

Small and Large Intestinal pathology, part 4

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Colonic Adenocarcinoma

- ▶ Most common malignancy of the gastrointestinal tract
- ▶ Small intestine is uncommonly involved by neoplasia.
- ▶ Peak: 60 to 70 years
- ▶ 20% under 50 years.
- ▶ Developed countries lifestyles and diet.
- ▶ **Low intake of vegetable fiber and high intake of carbohydrates and fat.**
- ▶ Aspirin or other NSAIDs have a protective effect.
- ▶ Cyclooxygenase-2 (COX-2) promotes epithelial proliferation.



Pathogenesis

- ▶ Heterogeneous molecular events.
- ▶ Sporadic >>>> familial.
- ▶ **Two pathways:**
- ▶ **APC/ β -catenin pathway >> increased WNT signaling**
- ▶ **Microsatellite instability pathway >> defects in DNA mismatch repair**

- ▶ Stepwise accumulation of multiple mutations



The APC / β -catenin pathway: chromosomal instability

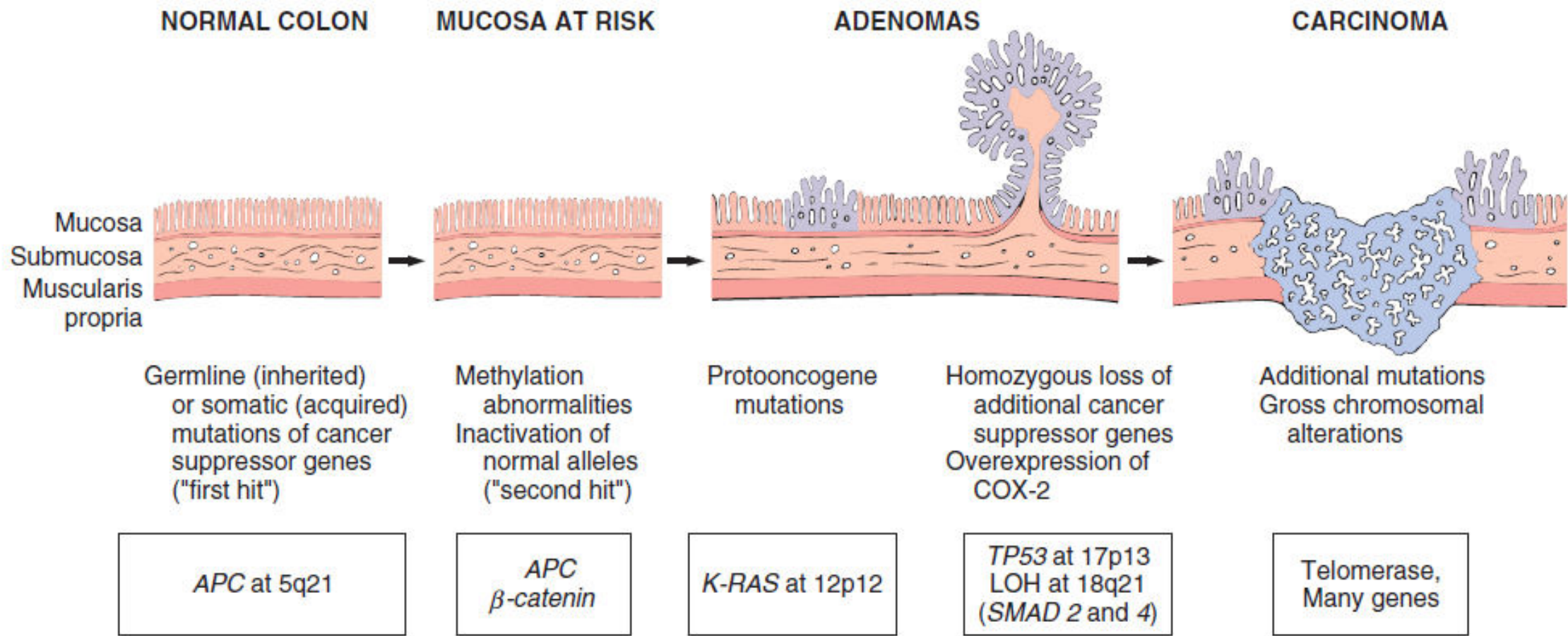
- ▶ *Classic adenoma carcinoma sequence.*
- ▶ **80% of sporadic colon tumors**
- ▶ Mutation of the APC tumor suppressor gene: EARLY EVENT
- ▶ *APC is a key negative regulator of β -catenin, a component of the WNT signaling pathway.*
- ▶ *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).*



- ▶ *Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >> promote proliferation.*
- ▶ *Additional mutations >> activation of KRAS (LATE EVENT) >> inhibits apoptosis.*
- ▶ *SMAD2 and SMAD4 mutations (tumor suppressor genes.)*

- ▶ **TP53 is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**
- ▶ TP53 inactivation mutation
- ▶ Expression of telomerase also increases as the tumor advances.



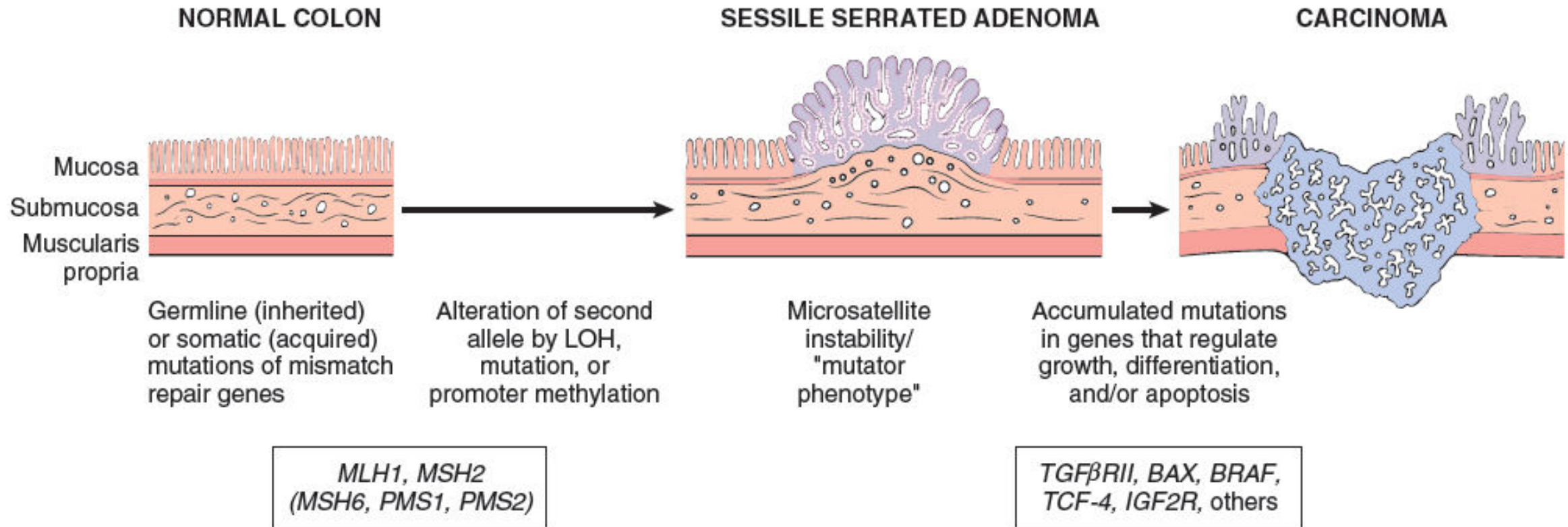


The microsatellite instability pathway

- ▶ DNA mismatch repair deficiency
- ▶ Loss of mismatch repair genes
- ▶ Mutations accumulate in microsatellite repeats
- ▶ *Microsatellite instability*

- ▶ Silent if microsatellites located in noncoding regions
- ▶ Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth and apoptosis (TGF-B and BAX genes)





Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	<i>APC</i>	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	<i>MSH2, MLH1</i>	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	<i>APC</i>	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	<i>MSH2, MLH1</i>	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma



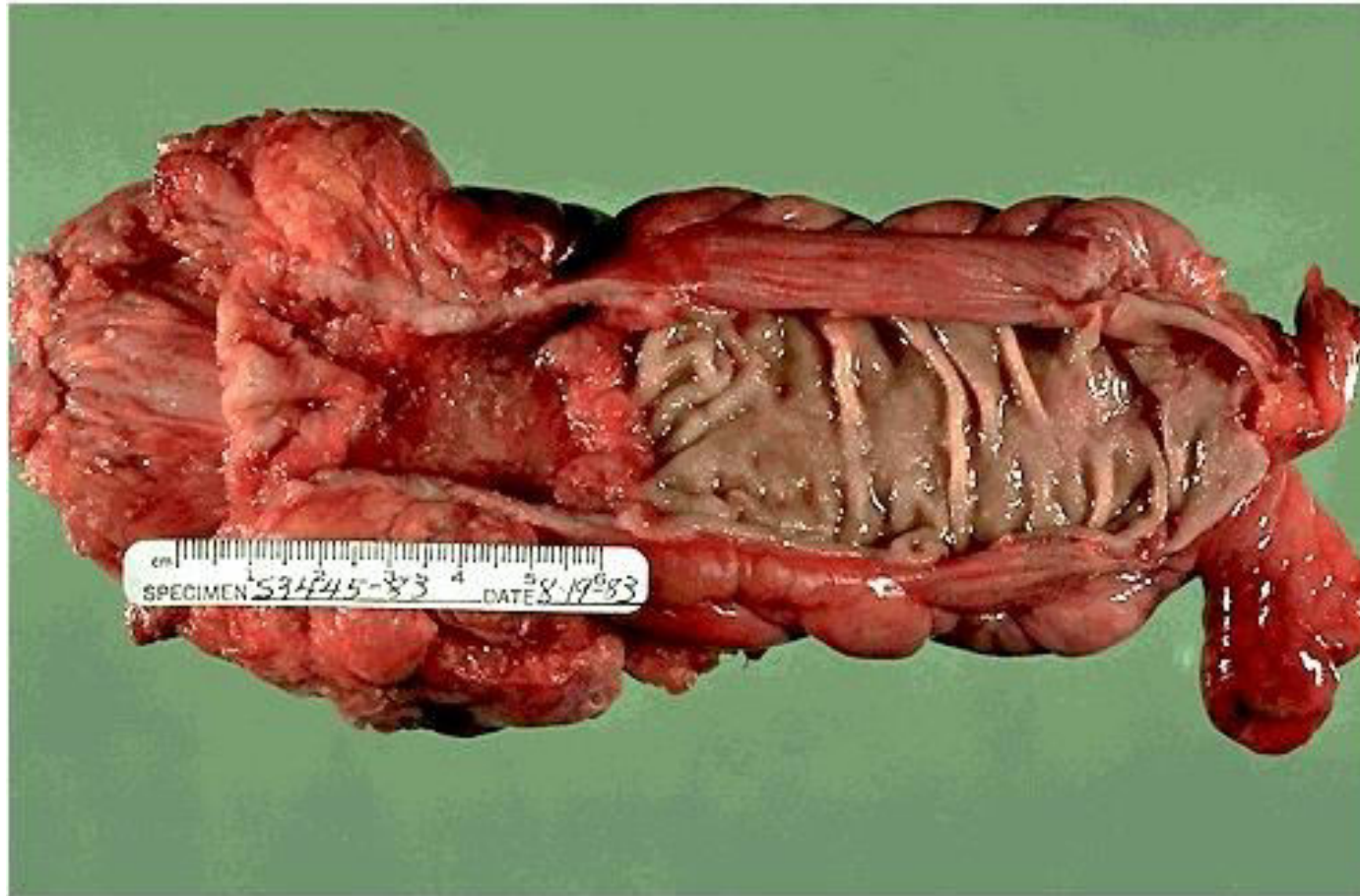
MORPHOLOGY

- ▶ **Macroscopic:**
- ▶ Proximal colon tumors: polypoid, exophytic masses
- ▶ Proximal colon: rarely cause obstruction.
- ▶ Distal colon: annular lesions “napkin ring” constrictions & narrowing

- ▶ **Microscopic:**
- ▶ Dysplastic GLANDS with strong desmoplastic response.
- ▶ Necrotic debris are typical.
- ▶ Some tumors give abundant mucin or form signet ring cells.



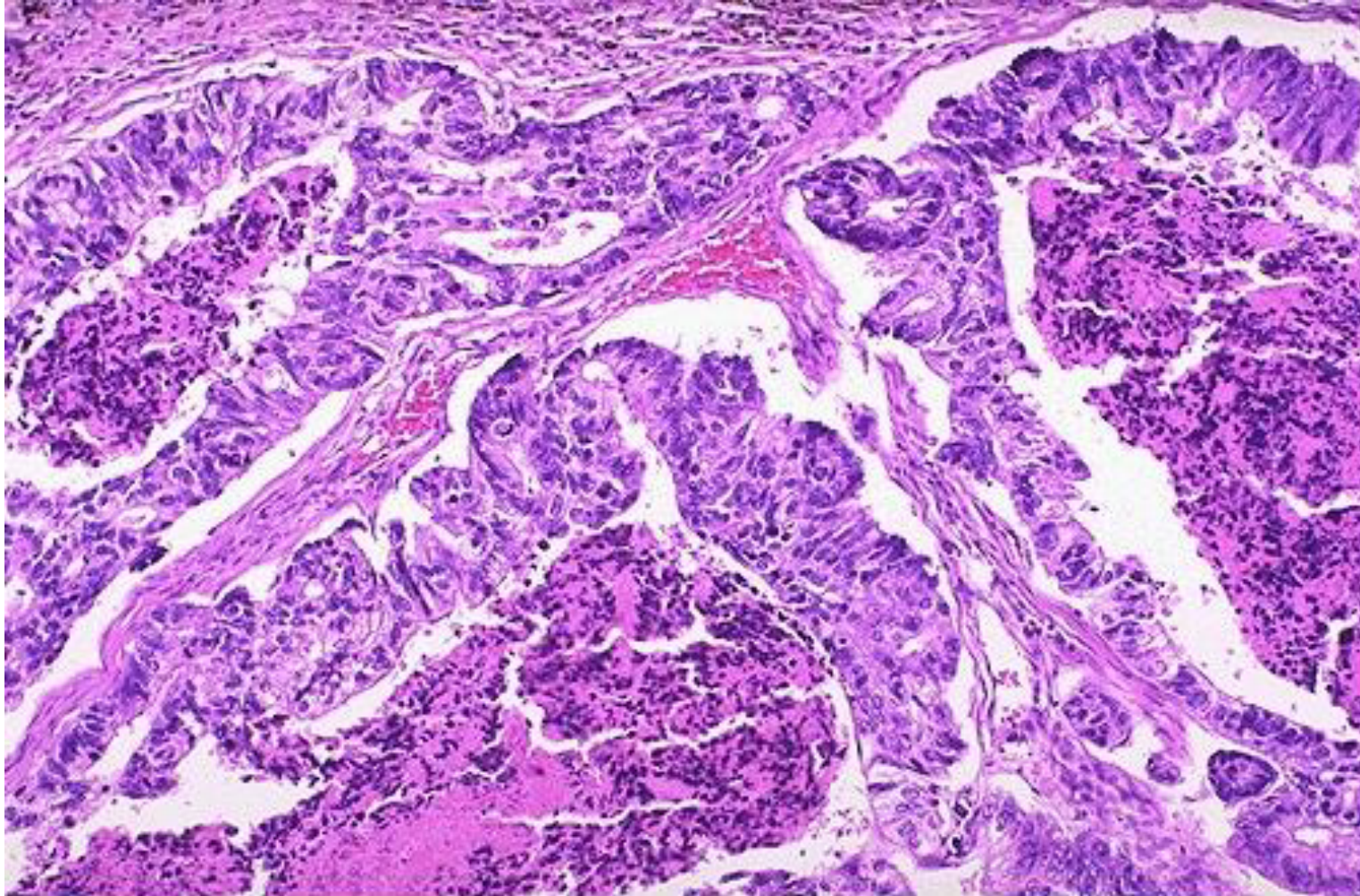
Rectosigmoid adenocarcinoma, napkin ring



Exophytic adenocarcinoma



Adenocarcinoma with necrosis



Clinical Features

- ▶ Endoscopic screening >> cancer prevention
- ▶ Early cancer is asymptomatic !!!!!!!
- ▶ Cecal and right side cancers: *Fatigue and weakness (iron deficiency anemia)*
- ▶ **Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.**

- ▶ *Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower-quadrant discomfort.*

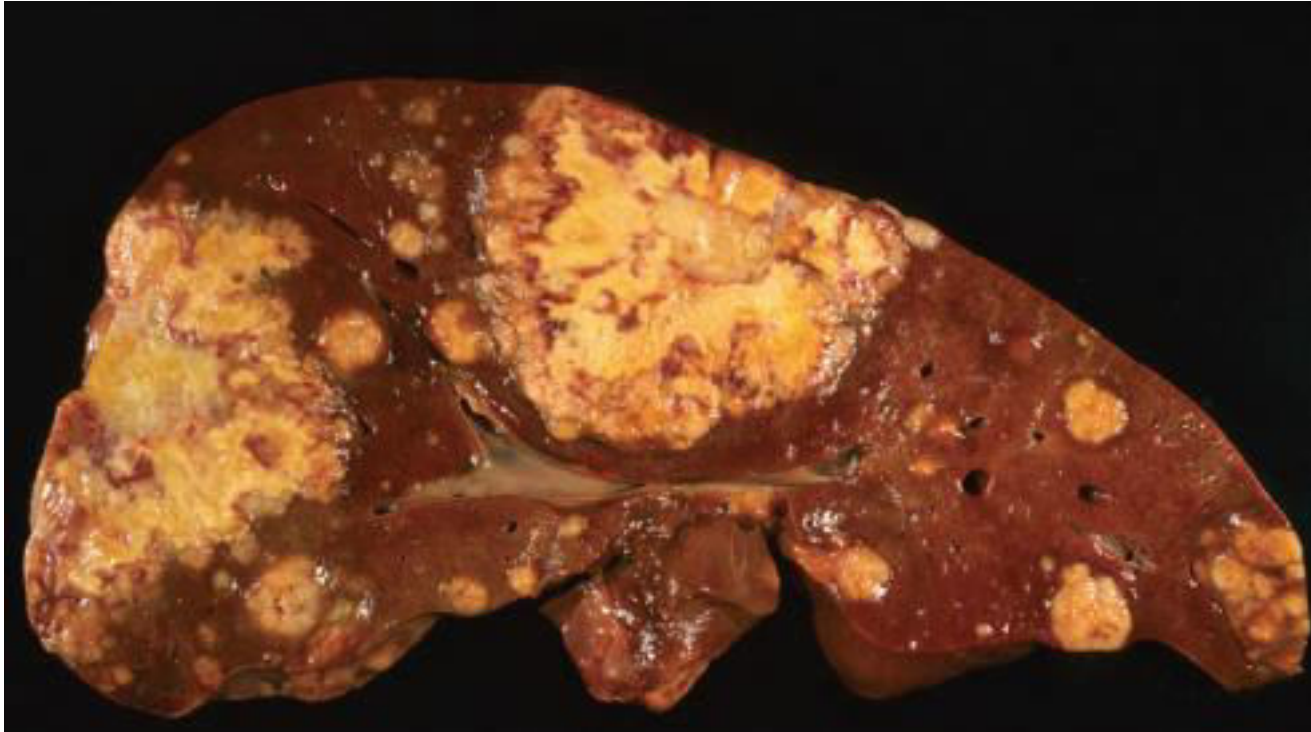


- ▶ Poor differentiation and mucinous histology >> poor prognosis
- ▶ *Most important two prognostic factors are*
- ▶ *Depth of invasion*
- ▶ *Lymph node metastasis.*

- ▶ *Distant metastases (lung and liver) can be resected.*



Liver metastasis.



Appendix

- ▶ Normal true diverticulum of the cecum

- ▶ ACUTE APPENDICITIS
- ▶ TUMORS OF THE APPENDIX



ACUTE APPENDICITIS

- ▶ Most common in adolescents and young adults.
 - ▶ May occur in any age.
 - ▶ Difficult to confirm preoperatively
-
- ▶ DDx:
 - ▶ Mesenteric lymphadenitis,
 - ▶ Acute salpingitis,
 - ▶ Ectopic pregnancy,
 - ▶ Mittelschmerz (pain associated with ovulation),
 - ▶ Meckel diverticulitis.



- ▶ Luminal obstruction in 50-80% of cases >> increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
- ▶ *Obstruction by fecalith, less commonly : gallstone, tumor, worms....*
- ▶ Diagnosis requires neutrophilic infiltration of the muscularis propria
- ▶ **Acute suppurative appendicitis >> more severe >> focal abscess formation.**
- ▶ **Acute gangrenous appendicitis >> necrosis and ulceration.**



Clinical Features

- ▶ Early acute appendicitis: periumbilical pain
- ▶ Later: pain localizes to the right lower quadrant,
- ▶ Nausea, vomiting, low-grade fever, mildly leukocytosis.
- ▶ A classic physical finding is *McBurney's sign* (McBurney's point).
- ▶ Signs and symptoms are often absent, creating difficulty in clinical diagnosis.

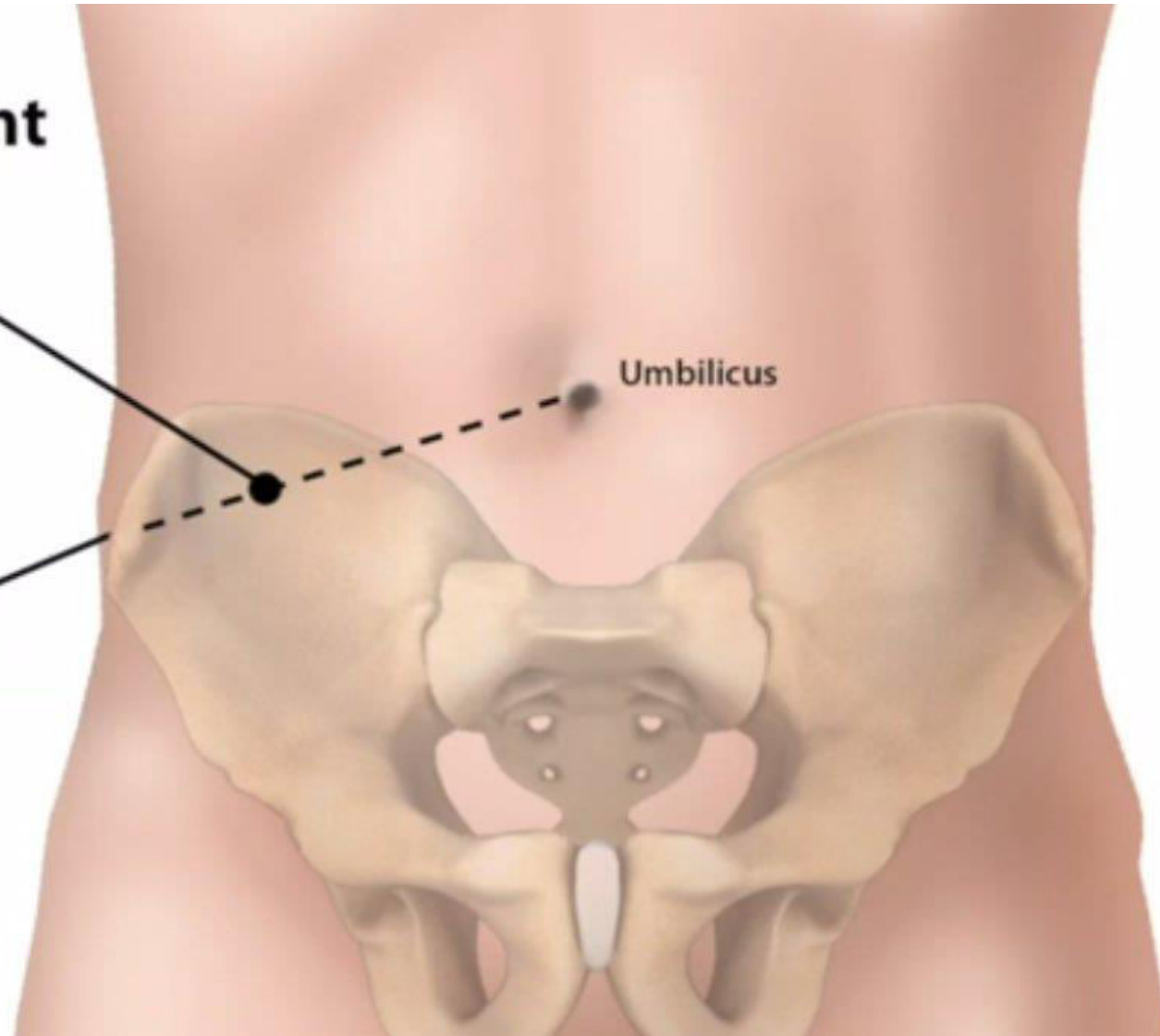


McBurney's Point

2/3 of the way from
umbilicus to ASIS

Anterior Superior Iliac Spine

Umbilicus



TUMORS OF THE APPENDIX

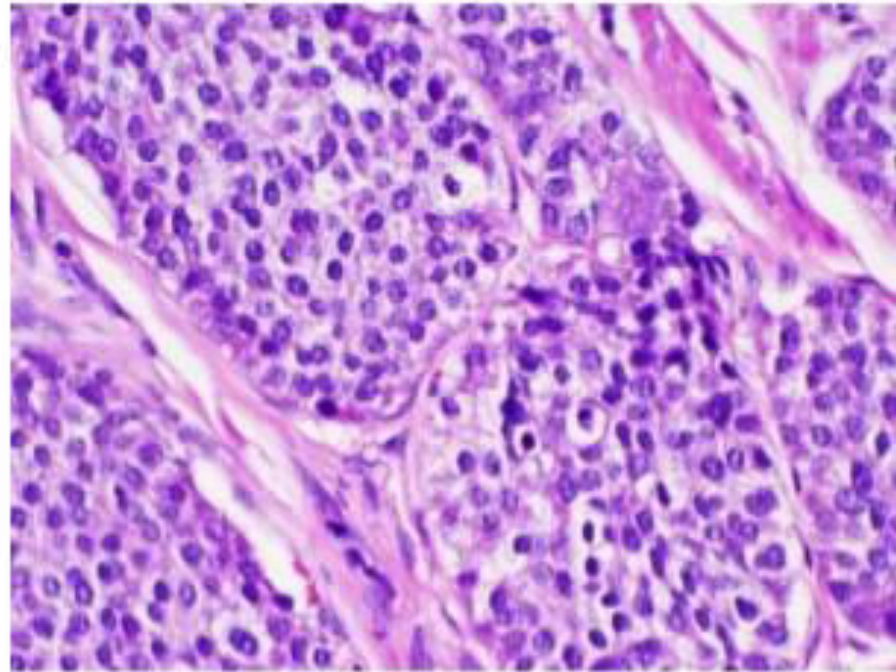
- ▶ **The most common tumor: *carcinoid* (neuroendocrine tumor)**
- ▶ Incidentally found during surgery or on examination of a resected appendix
- ▶ Distal tip of the appendix
- ▶ Nodal metastases & distant spread are rare.



Carcinoid tumor



Gross



Microscopic

