What are the preventative medical guidelines for adults?
It is recommended that adults get a health evaluation every 1 to 3 years, depending on their risk factors, and then annually after age 50. Male patients can be screened for prostate cancer after the age of 50, with appropriate patient education. Female patients are evaluated for cervical cancer at age 21 or earlier if indicated via a Pap test. In addition, females should be aware of breast cancer screening as early as age 18, with clinical breast exams and then mammography by the age of 40, unless the patient has risk factors, in which case imaging can start earlier. Colorectal carcinoma is evaluated at age 50 in both male and female patients, with a colonoscopy at age 50, then every 10 years, or an annual fecal occult blood test (FOBT) plus sigmoidoscopy every 5 years, or annual FOBT.

CLINICAL PEARL
High-sensitivity FOBT, sigmoidoscopy with FOBT, and colonoscopy are effective in decreasing colorectal cancer mortality.

What are some screening tests that could be recommended to this patient based on his age and symptoms?
Because this patient has not been seen by a doctor in a long time, he needs a health evaluation that includes history (including family history of disease), preventative screenings and counseling, updated immunization, and an age-appropriate physical exam. General counseling regarding diet, exercise, and substance use is recommended at every age. His pertinent evaluation in reference to his symptoms includes a colonoscopy.

The patient is referred to a gastroenterologist for a colonoscopy. His colonoscopy reveals four small polypoid lesions throughout his colon as well as a reddish irregular craterlike lesion in his rectum. The four polypoid lesions are removed entirely and the rectal lesion is biopsied.
TABLE 2.1  Polyps of the Large Intestine

<table>
<thead>
<tr>
<th>Inflammatory Polyps</th>
<th>Hamartomatous Polyps</th>
<th>Epithelial Polyps</th>
<th>Mesenchymal Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory pseudopolyp</td>
<td>Juvenile polyp</td>
<td>Hyperplastic polyp</td>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Prolapse type polyp</td>
<td>Peutz-Jeghers polyp</td>
<td>Sessile serrated polyp/adenoma</td>
<td>Granular cell tumor</td>
</tr>
<tr>
<td>Inflammatory myoglandular polyp</td>
<td></td>
<td>Conventional adenoma</td>
<td>Fibroblastic polyp</td>
</tr>
</tbody>
</table>

Figure 2.1  Hyperplastic polyp showing star-shaped glands with bland morphology as indicated by the arrow (haematoxylin and eosin [H&E] stain).

What kinds of polyps occur in the colorectal region?
The large intestine can have a multitude of different types of polyps (see Table 2.1). The patient was found to have three tubular adenomas and one hyperplastic polyp. Hyperplastic polyps are generally <5 mm and show a bland cytology with well-formed, elongated glands and crypts with serrated (saw tooth) or star-shaped appearance (see Fig. 2.1). Adenomas can be tubular, tubulovillous, villous, serrated, or flat. This patient had three traditional adenomas, which were all tubular. Tubular adenomas have at least low-grade dysplasia with the presence of architecturally noncomplex crypts with nuclei that are stratified or pseudostratified and remain at the lower half of the cytoplasm (see Fig. 2.2).

CLINICAL PEARL

Hyperplastic polyps are the most common type of polyp in the colon.
What are the risk factors for development of colorectal carcinoma?
The risk of developing colorectal carcinoma is affected by multiple factors, which can be constitutional or environmental (see Table 2.2). Family history of a first-degree relative and inflammatory bowel disease is a significant endogenous risk factor. Physical inactivity, obesity, red meat consumption, smoking, and alcohol use are all risk factors linked to colorectal carcinoma that are preventable.

### Clinical Pearl 2/3

**High-fat diets may increase the anaerobic gut flora, leading to a higher concentration of secondary bile acids, which may be carcinogens.**

**Clinical Pearl 2/3**

High folate intake is associated with a decreased risk of colorectal carcinoma.

**Clinical Pearl 2/3**

Colorectal cancer is the second leading cause of cancer-related deaths in the United States and the third most common cancer in men and in women.
Figure 2.2  Tubular adenoma showing pseudostratified nuclei arranged in a predominant tubular architecture as indicated by the arrow (H&E stain).

Figure 2.3  Rectal biopsy shows back-to-back glands with a complex architecture, loss of polarity, pseudostratification, nuclear hyperchromasia, and brisk mitotic activity (H&E stain).
What are the symptoms associated with left-sided versus right-sided colorectal carcinomas?
Most patients have general symptoms that include a change in bowel habit, abdominal distension, hematochezia, and constipation. Other symptoms that are not specific to colorectal carcinoma, but that are seen in many cancers, include weight loss, malaise, fever, and anemia. Left-sided carcinomas are more often associated with rectal bleeding, tenesmus, and alternating diarrhea and constipation, whereas right-sided carcinomas may have vague abdominal pain and anemia due to blood loss from ulceration of the tumor.

What is the mechanism for development of colorectal carcinoma?
Colorectal carcinoma begins as a benign adenomatous polyp (low-grade dysplasia), which then progresses to high-grade dysplasia, and eventually to an invasive carcinoma. The development of carcinoma is caused by the acquisition of multiple tumor-associated mutations causing genomic instability. Chromosomal instability, which is the loss of heterozygosity at APC, TP53, and SMAD4, is the most common genomic instability in colorectal cancer. It is characteristic of 80 to 85% of sporadic colorectal cancers. Another cause of genomic instability is DNA repair defects. This inactivation of genes required for repair of base–base mismatches can be inherited, as in hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome, or acquired in sporadic colorectal cancers. Aberrant DNA methylation is another mechanism of gene inactivation in patients with colorectal carcinoma.

Oncogenes RAS and BRAF, which activate the mitogen-activated protein kinase (MAPK) signaling pathway, also occur in colorectal carcinomas.

What are syndromes associated with development of colorectal carcinoma?
Less than half a percent of colorectal carcinomas are associated with genetic syndromes such as familial adenomatous polyposis (FAP), juvenile polyposis syndrome, Peutz-Jeghers syndrome, and Cowden syndrome. However, hereditary nonpolyposis forms are associated with a 2 to 3% incidence. The most common of these is Lynch syndrome, also known as HNPCC.

**CLINICAL PEARL**
Familial polyposis syndrome (FAP) is associated with >100 colon polyps (mostly tubular adenomas), mutation in APC gene, and either an epidermoid cyst, osteoma, or desmoid tumor.

**CLINICAL PEARL**
Peutz-Jeghers syndrome is associated with Peutz-Jegher–type polyps, melanotic mucocutaneous pigmentation, and sex cord tumors of the ovaries/testes.

**CLINICAL PEARL**
Cowden’s syndrome is associated with facial tricholemmomas, acral keratosis, oral mucosal papillomas, and colorectal polyps.

What is the management of colorectal carcinoma?
The management of colorectal carcinoma depends primarily on the stage of the cancer. Stage I is managed with surgical resection alone. Stage II management varies depending on the location of the cancer and may include surgery and/or chemotherapy/radiation. Stage III and IV patients may receive chemotherapy. Radiation may be useful in rectal cancers, although it is not often used in other parts of the colon, as those parts are not radiosensitive.
The patient is admitted to the hospital and prepped for surgery. He receives a rectosigmoid resection (see Fig. 2.4). Microscopically, the tumor appears to invade the muscularis propria (see Fig. 2.5). The surgical margins are negative, and there are 12 negative lymph nodes.

**CLINICAL PEARL**

The most common sites of colorectal cancer recurrence are the liver and lungs.

Pathologic staging of colorectal carcinoma depends on the depth of invasion of the bowel wall and surrounding structures, lymph node involvement, and distant metastasis. His final pathologic stage is T2N0M0 and clinical stage is I. He recovers quite well postoperatively and is sent home after 2 days.

**What is the prognosis of colorectal carcinoma?**

Survival is related to the stage of the disease. Patients with an invasive carcinoma into the submucosa (T1) or muscularis propria (T2) have a 5-year survival rate of 90%. Patients with tumors that invade into the pericolorectal tissues (T3) or visceral peritoneum (T4) without positive lymph nodes have a 5-year survival rate of 70%. When patients have positive lymph nodes with any T stage, their 5-year survival rate decreases to approximately 40%. Metastatic disease decreases the 5-year survival rate even further to 5%.

*Figure 2.4  Portion of rectosigmoid resection showing a craterlike reddish lesion with heaped up irregular borders as indicated by the arrow. Adjacent bluish green discoloration in mucosa due to tattooing during colonoscopy (Gross photograph).*
What kind of follow-up is recommended following treatment of colorectal carcinoma?

Medical history and physical exam should be performed every 3 to 6 months for 5 years. Carcinoembryonic antigen (CEA) levels should follow the same timing but only in patients with T2 or greater disease. An abdominal and chest computed tomography (CT) scan is recommended annually for 3 years. Additionally, when the tumor is located in the rectum, a pelvic CT scan is recommended.

A colonoscopy should be performed 1 year after surgery and then every 5 years. There is no recommendation for routine positron emission tomography (PET) scans, chest radiographs, or complete blood counts or liver function tests. Secondary therapy includes exercise, which maintains an appropriate body weight.

**CLINICAL PEARL**

CEA is an antigen produced by many colon cancers. It should not be used as a screening tool. However, it can be used preoperatively to follow the course of disease. CEA may be elevated prior to surgery but should return to normal 30 days postoperatively. If it remains elevated, it could be an indicator of recurrent disease.

**BEYOND THE PEARLS**

- Ninety percent of colorectal cancer deaths are preventable.
- Polypectomy can prevent colorectal carcinoma.
- It generally takes 10 to 15 years for an adenoma to become a carcinoma.
- Patients with familial adenomatous polyposis (FAP) may benefit from a preventative total proctocolectomy because of their increased risk of development of colorectal carcinoma.
BEYOND THE PEARLS—cont’d

- Although patients with Cowden syndrome have an increased number of colorectal polyps, they are mostly hamartomatous; therefore, they have a low rate of colorectal carcinoma.
- \textit{MACC1} is a gene that has been isolated as a potential contributor to metastatic disease in colorectal carcinoma.
- HNPCC is associated with multiple primary colorectal cancers, accelerated tumor progression, and increased risk of endometrial, gastric, and urothelial tumors.
- HNPCC is usually a poorly differentiated carcinoma with a marked lymphocytic infiltration.
- Patients with mismatch repair genes do not benefit from chemotherapy.
- 5-Fluorouracil is a potent inhibitor of thymidylate synthase. Without thymidylate synthase, tumor cells cannot form dTMP (a precursor of DNA synthesis).
- 5-Fluorouracil side effects include myelosuppression, angina, mucositis, hyperpigmentation, and cerebellar ataxia.

References


**Complaint/History:** A 61-year-old male with alternating diarrhea and constipation.

**Findings:** Abdominal distension and left lower quadrant tenderness.

**Labs/Tests:** Positive stool guaiac. Colonoscopy with four polyps and one craterlike mass.

**Diagnosis:** Invasive adenocarcinoma, multiple tubular adenomas, and a hyperplastic polyp.

**Treatment:** Surgery.