

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 (**considered familial**).
- ▶ 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 by NSAIDs and aspirin to inhibit COX-2, reducing smoking and alcohol consumption, weight reduction.**

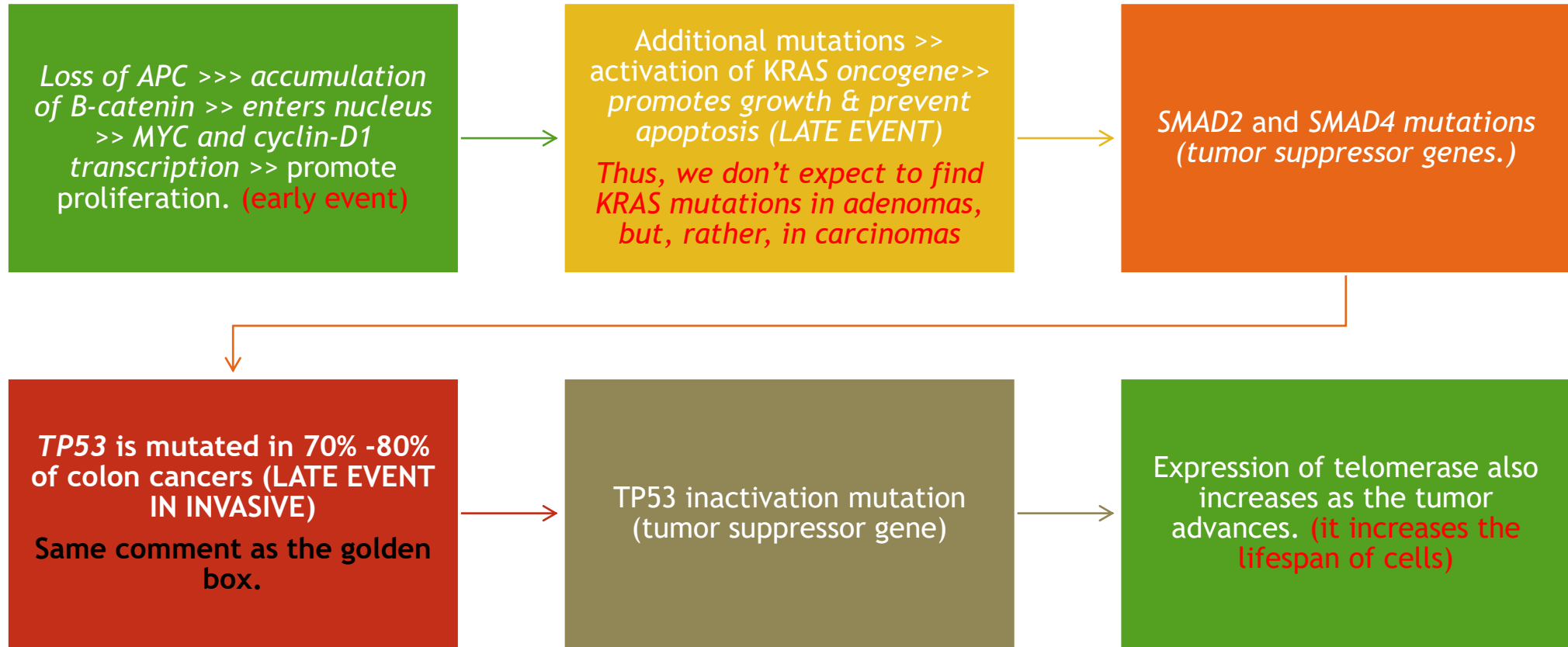
Pathogenesis

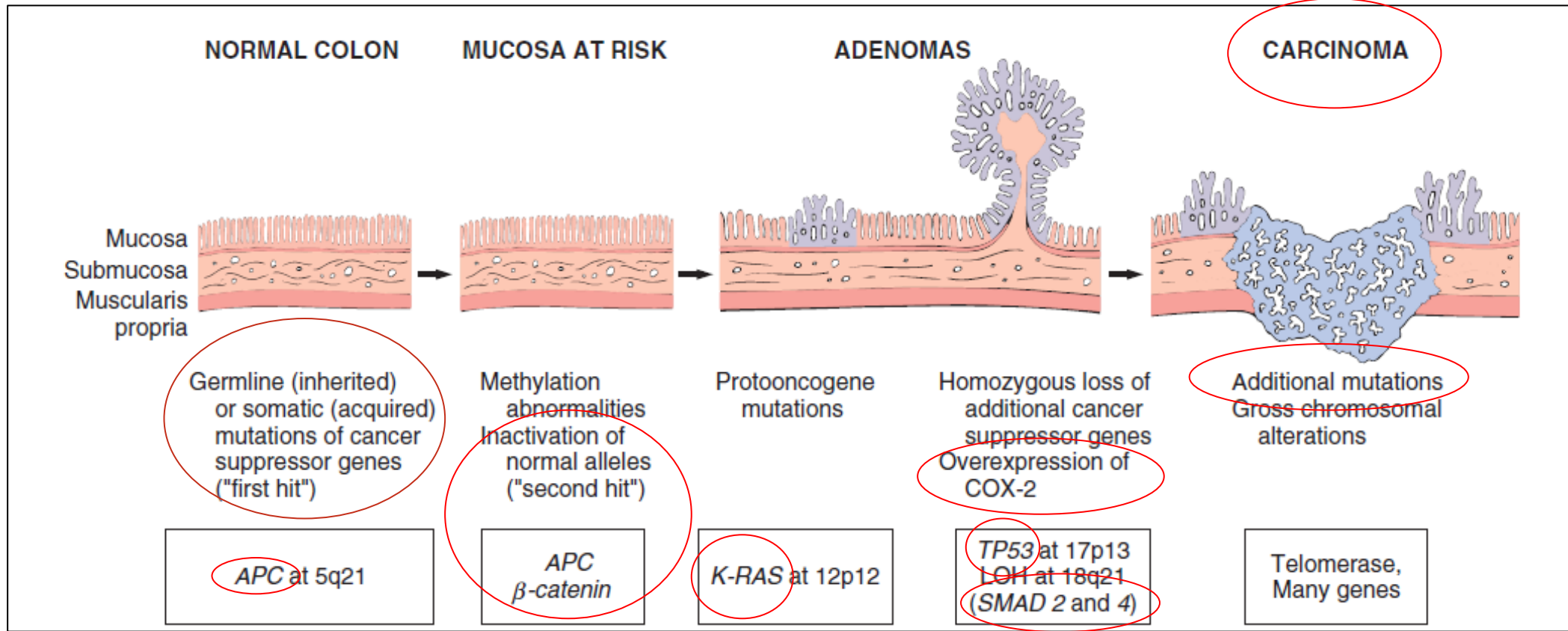
- ▶ Heterogeneous molecular events (genetic and epigenetic).
- ▶ Sporadic >>>> familial.
- ▶ **Two pathways:**
- ▶ **APC (remember, same gene in FAP)/ β -catenin pathway >> increased WNT signaling**
- ▶ **Microsatellite instability pathway due to defects in DNA mismatch repair (remember, same pathogenesis in HNPCC)**
- ▶ Stepwise accumulation of multiple mutations



The APC / β -catenin pathway: chromosomal instability

- ▶ *Classic adenoma-to-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, so **β -catenin accumulates**), a component of the WNT signaling pathway.*
- ▶ *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits) and progress to carcinoma. If 1st hit is germline (inherited), then we expect the 2nd mutation to occur and for the disease to manifest earlier.*
- ▶ *Chromosomal instability by deletions (hallmark)*



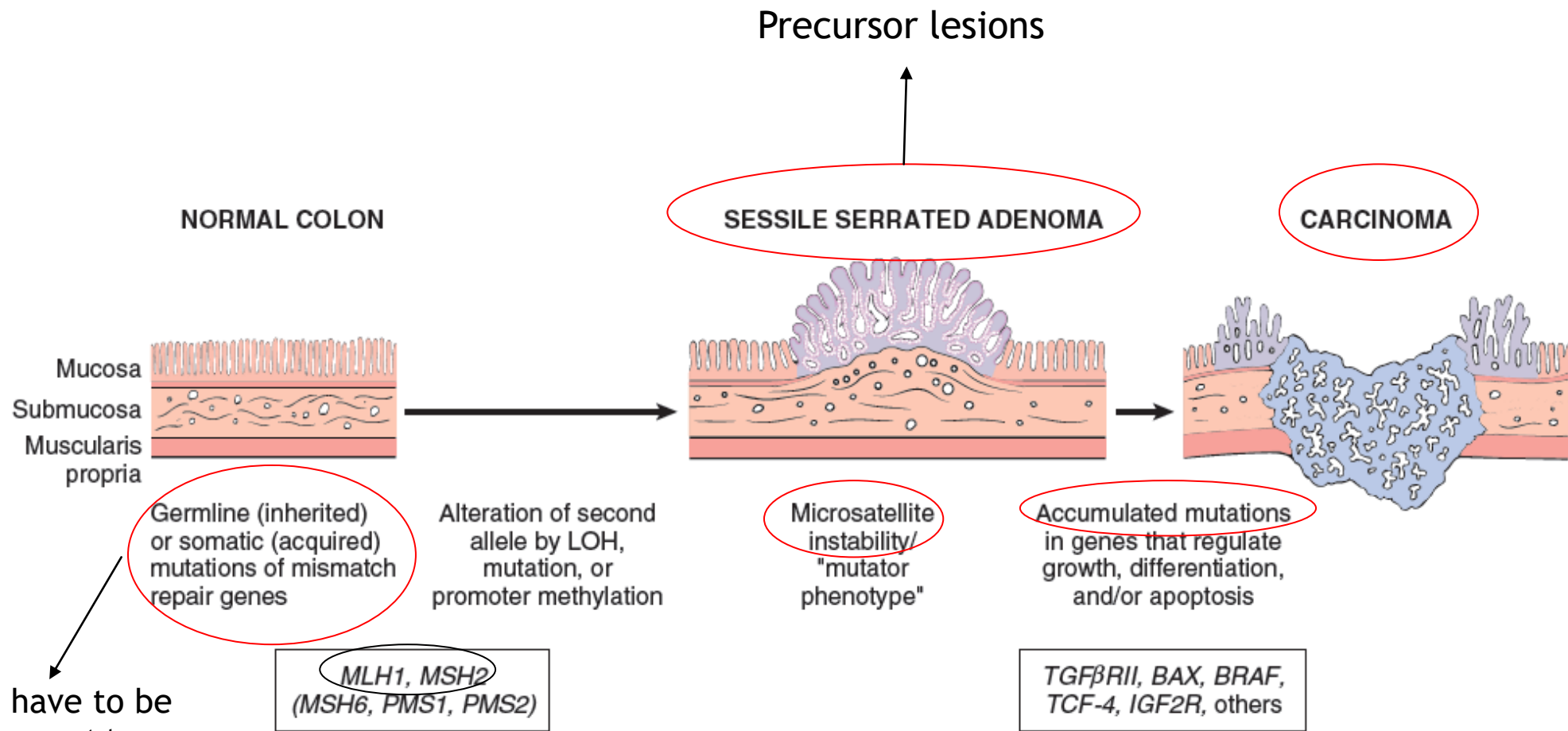




The microsatellite instability pathway

- ▶ 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 (**pro-apoptotic**) genes)
- ▶ BRAF mutations common **and occur later**. However, P53 and KRAS are absent , **which were present in chromosomal instability pathway.**



Both genes have to be defective here. 1st germline and 2nd somatic if inherited. Both somatic if tumor is sporadic

Therefore, we expect the age of onset to be earlier

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

Doctor read everything except for the histology. But, I recommend you go over it as it is a good revision and summary.

MORPHOLOGY

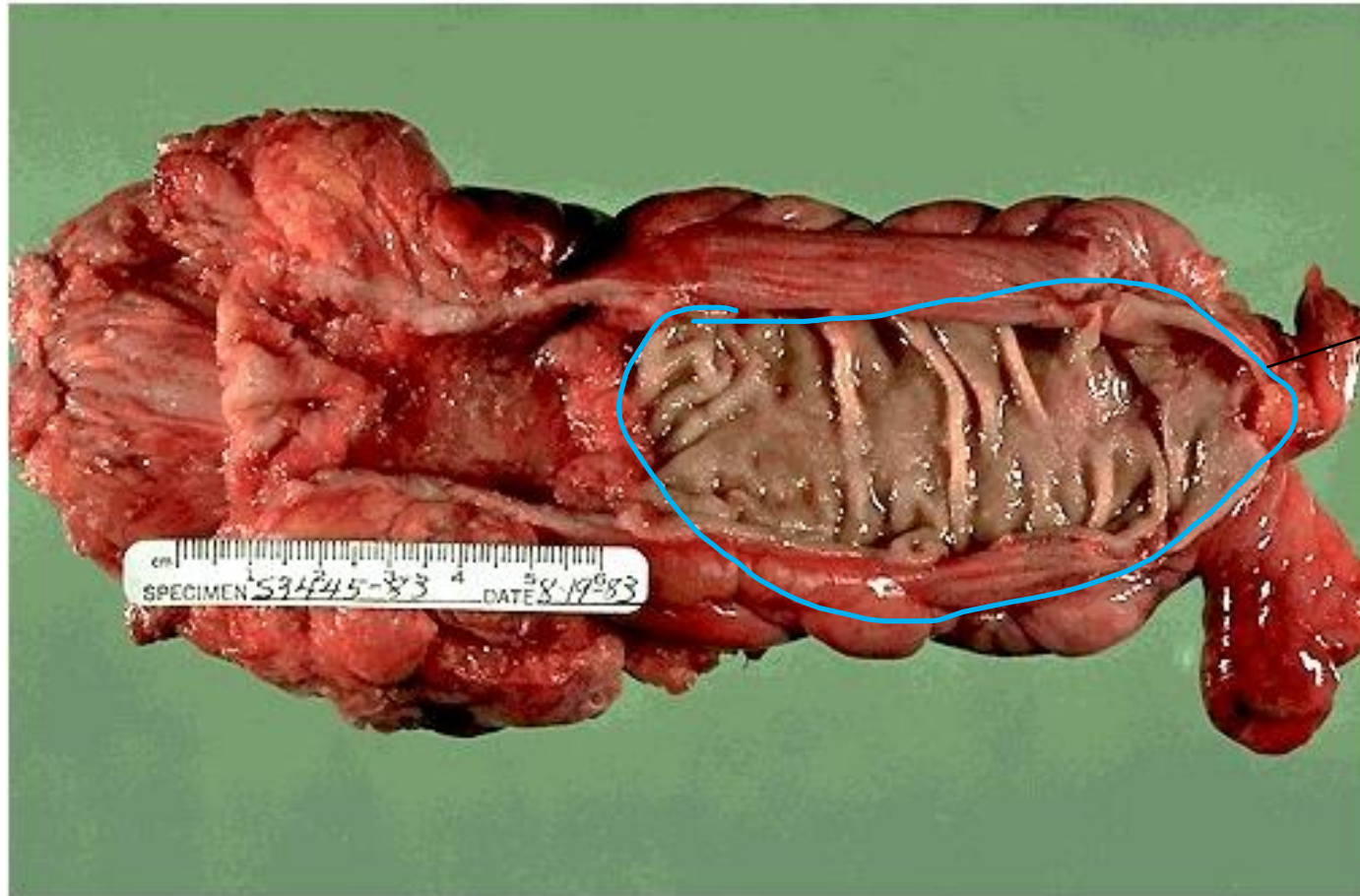
- ▶ **Macroscopic:**
- ▶ Proximal colon tumors: polypoid, exophytic masses
- ▶ Proximal colon: rarely cause obstruction. **Diameter of cecum is large.**
- ▶ Distal colon: annular lesions “napkin ring” constrictions & narrowing

- ▶ **Microscopic: proximal and distal are similar**
- ▶ Dysplastic GLANDS (**hyperchromasia, stratification, high N:C ratio**) with strong desmoplastic response (firm).
- ▶ Necrotic debris (dirty necrosis) are typical.
- ▶ Some tumors give abundant mucin (poor Px (**Px=prognosis**)) or form signet ring cells (**Similar to the diffuse type gastric adenocarcinoma**).

Napkin ring



Recto-sigmoid adenocarcinoma, napkin ring



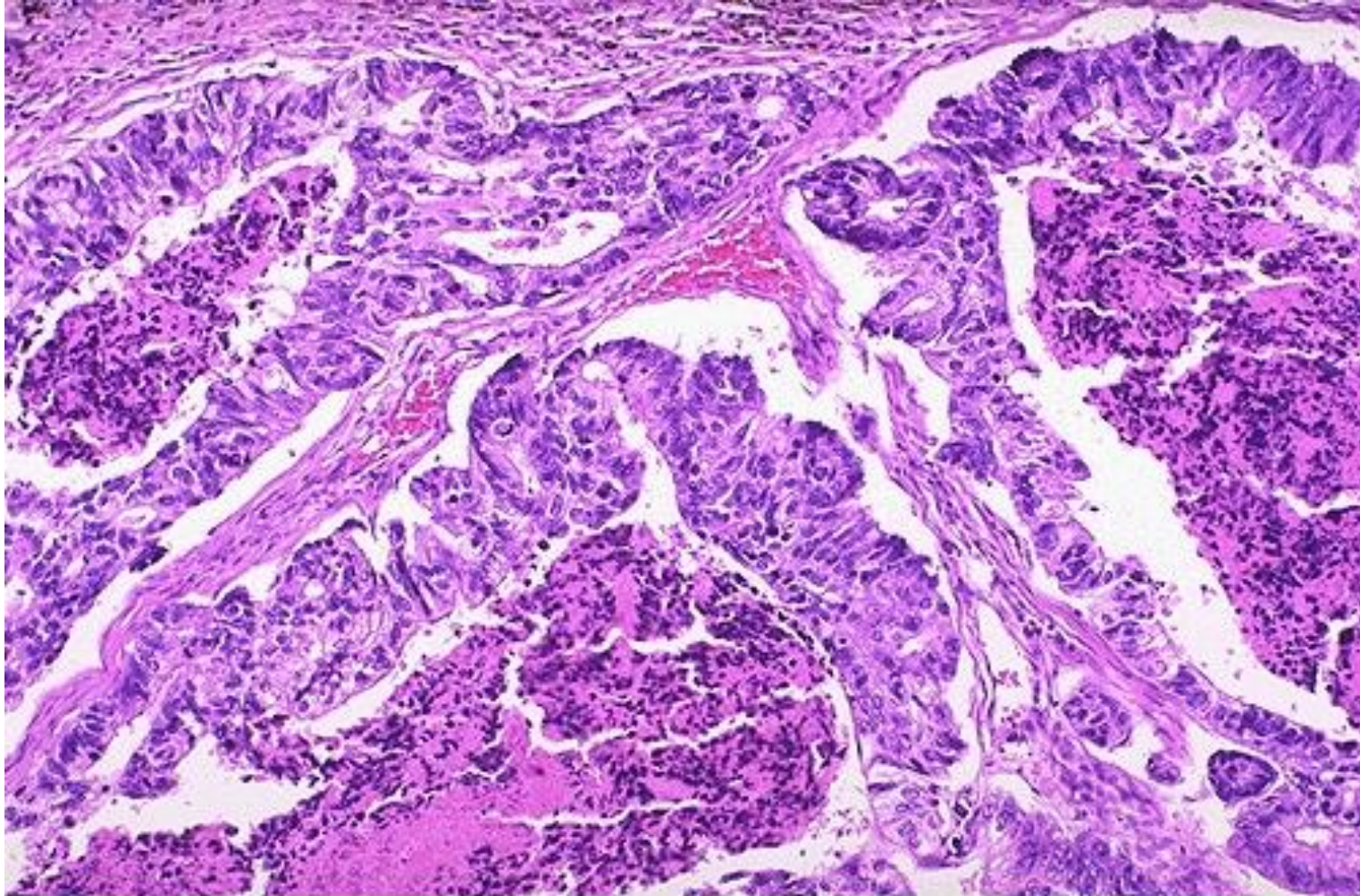
Normal mucosa,
has folds

Exophytic adenocarcinoma

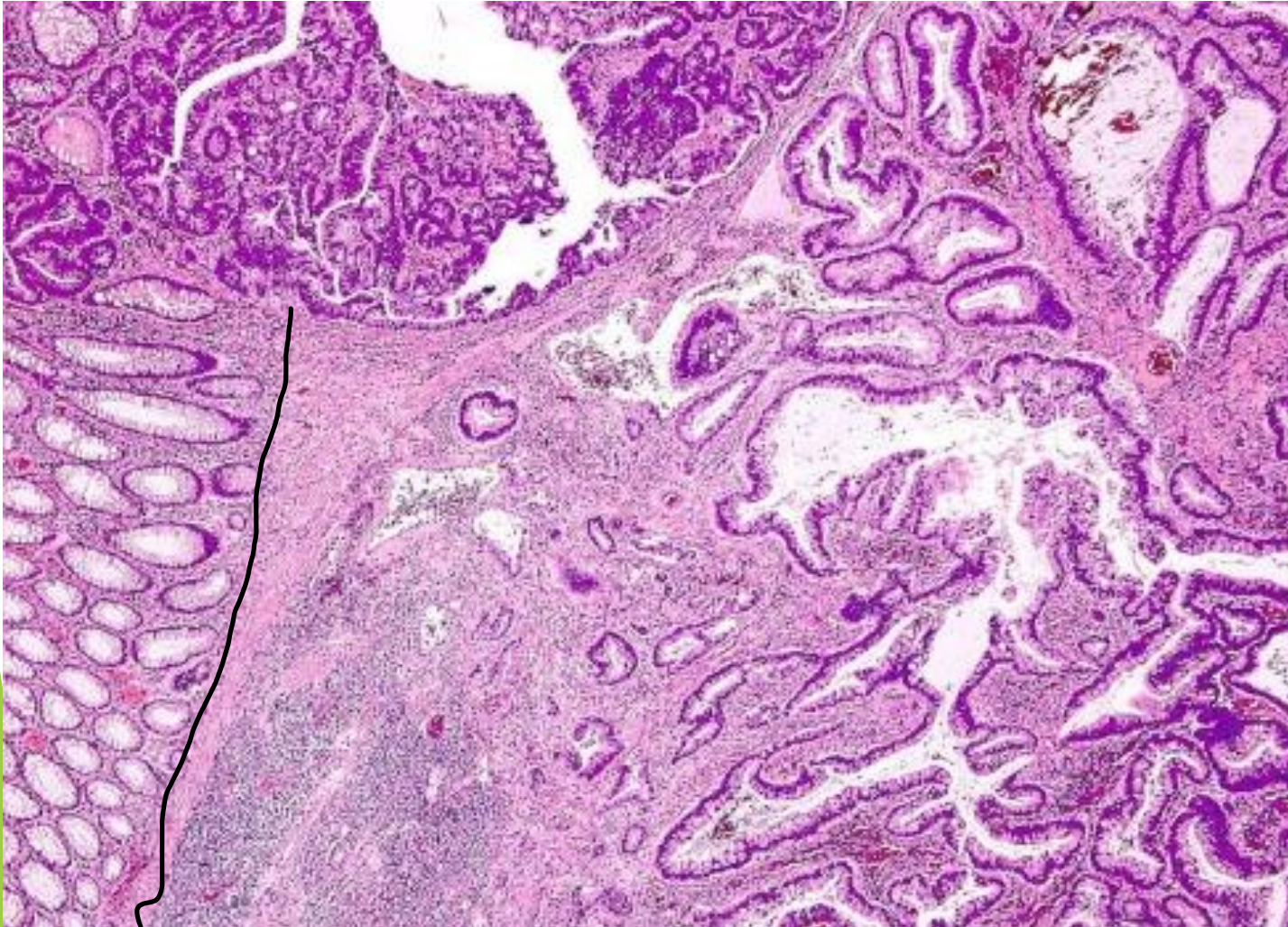


Can cause partial obstruction of lumen, only rarely causes complete obstruction because it usually occurs in cecum which has large diameter.

Adenocarcinoma with necrosis in the center of dysplastic glands



Invasive carcinoma



- ▶ To the left are the normal crypts of the colon, while to the right are the dysplastic.

Clinical Features

- ▶ Endoscopic screening >> cancer prevention **especially in families which have these cancers.**
- ▶ Early cancer is asymptomatic, **that's why some cancers present at advanced stages !!!!!!!**
- ▶ Cecal and right-side cancers: Fatigue and weakness (iron deficiency anemia **caused by chronic blood loss**)
- ▶ ***Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.***
- ▶ Left sided carcinomas: occult bleeding (**not bright red, patient cannot see it**), changes in bowel habits (**constipation, diarrhea and abdominal pain**), cramping left lower-quadrant discomfort.

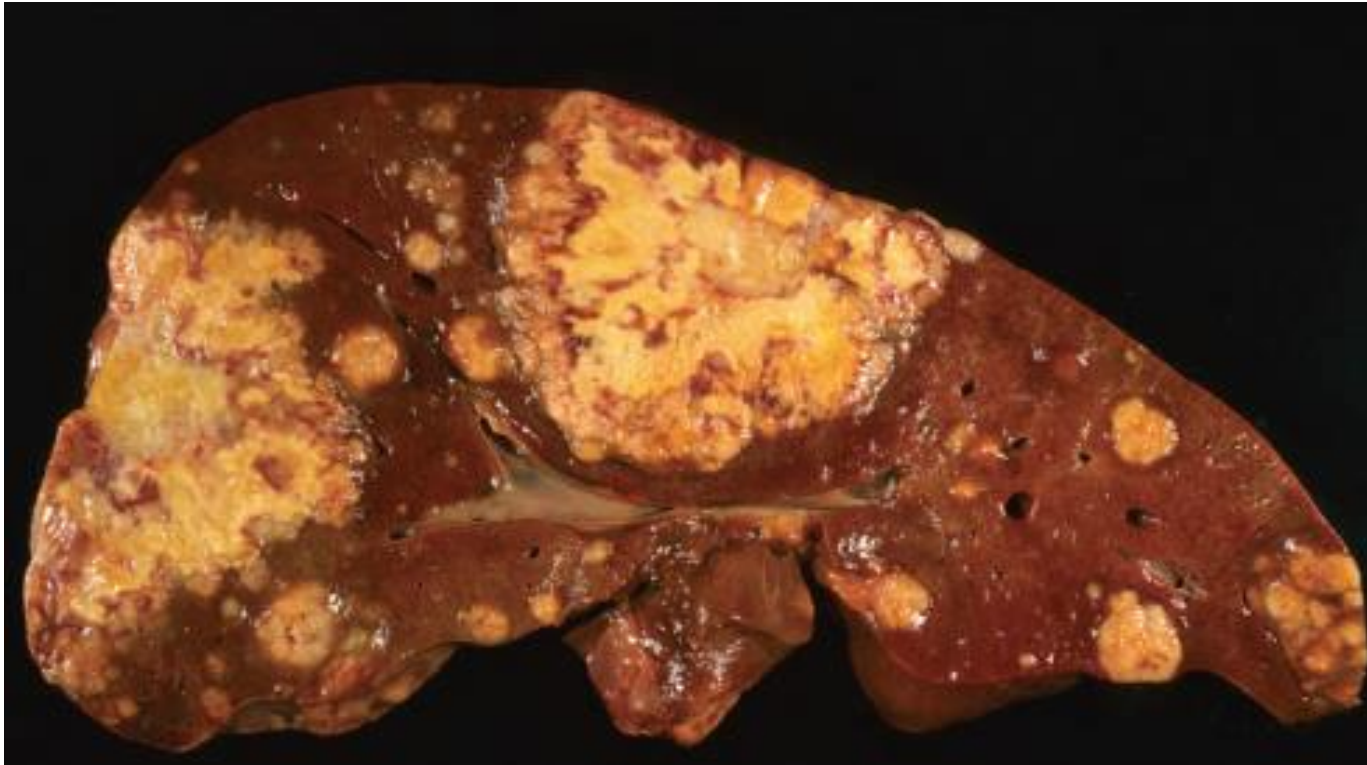
Prognosis:



- ▶ Poor differentiation and mucinous histology >> poor prognosis
- ▶ *Most important two prognostic factors are*
 1. *Depth of invasion (mucosa, submucosa, MP, serosa), if only mucosa invaded, 5-year survival rate is high, almost 100%.*
 2. *Lymph node metastasis. (needs Rx and Chemox)*
- ▶ **Both determined by histopathologic examination after surgical resection) for TNM classification of tumors (T=depth of invasion, N= lymph node metastasis, M=metastasis)**

In addition:

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



Tan-to-yellow
colour

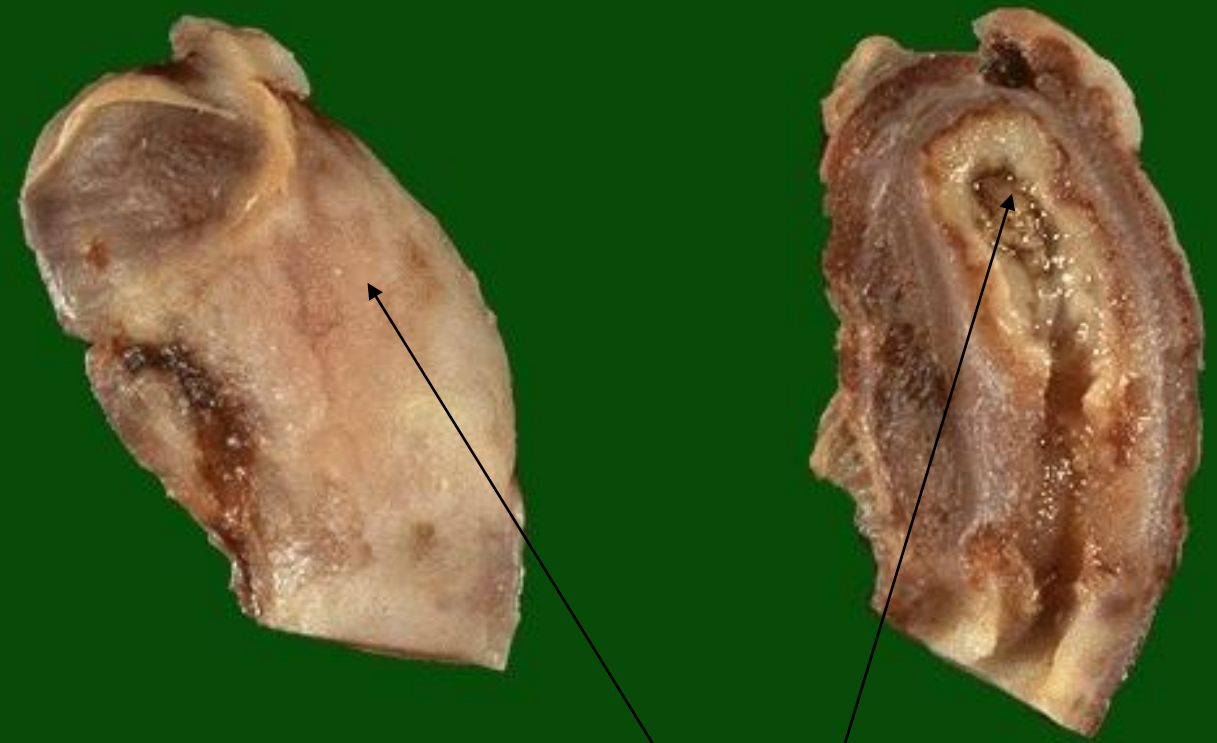
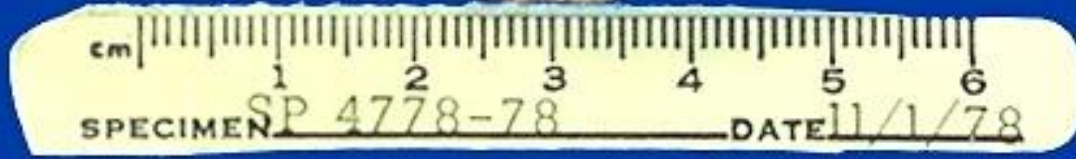
Liver metastasis.

Appendix diseases:

- ▶ Normal true diverticulum of the cecum
- ▶ ACUTE APPENDICITIS
- ▶ TUMORS OF THE APPENDIX **not common**

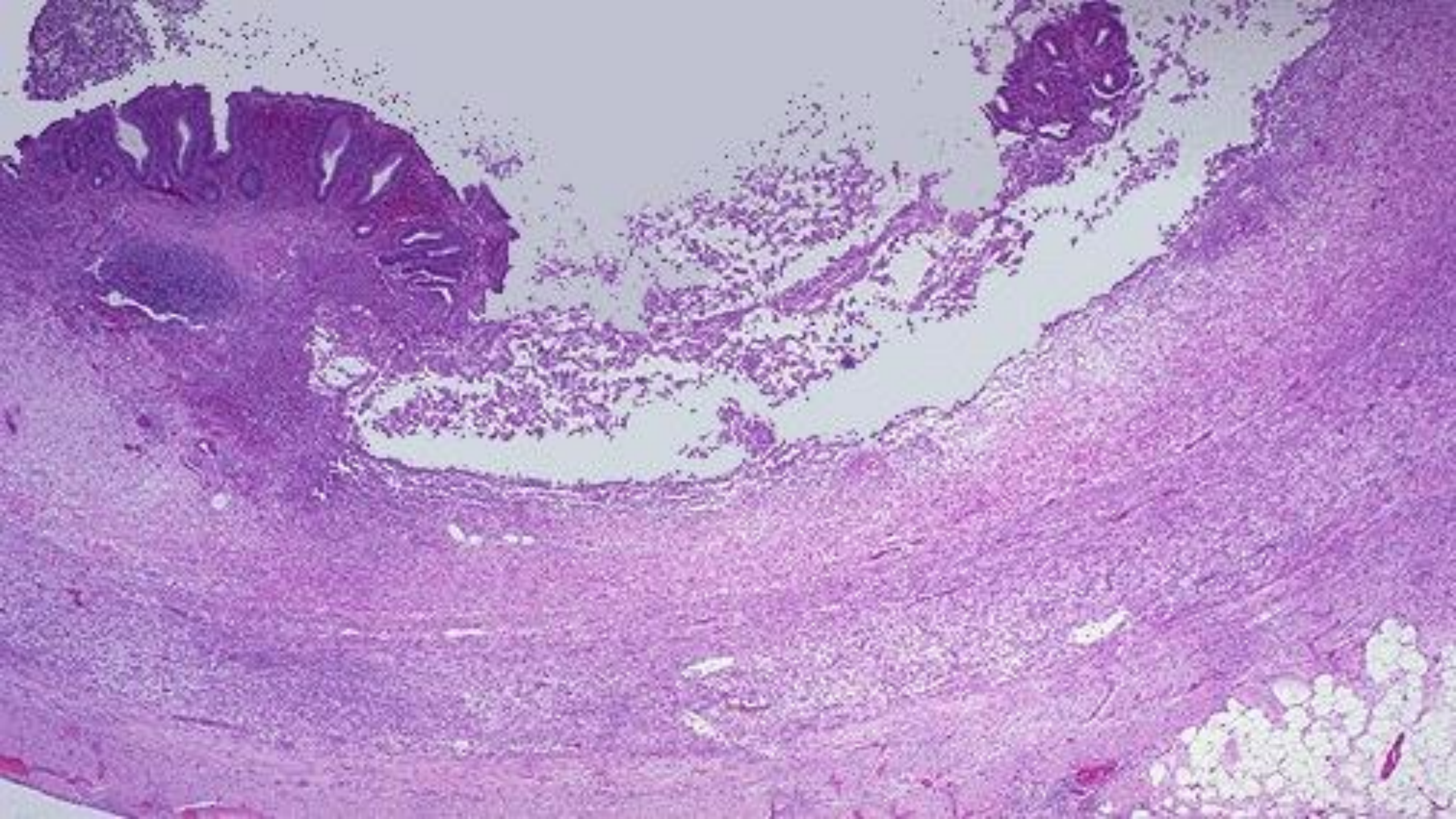
ACUTE APPENDICITIS

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

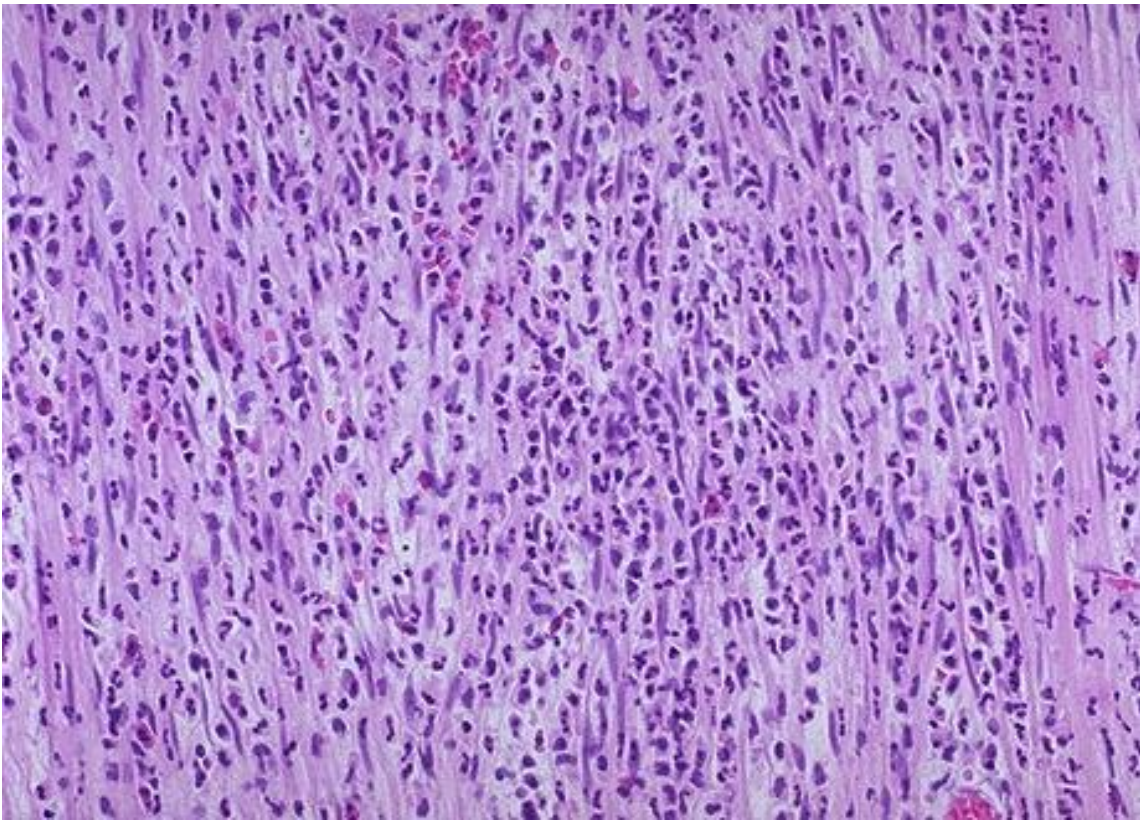


Normal appendix versus acute appendicitis

Yellowish exudate



Acute appendicitis: neutrophils after surgery to confirm



- ▶ It is natural, in some cases, to find normal appendix after surgery but it is to protect the patient from sequelae of ruptured gangrenous appendicitis.

DDx of acute
appendicitis:
rule out causes
of acute
abdominal pain

- ▶ Mesenteric lymphadenitis,
- ▶ Acute salpingitis (inflammation of fallopian tubes, in women of childbearing age),
- ▶ Ectopic pregnancy,
- ▶ Mittelschmerz (pain associated with ovulation),
- ▶ Ovarian cysts torsion
- ▶ Rupture Meckel diverticulitis
- ▶ Crohn disease due to terminal ileocecal valve inflammation.

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

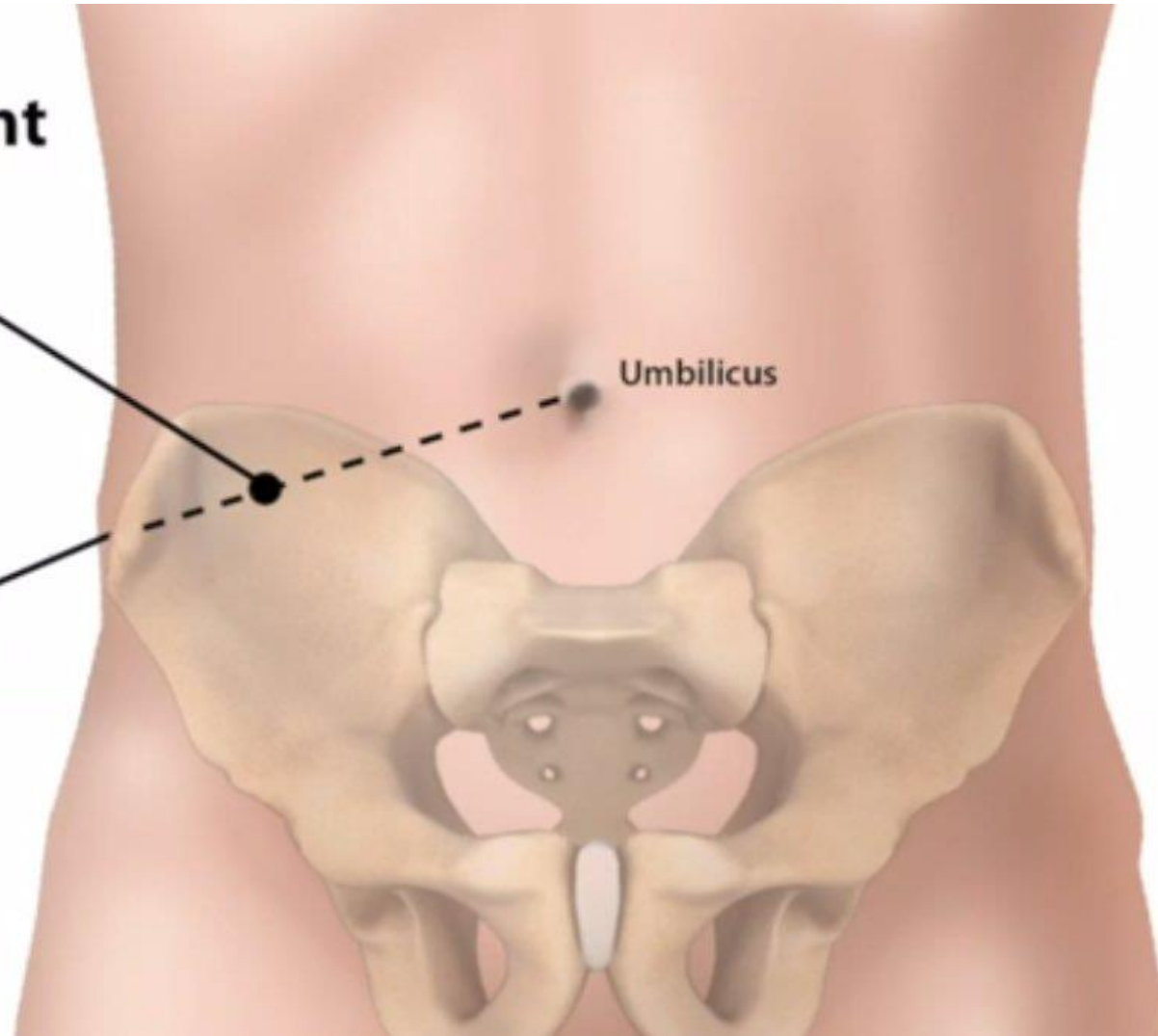
- ▶ Early acute appendicitis: periumbilical pain
- ▶ Later: pain localizes to the right lower quadrant,
- ▶ Nausea, vomiting, low-grade fever, mildly leukocytosis.
- ▶ A classic physical finding is *McBurney's sign* (McBurney's point).
- ▶ Signs and symptoms are often absent, creating difficulty in clinical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

McBurney's Point

2/3 of the way from
umbilicus to ASIS

Physician presses here
and then releases
pressure, if patient
complains of pain, this
is the McBurney's Sign

Anterior Superior Iliac Spine



TUMORS OF THE APPENDIX

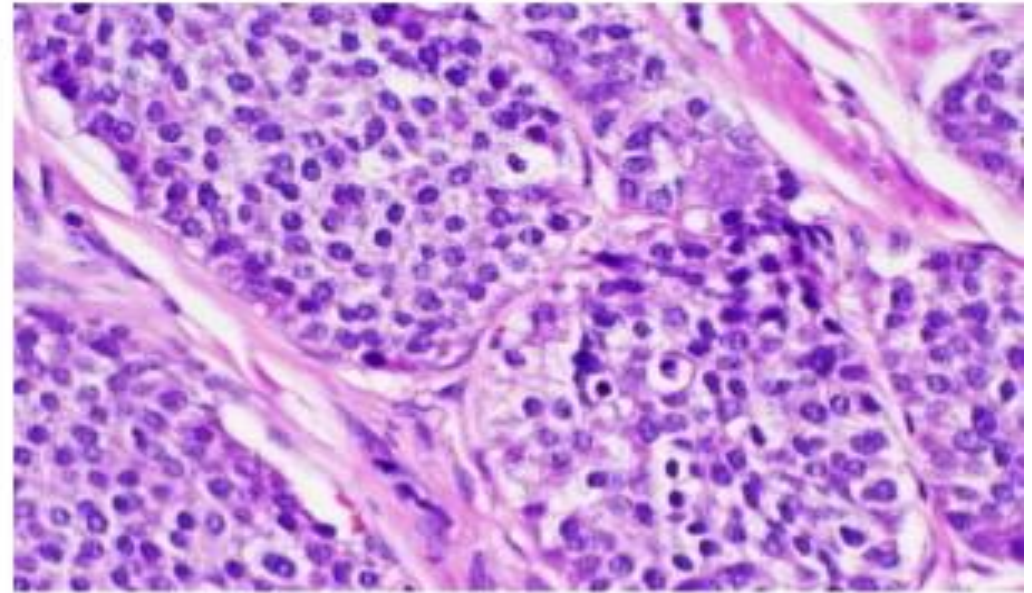
- ▶ **The most common tumor: *carcinoid* (neuroendocrine tumor)**
- ▶ Incidentally found during surgery or on examination of a resected appendix
- ▶ Distal tip of the appendix
- ▶ Nodal metastases & distant spread are rare.

Carcinoid tumor



Gross

nesting



Salt-and-pepper
chromatin

Microscopic

The background features abstract, overlapping geometric shapes in various shades of green, ranging from light lime to dark forest green. These shapes are primarily located on the left and right sides of the frame, creating a modern, layered effect. The central area is a plain white space.

Good Luck!