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Colorectal Cancer

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Et al.

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Summary and Key Points

1. Colorectal cancer is a common cancer which may be largely preventable by screening.
2. There are well defined genetic syndromes which result in a markedly increased risk of developing colon cancer.
3. Colon cancer that has not spread to distant organs is usually treated primarily by surgical resection.
4. Rectal cancer has a higher probability of relapsing locally than colon cancer, and so is often treated initially with a combination of chemotherapy, radiation, and surgery.
5. Adjuvant chemotherapy may be given after resection of either colon or rectal cancer to lower the risk of cancer recurrence.
6. Metastatic colorectal cancer is not currently curable. While chemotherapy can prolong life in patients with metastatic disease, the primary goal of treatment is palliation of symptoms.

Introduction

Colorectal cancer is one of the most common types of cancer to affect individuals in the United States. It is the third most frequently diagnosed cancer as well as the third leading cause of cancer death among men and women. There were 150,000 new cases and nearly 50,000 deaths from colorectal cancer in the year 2008. Fortunately, these numbers have been decreasing since the late 1990s, largely attributable to increased screening for colorectal cancer and the removal of precancerous polyps.

Etiology

Colon and rectal cancers develop from changes in the mucosa, the inner lining of the intestine, that occur over time. (Figure 1) This progression is referred to as the "adenoma to carcinoma" sequence, and is a result of alterations in the DNA of the colonocytes. This sequence can be affected by genetic mutations passed among families, the most common of which are the adenomatous polyposis coli (APC) gene and mismatch repair (MMR) gene mutations. APC gene mutations are responsible for Familial Adenomatous Polyposis (FAP) syndrome. Patients with FAP will acquire hundreds or thousands of colonic polyps by the age of 20 and have a near 100% chance of developing colorectal cancer, usually before the age of 40. MMR gene mutations are included in Hereditary Non-Polyposis Colon Cancer (HNPCC) syndrome. A thorough family history is necessary to help determine if an individual is at risk for one of these familial conditions.

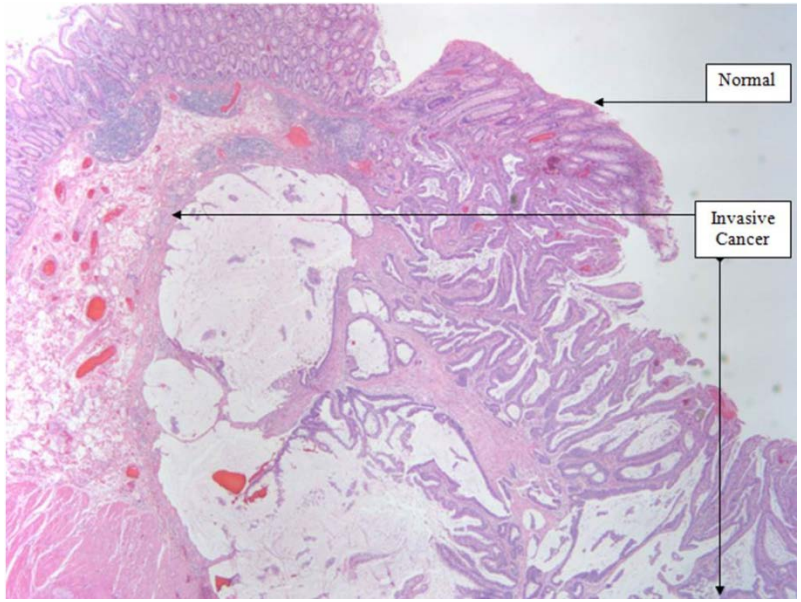

Figure 1. (H&E stain, 2x magnification). Transition from normal colonic mucosa (left) to invasive well- differentiated adenocarcinoma (right). University of Massachusetts Medical School. Department of Pathology.

These inherited conditions, while important, only account for a small minority of colon cancers. This means that most patients who develop colorectal cancer will have no significant family history. These cancers develop from acquired DNA mutations due to environmental factors acting on the colonic mucosa. Other causative factors that have been implicated in colorectal carcinogenesis include a high fat, low fiber diet and chronic inflammatory conditions such as inflammatory bowel disease.

Screening

As almost all colorectal malignancies start out as precancerous polyps, they can be identified and removed at the time of screening colonoscopy. (watch 2.44 minute movie) Currently, screening of the general population for colon cancer is recommended beginning at age 50, though it should be done earlier for patients with risk factors or family history. For the general population, annual stool testing by fecal occult blood, fecal immunochemical test (FIT), stool DNA test (sDNA) and flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, double-contrast barium enema every 5 years* or CT colonography (virtual colonoscopy, Figure 2) every 5 years are recommended. If any of the other tests are positive, then colonoscopy should follow immediately.

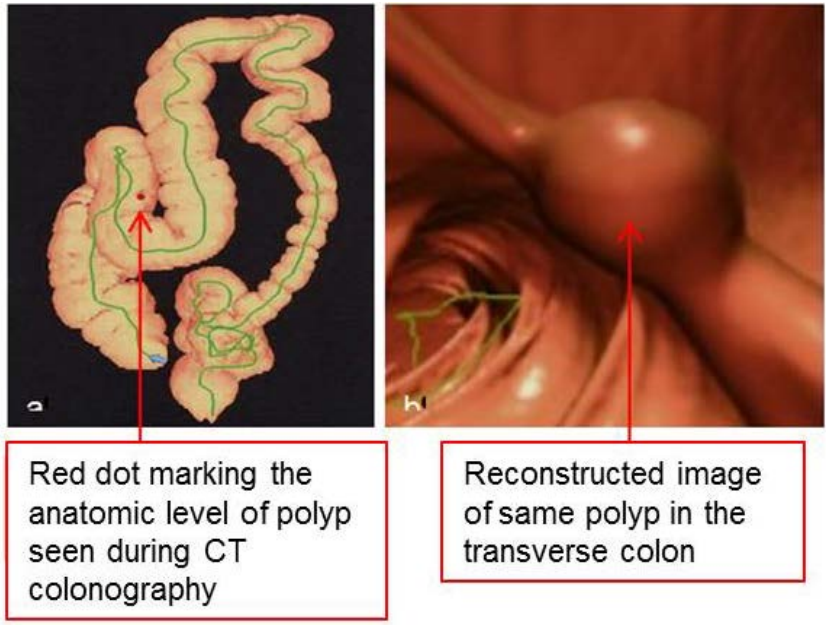

Figure 2. 3D images from a screening CT Colonography (virtual colonoscopy) demonstrate a 1.5 cm polyp in the proximal transverse colon. University Massachusetts Medical School. Department of Radiology.

Adherence to these screening recommendations will contribute to continued decline in the incidence of colon cancer that has been observed over the last twenty five years. It is important that physicians and patients realize that screening will not eliminate colon cancer. Screened patients still develop invasive cancer, probably due to lesions missed at colonoscopy, incomplete resection of polyps or predisposition to cancer because of genetics, lifestyle or other factors.[1]

Pathology

Cancers of the colon and rectum originate from the mucosa, the epithelial lining of the gastrointestinal tract. For this reason, these tumors are almost exclusively adenocarcinomas. (Figures 3a-c) There are rare reports of squamous cell carcinomas in the low rectum, though there is debate whether these are truly anal cancers arising in the transitional epithelium of the anal canal. Other tumor types such as lymphoma, carcinoid, gastrointestinal stromal tumor (GIST), and melanoma are less common in the colon and rectum and have different modalities of treatment. Though a full discussion of these tumors is outside the scope of this chapter, their presence highlights the importance of biopsy to obtain a tissue diagnosis when dealing with a newly discovered colon or rectal mass

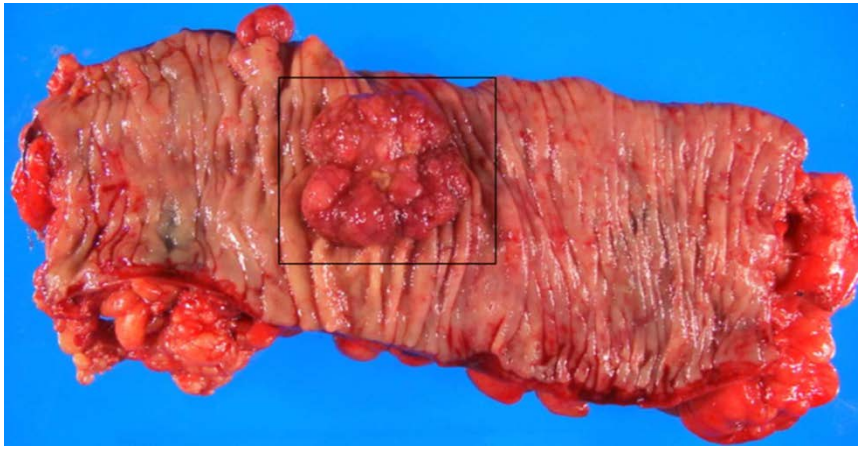

Figure 3a. Gross image of colon resection: Polypoid lesion of invasive adenocarcinoma (see next figure). University of Massachusetts Medical School. Department of Pathology.

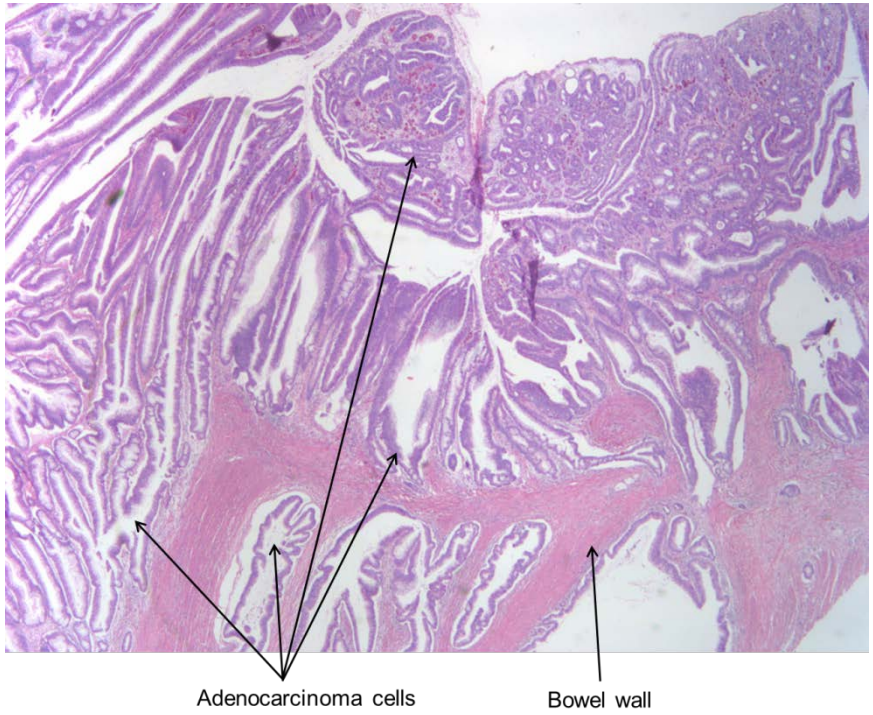

Figure 3b. (H&E stain, 2x magnification) Invasive adenocarcinoma, moderately differentiated. Note the intermingling of the malignant tumor and benign bowel wall tissue. University of Massachusetts Medical School. Department of Pathology.

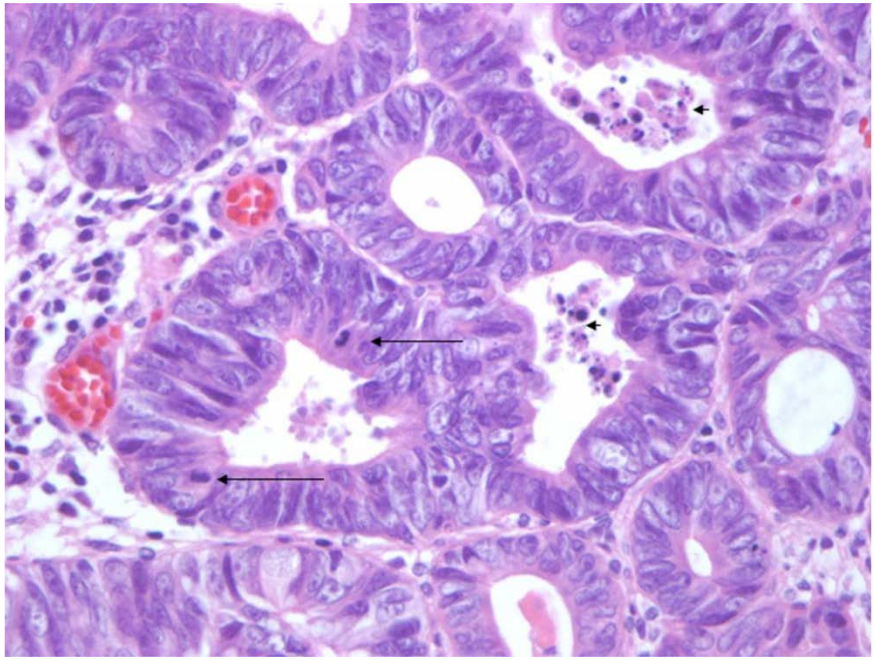

Figure 3c. (H&E stain, 40x magnification) High power of the malignant cells. Note the necrotic cells within the glandular lumen (short arrows). There is often extensive necrosis associated with colonic adenocarcinomas. The nuclei show size variation, prominent nucleoli, crowding, loss of polarity and mitotic figures (long arrows). University of Massachusetts Medical School. Department of Pathology.

Staging

Staging of colorectal cancer is performed once the diagnosis is confirmed by tissue biopsy of the primary lesion. This staging protocol, often referred to as a metastatic workup, is slightly different for colon cancer than rectal cancer. In colon cancer the primary concern is identification of distant metastatic disease, as this may change the treatment plan in regards to surgical resection (Figures 4, 5 & 6). While distant metastases are also a worry in new rectal cancers, staging of these tumors also includes in depth evaluation of the primary lesion given the concern for local invasion (Figure 7).

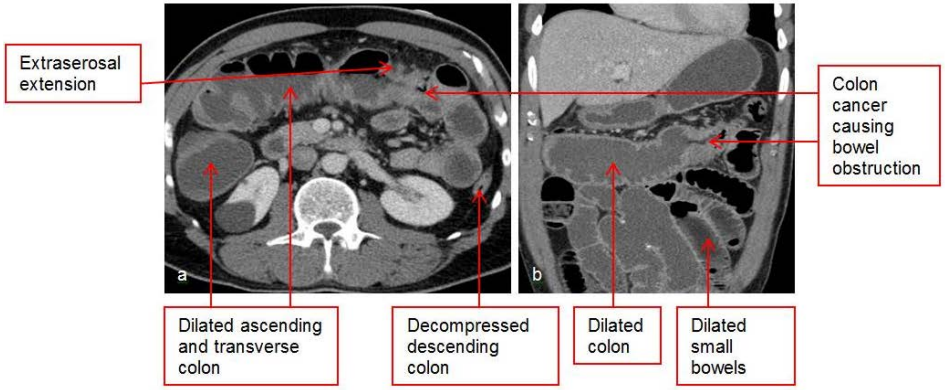

Figure 4. Sixty-one year-old male patient presenting with bowel obstruction. Axial plane (a) and coronal plane (b) images from a contrast-enhanced CT scan of the abdomen and pelvis, demonstrate an “apple core” lesion in the distal transverse colon causing bowel obstruction. Patient underwent left hemicolectomy that confirmed the diagnosis of transverse colon adenocarcinoma. Note the presence of extramural soft tissue nodule (a) suggestive of extraserosal extension. University of Massachusetts Medical School. Department of Radiology.

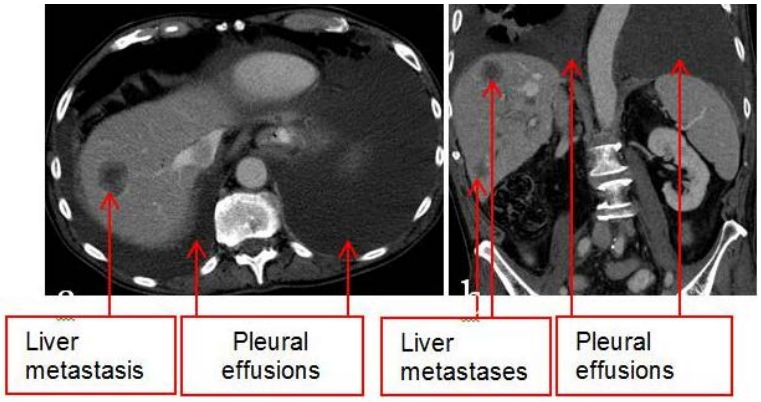

Figure 5. Seventy-five year-old female patient with newly diagnosed colon cancer. Axial plane (a) and coronal plane (b) images from a contrast-enhanced CT scan of the abdomen and pelvis, demonstrate multiple liver lesions and bilateral pleural effusions. Ultrasound-guided biopsy of the liver lesions and diagnostic thoracentesis, confirmed the diagnosis of liver metastases and

malignant pleural effusions. University of Massachusetts Medical School. Department of Radiology.

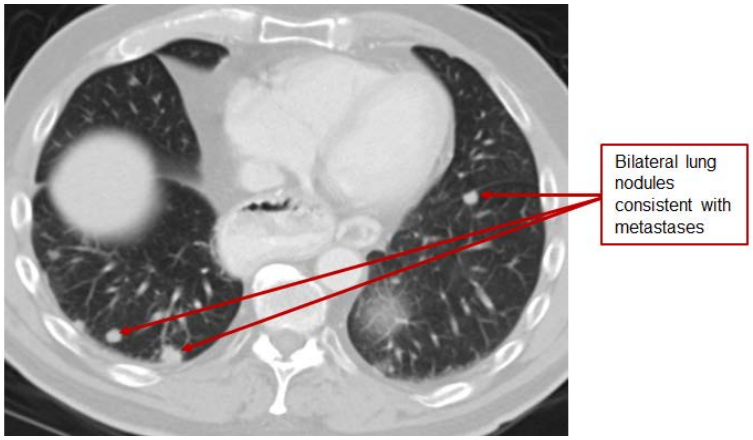

Figure 6. Sixty-nine year-old male patient with known metastatic colon cancer. Lung window image form a CT scan of the chest demonstrates multiple lung metastases in both lower lobes. University of Massachusetts Medical School. Department of Radiology.

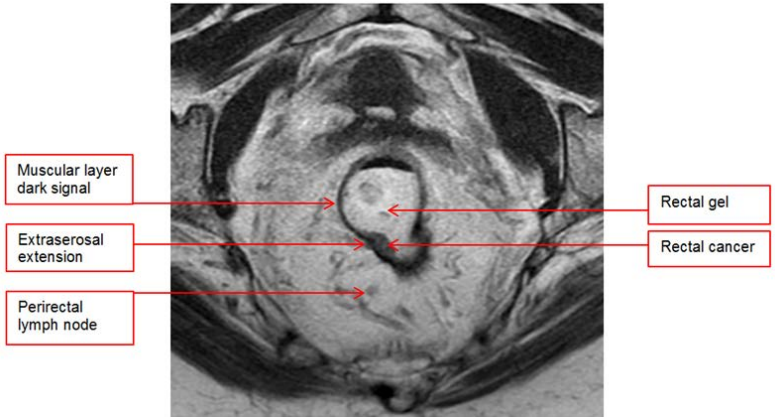

Figure 7. Eighty-six year-old female patient with newly diagnosed rectal cancer. Axial T2-weighted image through the rectum from a rectal cancer protocol MRI examination, demonstrates a 2.2 cm rectal cancer. A soft tissue nodule is seen extending beyond the muscular layer (dark signal) and is suggestive of extraserosal extension. A perirectal lymph node was also present. Rectal gel is used to distend the lumen for better visualization of rectal tumors. University of Massachusetts Medical School. Department of Radiology.

For a new colon cancer, staging primarily includes a CT scan of the chest, abdomen and pelvis with oral and intravenous contrast (Figure 4.. This study allows evaluation of the mesenteric lymph nodes surrounding the primary tumors (which often are not visible if they are not enlarged) as well as the liver (Figure 5) and lungs (Figure 6), two common locations of metastasis from colonic adenocarcinoma.

Patients will also have blood work drawn in the form of a complete blood count with platelets, blood chemistries, and carcinoembryonic antigen (CEA) level, which is a protein that is often elevated in colon cancer. This level does not affect initial treatment decisions, but is used as a baseline for comparison with levels drawn during post-treatment surveillance for recurrent or metastatic disease.

Rectal cancers present a slightly greater challenge in regards to staging, as their confined location within the pelvis and proximity to other structures leads to greater consequences from local invasion. Rectal cancer staging includes all of the elements listed above for colonic malignancies along with further evaluation of the primary tumor. First, a rigid proctoscopy is necessary to determine the level of the tumor within the rectum, often measured as the distance from the anus. This location has implications in surgical planning and when considering preoperative treatment.

Endorectal ultrasound (ERUS) is one test that is used to evaluate the depth of penetration of the cancer into or through the wall of the rectum. This study also allows visualization of the mesorectum, where the lymph nodes draining the rectum are located. ERUS requires an ultrasound probe to be placed in the rectum, which is often done at the same time as the rigid proctoscopy.

Another newer modality being used to stage rectal cancers is magnetic resonance imaging (MRI.) Pelvic MRI is very sensitive in evaluating the lymph nodes of the mesorectum, and newer high resolution MRI protocols have provided excellent image quality of the primary tumor, allowing accurate determination of depth of invasion as well (Figure 7). MRI is particularly useful in patients who have a bulky tumor or rectal

stricture that does not allow successful performance of ERUS. Oftentimes these studies are used in combination to get the most accurate staging information for each patient.

All of the information that is obtained during the staging workup is put together to develop the clinical stage of the cancer. This becomes the pathologic stage once the tumor has been resected and microscopically evaluated.

Principles of Treatment

The main principle of treatment for either colon or rectal cancer is complete removal of the tumor with negative margins whenever this is anatomically possible. When metastatic disease is present or a tumor is considered surgically unresectable, the focus of treatment shifts to limiting the progression of the cancer and palliating the patient's symptoms.

In the absence of distant metastasis (stage IV disease) patients with colon cancer undergo surgical resection as the primary method of treatment (see movie clip Colorectal Cancer Surgery). The goal of surgery is to remove the primary tumor along with all associated lymph nodes. If the final pathology shows involvement of the lymph nodes by the cancer or deep invasion through the wall of the colon, patients will be offered adjuvant chemotherapy to reduce the chance of developing recurrence or metastatic cancer. Radiation therapy is only given in cases where an incomplete surgical resection is performed, indicated by positive margins on the surgical specimen or tumor fixation to a normal structure, such as abdominal wall.

Patients with rectal cancer are often treated with combination, or multimodal treatment. While those with stage I cancers can often be cured with surgery alone, these unfortunately represent a minority of cases. For stage II and III cancers, patients are given preoperative or "neoadjuvant" chemotherapy and radiation treatment to limit local invasion and increase the likelihood that surgery will be successful. Depending on the location of the tumor, surgical resection may require a temporary or permanent stoma (colostomy or ileostomy), where the stool drains into a bag through the abdominal wall. Patients who receive chemotherapy and radiation preoperatively will then undergo chemotherapy postoperatively to reduce the chance of developing recurrence or metastatic cancer.

Patients with stage IV colorectal cancer are those whose tumor have spread to other distant organs, or have grown so extensively that it invades other nearby organs. In these patients, the focus shifts to evaluating the site and extent of their metastasis. As mentioned earlier, the liver and lungs are common locations of metastatic deposits in colorectal cancer. In cases of isolated metastatic disease to one of these locations, it is possible to still proceed with surgery to affect a cure by removal of the colonic tumor and the metastatic implant. If a patient is likely to live long enough to suffer the consequences of tumor progression, surgery and/or radiotherapy (for rectal cancer) to attempt to achieve local control may be indicated. Widely metastatic disease is treated with palliative chemotherapy; radiation and surgery are reserved for treatment of complications and symptoms.

Conclusions

Cancers of the colon and rectum are quite common and can be cured if discovered and treated in their earliest stages. Most of these tumors can be prevented through the use of screening colonoscopy. A majority of cancers occur in individuals over age 50, though any patient presenting with symptoms suggestive of cancer should be thoroughly evaluated. With a multidisciplinary approach involving surgeons, oncologists, and radiation oncologists, even the most challenging patients can be treated with encouraging results and high chance of cure

Thought Questions

1. Death from colorectal cancer can be prevented by screening programs. Further, screening by colonoscopy can lower the incidence of colon cancer. How do the results of colon cancer screening by colonoscopy differ from the results of breast cancer screening by mammography?

   Your answer:

   Expert Answer

2. Inherited mutation of APC causes FAP; acquired mutation of APC in colonocytes is a very common early event in the development of sporadic colon cancers. How are mutations in APC and their effect on colorectal cancer similar to and different from the effects of mutations in BRCA1 and BRCA2 on breast cancer?

   Your answer:

   Expert Answer

3. Radiation therapy after complete (R0) resection of rectal cancer clearly lowers the risk of local relapse of the tumor. However, radiation therapy after complete resection of colon cancer does not affect local relapse risk. Why should there be a difference in the effectiveness of radiation between completely resected rectal and colon cancers?

   Your answer:

   Expert Answer

4. What symptoms would uncontrolled colon cancer cause?

   Your answer:

   Expert Answer

5. What symptoms would uncontrolled rectal cancer cause?

   Your answer:

   Expert Answer:

Glossary

Colonocytes- Mature, non-dividing epithelial cells that form the colonic epithelium

Colostomy- A portion of the large intestine is brought through the abdominal wall ending in an opening outside the body. Stool is pushed out into a special bag, which has to be fixed to the abdominal wall.

Ileostomy- A portion of the ilium is brought through the abdominal wall ending in an opening outside the body. Liquid stool (since the water absorption function of the colon is lost) is pushed out into a special bag, which has to be fixed even more tightly to the abdominal wall.

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