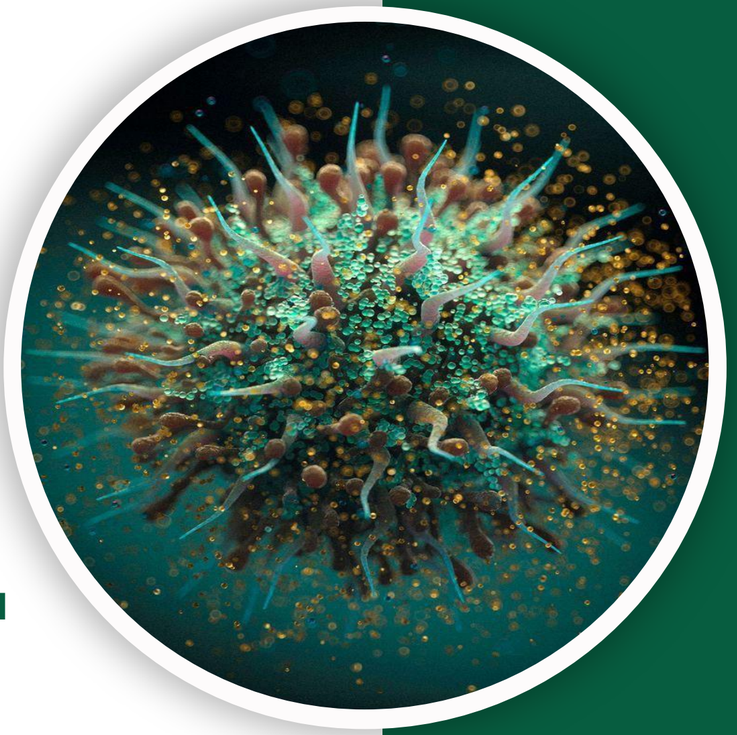
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | MID 8

Intestinal Diseases Pt.4



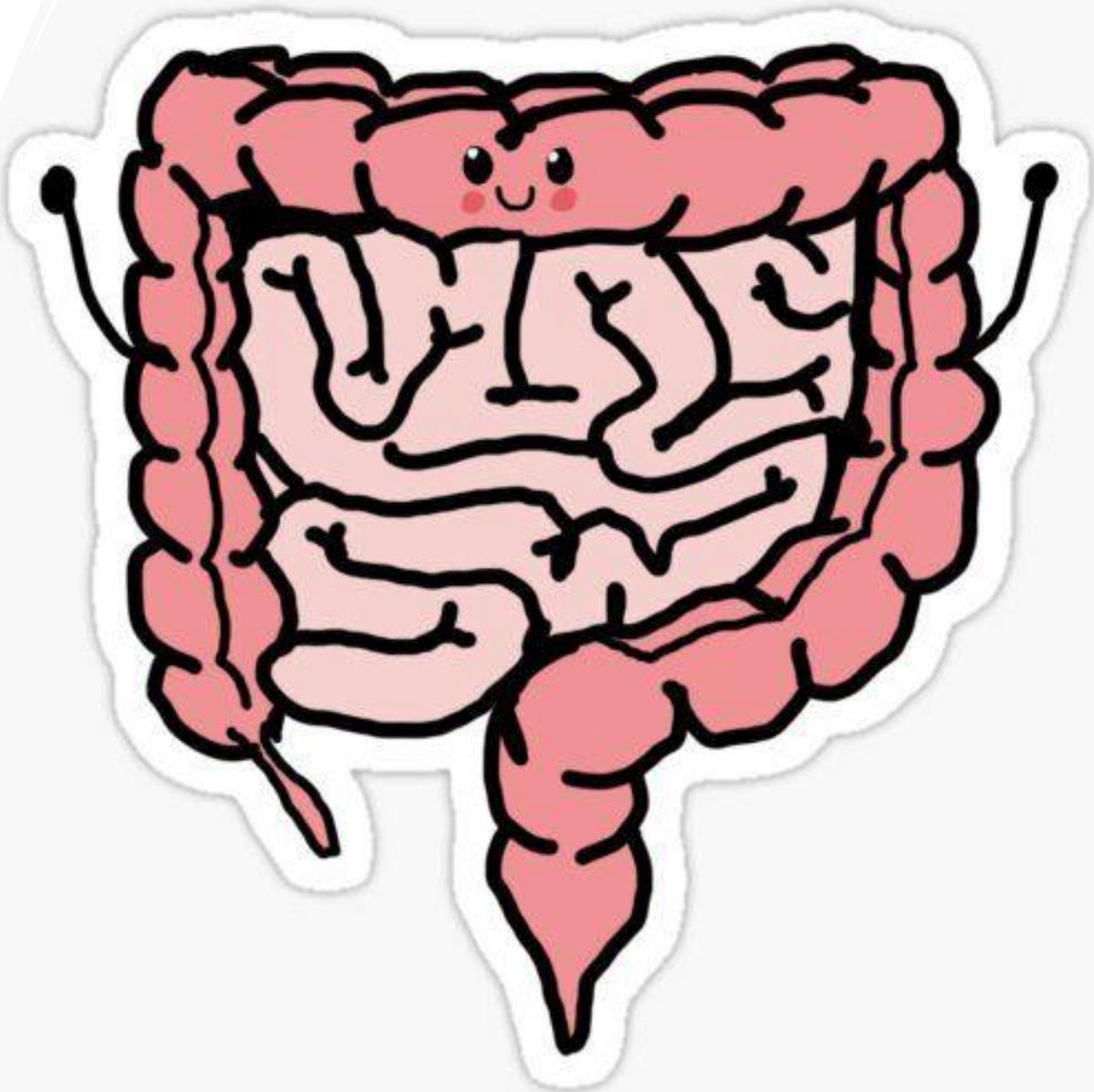
Written by : DST

Reviewed by : Tala Othman

Batool Zayed

Intestinal pathology part 4

- Manar Hajeer, MD, FRC Path
University of Jordan, School of medicine



Diseases of the intestines

As was mentioned before, the diseases of the intestine are divided into:

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

This lecture discusses the neoplastic conditions

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 incidence of colon cancer:
  - *60-70 years of age
  - *males>females
  - * Some cases present before 50 (<20%) . (some of these cancers before the age of 50 are considered familial.)
- Developed countries lifestyles and diet are considered risk factors for the development of colonic adenocarcinoma.
- The risk factors are mostly related to :
  - **Low intake of vegetable fiber and high intake of carbohydrates and fat.**
  - **Obesity, smoking and alcohol.**
- The use of aspirin or other NSAIDs has a protective effect because they inhibit (Cyclooxygenase-2 (COX-2) expressed in 90% of carcinomas, even adenomas. This enzyme promotes epithelial proliferation and inhibition of this enzyme will lead to inhibition of this proliferation and protect against colon cancer).
- **Prevention:** 1 **dietary modification** (Diets high in vegetables and low in carbohydrates and fat)
  2 **pharmacologic chemoprevention.** (By use of NSAIDs and aspirin to inhibit the COX2)
  3 Body weight reduction
  4 Smoke and alcohol cessation

Pathogenesis

- Heterogeneous molecular events (genetic and epigenetic **mutations**).
- Sporadic >>>> familial. **(sporadic much more common than familial)**

- **Two pathways** of carcinogenesis:

1. **APC/β-catenin pathway > leads to increased WNT signaling**
   → Same gene mutation involved in FAP syndrome
2. **Microsatellite instability pathway due to defects in DNA mismatch repair gene**
   → Same pathway as the (HNPCC)

- In both pathways there's a Stepwise accumulation of multiple mutations

FAP = Familial adenomatous polyposis
HNPCC = hereditary nonpolyposis colorectal cancer

The APC/β-catenin pathway: chromosomal instability pathway

APC = adenomatous polyposis coli

- Classic *adenoma carcinoma sequence* (progression from an adenoma to carcinoma). Involved in *80%* of sporadic colon tumors
- The earliest event is the mutation of the *APC* tumor suppressor gene: EARLY EVENT

•*APC is a key negative regulator of β-catenin (promotes degradation).* It's *a component of the WNT signaling pathway.*

- → When APC is mutated, this negative regulation is lost which leads to build up of B-catenin

•*Both copies of APC should be inactivated* or mutated in order *for adenoma to develop* , and for the adenoma to progress to carcinoma.

- And for both copies to be inactivated we need *(1st and 2nd hits).*

→ If 1st hit is inherited or a germline mutation then the 2nd hit will occur at an earlier age, and the tumor will present at an earlier age; like what happens in inherited cancer syndromes.

- It's called the *chromosomal instability pathway* because we have these mutations *by* chromosomal *deletions (hallmark)*

Loss of APC **gene (inhibition)**

↓

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)

- APC mutations are earlier events and KRAS and TP53 mutations are late event (found in invasive carcinoma not adenoma)

SMAD2 and *SMAD4 mutations (tumor suppressor genes.)*

TP53 **is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**

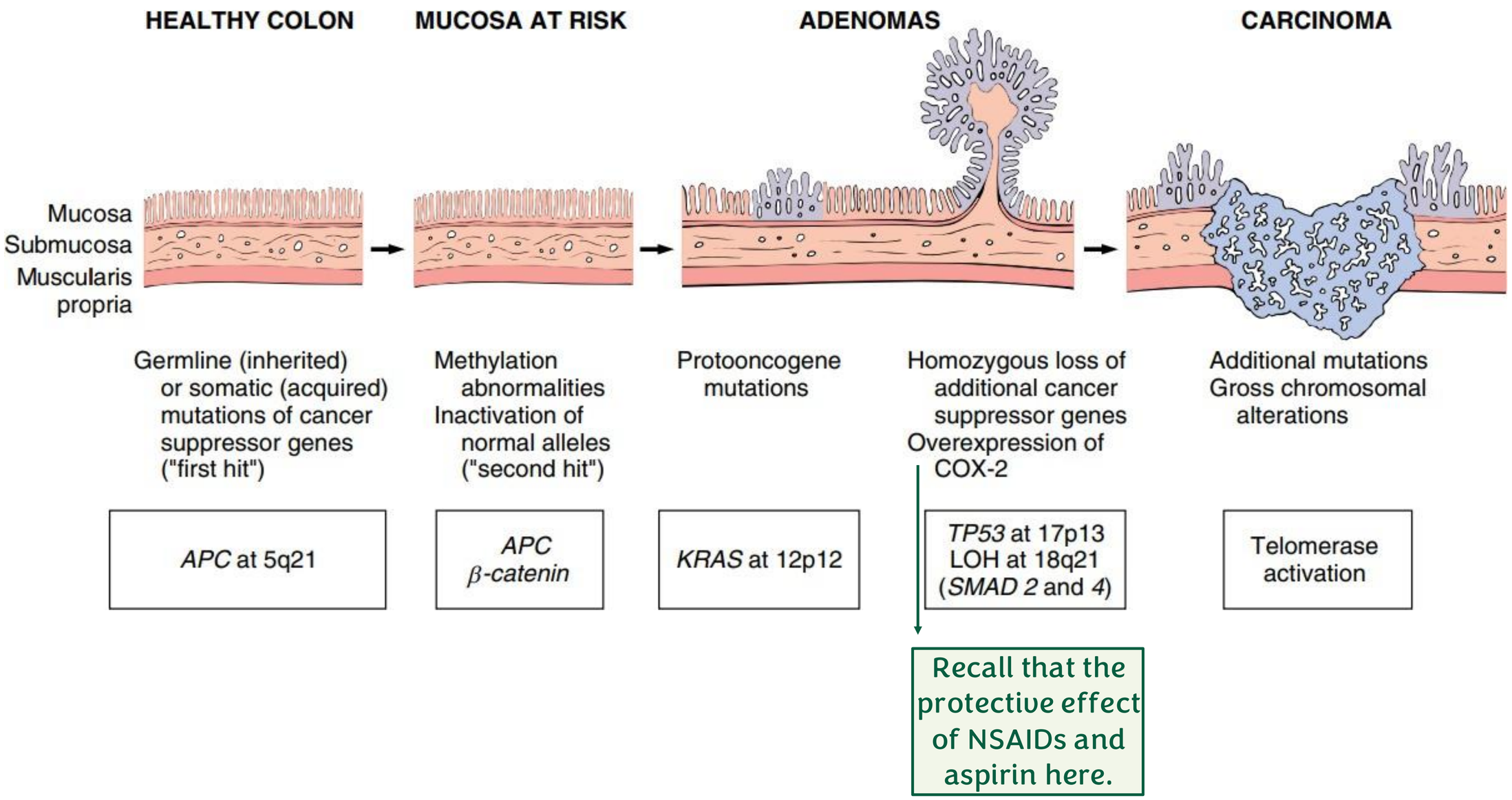
TP53 inactivation mutation (Tumor suppressor gene)

Expression of telomerase also increases as the tumor advances.

↓

This increases the lifespan of cells.

You can refer to the lecture 7:08- 8:30, where the doctor explains the same steps mentioned in the previous slide on this image.



The microsatellite instability pathway

NOT chromosomal instability pathway because the problem is in the microsatellite repeats in the DNA

- DNAmismatch repair deficiency (Loss of genes) (loss of function mutation)
- Mutations accumulate in microsatellite repeats of DNA (mostly non-coding), which results in microsatellite instability

- Microsatellite repeats are mostly noncoding , and the effect of mutation is **silent** (no effect) if microsatellites located in noncoding regions
- Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth (TGF-B gene) and apoptosis (BAX gene which is proapoptotic)
  → which leads to cell growth and inhibition of apoptosis and tumor development.

- BRAF mutations occur later and common. However, P53 and KRAS (which were described in the chromosomal instability pathway) are absent here..

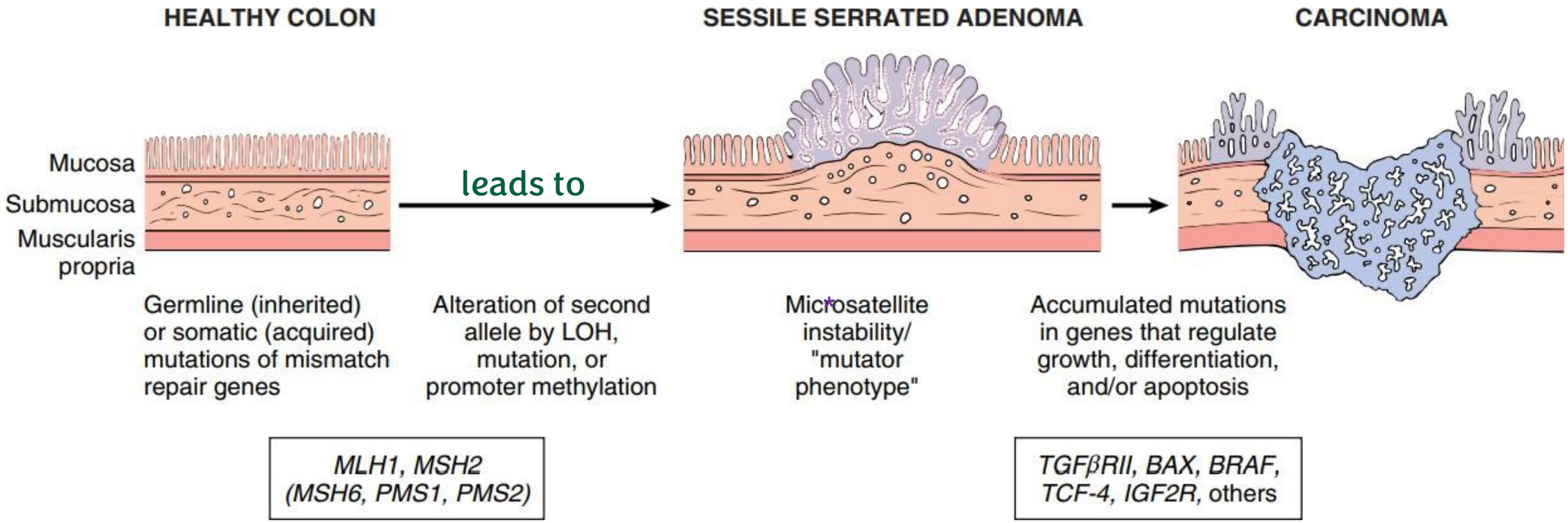
Again, we need both alleles of the genes to be inactivated for the tumor to be expressed

- If the tumor is intertied the first one is germline mutation and the second is somatic
- If the tumor is sporadic then both alleles will be inactivated in a somatic acquired pathway

Here we're talking about the mismatch repair genes like MLH1 and MLH2 mutations.

Microsatellite instability and cellular proliferation and the appearance of the precursor lesion of these tumors which is called sessile serrated adenoma; as was discussed in the previous lecture .

This will eventually progress into an invasive carcinoma by acquiring more mutations like the BRAF gene.



The whole table was read by the doctor in the lecture 11:03–12:49 but nothing extra was mentioned.

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. → because the diameter of the cecum or the right side of the colon is large.
- Distal colon: annular lesions “napkin ring” constrictions & narrowing → present most of the time with obstruction.

Microscopic:

- Dysplastic GLANDS with strong desmoplastic response (firm).
- Dysplastic glands displaying hyperchromasia, stratification, high N/C ratio, and a strong desmoplastic or fibrotic response. That's why these tumors tend to be firm
- Necrotic debris (dirty necrosis) are typical.
- Some tumors give abundant mucin (poor Px) or form signet ring cells.

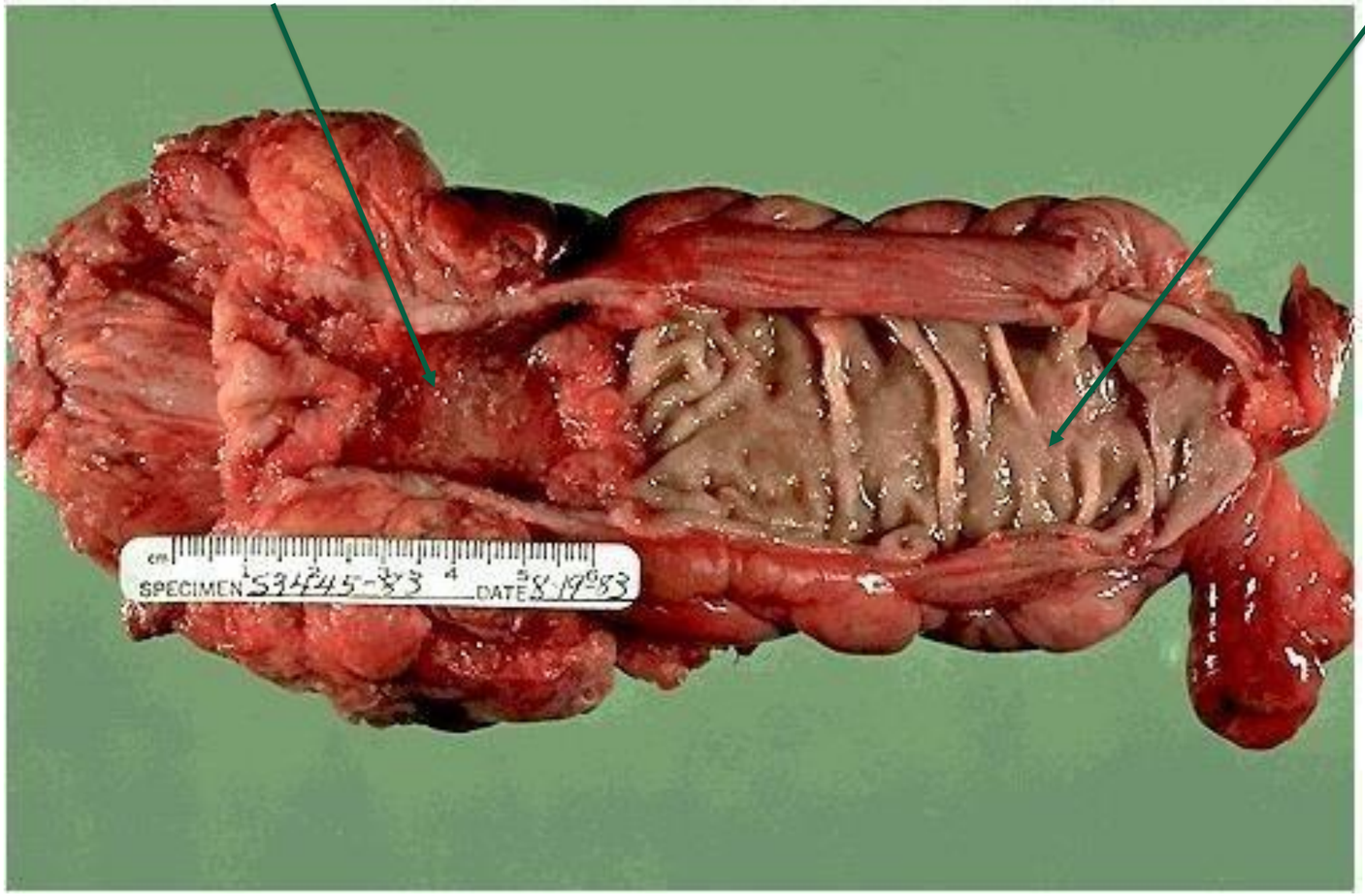
Napkin ring

This is the napkin ring appearance which is used to describe tumors in distal colon that cause narrowing with obstructive symptoms.

Recto-sigmoid adenocarcinoma, napkin ring

napkin ring / constructive appearance

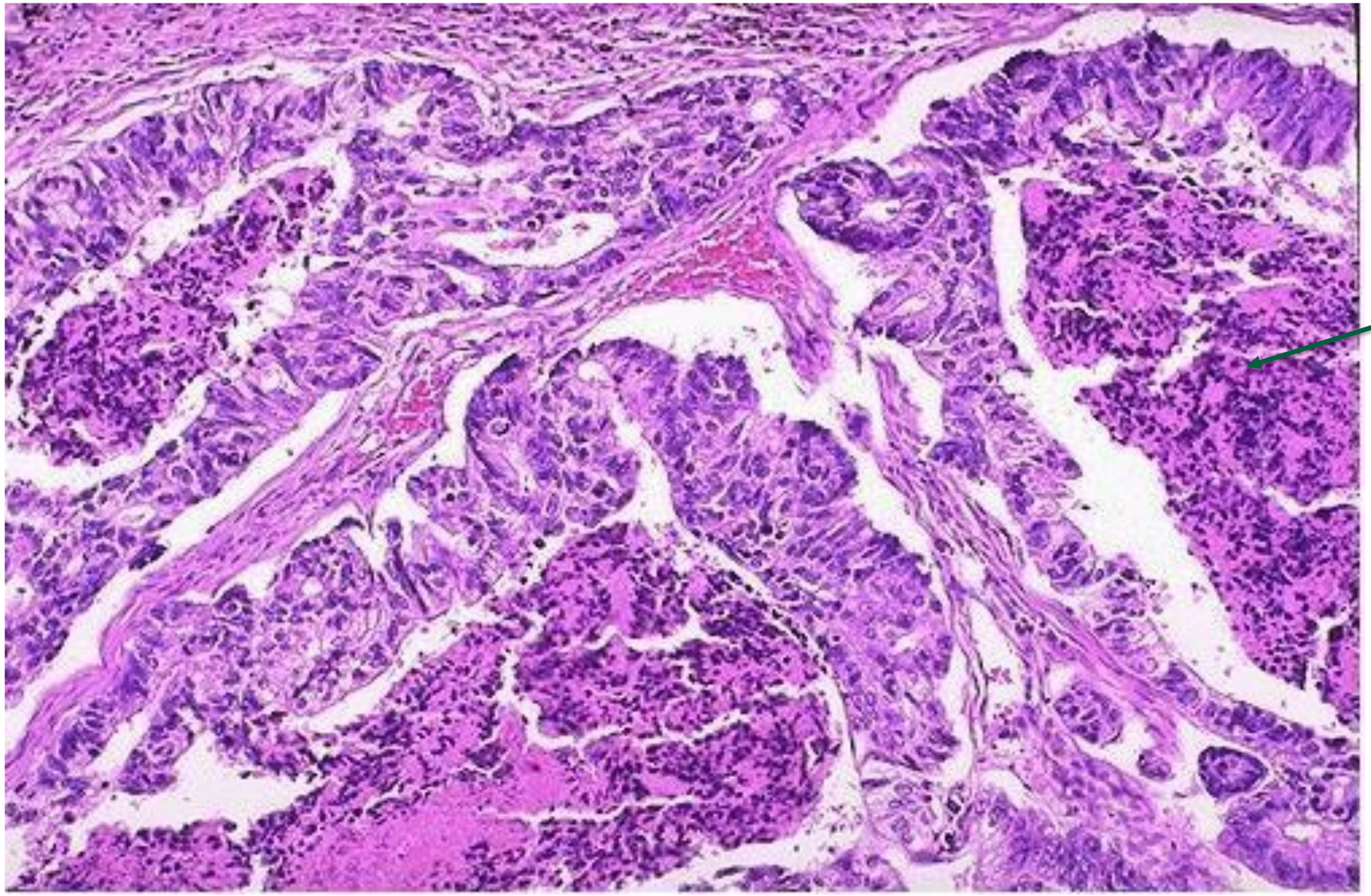
Normal mucosa with folds



Exophytic adenocarcinoma

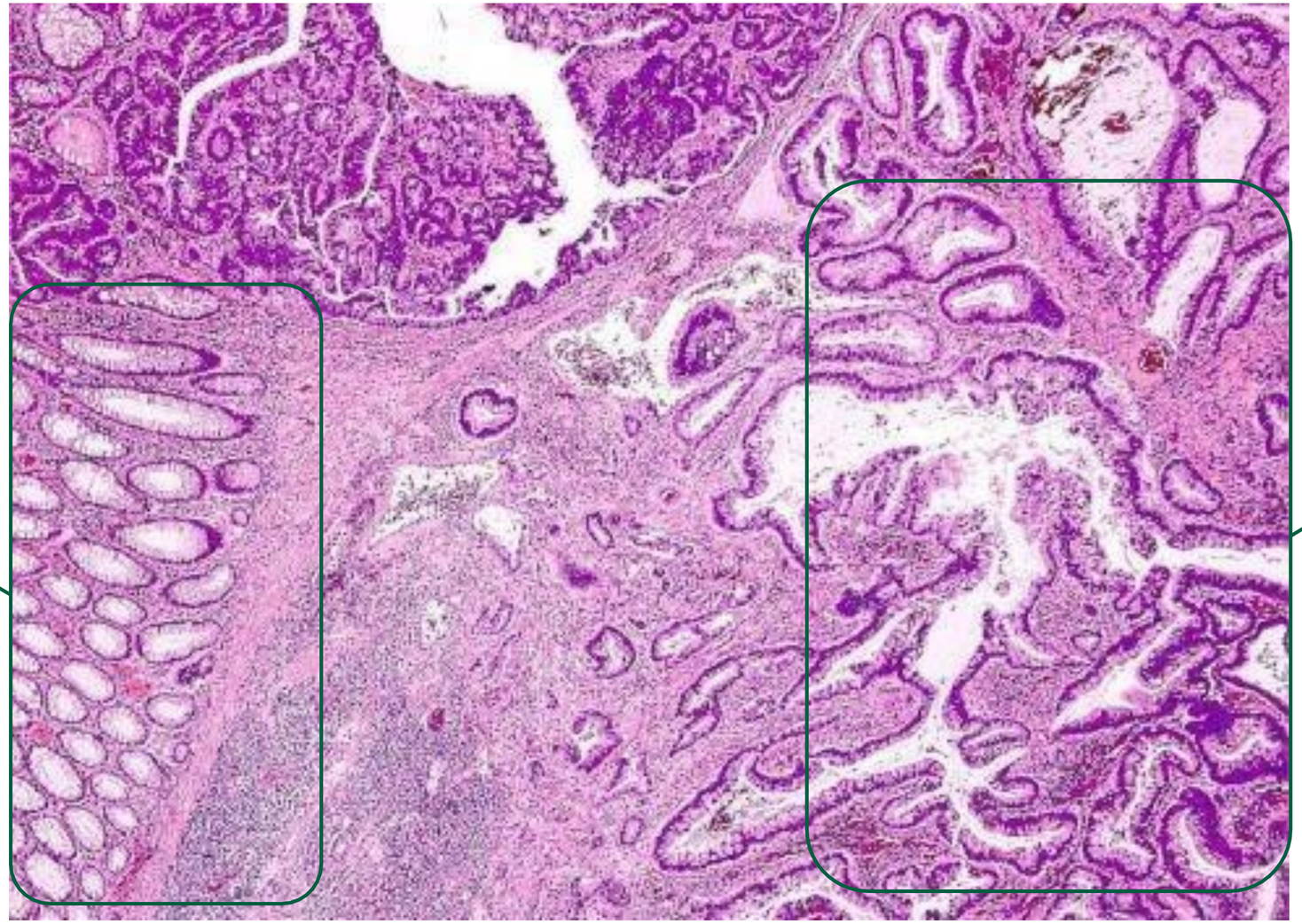
Mass projecting to the lumen of the bowl that can cause **partial** obstruction. Rarely causes complete obstruction due to it occurring mostly in the right side of the colon or cecum which has a large diameter.

Adenocarcinoma with necrosis



Dirty necrosis in the center of the dysplastic gland.

Invasive carcinoma



Normal crypts of the colon

Dysplastic invasive component

Clinical Features

- Endoscopic screening >> cancer prevention
- Especially in patients with a family history of colon cancer at an early age of onset
- Early cancer is asymptomatic !!!!!!!!
- That's why some cancers may present at an advanced stage 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.**
- Right-sided cancers or cecal cancers present with prolonged blood loss leading to iron deficiency anemia, fatigue & weakness.
- Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower-quadrant discomfort.

Occulted bleeding is a bleeding that is not visible to the patient –not bright red– and may go unnoticed. It needs Laboratory investigations because it is a chronic low volume of blood loss that can lead to iron deficiency anemia.

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)*** Second most important prognostic factor

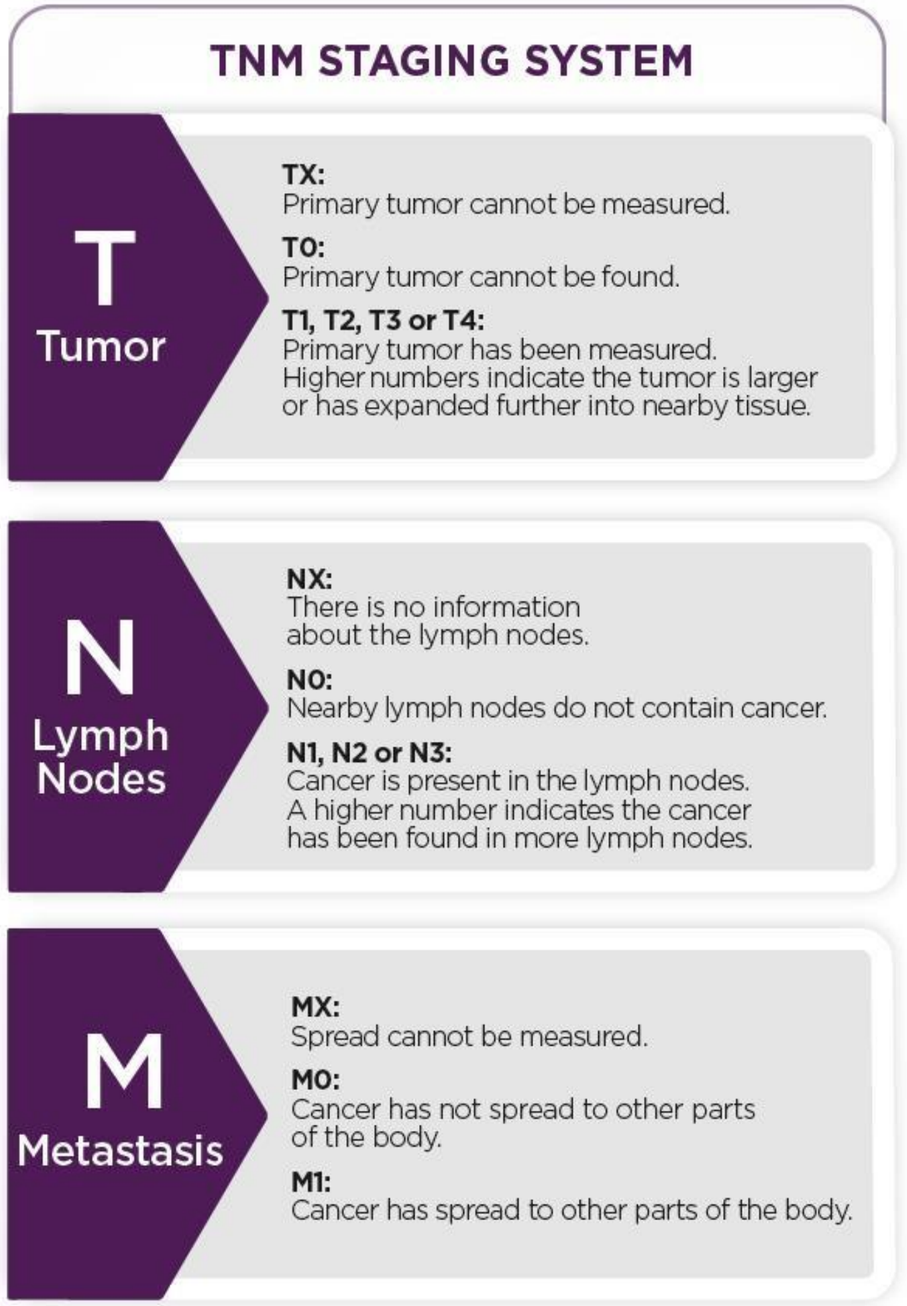
If the tumor invades only the mucosa, then the five-year survival is very high, and it approaches 100%.

In addition:

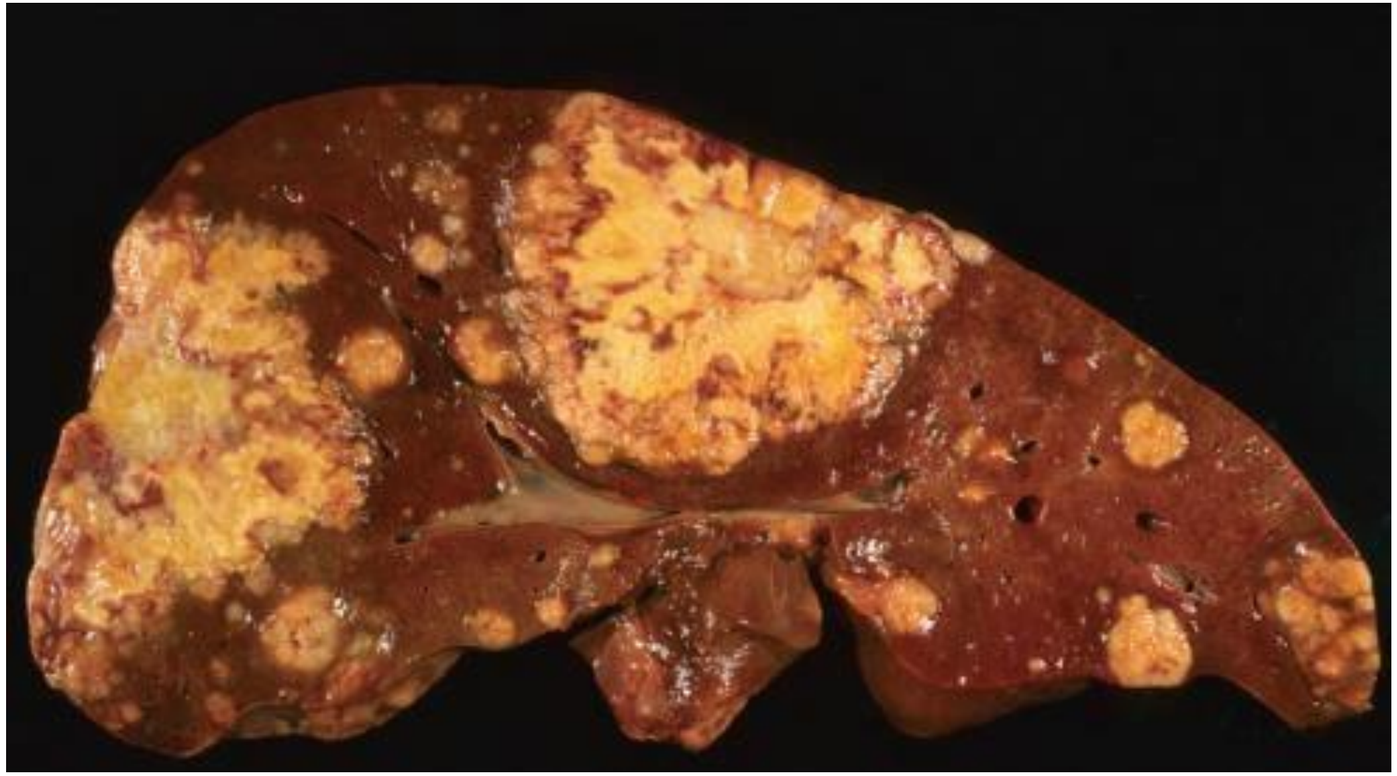
- *Distant metastasis to liver (most common) and lung. (solitary mets can be resected).*
- *Tumors w/ microsatellite instability (immune checkpoint inhibitor therapy)*

In the **TNM** staging classification
T: depth of invasion
N: lymph node metastasis.
We find this through the histopathological examination of the tumor after resection

- **Microsatellite instability** is detected by immunohistochemical staining for the DNA mismatch repair gene mutations.
- Patients with any type of colon cancer are tested for **microsatellite instability** by immunohistochemical staining for DNA mismatch repair gene mutations. If they have microsatellite instability or loss of these DNA mismatch repair genes, they can use immune checkpoint inhibitor therapy which is a targeted therapy.



~Added for clarification



This is a liver metastasis -yellow colored tumor- in a patient with colon cancer.

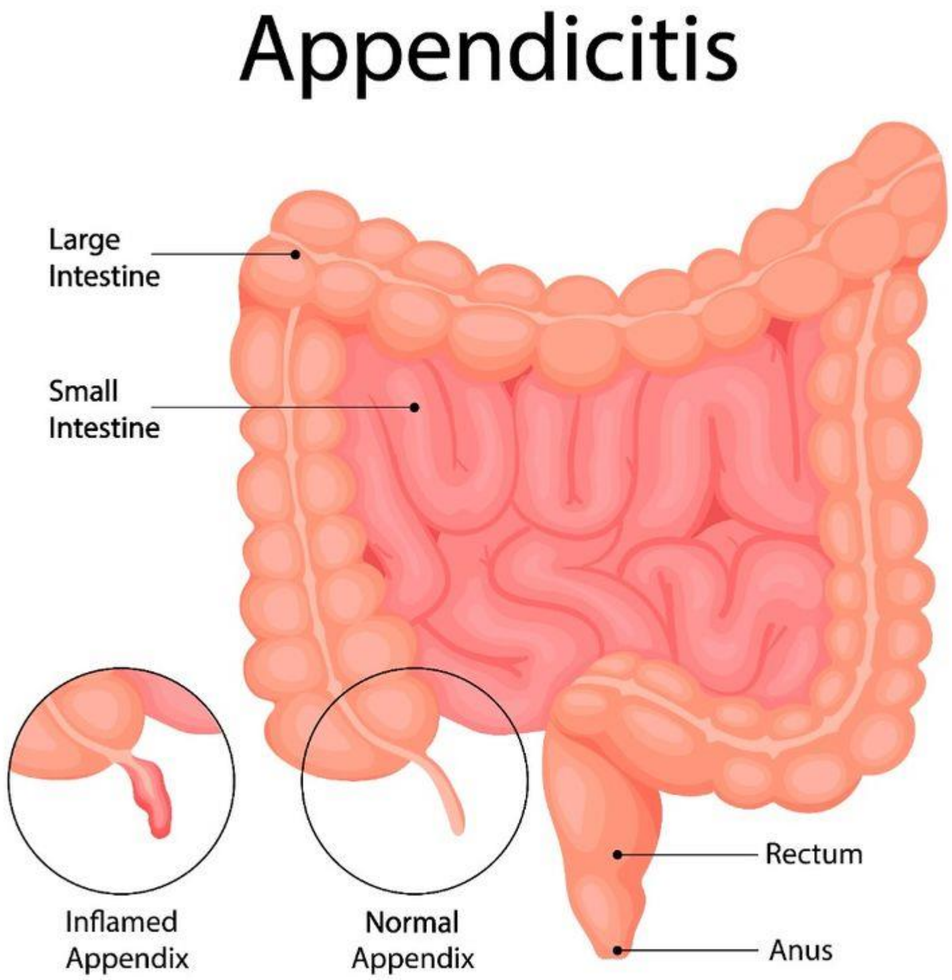
- Liver metastasis.

~Added for clarification

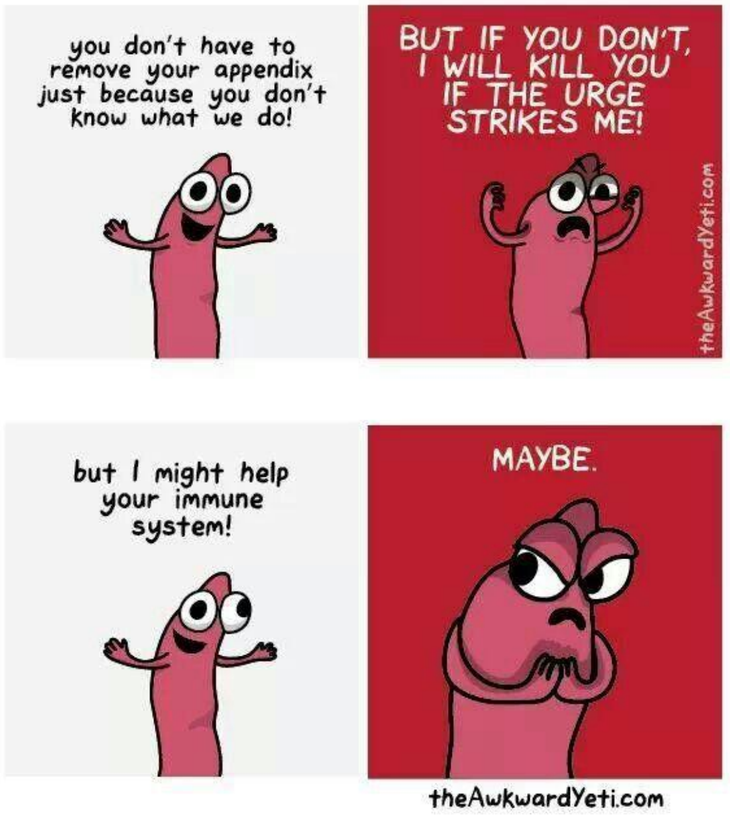
Appendix diseases:

- Normal true diverticulum of the cecum

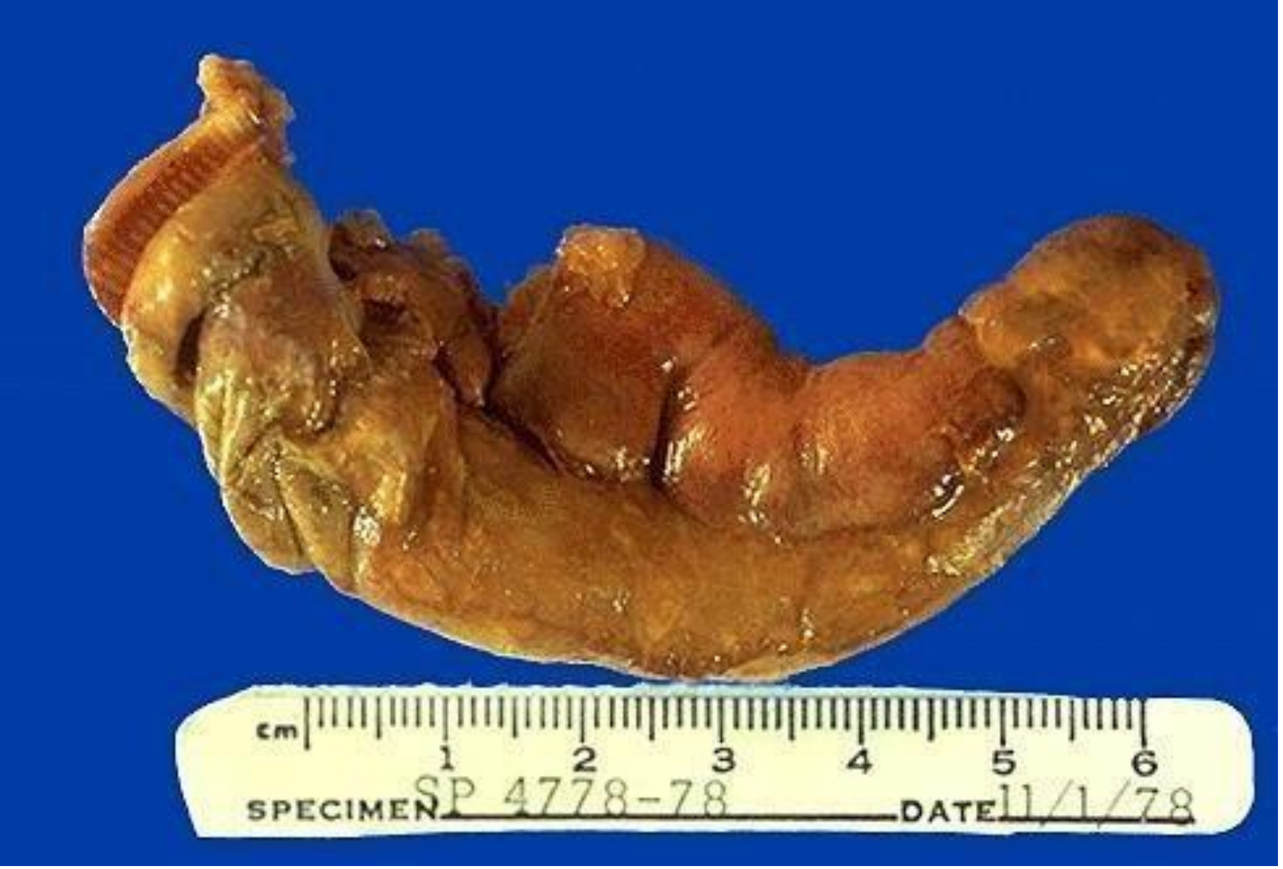
- ACUTE APPENDICITIS number “1”
- TUMORS OF THE APPENDIX not common

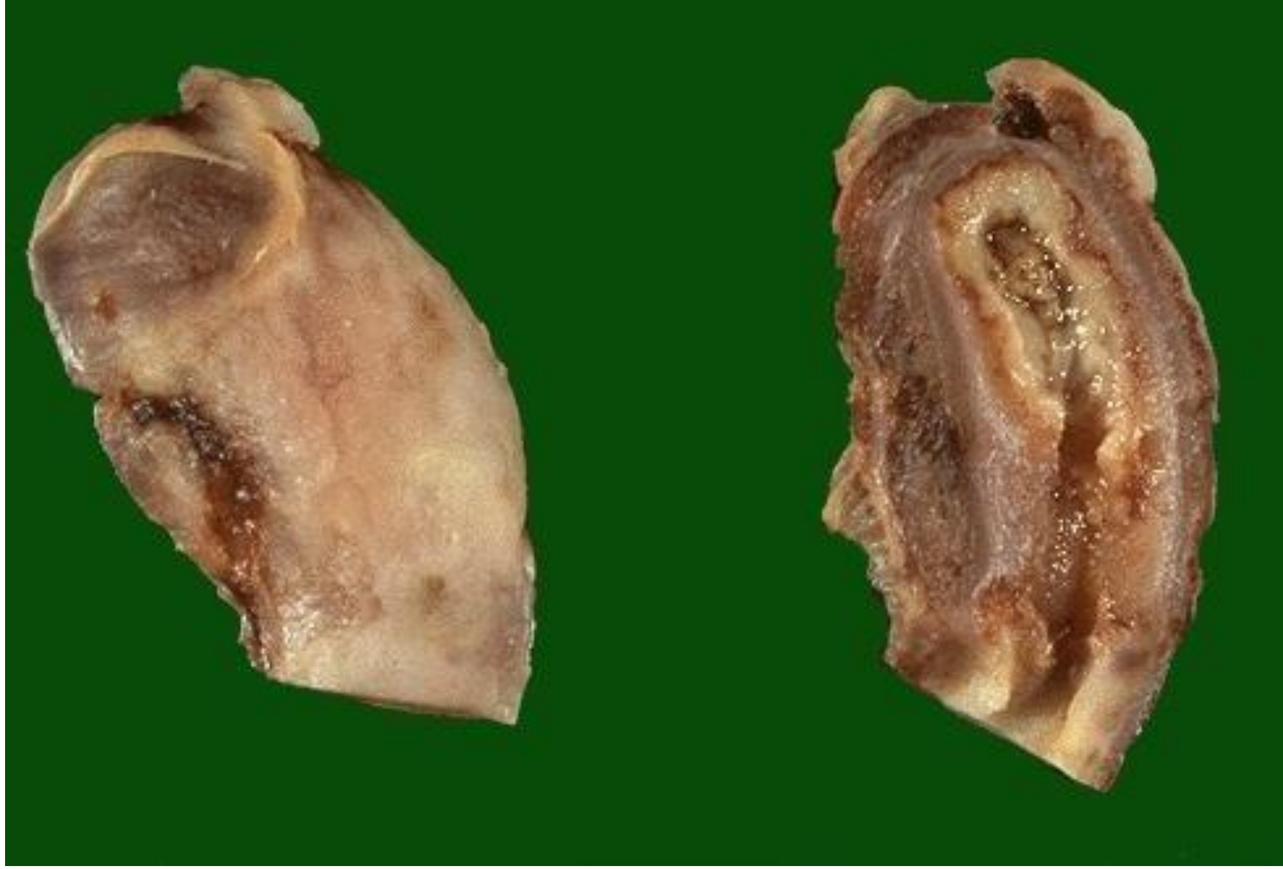


ACUTE APPENDICITIS



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





Normal appendix with glistening serosal surface.

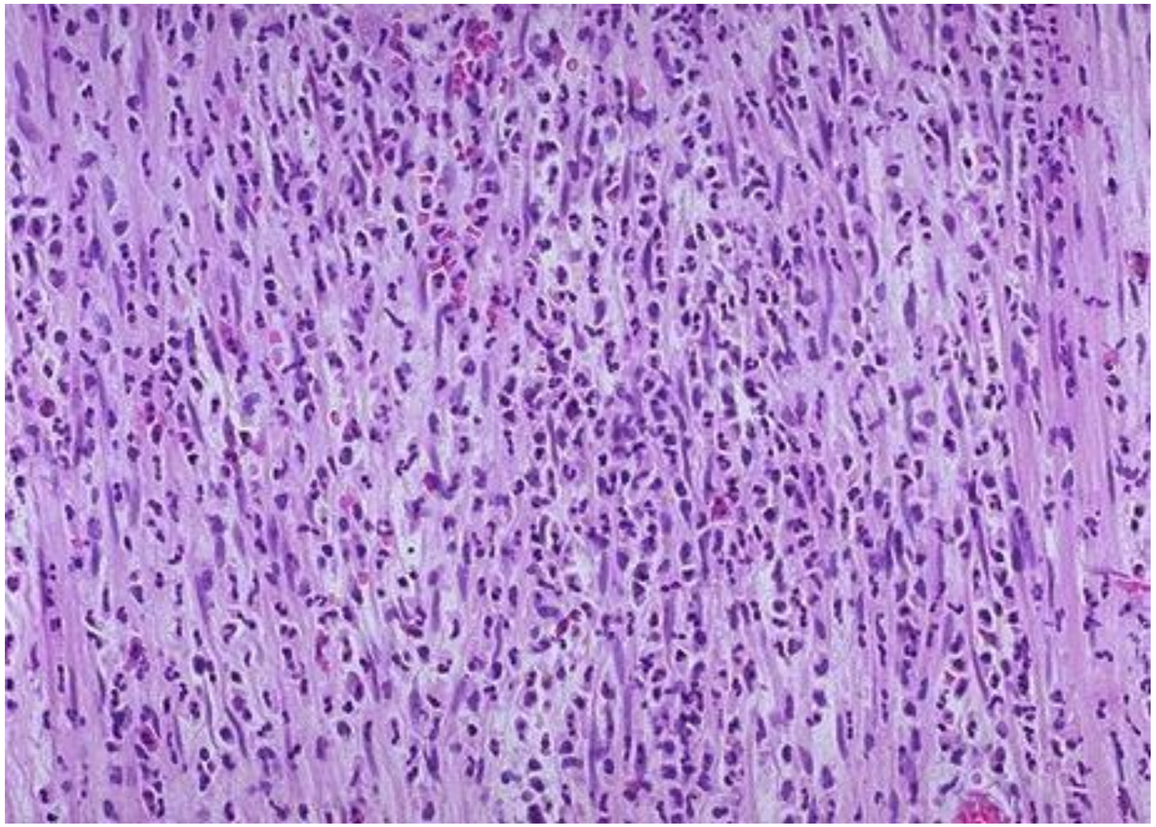
Appendix with acute appendicitis, serosa is dusky and covered by yellowish exudates, and the mucosa is also covered by a yellowish exudate.

Normal appendix versus acute appendicitis

To diagnose appendicitis, we need to confirm histopathological infiltration of the muscularis propria by neutrophils, sometimes associated with ulceration of the wall. So, a diagnosis is suspected preoperatively, but it is confirmed after surgical removal and histopathological evaluation of the appendix.

Acute appendicitis:

neutrophils



Numerous neutrophils, infiltrating the wall.

Sometimes, the appendix is removed even when it is healthy and not inflamed. There is an acceptable margin for this error, especially since appendicitis is dangerous–the appendix could rupture and spread the infection.

When the patient complains of acute abdominal pain. In addition to acute appendicitis, we have to rule out other causes of acute abdominal pain, like:

DDx of acute appendicitis:

When a female patient complains of acute abdominal pain which acute appendicitis is suspected. You should first exclude gynecologic causes of abdominal pain.

- Mesenteric lymphadenitis,
  usually follows an upper respiratory tract infection in children, and females of childbearing age
- Acute salpingitis,
  inflammation of the fallopian tube
- Ectopic pregnancy,
- Mittelschmerz (pain associated with ovulation),
- Ovarian cysts torsion
- Rupture Meckel diverticulitis
- Crohn disease.
  due to terminal ileocecal valve inflammation

Pathogenesi s:

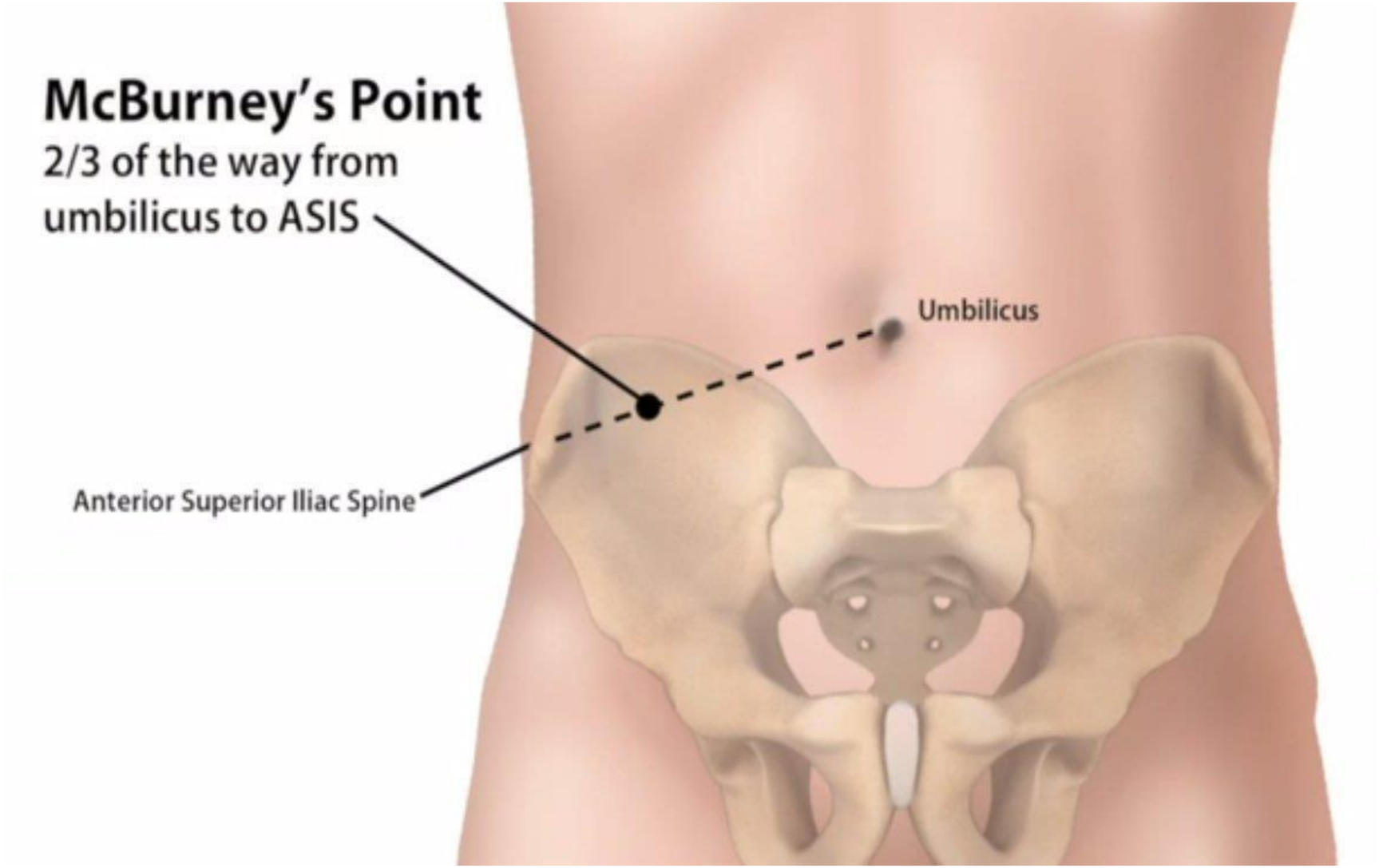
- Increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
- Luminal obstruction in 50-80% of cases by fecalith (small mass-like stone of stool), less commonly : gallstone, tumor, worms….

- 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 non-specific, disappears after a while, then localizes in the lower right quadrant.
- Later: pain localizes to the right lower quadrant,
- Nausea, vomiting, low-grade fever, mildly leukocytosis.(elevated white blood cell count)
- A classic physical finding is *McBurney's sign* (McBurney's point).
- Signs and symptoms are often absent, creating difficulty in clinical diagnosis.

McBurney's sign rebound tenderness at McBurney's point

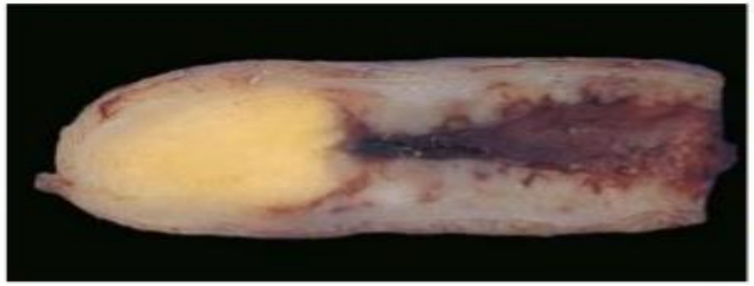


The surgeon deeply presses on the point between the anterior superior iliac spine and the umbilicus one third to the anterior superior iliac spine, then releases pressure. The patient will complain of severe pain which is considered a sign of appendicitis.

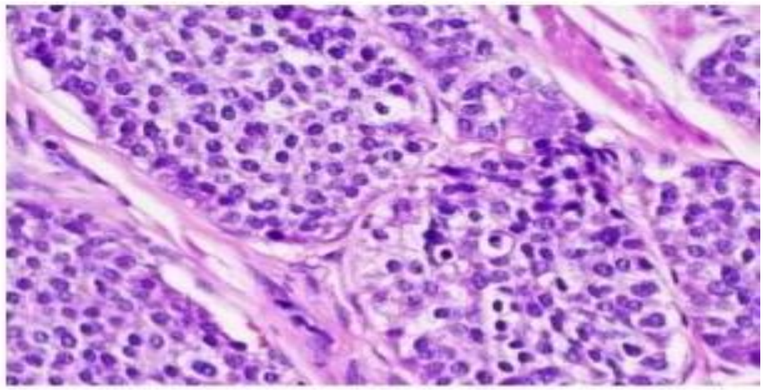
TUMORS OF THE APPENDIX

- The most common tumor: *carcinoid (*neuroendocrine tumor) like the neuroendocrine tumor of the stomach.
- Incidentally found during surgery or on examination of a resected appendix Distal tip of the appendix the most common location
- Nodal metastases & distant spread are rare.
- tumors behave in an indolent fashion with a good Prognosis

Carcinoid tumor



Gross



Microscopic

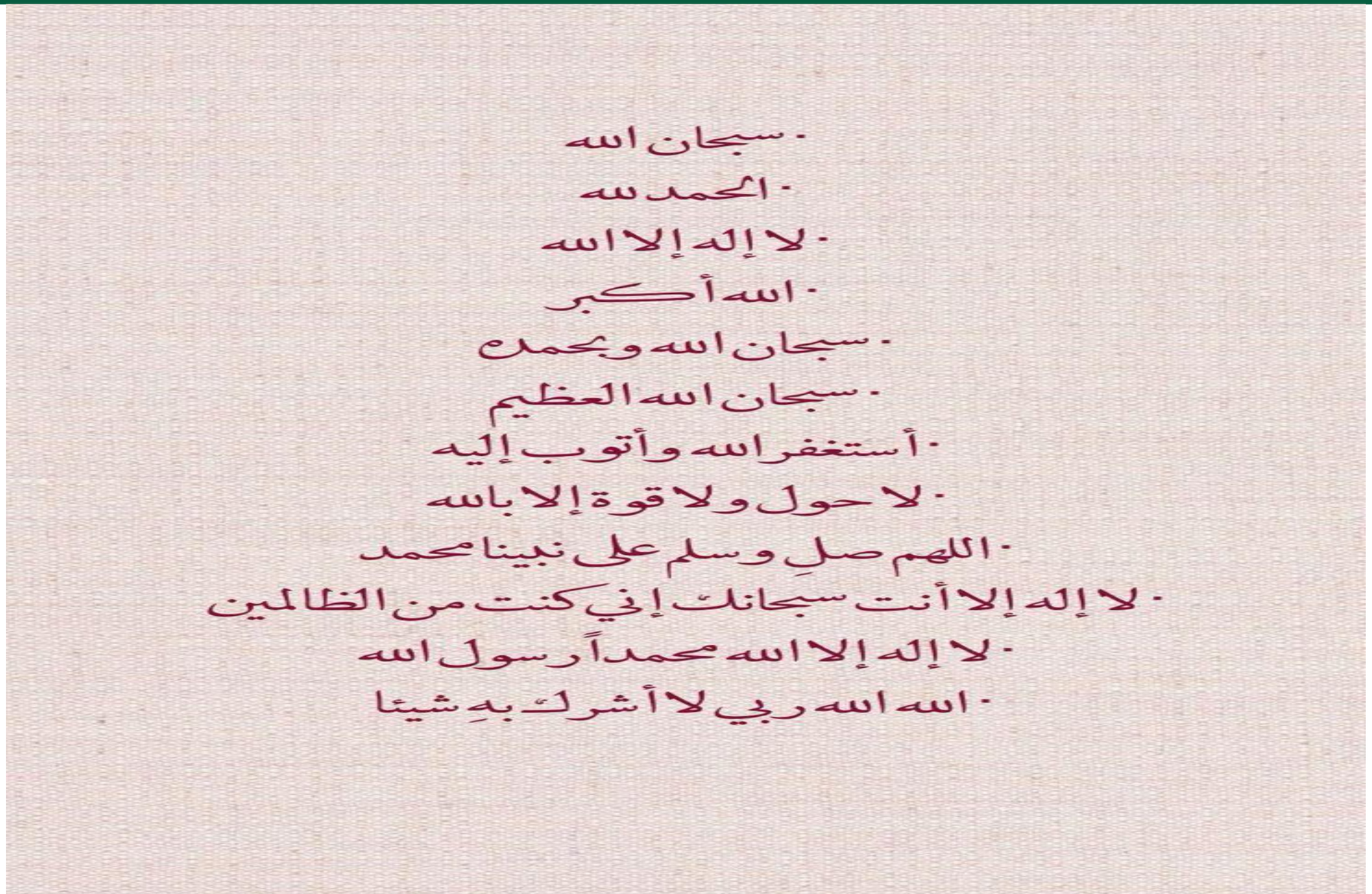
Tend to be on the tip of the appendix with yellow discoloration

The tumor shows a nesting pattern with salt and pepper chromatin, typical of a neuroendocrine tumor.

Test yourself on this lecture!

Additional Resources:

رسالة من الفريق العلمي:



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			