Intestinal pathology, part 4

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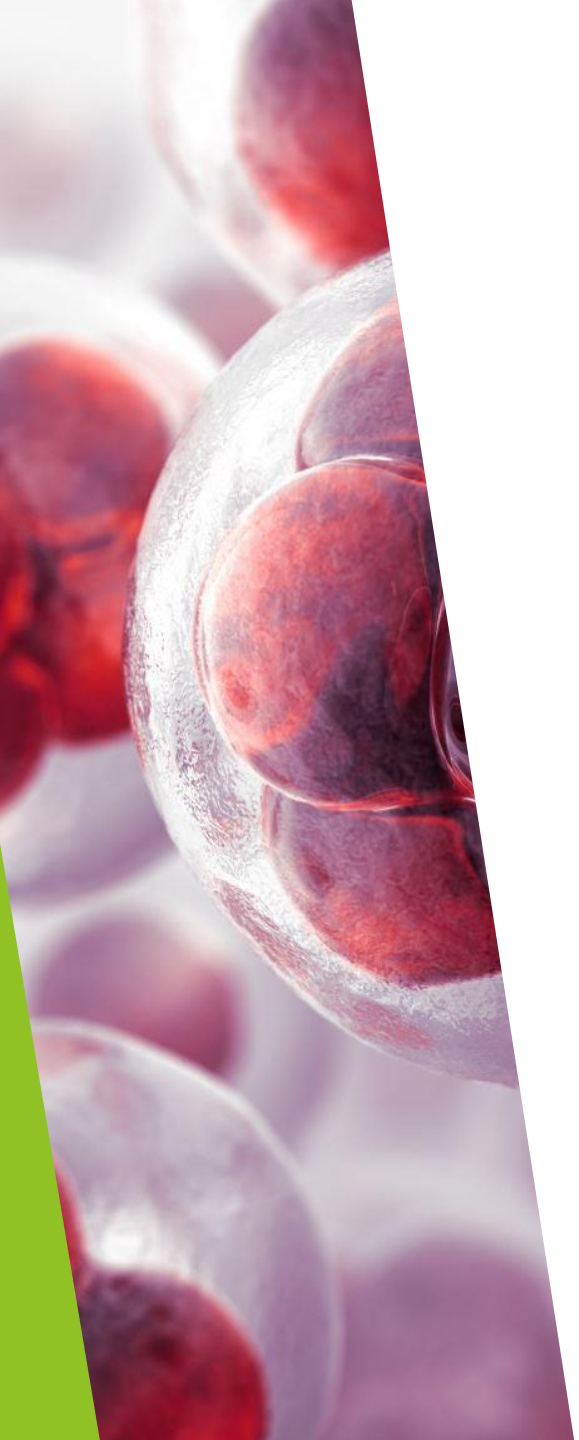
Diseases of the intestines

- Intestinal obstruction
- Vascular disorders
- Malabsorptive diseases and infections
- Inflammatory intestinal disease.
- Polyps and **neoplastic diseases**

Colonic Adenocarcinoma

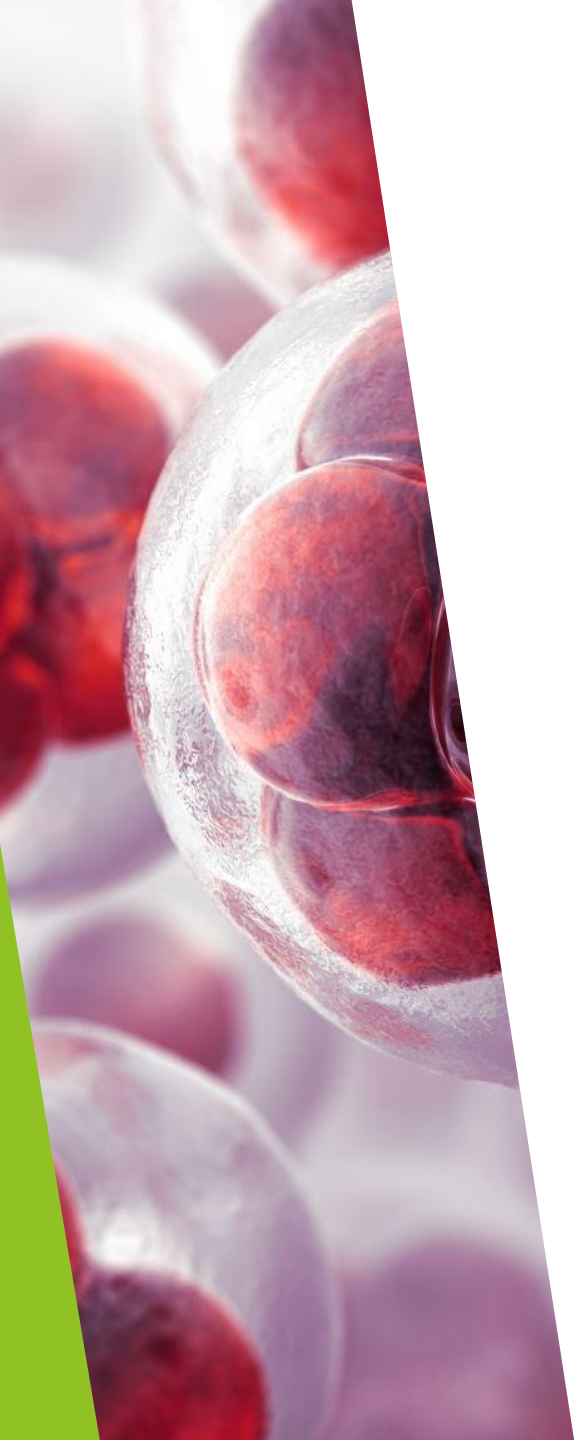
- Most common malignancy of the gastrointestinal tract (2nd cause of cancer related death after lung cancer)
- Small intestine is uncommonly involved by neoplasia.
- Peak: 60-70 years, males>females, <20% before 50.
- Developed countries lifestyles and diet.
- **Risk factors: Low intake of vegetable fiber and high intake of carbohydrates and fat. Obesity, smoking and alcohol.**
- Aspirin or other NSAIDs have a protective effect (Cyclooxygenase-2 (COX-2) expressed in 90% of carcinomas, even adenomas, promotes epithelial proliferation).
- **Prevention: dietary modification, pharmacologic chemoprevention.**



Pathogenesis

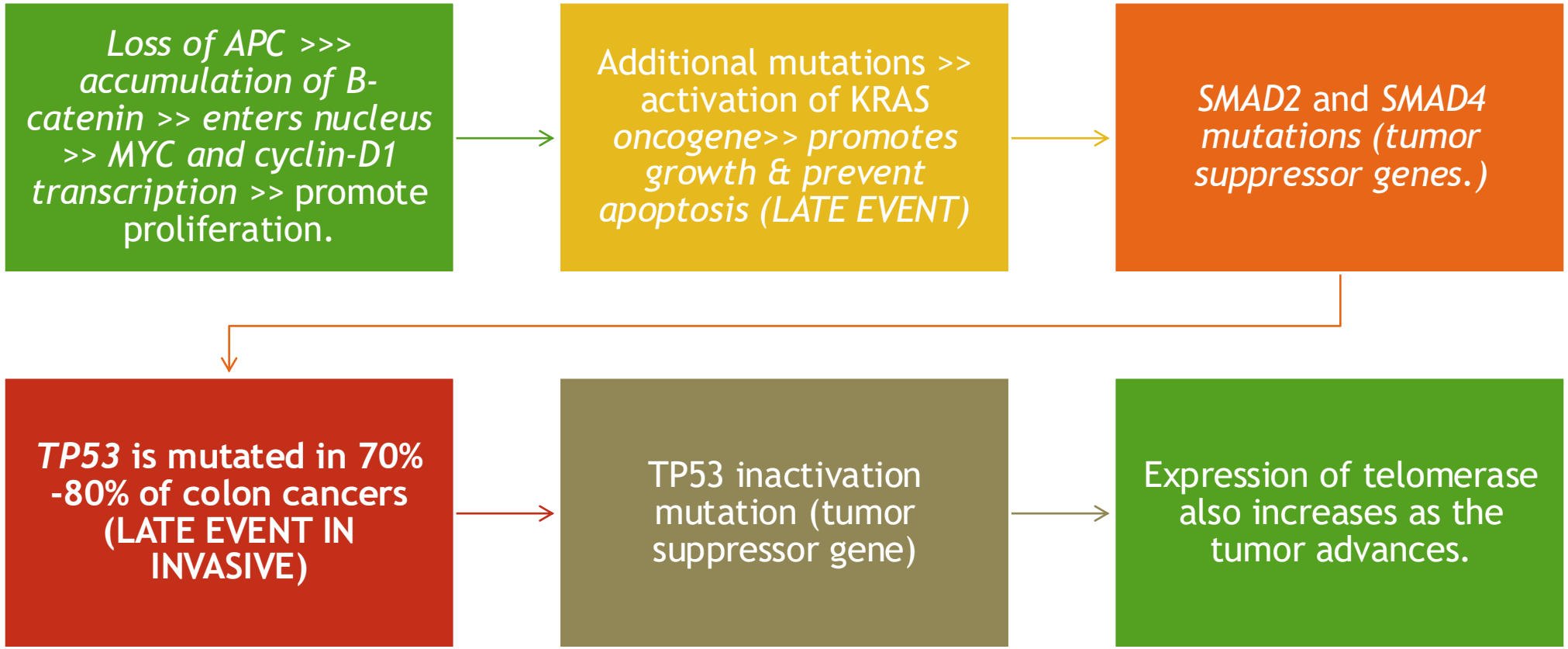
- Heterogeneous molecular events (genetic and epigenetic).
- Sporadic >>>> familial.
- **Two pathways:**
- **APC/ß-catenin pathway >> increased WNT signaling**
- **Microsatellite instability pathway due to defects in DNA mismatch repair**

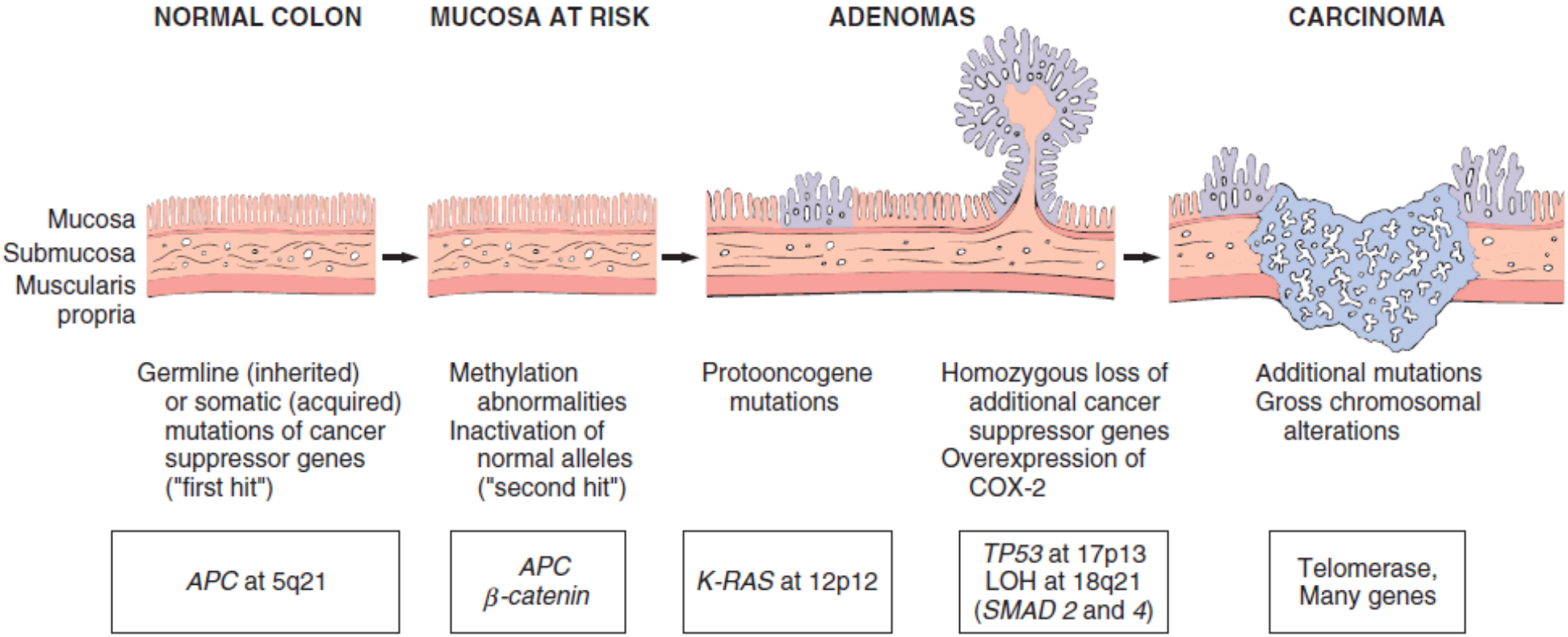
- Stepwise accumulation of multiple mutations

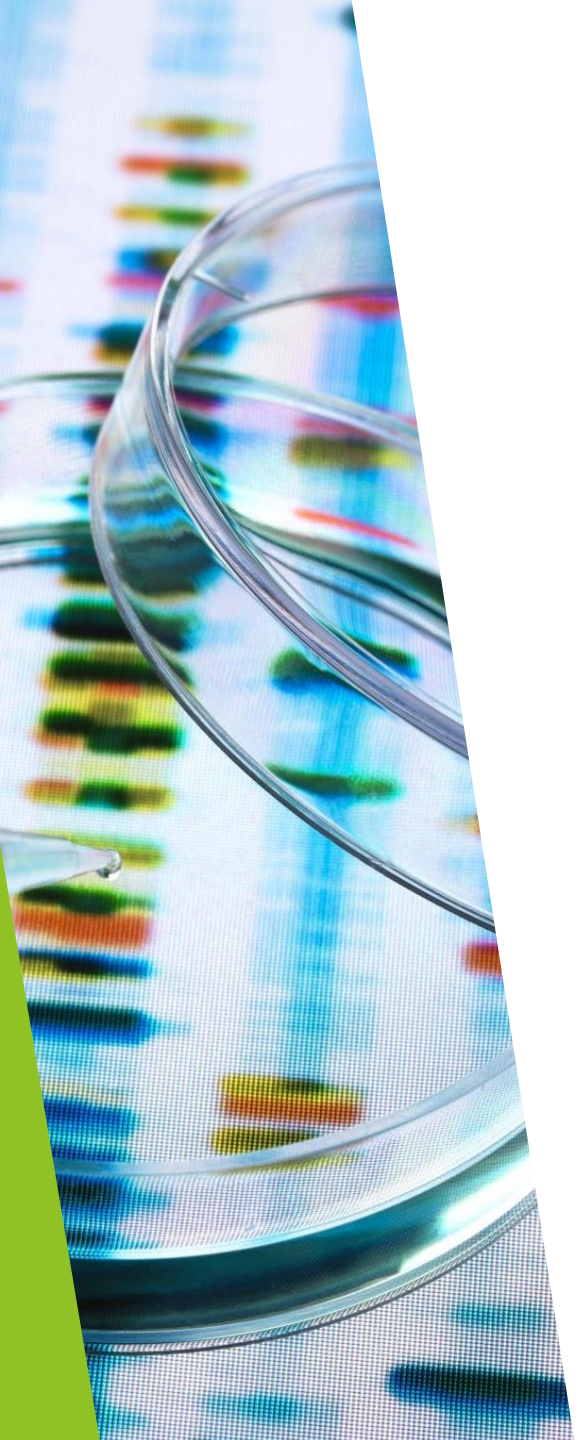


The APC/β-catenin pathway: chromosomal instability

- **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 (promotes degradation), a component of the WNT signaling pathway.*
- *Both copies of APC should be inactivated for adenoma to develop (1^{st} and 2^{nd} hits).*
- ***Chromosomal instability by deletions (hallmark)***


Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >> promote proliferation.
Additional mutations >> activation of KRAS *oncogene>> promotes growth & prevent apoptosis (LATE EVENT)*
SMAD2 and *SMAD4 mutations (tumor suppressor genes.)*
***TP53* is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**
TP53 inactivation mutation (tumor suppressor gene)
Expression of telomerase also increases as the tumor advances.

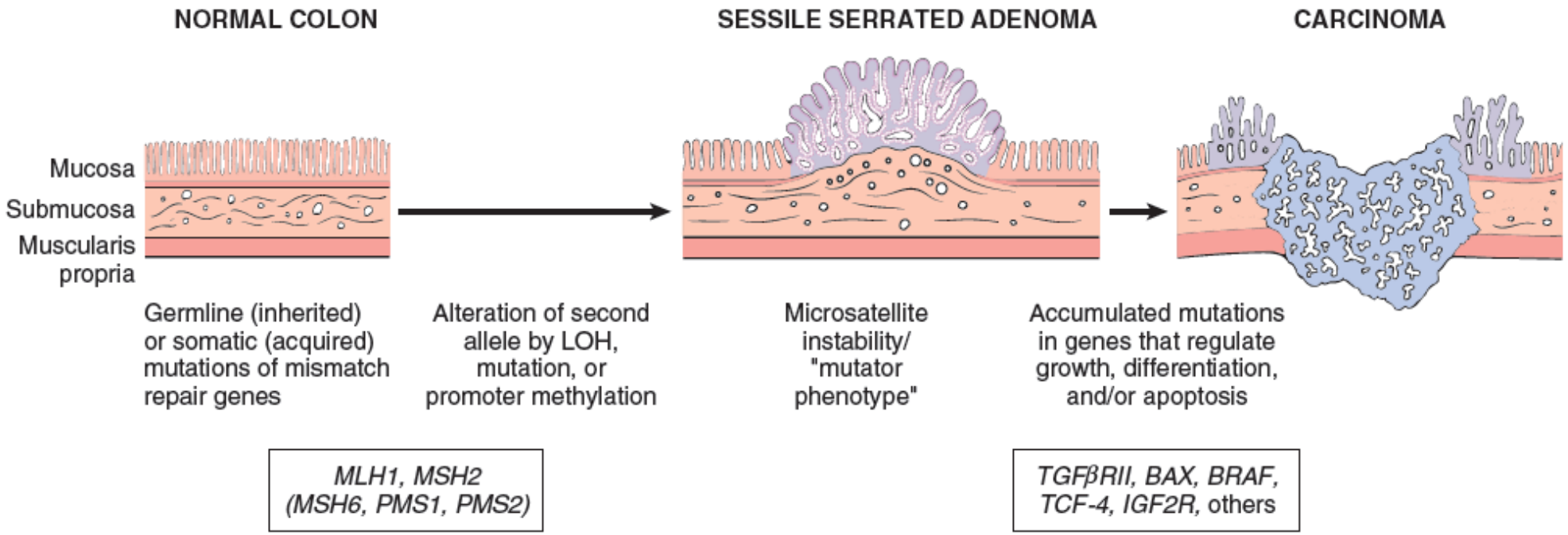

NORMAL COLON
MUCOSA AT RISK
ADENOMAS
CARCINOMA
Mucosa
Submucosa
Muscularis propria
Germline (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")
Methylation abnormalities
Inactivation of normal alleles ("second hit")
Protooncogene mutations
Homozygous loss of additional cancer suppressor genes
Overexpression of COX-2
Additional mutations
Gross chromosomal alterations
APC at 5q21
APC
β-catenin
K-RAS at 12p12
TP53 at 17p13
LOH at 18q21
(SMAD 2 and 4)
Telomerase,
Many genes



The microsatellite instability pathway

- DNA mismatch repair deficiency (Loss of genes)
- Mutations accumulate in microsatellite repeats (mostly non-coding)
- 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)
- BRAF mutations common. However, P53 and KRAS are absent


NORMAL COLON
SESSILE SERRATED ADENOMA
CARCINOMA
Mucosa
Submucosa
Muscularis propria
Germline (inherited) or somatic (acquired) mutations of mismatch repair genes
Alteration of second allele by LOH, mutation, or promoter methylation
Microsatellite instability/ "mutator phenotype"
Accumulated mutations in genes that regulate growth, differentiation, and/or apoptosis
MLH1, MSH2 (MSH6, PMS1, PMS2)
TGFβRII, BAX, BRAF, TCF-4, IGF2R, others

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

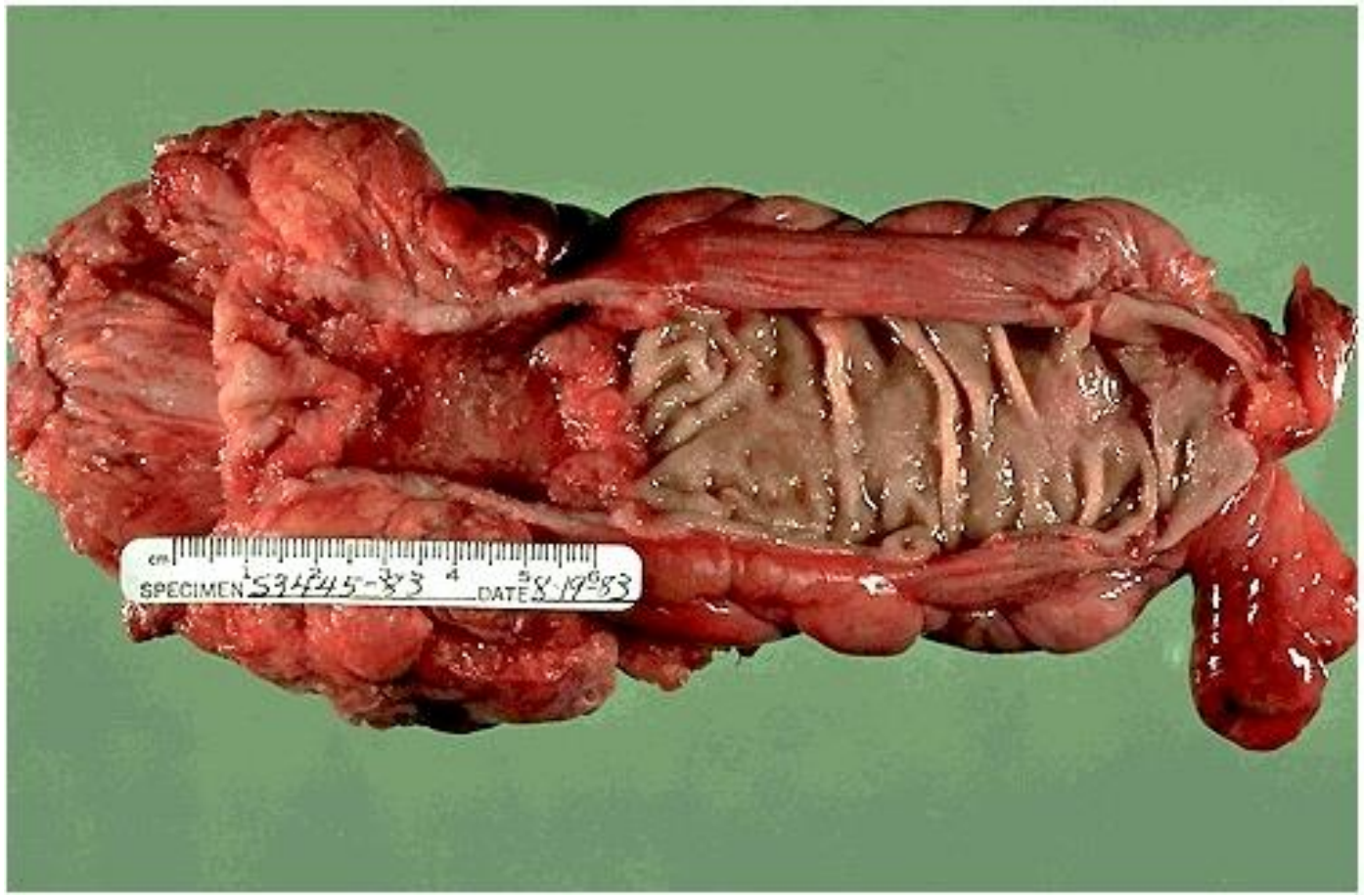
MORPHOLOGY

- **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 (firm).
- Necrotic debris (dirty necrosis) are typical.
- Some tumors give abundant mucin (poor Px) or form signet ring cells.

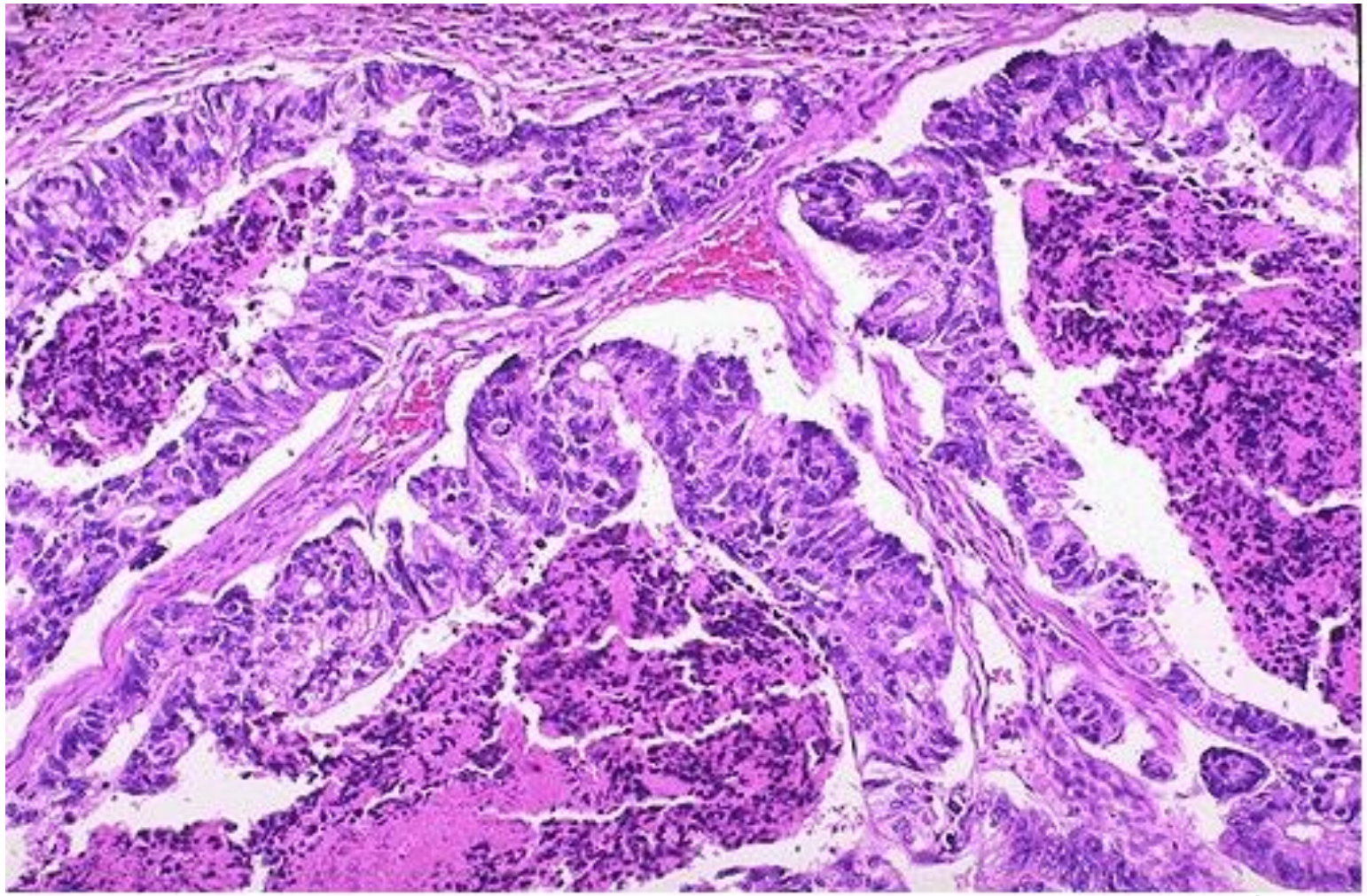
Napkin ring

Recto-sigmoid adenocarcinoma, napkin ring

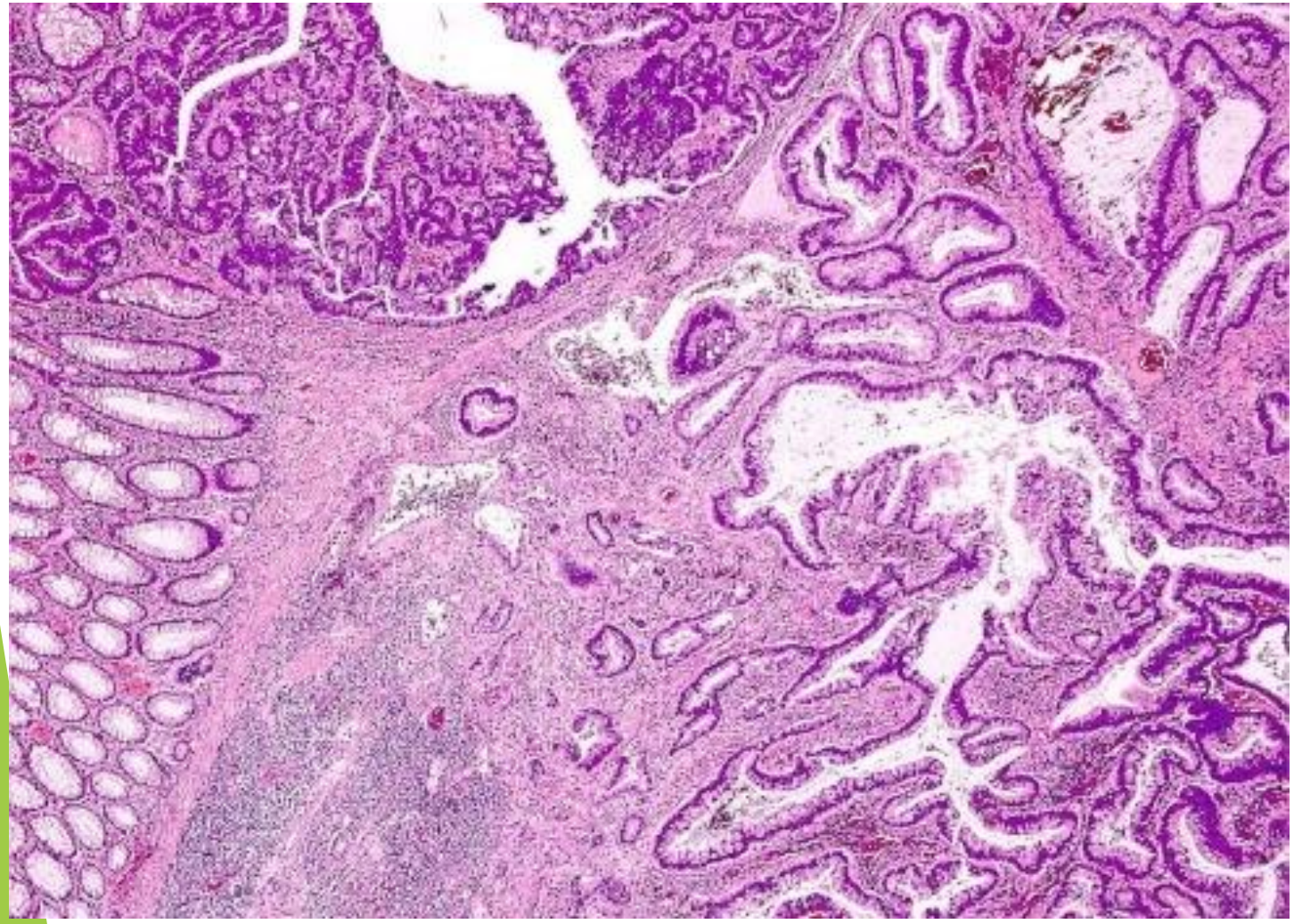


Exophytic adenocarcinoma

Adenocarcinoma with necrosis



Invasive carcinoma



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.

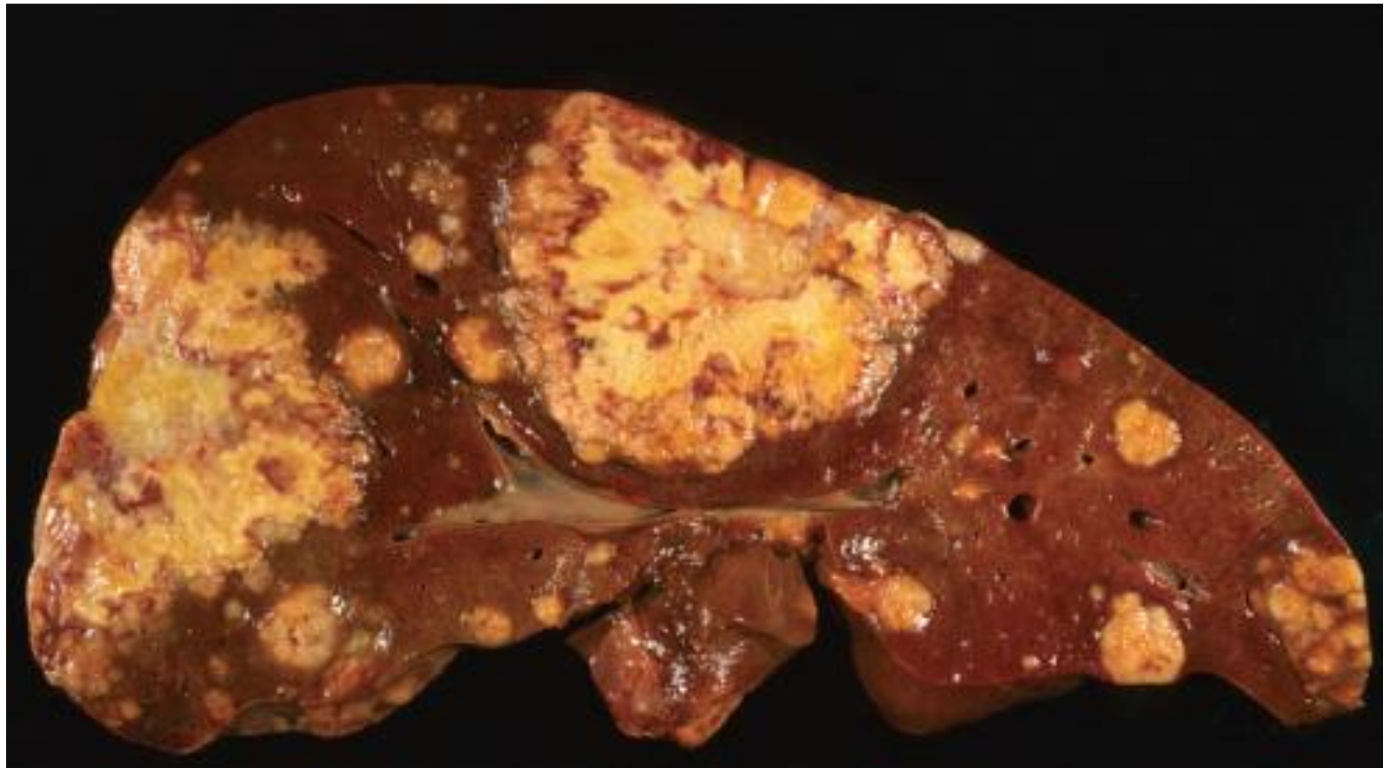
Prognosis:

- Poor differentiation and mucinous histology >> poor prognosis
- ***Most important two prognostic factors are***

1. ***Depth of invasion (mucosa, submucosa, MP, serosa)***
2. ***Lymph node metastasis. (needs Rx and Chemox)***

In addition:

- *Distant metastasis to liver (most common) and lung. (solitary mets can be resected).*
- *Tumors w/ microsatellite instability (immune checkpoint inhibitor therapy)*



Liver metastasis.

Appendix diseases:

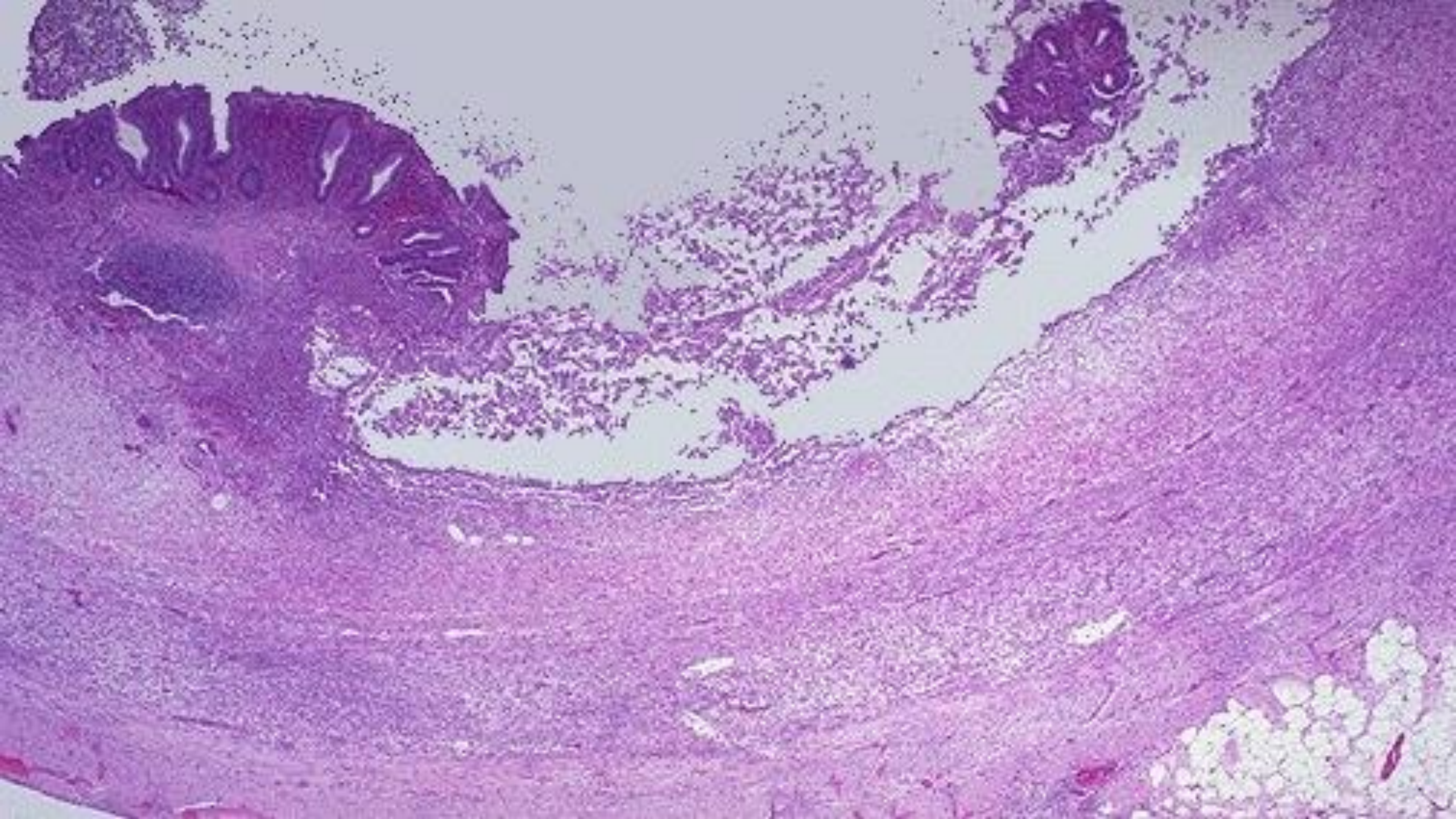
- Normal true diverticulum of the cecum

- ACUTE APPENDICITIS
- TUMORS OF THE APPENDIX

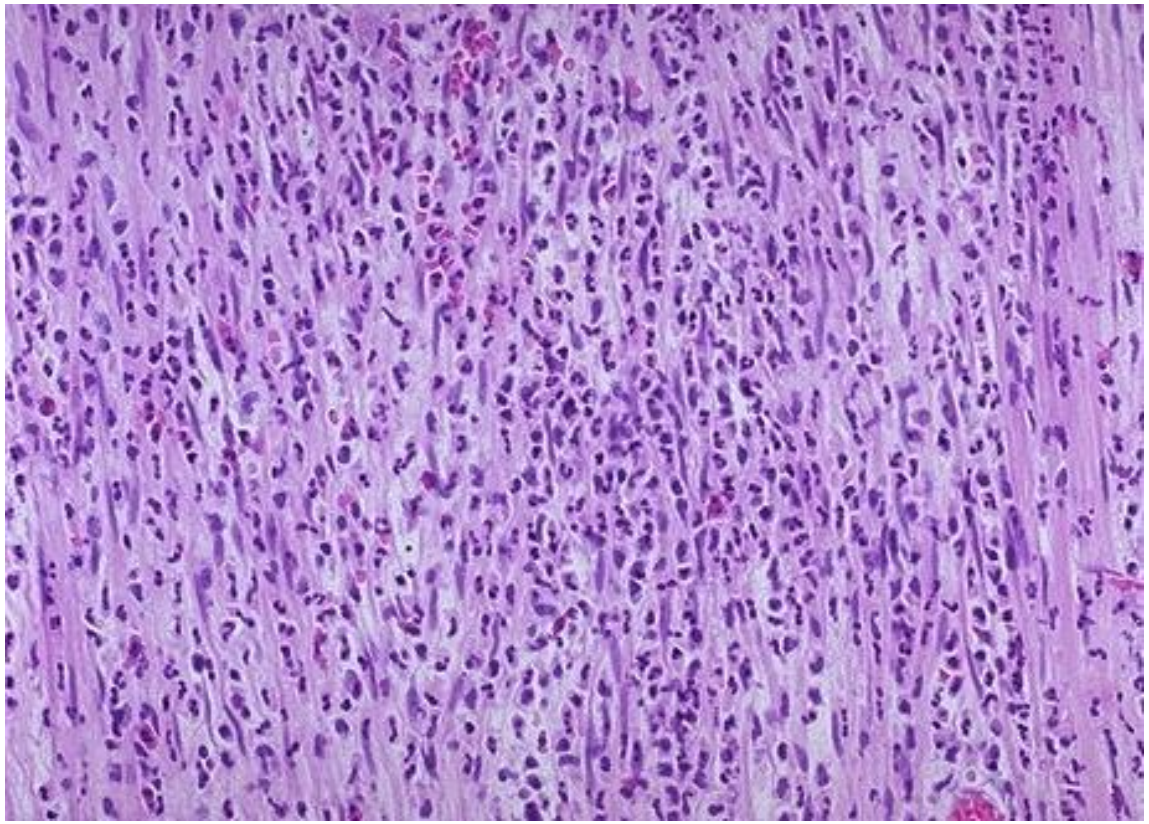
ACUTE APPENDICITIS

- Most common in adolescents and young adults.
- May occur in any age.
- Difficult to confirm preoperatively, surgical emergency.

Normal appendix versus acute appendicitis



Acute appendicitis: neutrophils



DDx of acute appendicitis:

- Mesenteric lymphadenitis,
- Acute salpingitis,
- Ectopic pregnancy,
- Mittelschmerz (pain associated with ovulation),
- Ovarian cysts torsion
- Rupture Meckel diverticulitis
- Crohn disease.

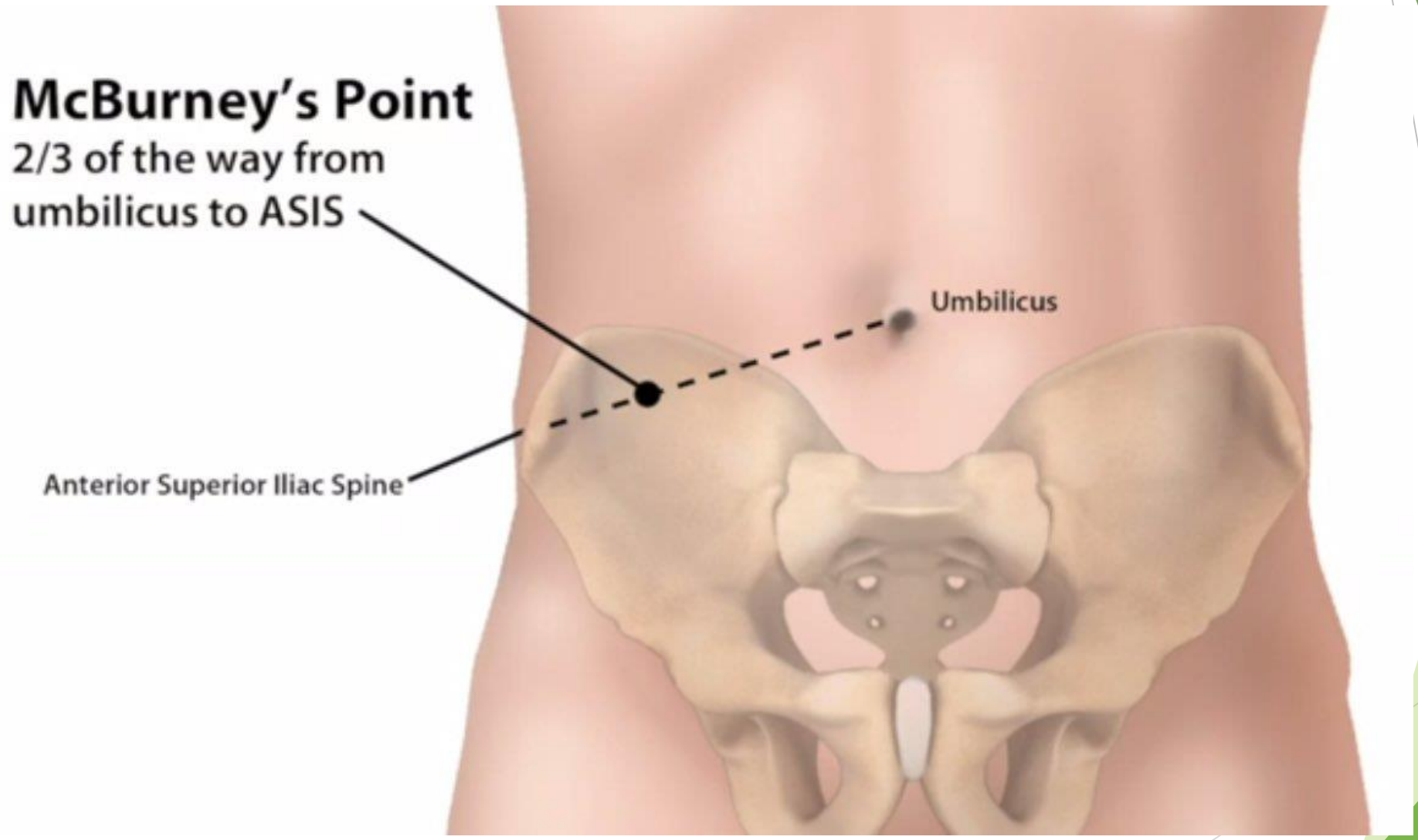
Pathogenesis:

- Increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
- Luminal obstruction in 50-80% of cases by fecalith (small mass-like stone of stool), less commonly : gallstone, tumor, worms….

- Diagnosis requires neutrophilic infiltration of the muscularis propria
- **Acute suppurative appendicitis >> more severe >> focal abscess within wall.**
- **Acute gangrenous appendicitis >> gangrenous necrosis and ulceration>> rupture.**

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.

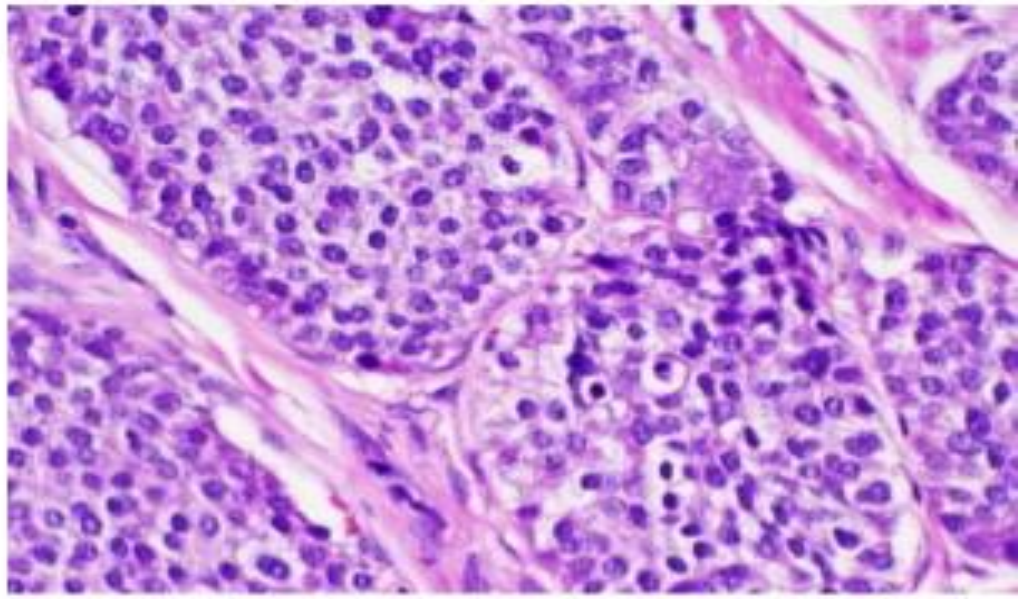

McBurney's Point
2/3 of the way from
umbilicus to ASIS
Umbilicus
Anterior Superior Iliac Spine

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