Sporadic (Nonhereditary) Colorectal Cancer: Introduction

Colorectal cancer affects about 5% of the population, with up to 150,000 new cases per year in the United States alone. Cancer of the large intestine accounts for 21% of all cancers in the US, ranking second only to lung cancer in mortality in both males and females. It is, however, one of the most potentially curable of gastrointestinal cancers. Colorectal cancer is detected through screening procedures or when the patient presents with symptoms. Screening is vital to prevention and should be a part of routine care for adults over the age of 50 who are at average risk. High-risk individuals (those with previous colon cancer, family history of colon cancer, inflammatory bowel disease, or history of colorectal polyps) require careful follow-up.

There is great variability in the worldwide incidence and mortality rates. Industrialized nations appear to have the greatest risk while most developing nations have lower rates. Unfortunately, this incidence is on the increase. North America, Western Europe, Australia and New Zealand have high rates for colorectal neoplasms (Figure 2).

Symptoms
Colorectal cancer does not usually produce symptoms early in the disease process. Symptoms are dependent upon the site of the primary tumor. Cancers of the proximal colon tend to grow larger than those of the left colon and rectum before they produce symptoms.

Abnormal vasculature and trauma from the fecal stream may result in bleeding as the tumor expands in the intestinal lumen. Typically, blood is mixed in with the stool and may not be obvious to the patient (occult bleeding). Patients may present with iron deficiency anemia. Alternatively, tumors of the anus, sigmoid colon and rectum may give rise to hematochezia or blood in the stool that is readily apparent.

As colon cancer grows, several symptoms may appear. Obstruction of the colonic lumen may produce symptoms of abdominal distension, pain, nausea, and vomiting. Obstruction of the gastrointestinal tract suggests a large tumor and a poorer prognosis.

Other symptoms of colorectal cancer may suggest an invasive process. Invasive tumors can penetrate the muscularis propria and invade adjacent tissue. This results in pain and may initiate symptoms specific to the site of invasion. Tenesmus is produced by tumor invasion into the rectum; bladder penetration may produce urinary symptoms such as pneumaturia. Pelvic invasion may produce perineal or sacral pain, and colonic perforation may result in an acute abdominal pain.

Some tumors produce a wasting syndrome. Cancer cachexia is characterized by loss of appetite, weight and strength. The wasting occurs despite the fact that most patients with colorectal cancer do not have hypermetabolic energy expenditure. Cancer cachexia is common in patients with advanced gastrointestinal malignancies.

Pathophysiology
Basic and clinical research efforts in colorectal cancer began in the 1980’s and continue to accumulate new information. Great strides have been made in understanding the pathogenesis. Epidemiologic studies have contributed to our understanding of the role diet may play in this disease. Additionally, studies have confirmed a genetic scheme in pathogenesis that has validated a multi-step process in the colon and rectum.

Adenomatous polyps and adenocarcinoma are epithelial tumors of the large intestine and the most common and clinically significant of intestinal neoplasms. The potential for polyps or adenomas to develop into cancer increases with patient age. Adenomas greater than 1 cm, with extensive villous patterns are at increased risk of developing into carcinomas (Figure 3).

The development of cancer of the colon and rectum is thought to be influenced by diet, genetic, and environmental factors. The incidence of colorectal cancer increases with age beginning at 40 but remains relatively low until the age of 50 and then rapidly accelerates. This prevalence appears to double with each successive decade until about age 80. Those with a personal history of adenomas or colorectal cancer are at increased risk. Individuals with a family history of colorectal cancer or adenomas, various genetic polyposis and nonpolyposis syndromes, other cancers, and inflammatory bowel disease are also at higher risk of developing colorectal cancer. It is important to note, however, that most patients have no identifiable genetic risk factors (Figure 4).
Colorectal adenomas have a potential to progress to malignancy. Malignancy may spread by direct extension into other organs in the abdominal cavity. Invasion of the lymph vessels leads to lymph node metastases and invasion through the blood stream (hematogenous) can result in metastasis to distant sites such as the liver. Figure 5. Illustrates the distribution of colorectal tumors.
Sporadic (Nonhereditary) Colorectal Cancer: Anatomy

The lower gastrointestinal tract is divided into the cecum, ascending, transverse, descending colon, sigmoid colon, and rectum. The large intestine (colo rectum) begins at the cecum, which is a pouch of approximately 2 to 3 inches in length. Ileal contents empty into the cecum through the ileocecal valve. The appendix extends from the base of the cecum. The ascending colon rises from the cecum along the right posterior wall of the abdomen, to the right upper quadrant and to the undersurface of the liver. At this point, it turns toward the midline (hepatic flexure) becoming the transverse colon. The transverse portion crosses the abdominal cavity toward the spleen in the left upper quadrant. At this point, it turns downward at the splenic flexure. Continuing along the left side of the abdomen, the descending colon turns medially and inferiorly to form the S-shaped sigmoid colon. The rectum makes up the last 5 to 10 inches of the large intestine, beginning from the end of the sigmoid colon down to the anal canal (Figure 6). The rectum is located within the pelvis and is not a true intra-abdominal structure. The diameter of the rectum is larger than that of the colon, and serves primarily as a storage reservoir.

![Image of colorectal anatomy]

**Figure 6.** Normal colorectal anatomy. A, anatomy of the colon; B, anatomy of rectum.

The pelvic musculature, or levator ani muscles and the internal and external anal sphincter muscles, bind the most distal rectum and anus. The sphincter muscles maintain bowel continence.

The entire large intestine is approximately 5 to 6 feet in length with a diameter that varies from 1–2 inches. It is the site of salt and water absorption. Glands secrete large quantities of alkaline mucus that lubricates the intestinal contents and neutralizes acids formed by bacteria in the intestine. These bacteria aid in decomposition of undigested food residue, unabsorbed carbohydrates, amino acids, cell debris, and dead bacteria through the process of segmentation and putrefaction. Short-chain fatty acids formed by bacteria from unabsorbed complex carbohydrates provide an energy source for the cells of the left colon. Maintenance of potassium balance is also performed by the colon where the epithelium absorbs and secretes potassium and bicarbonate.
Sporadic (Nonhereditary) Colorectal Cancer: Causes

Diet
Diet is considered a determinant of increased risk in the development of colorectal cancer. Although it is difficult to ascertain which components of the diet are most important in conferring risk cancer, compelling evidence suggests a strong dose-related association between red meat and fat intake and colorectal cancer.

While consumption of animal fat is positively associated with colon cancer, consumption of fish and skinless chicken is associated with lower risk. Higher cholesterol values (a reflection of total dietary fat intake) correlate significantly with later tumor development. Obesity in middle age is also associated with increased risk of colon cancer in men; increased physical activity appears to eliminate this risk.

Dietary fiber demonstrates a protective effect in the pathophysiology of colorectal cancer. Diets rich in vegetables and high fiber grains demonstrated significant protection against fatal colorectal cancer, as revealed in a prospective study of more than 760,000 people. Fiber appears to have a number of mechanisms responsible for its protective effects. First, fiber decreases the fecal transit time by increasing stool bulk. Fiber also appears to dilute the concentration of other colonic constituents, which tend to minimize contact between carcinogens and colon epithelium. In addition, fiber is not digested or absorbed in the small intestine but undergoes fermentation in the presence of the colonic flora. This reduces fecal pH and generates short-chain fatty acids (certain short-chain fatty acids can protect isolated colonic epithelial cells).

Diet appears to play a significant role in determining the incidence of colorectal cancers in the general population. Although the international incidence of colorectal cancer varies widely, groups migrating from low-risk to high-risk regions experience an increase in the incidence of the disease. Diets high in fat and low in fiber have consistent associations with increased colorectal cancer risk. Suggestions for diet modification to reduce cancer risk include: reduced caloric intake, reduction of dietary fat to less than 35% of caloric consumption, increased consumption of fresh fruit and vegetables with at least 25 g of fiber (see Lifestyle) (link to hereditary colon cancer web site Lifestyle section). Those using aspirin have less colorectal cancer than the rest of the population. Though the mechanism by which aspirin and NSAIDs exert a protective effect against tumor formation is speculative, studies have revealed a significant reduction in relative risk of colon cancer death among users (aspirin use more than 16 times per month).

Genetics
Colorectal cancer, or a predisposition to this disease, may be inherited. In particular, familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which affected patients have 100 percent risk of colorectal cancer development. A mutation of the APC gene (adenomatous polyposis coli (APC)) on chromosome 5 causes this disease. Gene testing is available to identify patients with this genetic mutation. Sporadic colorectal cancer is the term given to those patients who are affected with the disease, but have no family history of this condition.

Hereditary nonpolyposis colorectal cancer (Lynch syndrome or HNPCC), an autosomal dominant disorder, is a disease in families where multiple members have colorectal and other forms of cancer. The syndrome causes right-sided colon cancer and may produce primary cancers in other sites. Researchers have isolated five mutated genes associated with HNPCC: human MutS homolog 2 gene (hMSh2), MutL homolog 1 gene (hMLh1), human PMS homolog 1 gene (hPMS1), and human PMS homolog 2 gene (hPMS2) and MSH6 (MS homolog 6 gene). Hereditary nonpolyposis colorectal cancer is characterized in families with at least three members with colorectal cancer (one must be a first degree relative of the other two), at least two successive generations affected, and diagnosis of one relative before the age of 50 (Amsterdam criteria).

Ulcerative Colitis and Crohn’s Disease
Ulcerative colitis and Crohn’s disease are inflammatory conditions of the intestines; both are known risk factors for colorectal cancer. The risk of development of colorectal cancer is related to the severity and duration of the disease. Patients with ulcerative colitis and Crohn’s disease should undergo colonoscopic surveillance for epithelial dysplasia, a precursor to cancer, at routine intervals. Surveillance should be performed every 1–2 years in patients with 8-10 years duration of disease and annually in those with disease history of over 15 years.

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Sporadic (Nonhereditary) Colorectal Cancer: Diagnosis

Overview
Because colorectal cancer and polyp are usually asymptomatic during the early stages, patient screening is critical to reduce the morbidity and mortality. Currently, the mainstay of screening involves fecal occult stool testing and bowel examination either by endoscopy or barium enema.

Fecal Occult Blood Testing
Neoplasm in the colon and rectum are known to bleed early in their development. An inexpensive, easy to perform screening tool is the guaiac test for occult blood in the stool.

The test uses the peroxidase activity of hemoglobin to cause a change in a reagent. Patients are asked to consume diets high in fiber, restrict red meat consumption, vitamin C, and NSAID drugs for several days prior to testing. Since adenomas or tumors bleed intermittently, samples are taken from three successive stool specimens. Positive results indicate the need for complete examination of the colon. The sensitivity of fecal occult blood testing ranges from 30–92% with a specificity of 98%.

Barium Enema
A barium enema is a radiological examination of the rectum and the entire colon. Prior to a barium x-ray, the patient may have to undergo a preparation that includes a liquid diet and enemas or cathartics to clear stool from the colon. This preparation may differ from exam to exam and from one physician to the next. Prior to this exam, a barium preparation (a contrast agent) is administered through a rectal tube (Figure 7).

The barium enema has been used for many years to diagnose polyps and colon cancers. Single contrast examination is usually not sensitive enough and has been replaced by double contrast studies. The double contrast barium enema is a diagnostic procedure that can provide important information about colonic stricture or obstruction (Figure 8).

The utility of double contrast barium radiography is dependent upon the skill of the radiologist in reading the subtleties of the resultant film. Additionally, successful studies are dependent upon the patient’s preparation and cooperation during the procedure. No sedation is required. The entire colon may be examined, though overlapping loops of the bowel and the flexures are difficult areas to interpret. The complication rate with the procedure is very low; the rate of perforation is 1 in 25,000 examinations. The sensitivity of double contrast barium enema ranges from 39–90%. The addition of flexible sigmoidoscopy to double contrast barium enema improves the diagnostic yield.
Endoscopic Diagnosis

Flexible Sigmoidoscopy
Flexible sigmoidoscopy may be used to screen for colorectal cancer. A flexible fiberoptic tube is introduced through the rectum and slowly advanced toward the splenic flexure. This allows for visualization of the lumen. The physician may inspect the bowel for polyps and lesions from the anus to the descending colon (Figure 9). Because this region is the site of 60% of all neoplasms, flexible sigmoidoscopy along with fecal occult blood testing provides an effective screening tool for colorectal cancer.

![Figure 9: Position of the sigmoidoscope in the colon; B, endoscopic view; C, detail of the colonoscope tip.](image)

No rigorous preparation is required for sigmoidoscopy other than two Fleet's Enemas and Magnesium Citrate (link to preparation instructions in direct access endoscopy section). Sedation is not required for this procedure, which may be performed by general internists and/or endoscopic technicians with appropriate training. The procedure has a low complication rate with perforation occurring in only 1–2 per 10,000 exams. Biopsies of suspicious lesions for histological examination may be obtained during this procedure. Figure 10 illustrates patient positioning and the endoscopy room set-up for flexible sigmoidoscopy and colonoscopy procedures.

![Figure 10: Patient positioning and room set-up for sigmoidoscopy and colonoscopy.](image)

Colonoscopy
Colonoscopy is the most widely used diagnostic method to study the colon and has the highest diagnostic sensitivity and specificity of all available tests. Ninety to 95% of the colon can be examined in most studies (Figure 11).
The patient prepares for the procedure using a nonabsorbable gastrointestinal lavage solution and/or the administration of laxatives. Intravenous analgesia and sedation are administered during the examination. The examination does carry an extremely small risk of complications (0.1–0.3% risk of hemorrhage and perforation). Colonoscopy offers the flexibility of performing mucosal biopsy of suspicious regions and the ability to perform endoscopic polypectomy. Figure 13 illustrates a sessile polyp, a pedunculated polyp, and an adenocarcinoma of the colon with corresponding endoscopic views.

This single test, which usually takes 60 minutes or less to complete, may be both diagnostic and therapeutic. The sensitivity of colonoscopy for the detection of polyps greater than or equal to 1 cm and tumors is greater than 95%. Colonoscopy is the preferred procedure for diagnosis of symptomatic patients. At the present time it is the “gold standard” for the diagnosis of colorectal neoplasms.

Screening

Educational campaigns and screening strategies targeted at high-risk groups are urgently needed to increase the public’s awareness of colorectal cancer screening for prevention and early detection. Colon cancer screening is one way that everyone can improve his or her chances against colon cancer. Early detection is essential to ensure survival if cancer is found. When polyps or very early cancer are found, the cure rate is close to 100%. Screening has led to a decline in the number of deaths from colon cancer over the last 20 years. The combination of screening and prevention will have the biggest impact in our efforts against colorectal cancer.

A variety of national organizations involved with the diagnosis and treatment of colorectal cancer developed the following guidelines for screening.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Suggested screening</th>
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<tbody>
<tr>
<td>Asymptomatic, greater than 50 years, no risk factors</td>
<td>Annual fecal occult blood test with flexible sigmoidoscopy every 5 years</td>
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<tr>
<td></td>
<td>Double contrast barium enema every 5 years</td>
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<tr>
<td></td>
<td>Colonoscopy every 10 years</td>
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Table 1. Patients at average risk for colorectal cancer (CRC)
Table 2. Patients at increased risk for colorectal cancer (CRC)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Suggested screening</th>
</tr>
</thead>
</table>
| First degree relative with CRC or adenomatous polyps diagnosed at or greater than age 60 | Begin screening at age 40  
Annual fecal occult blood test and flexible sigmoidoscopy every 5 years  
Double contrast barium enema every 5 years  
Colonoscopy every 10 years |
| First degree relative with CRC or adenomas before age 60 | Begin screening at age 40 years or 10 years earlier than the earliest diagnosis in the family  
Colonoscopy every 3-5 years  
Double contrast barium enema every 5 years |
| 2 or more first degree relatives with CRC | Begin screening at age 40 or 10 years earlier than the earliest diagnosis in the family  
Colonoscopy every 3-5 years  
Double contrast barium enema every 5 years |
| Second or third degree relatives with CRC | Annual fecal occult blood test and flexible sigmoidoscopy every 5 years  
Double contrast barium enema every 5-10 years  
Colonoscopy every 10 years* |
| Adenomatous polyps removed | Colonoscopy every 3 years  
If normal then every 5 years |
| Resected CRC | Colonoscopy within 1 year of resection  
If normal, subsequent exams at 3-5 years |
| Family history of FAP | Genetic counseling  
Flexible sigmoidoscopy beginning at puberty |
| Family history of HNPCC | Colonoscopy every 1-2 years, at age 20-30  
Colonoscopy every year at age 40 |
| Inflammatory bowel disease | 8 years of IBD (panscolitis), colonoscopy every 1-2 years  
15 years left sided IBD, colonoscopy every 1-2 years |
* Colonoscopy may be started at a younger age depending on the number and age of the second- and/or third-degree relatives with colon cancer.

Table 3. TNM Classification and Duke's Classification

<table>
<thead>
<tr>
<th>Staging</th>
<th>Dukes' Classification (Astler-Coller modification)</th>
</tr>
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<tbody>
<tr>
<td>The vast majority of colorectal cancers are adenocarcinomas, tumors that arise from the colon mucosa cells. While most adenocarcinomas are well or moderately differentiated, approximately 15% are poorly or undifferentiated tumors. These tumors are associated with a poorer prognosis. Mucinous or colloid carcinomas (with moderate to prodigious mucin production) are also associated with less favorable 5-year survival rates.</td>
<td></td>
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<tr>
<td>Tumors are “staged” according to evidence of invasion into the intestinal wall or evidence of spread. There is a close correlation between advancing stage and cancer mortality. Tumor size does not appear to be important in terms of outcome. The aggressiveness of colorectal cancer is based upon its ability to grow and invade the colonic wall, lymphatics, and blood vessels. Below are the classifications of tumor stage currently used.</td>
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<table>
<thead>
<tr>
<th>TNM Classification (American Joint Commission on Cancer)</th>
<th>Dukes' Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stages</strong></td>
<td><strong>T</strong></td>
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<tr>
<td>Stage 0</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3N0M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1N1M0 or T2N1M0</td>
</tr>
<tr>
<td></td>
<td>T3N1M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

Table 3. TNM Classification and Duke's Classification
TX – primary tumor cannot be assessed.
T0 – no evidence of primary tumor.
Tis – carcinoma in situ: intraepithelial or invasion of lamina propria.
T1 – tumor invades submucosa.
T2 – tumor invades muscularis propria.
T3 – tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissues.
T4 – tumor directly invades other organs or structures and/or perforates visceral peritoneum.
NX – regional lymph nodes cannot be assessed.
N0 – no regional lymph node metastasis.
N1 – metastasis in 1–3 regional lymph nodes.
N2 – metastasis in 4 or more regional lymph nodes.
MX – distant metastasis cannot be assessed.
M0 – no distant metastasis.
M1 – distant metastasis.

Figure 13 illustrates the stages of colon cancer.
Sporadic (Nonhereditary) Colorectal Cancer: Therapy

Endoscopic Therapy

Colonoscopy

Most adenomatous polyps can be completely and safely removed during colonoscopy. Small polyps (<5mm) should be biopsied to determine whether they are hyperplastic polyps or adenomas. Polyps are removed with biopsy forceps (Figure 14), or snare resection (Figure 15) with or without cautery.

Pedunculated polyps can be resected with application of cautery through a snare localized around the polyp stalk.

Some sessile polyps require special techniques. Saline is injected into the submucosa area in order to elevate the polyp and facilitate removal by snare (Figure 16).

Large sessile polyps may be resected piecemeal with snare and cautery current. In cases of unsuccessful resection of the polyp, the patient is referred for surgery.

When large polyps are involved, it may be useful to mark the polypectomy site with India ink (Figure 17). Site tattooing may help localize the area during subsequent surveillance colonoscopies and may assist the surgeon in locating the area to be resected.
The most common complications of colonoscopy and polypectomy are bleeding or bowel perforation, which occurs in 0.1%–0.2% of procedures. When performing polypectomies of large polyps (Figure 18), use of excessive cautery may cause perforation or full wall thickness burn (postpolypectomy coagulation syndrome). These complications tend to occur more frequently in the right colon.

Post-polypectomy Management
Patients with only a small (<1cm) tubular adenoma do not have an appreciable increased risk of colorectal cancer and the general screening guidelines should be followed. For polyps larger than 1 cm or for multiple polyps, follow-up colonoscopies should be performed every year. In patients who have a suboptimal initial examination, colonoscopy should be repeated at 3 months. After one negative 1-year follow up, subsequent surveillance intervals may be increased to 3 years. If subsequent colonoscopy is not possible, a flexible sigmoidoscopy and an air contrast barium enema should be performed. However, it is important to individualize surveillance according to age and comorbidity of the patient.

Surgical Therapy
Colon Cancer
The mainstay for the treatment of colorectal cancer is surgical resection. The goals of surgical therapy are to:
1. Remove the cancer completely with clear margins.
2. Resect adjacent draining lymph node.
3. Avoid excessive disruption or spillage of tumor cells.
4. Reconstruct the bowel, if possible, in order to achieve intestinal continuity and normal or near normal bowel function postoperatively.

The type of resection depends on a variety of factors including the location of the tumor, the presence of other associated cancers or polyps, the stage of the cancer, the risk of development of other colon cancer in the future, and finally, the patient’s preference. The method of reconstruction or anastomosis for colon resection can vary. Some surgeons use manual suturing either in one or two layers, others prefer one of various stapling techniques.

Colorectal resection, including regional lymph nodes, is based on the blood supply to the bowel (Figure 19). A variety of types of colorectal resections are possible.
A right hemicolectomy (Figure 20) is the surgical procedure performed for patients with cancer between the cecum and ascending colon.

A transverse colectomy (Figure 21) is performed for tumors in the transverse colon. The middle colic artery is ligated and the ascending and descending colon are anastomosed.

Extended right colectomy is performed in cases in which the cancer is located in the proximal or mid transverse colon (Figure 22). This resection requires removal of the terminal ileum, cecum, ascending colon, hepatic flexure and a portion of the transverse colon.
Left hemicolectomy (Figure 23) is the procedure for tumors of the descending colon. The left colic artery is ligated, the splenic flexure and descending colon removed and the transverse and upper sigmoid colon anastomosed.

Sigmoid colectomy removes tumors of the sigmoid colon (Figure 24). The upper rectum and descending colon are anastomosed.

**Rectal Cancer**

The surgical management of rectal cancer can be particularly complicated, depending on the location of the tumor. There are a variety of surgical procedures that are available to patients with rectal cancer ranging from local excision to radical abdominoperineal resection. Accurate preoperative staging determining depth of invasion and lymph node involvement is essential in selection of the appropriate operative procedure. CT or MRI and endorectal ultrasound are diagnostic tests used for staging of the tumor.

The three options for management of rectal cancers include local excision, restorative anterior or low anterior resection, and abdominal perineal resection with permanent colostomy.

The low anterior resection is suitable for lesions located in the upper two-thirds of the rectum. This sphincter-sparing operation can be performed for cancers in the middle and lower third of the rectum with low colocolonic anastomosis at the level of the pelvic floor (Figure 25).
Coloanal reconstructions are alternatives to permanent colostomy. Construction of a colon J-pouch creates a neorectal reservoir that can reduce frequency and urgency of bowel movements and nocturnal bowel movements in selected cases (Figure 26).

These radical “transabdominal” resections are recommended for most cancers at risk for recurrence (higher than stage T1 or poorly differentiated with lymphatic or vascular involvement). The selection of surgical procedure should be guided toward the prevention of pelvic recurrence. Total mesorectal excision with a low anterior resection or an abdominoperineal resection is the optimal surgical procedure for rectal cancer. Total mesorectal excision removes the rectal mesentery as an intact unit. This reduces local recurrence along with preserving sexual function, urinary function, and continence.

Abdominoperineal resection is used when the lesion is in the lowest part of the rectum (Figure 27) typically involving the anal musculature. A colostomy allows for drainage of waste through an opening in the abdominal wall.
Transanal excision is occasionally used for local therapy in selected cases. Local excision is typically considered for small tumors (less than 3–4 cm in diameter), within 6–8 cm of the anal verge, and with limited circumferential involvement (less than one third of rectal circumference). Tumors should be moderately- to well-differentiated and be T1 on transrectal ultrasound. A 1-cm margin of grossly normal mucosa beyond the edge of the tumor is ideal, although 5-mm is acceptable. A full thickness rectal wall excision to the perirectal fat layer is performed. Local excision reduces perioperative complications and preserves anorectal, bladder, and sexual function. Studies have demonstrated about a 90% recurrence-free survival rate in patients with T1 well-to–moderately differentiated rectal tumors without venous or lymph vessel invasion.

**Chemotherapy**

**Adjuvant Therapy for Colon Cancer**

In cases of Stage III and some Stage II cancers, postoperative adjuvant chemotherapy is often recommended. Randomized trials have demonstrated statistically improved survival in such patients. Typically, combination chemotherapy is administered (e.g. 5-fluorouracil plus leucovorin) for a six-months following surgical resection. It is administered on an outpatient basis, most patients do not lose their hair, and are able to continue usual daily activities. This therapy is usually well tolerated, however, common complications of adjuvant chemotherapy include diarrhea, neutropenia, and stomatitis.

**Adjuvant Therapy for Rectal Cancer**

Postoperative adjuvant chemotherapy combined with radiation therapy has been shown to improve outcomes in patients with transmural or node positive rectal cancers. Combined chemotherapy and radiation improve local control and increase overall survival. A National Institutes of Health consensus conference on rectal cancer recommended combined postoperative chemotherapy and radiation as the standard of care for patients with Stage II and III rectal cancers.

Preoperative chemoradiation therapy is being used with increased frequency in patients with rectal cancer. The advantages of preoperative therapy include increased sphincter preservation, less small intestinal radiation injury, and improved bowel function. Typically, preoperative therapy is reserved for those tumors with evidence of nodal or transmural disease.

Radiation therapy is typically administered with chemotherapy for a six-week period. Chemotherapy alone is then administered for an additional four months. When given preoperatively, the combined chemoradiation is given for six weeks, followed by a break of 4–10 weeks before surgery. An additional four months of chemotherapy is given postoperatively.

**Surveillance**

Postoperative surveillance of colorectal cancer is critical due to the risk of recurrence, especially in cases with serosal or lymphatic involvement. Eighty-five percent of recurrences become evident within the first three years after surgery. Initially, patients should be seen at 3–6 month intervals for 3 years. Subsequently, they should be seen every 6–12 months for 5 years. Repeat colonoscopy should be performed after one year and every 1–3 years afterward to detect new polyps or cancer. For patients who underwent anterior resection of a rectal cancer, serial digital rectal examination or proctoscopy may also be indicated.

Routine evaluation with history, physical exam, and carcinoembryonic antigen (CEA) serum levels, are the backbone of the post-surgical evaluation and the mainstay of the detection of recurrent disease. Measuring CEA levels every 3–4 months in patients treated for Stage II and III disease for at least the first two years after resection, and then every six months for the next three years is considered an adequate surveillance strategy. Elevation in CEA level has been shown to correlate with recurrence of tumor and/or presence of metastasis. History and physical exam should be performed every 3–6 months for the first three years, and annually thereafter.

Colonoscopy should be performed annually for five years for patients who have been diagnosed with colorectal cancer and then every other year or every third year. Rather than detecting recurrence, the role of colonoscopy is to detect metachronous polyps or cancers.

**Ongoing Research**

Active efforts to elucidate the interactions of genetic and environmental factors of colorectal cancer are underway. Understanding the pathogenesis of colorectal cancer will enable us to tailor appropriate therapies and establish surveillance and prevention protocols.

Evaluation of recombinant vaccines for colon cancer has begun with the concurrent technologies in the fields of molecular biology and immunology. New models for understanding colorectal cancer resistance to chemotherapy are being developed. Alterations in genes involved in the regulation of the cell cycle or in DNA damage repair may result in a cell becoming resistant to chemotherapy. Clinical trials are underway to study different combinations of chemotherapy in specific sets of patients who share similarities in their tumor genetic profile.

Novel approaches for advanced or metastatic disease are also being developed. New techniques of surgical resection and ablation for liver metastases can allow for lower morbidity and improved survival, using minimally invasive approaches. New drugs and drug combinations are also being studied both in the advanced and adjuvant setting.
Advanced Rectal Cancer

Endoscopic Therapy
For patients with obstructive unresectable rectal cancer, endoscopic therapy using the neodymium-yttrium-aluminum-garnet (Nd:YAG) laser is an alternative to recanalize the rectal lumen. Electrofulguration using a heater probe has also been used for palliative therapy. Another approach for patients who are poor surgical candidates is photodynamic therapy (PDT). In this procedure, patients are sensitized with a hematoporphyrin derivative, which is taken up preferentially by the tumor cells. At this point, phototherapy is performed using a laser beam applied through a flexible optical fiber directed at the tumor. The laser sensitizes the protoporphyrin ultimately inducing apoptosis of the tumor cells. This technique is still considered experimental. Complications associated to endoscopic therapy with Nd:YAG laser are bleeding and perforation.

Colonic Stents
Obstruction is a presenting symptom in a significant number of patients with colorectal cancer. Many of these patients are elderly, dehydrated, or unstable due to significant co-morbidities and are, therefore, poor operative risks. Emergent surgical intervention in this group of patients is associated with high morbidity and mortality. Endoscopic placement of an expandable colonic stent provides effective nonsurgical decompression of large bowel obstruction and avoids surgery. The technique has been shown to be effective in resolving obstruction in the majority of patients. In a study conducted in Spain, 38 patients received colonic stents. All except two patients had clinical and radiographic resolution of their large bowel obstructions within 48 hours without complications.

Preoperative colonic decompression with an expandable stent often allows postponement of surgery until there can be adequate bowel cleansing and/or stabilization of the patient's general health. The utility of the stent lies in the fact that its role may be changed from preoperative to palliative when disease staging dictates. Stenting is a useful therapeutic modality in non-operative patients to preserve quality of life and keep these patients out of the hospital. Endoscopic colonic stenting appears to be safe, effective and has lasting results in the management of patients with large bowel obstruction.

Colonic stents may be placed endoscopically in a relatively short period of time with very few complications. Guide wires are advanced across the stenosis or obstruction with fluoroscopic and/or endoscopic guidance. The guide wire is then substituted with a stiffer one. This is followed by the stent delivery system over the guide wire in which the stent is deployed across the stricture. Long strictures may require overlapping endoluminal colonic wall stents.

Follow-up studies, using larger numbers of patients for longer periods of time, are needed to accurately assess the utility of this therapeutic modality.

Recurrent or Advanced Colorectal Cancer
Unfortunately, about 20% of patients with colorectal cancer have metastatic disease (Stage 4) at the time of presentation. Even in those patients with localized disease, up to 40% will go on to develop recurrence.

Local recurrence at the site of the original tumor is relatively uncommon with colon cancer. In contrast, local or pelvic recurrence is seen with rectal cancer in up to 20% of cases. Initial resection, with total mesorectal excision significantly reduces the risk of developing pelvic recurrence.

The liver is the most common site of distant metastatic disease. Up to two thirds of initial recurrence will be in the liver. In many of these patients, the liver will be the only site of disease. Other sites may include the lung, abdominal (extrahepatic), bone and brain.

Treatment of recurrent or advanced colorectal cancer depends on the site and extent of metastatic disease. Surgical therapy, systemic or regional chemotherapy, and radiation therapy may all play a role.

Liver Metastases
Liver resection of isolated or limited hepatic metastases from colorectal cancer can offer a potential cure and should be considered if indicated. Improved surgical techniques have resulted in significant improvement in outcomes following even major liver surgery and 5-year survival rates can exceed 50%.

Other surgical approaches in unresectable patients include intratumoral ablation approaches such as radiofrequency ablation (RFA) and cryotherapy. Regional chemotherapy directed to the liver may be used following surgical implantation of a hepatic arterial infusion pump. Such chemotherapy can be used in cases of unresectable disease confined to the liver. It may also be used as an adjuvant therapy following complete resection.

Chemotherapy
Systemic chemotherapy is recommended in the case of disseminated metastatic colorectal cancer. Multi-drug therapy including 5-fluorouracil and leucovorin are usually used. Another agent, irinotecan (CPT-11) has been shown to improve efficacy. Other drugs, including oxaliplatin have also shown activity. Combination chemotherapy has been shown to have response rates as high as 40% and is associated with marginal but significant prolongation in survival. Moreover, systemic chemotherapy can be used in conjunction with surgical therapy and regional chemotherapy in selected cases.

Radiation Therapy
Radiation therapy for recurrent or advanced disease is generally used for palliative purposes. Bulky unresectable primary colorectal cancer can be successfully controlled in many cases. Symptomatic recurrences in some areas such as bone, brain, retroperitoneum, or pelvis can be treated with radiation therapy.