resection to a sphincter-sparing low anterior resection.

CONCLUSION

Although colorectal cancer is a leading cause of death in the United States, improvements in our understanding of the pathogenesis and risk factors have led to improved survival rates in recent years. Screening programs for colorectal cancer have resulted in improved management of precancerous polyps and in detection of cancer at an earlier stage. An understanding of the genetics of familial colorectal cancer syndromes has led to increased surveillance of people whose family history puts them at increased risk of developing cancer.

Treatment of colorectal cancer consists of surgical resection with adjuvant chemotherapy and/or radiation therapy as indicated. The current standard adjuvant therapy for stage III colon cancer is 5-FU with leucovorin. Research to optimize adjuvant chemotherapy for stage II colon cancer is ongoing. Rectal carcinomas usually require combined radiation and chemotherapy in addition to surgical therapy; the optimal timing and sequence of these modalities is also under investigation. Future advances in the treatment of colorectal cancer will depend on our improved understanding of the molecular genetic mechanisms in the development of colorectal cancer and the development of new pharmacologic and genetic therapeutic measures as an adjunct to resective surgery.

REFERENCES


