GNB

Pathology

2019

Colonic tumors and polyps-2:
Malignant Tumors of Intestine

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Objectives:

Colon cancer:

- Describe the epidemiology of colon cancer.
- List genetic pathways for the development of colon cancer
- Compare the pathology (gross and microscopic features) and clinical features of right-sided colonic adenocarcinoma and left-sided colorectal adenocarcinoma.
- Describe the relationship between prognosis and the various stages of cancer of the colon and rectum as noted in the TNM (tumor-nodes-metastasis) classification and staging system.
- Describe the relationship between carcinoembryonic antigen (CEA) and recurrence following resection of the primary tumor.
- Mention the significant of carcinoid tumor and its features

Tumors of the small and large intestines

Carcinoma

Carcinoid tumor

Lymphoma

- Adenocarcinoma of the colon is the most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide.

- The small intestine accounts for 75% of the overall length of the GI tract, is an uncommon site for benign and malignant tumors.
- Among malignant small intestinal tumors, adenocarcinomas and well-differentiated neuroendocrine (carcinoid) tumors have roughly equal incidence, followed by lymphomas and sarcomas.

Epidemiology of colon cancer

Malignant Tumors of Large Intestine

Adenocarcinoma

- Adenocarcinoma of the colon is the most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide.
- Constitutes 98% of all cancers in the large intestine.
- incidence peaks at 60 to 70 years of age

Epidemiology of colon cancer

Malignant Tumors of Large Intestine

Adenocarcinoma

Predisposing factors

1. IBD, adenomas, polyposis syndrome.
2. Diet appears to play an important role in the risk for colon cancer:
   - Low fibre diet.
   - High fat content.
   - Alcohol
   - Reduced intake of vit A, C & E.

- It is theorized that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota. This change may increase synthesis of potentially toxic oxidative by-products of bacterial metabolism, which would be expected to remain in contact with the colonic mucosa for longer periods of time as a result of reduced stool bulk. High fat intake also enhances hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria.

- Several epidemiologic studies suggest that aspirin or other NSAIDs have a protective effect. This is consistent with studies showing that some NSAIDs cause polyp regression in FAP patients in whom the rectum was left in place after colectomy.

Adenocarcinoma of Large Intestine

Carcinogenesis

- Two pathogenetically distinct pathways for the development of colon cancer, both seem to result from accumulation of multiple mutations:
  1- The APC/B-catenin pathway (85 %)
  2- The DNA mismatch repair genes pathway

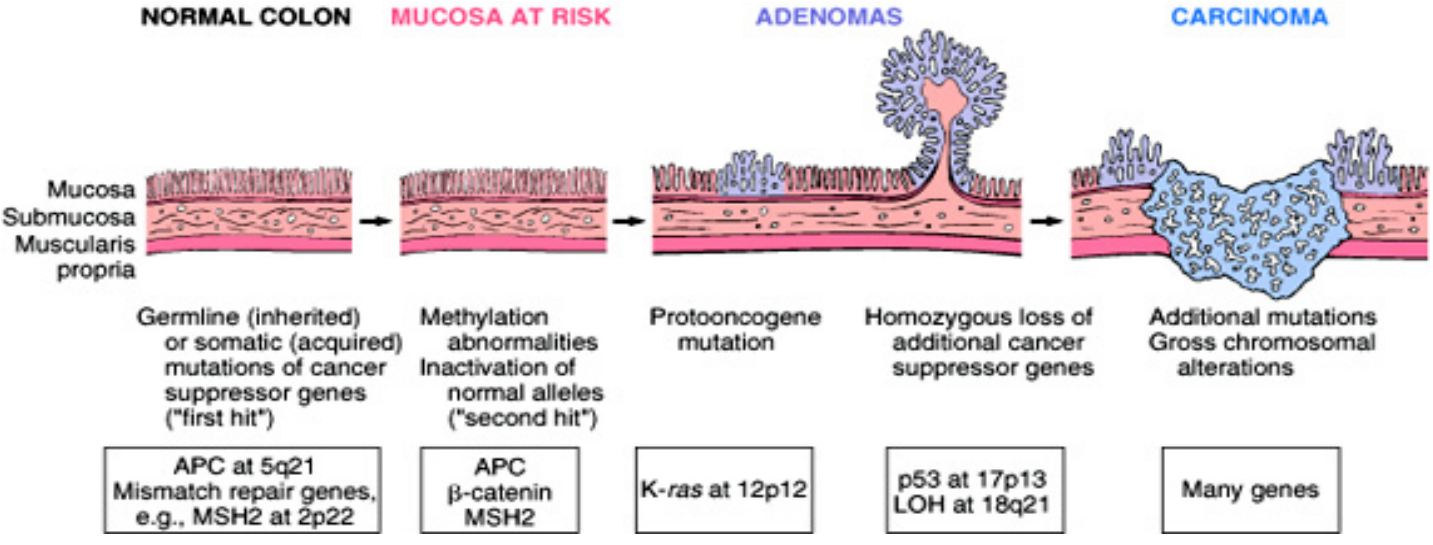
Adenocarcinoma of Large Intestine

Carcinogenesis

1- The APC/B-catenin pathway (85 %)

- chromosomal instability that results in stepwise accumulation of mutations in a series of oncogenes and tumor suppressor genes.

adenoma-carcinoma sequence



Familial Adenomatous Polyposis

- Hereditary mutation of the APC gene is the cause of familial adenomatous polyposis (FAP), where affected individuals carry an almost 100% risk of developing colon cancer by age 40 years
  .

Malignant Tumors of Large Intestine Adenocarcinoma

Carcinogenesis

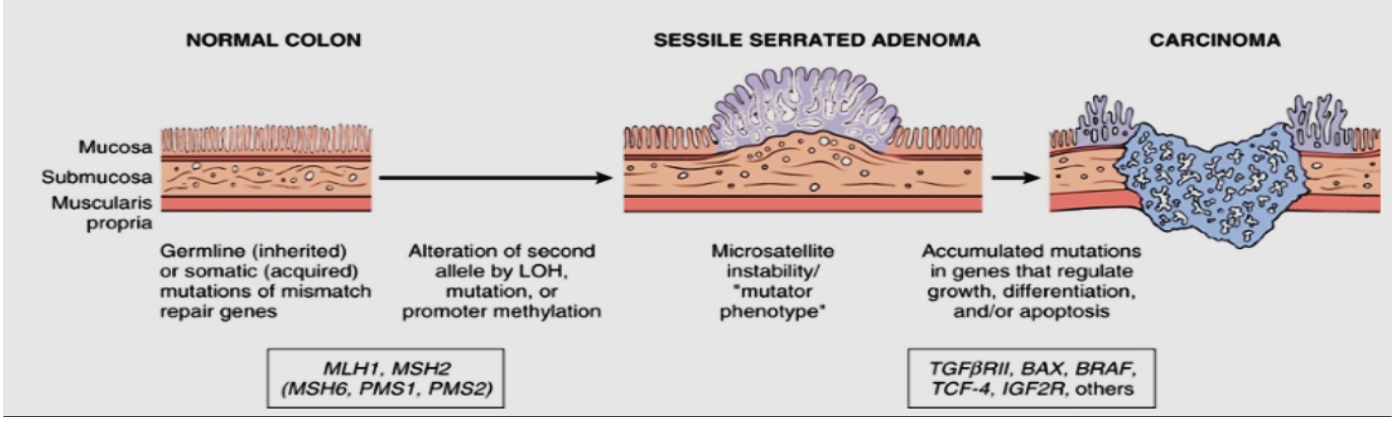
2- The DNA mismatch repair genes pathway

(These are referred to as MSI high, or MSI-H, tumors:)

- 10% to 15% of sporadic cases.
- There is accumulation of mutations

- Five DNA mismatch repair genes (MSH2, MSH6, MLH1, PMS1, AND PMS2)
- give rise to the hereditary non polyposis colon carcinoma (HNPCC) syndrome.

Hereditary non polyposis colon carcinoma syndrome (Defects in mismatch repair genes)



This result in microsatellite instability and permit accumulation of mutations in numerous genes

If these mutations affect genes involved in cell survival and proliferation, cancer may develop

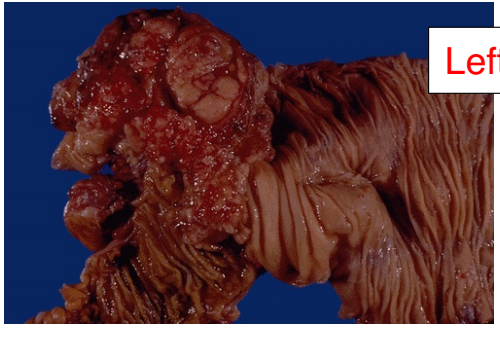
It progress from normal to sessile serrated adenomas to adenocarcinoma

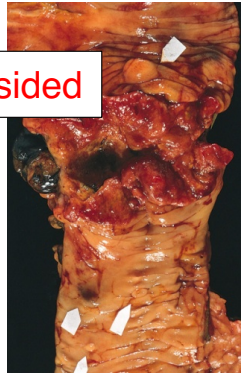
May produce abundant mucin that accumulates within the intestinal wall, and these carry a poor prognosis

Colorectal Carcinoma

Morphology

- 70% are in the rectum, rectosigmoid and sigmoid colon.
- Left-sided carcinomas tend to be annular, encircling lesions with early symptoms of obstruction.
- Right-sided carcinomas tend to grow as polypoid, fungating masses, obstruction is uncommon.

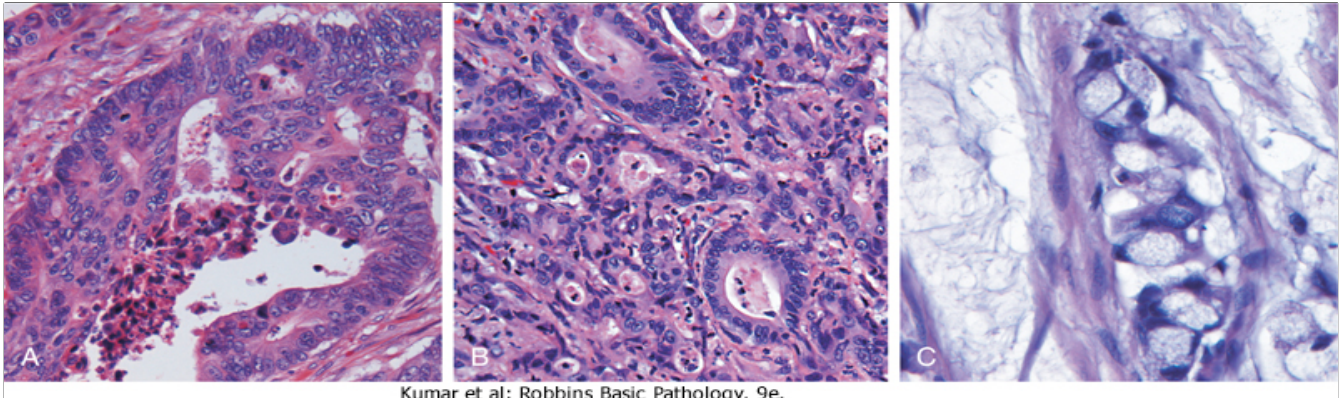




Colorectal Carcinoma

Morphology

- Adenocarcinoma: consist of infiltrating glands lined by atypical cells
- Mucinous adenocarcinoma secret abundant mucin that may dissect through cleavage planes in the wall.



Adenocarcinoma: infiltrating glands lined by atypical cells

Mucinous adenocarcinoma

Signs and symptoms

- PR bleeding: If located closer to the anus
- Change in bowel habit, feeling of incomplete defecation
- Bowel obstruction: A tumor that is large enough to fill the entire lumen of the bowel
- Right-sided lesions are more likely to bleed while left-sided tumors are usually detected later and could present with bowel obstruction.

Colorectal Carcinoma

Serum levels of carcinoembryonic antigen (CEA) are related to tumor size and extent of spread. They are helpful in monitoring for recurrence of tumor after resection.

TNM Staging of Colon Cancers is used for staging

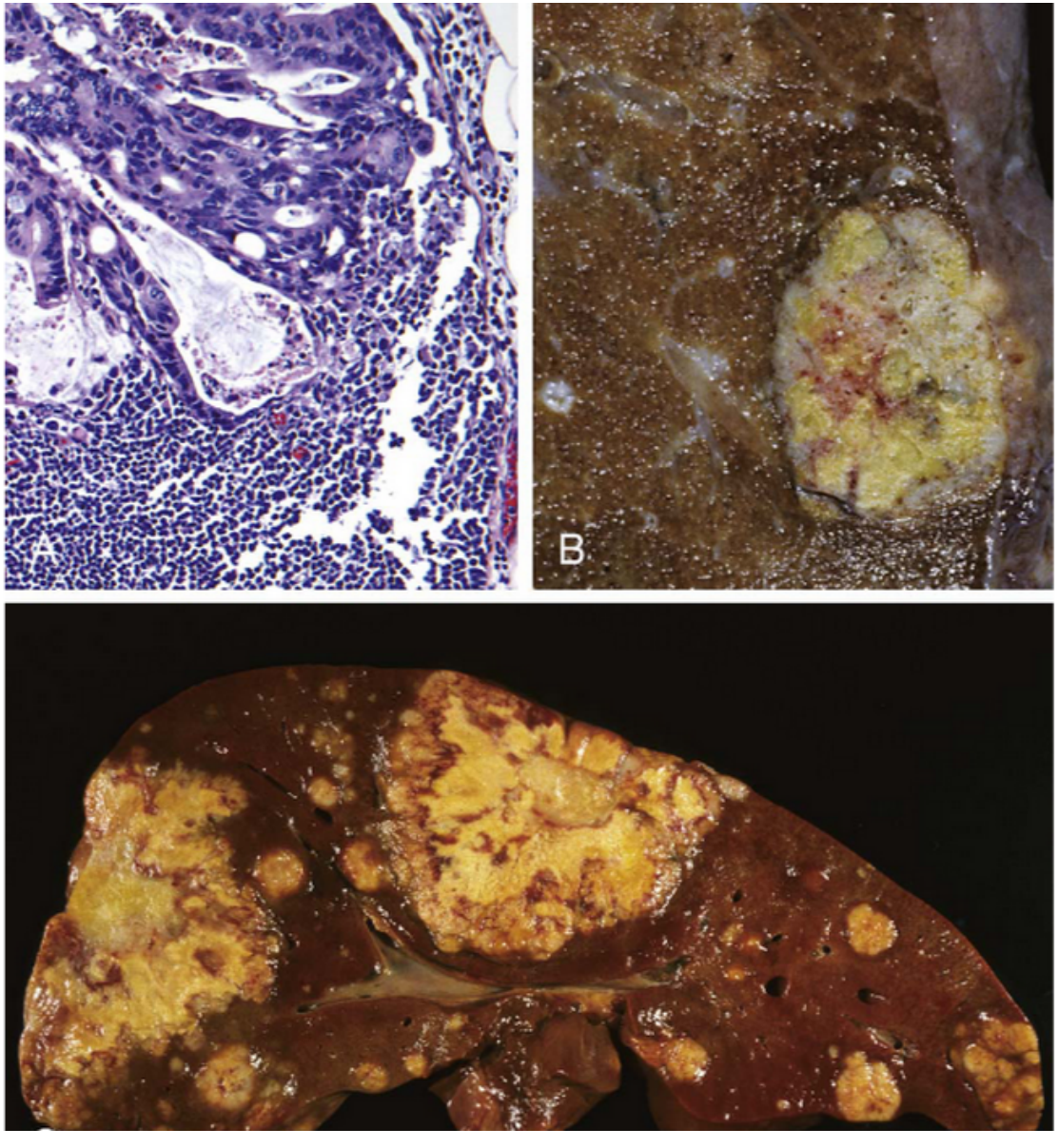
Table 14-8. AJCC Tumor-Node-Metastasis (TNM) Classification of Colorectal Carcinoma

Designation	Description
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades into, but not through, muscularis propria
T3	Tumor invades through muscularis propria
T4	Tumor invades adjacent organs or visceral peritoneum
Regional Lymph Nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or seeding of abdominal organs

AJCC, American Joint Committee on Cancer.

Table 14-9. AJCC Colorectal Cancer Staging and Survival

Stage*	Tumor-Node-Metastasis (TNM) Criteria			5-Year Survival (%)
	T	N	M	
I	T1, T2	N0	M0	74
II				
IIA	T3	N0	M0	67
IIB	T4	N0	M0	59
III				
IIIA	T1, T2	N1	M0	73
IIIB	T3, T4	N1	M0	46
IIIC	Any T	N2	M0	28
IV	Any T	Any N	M1	6


A
B

Colorectal Carcinoma

- The most important prognostic factors are depth of invasion and the presence or absence of lymph node metastases and distant metastasis.

Malignant Small Intestinal Neoplasms

- In descending order of frequency:
  - Carcinoid
  - Adenocarcinomas
  - Lymphomas
  - Leiomyosarcomas.

Small Intestinal Neoplasms

Carcinoid Tumors

- Neoplasms arising from endocrine cells found along the length of GIT mucosa.
- The peak incidence: sixth decade, but they may appear at any age.
- They compose less than 2% of colorectal malignancies
- almost half of small intestinal malignant tumors:
  - 60 to 80% appendix and terminal ileum
- 10 to 20% rectum.

Carcinoid Tumors

Behavior

- Aggressive behavior correlates with:

1. Site of origin:

   Appendiceal and rectal carcinoids infrequently metastasize, even though they may show extensive local spread

   90% of ileal, gastric, and colonic carcinoids that have penetrated halfway through the muscle wall have spread to lymph nodes and distant sites at the time of diagnosis, especially those larger than 2 cm in diameter.

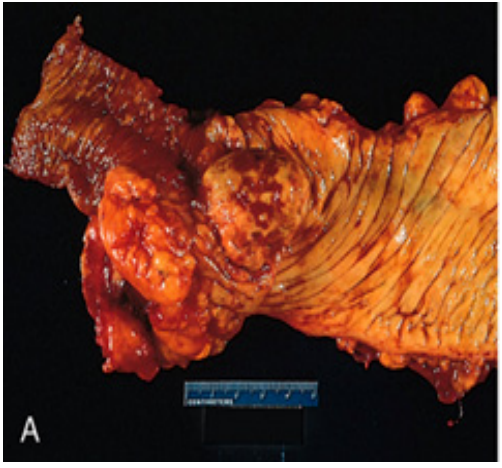
2. Depth of local penetration
3. Size of the tumor

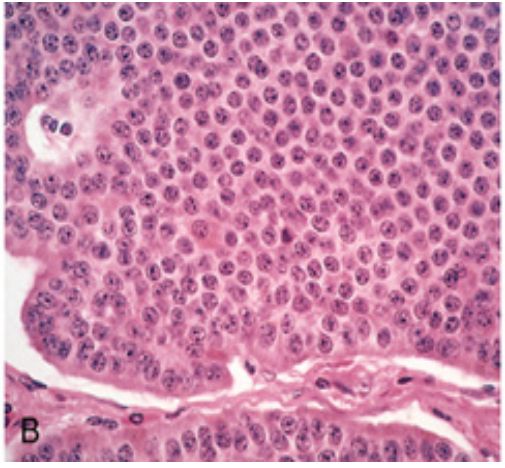
Small Intestinal Neoplasms

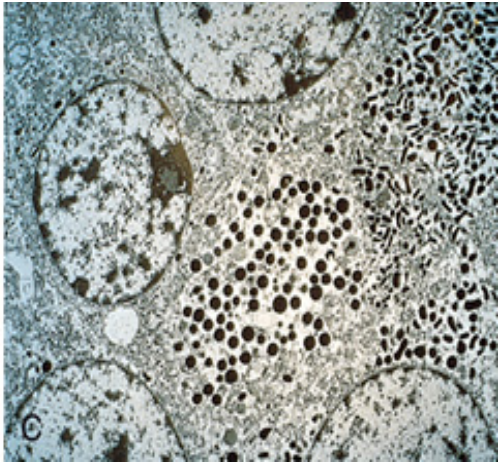
Carcinoid Tumors

Morphology

- A solid, yellow-tan appearance
- The cells are monotonously similar, having a scant, pink granular cytoplasm and a round-to-oval stippled nucleus.
- **Ultrastructral features: neurosecretory electron dense bodies in the cytoplasm**







Small Intestinal Neoplasms

Carcinoid Tumor

Clinical features

- Asymptomatic
- May cause obstruction, intussusception or bleeding.
- May elaborate hormones: Zollinger-Ellison, Cushing's carcinoid or other syndromes.

Small Intestinal Neoplasms

Carcinoid tumor

Carcinoid syndrome

- 1% of carcinoid tumor & in 20% of those of widespread metastasis
- Paroxymal flushing, episodes of asthma-like wheezing, right-sided heart failure, attacks of watery diarrhea, abdominal pain,
- The principal chemical mediator is serotonin
- The syndrome is classically associated with ileal carcinoids with hepatic metastases.

Clinical findings

- Due to serotonin and other bioactive compounds (e.g., histamine, bradykinin)
  - Flushing of the skin (75%–90% of cases)

    Due to vasodilation; may be triggered by emotion, alcohol, other foods
  - Diarrhea (>70% of cases)

    Increased bowel motility from serotonin
  - Intermittent wheezing and dyspnea (25% of cases)

    Due to bronchospasm
  - Facial telangiectasia
  - Tricuspid regurgitation and pulmonary stenosis

    Serotonin increases collagen production in the valves.

Serotonin and diarrhea

- Patients with carcinoid syndrome often suffer from diarrhea, which has both a secretory and a motor component. The secretory component of carcinoid diarrhea is attributable to excessive serotonergic stimulation of submucosal secretomotor neurons; the motor component includes faster small bowel and colon transit and an exaggerated tonic response of the colon to ingestion of a meal

Small Intestinal Neoplasms

Lymphoma

- Most often low-grade lymphomas arising in mucosal-associated lymphoid tissue (MALT) lymphoma or high-grade non-Hodgkin's lymphomas of B cell type.
- May occur in any part of the intestine;
- The ileocecal region is a favored site for Burkitt's lymphoma.

• A

1. Neurosecretory electron dense bodies
2. Occult blood in stool
3. Worst prognosis
4. Intussusception
5. Excess extracellular mucin
6. Serotonin
7. Round and uniform nuclei
8. Carcinoembryonic antigen
9. Annular lesions
10. Polypoid, exophytic masses
11. Sessile serrated adenomas

• B

A. Right-sided adenocarcinomas

B. Left-sided adenocarcinomas

C. Carcinoid Tumor

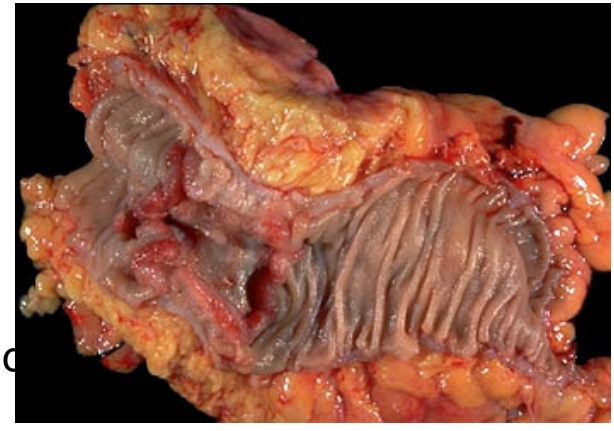
A

1. FAP
2. MSH2
3. APC
4. MSH6
5. K-RAS
6. MLH1
7. P53
8. PMS1
9. DCC
10. PMS2
11. HNPCC

B

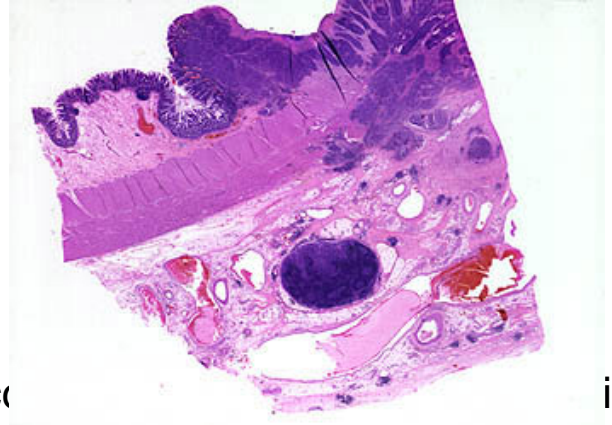
1. The APC/B-catenin pathway
2. The DNA mismatch repair genes pathway

- Left colon, carcinc

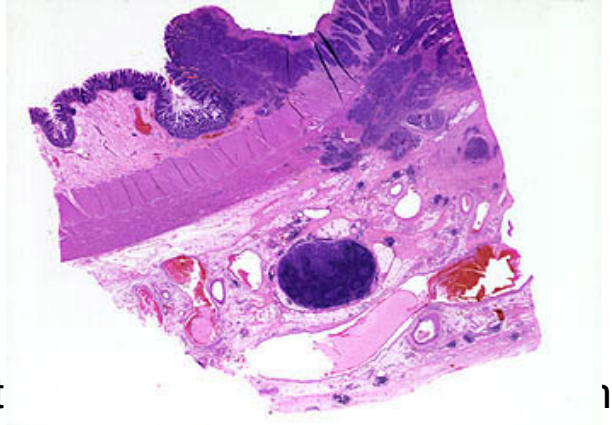


This specimen from the left colon shows an annular, encircling, and constricting cancer. The margins of the cancer are heaped-up and firm, and the mid-region is ulcerated.

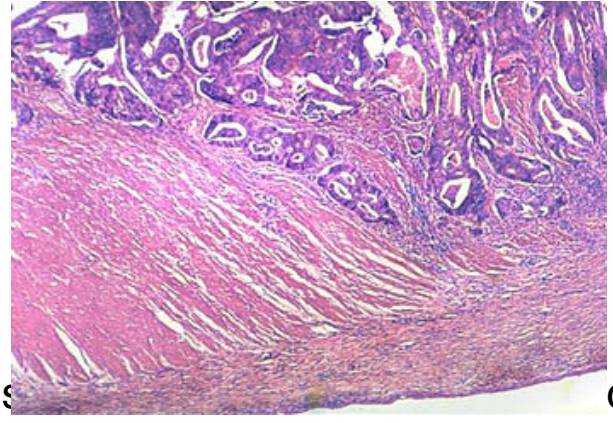
Left-sided colon cancers come to attention by producing occult bleeding and changes in bowel habits (i.e., constipation and cramping in the left lower quadrant).



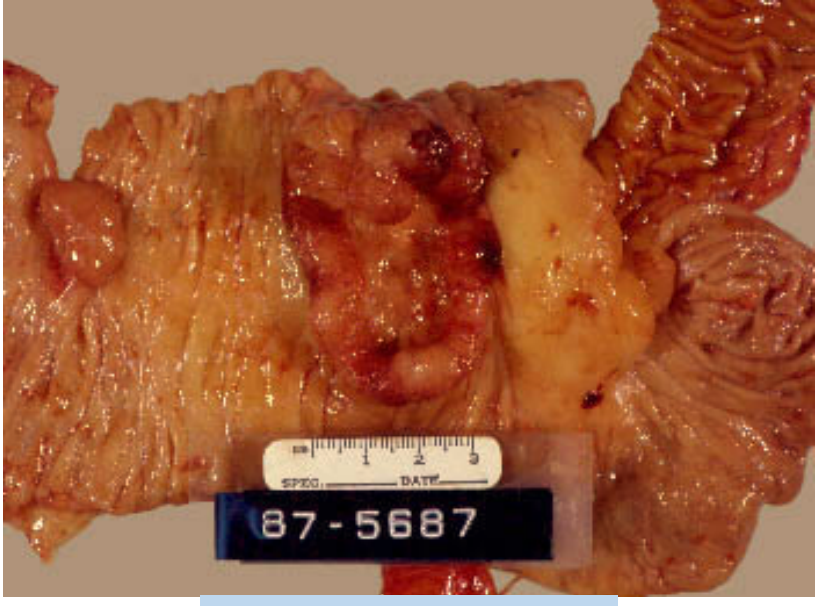
- The carcinoma is c iltrating the muscularis propria, serosa, and mesentery. The TNM classification is based on the extent of invasion, number of lymph nodes involved, and extent of metastatic involvement. The deeper tumor extends into the muscularis propria, and as lymph nodes become involved, the prognosis worsens.
- T—extent of invasion
- N—number of lymph nodes involved
- M—extent of metastatic involvement



- Assuming this pat ıetastasis, what stage is this carcinoma?
  The TNM stage for the current case would be T3N0MX.
- T3—extends through the muscularis propria
- N0—no lymph node involvement
- MX—extent of metastatic involvement unknown

- malignant glands  colon infiltrating the muscularis propria.

What is the mode of spread of this cancer?
Colonic carcinomas spread by local extension to adjacent structures. The favored sites of metastases are regional lymph nodes, liver, lungs, and bones.



Cecal adenocarcinoma

Tumors in the proximal colon tend to grow as polypoid, fungating, ulcerating masses. Obstruction is uncommon. About 25% of colon carcinomas are located in the cecum or ascending colon. Note the adjacent pedunculated adenomatous polyp. Most colon cancers develop from adenomatous polyps (the adenoma-carcinoma sequence).

Cecal and right colon cancers most often come to clinical attention by the appearance of fatigue, weakness, and iron-deficiency anemia.

Diverticulosis