



PATHOLOGY



بسم الله الرحمن الرحيم



MID | Lecture 8

Intestinal Diseases (Pt.4)

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Isra'a Mohammad

وَإِنْ تَوَلَّوْا يَسْتَبَدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَلَكُمْ

اللهم استعملنا ولا تستبدلنا



Intestinal pathology, part 4

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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 of the cases present** before 50 (<20%) . (**some of these cancers before the age of 50 are 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 pathway involved in FAP syndrome**
 2. Microsatellite instability pathway due to defects in DNA mismatch repair
→ **Same pathway as the (HNPCC)**
- ▶ **In both pathways there's a** Stepwise accumulation of multiple mutations

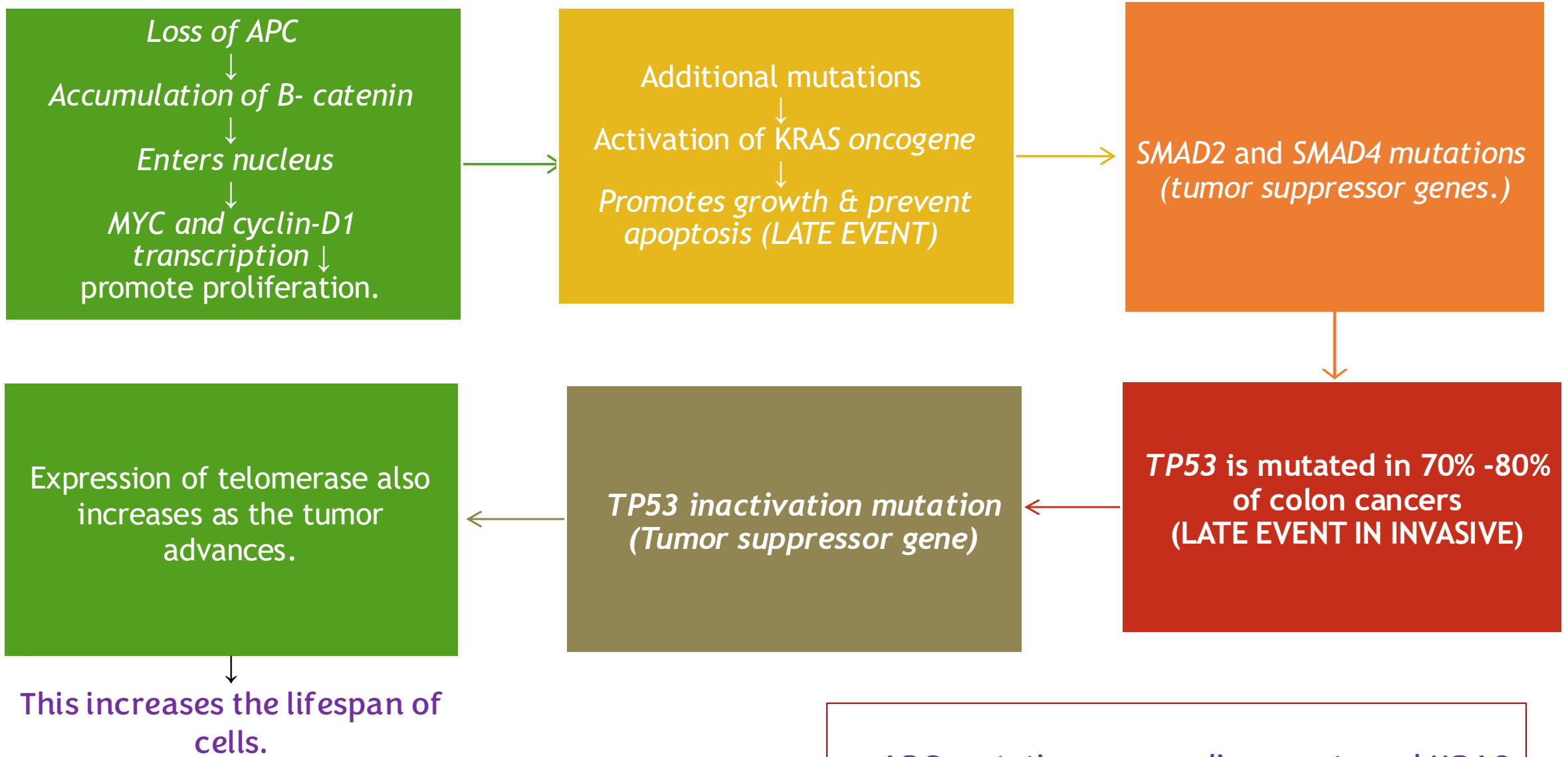
FAP = Familial adenomatous polyposis

HNPCC = hereditary nonpolyposis colorectal cancer

APC = adenomatous
polyposis coli

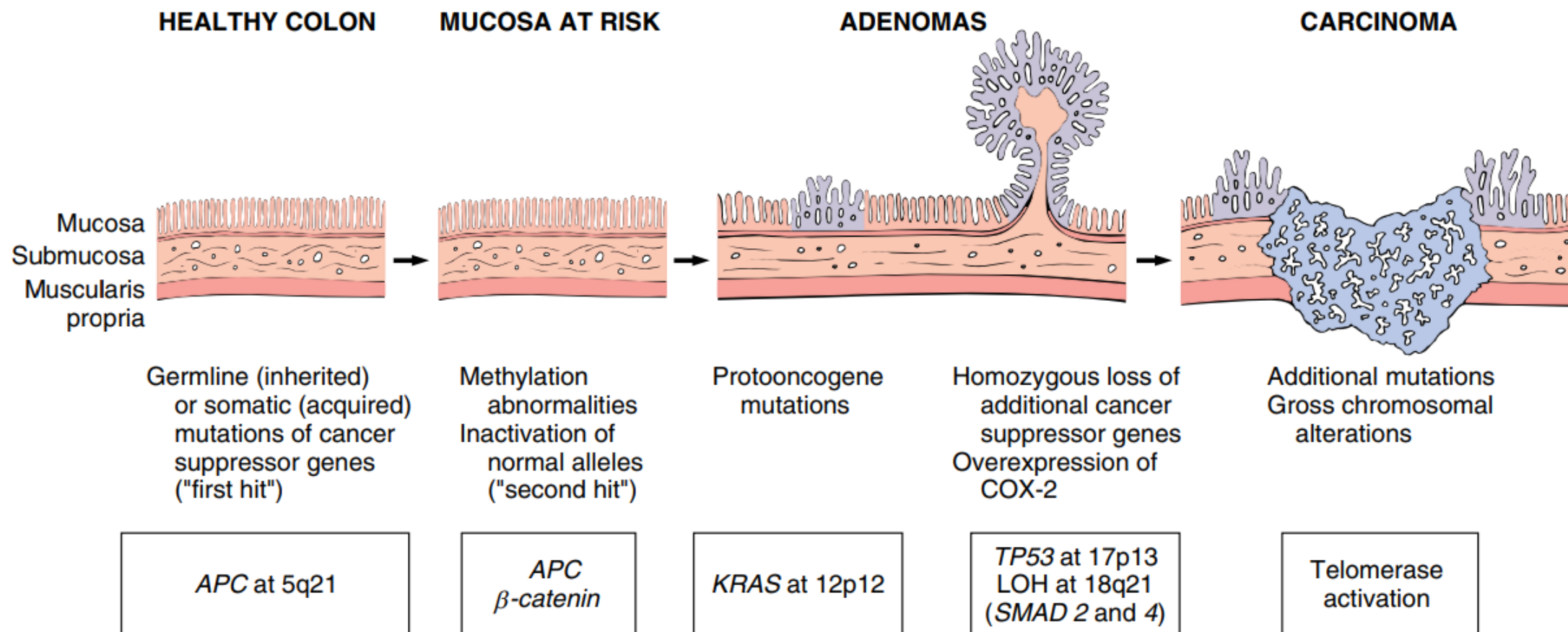
The APC / β -catenin pathway: chromosomal instability

- ▶ 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 β -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* because we have these mutations by chromosomal deletions (hallmark)



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

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.



Recall that the protective effect of NSAIDs and aspirin here.

The microsatellite instability pathway

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

- ▶ DNA mismatch repair deficiency (Loss of genes) (loss of function)
- ▶ 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 later and common. However, P53 and KRAS (which were described in the chromosomal instability pathway) are absent here..

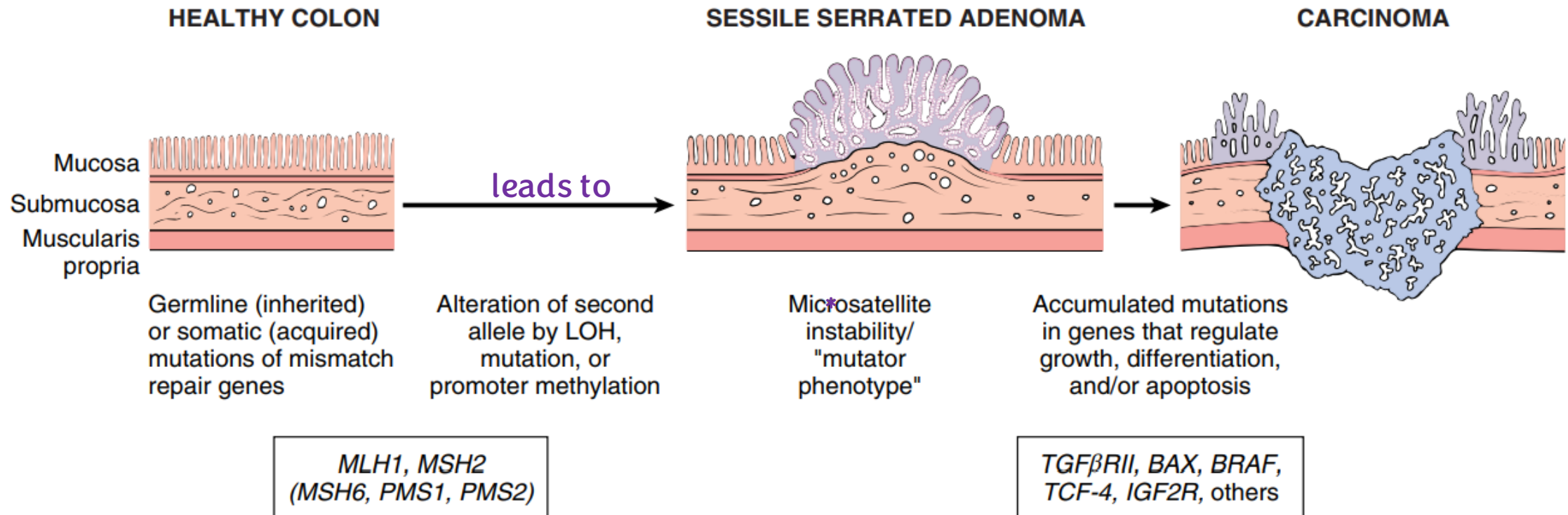
Again, we need both alleles of the genes to be inactivated for the tumor to be expressed

- If the tumor is inherited 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	<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. → 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).
- ▶ Necrotic debris (dirty necrosis) are typical.
- ▶ Some tumors give abundant mucin (poor Px) or form signet ring cells.

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

Napkin ring

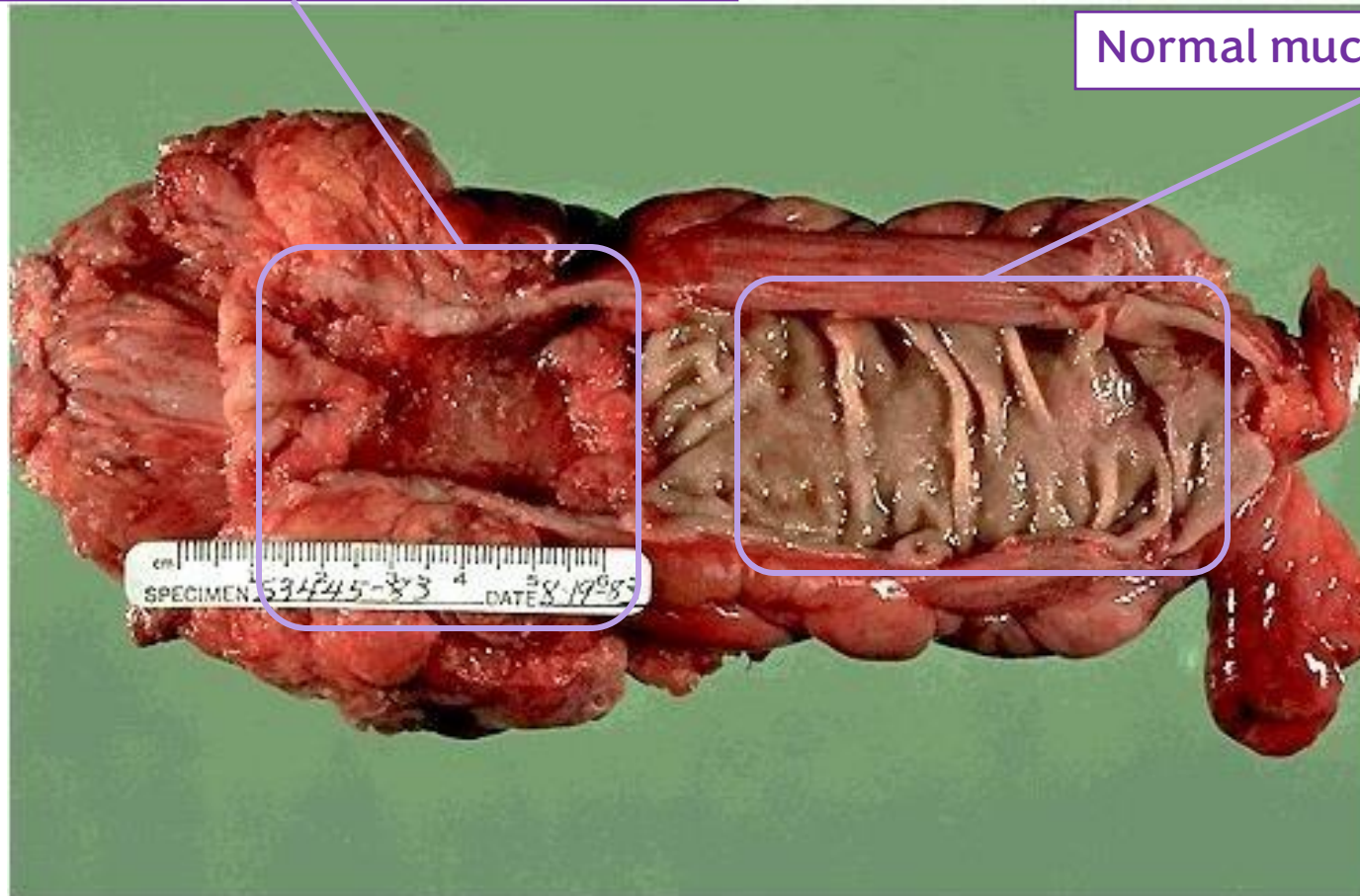


This is the napkin ring appearance which is used to describe tumors in distal colon that cause narrowing with obstructive symptoms.

Recto-sigmoid adenocarcinoma, napkin ring

napkin ring / constructive appearance

Normal mucosa with folds

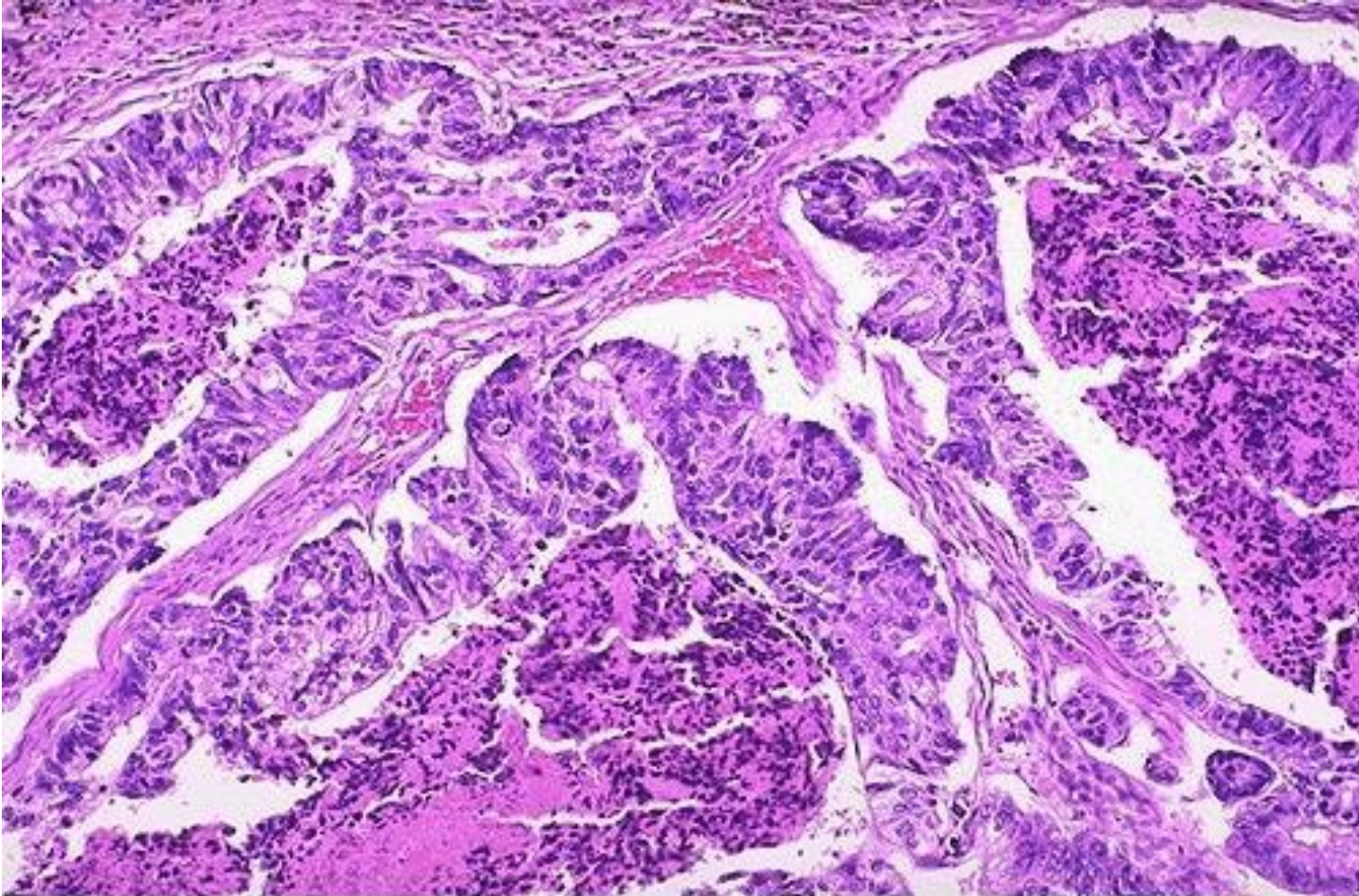


Exophytic adenocarcinoma



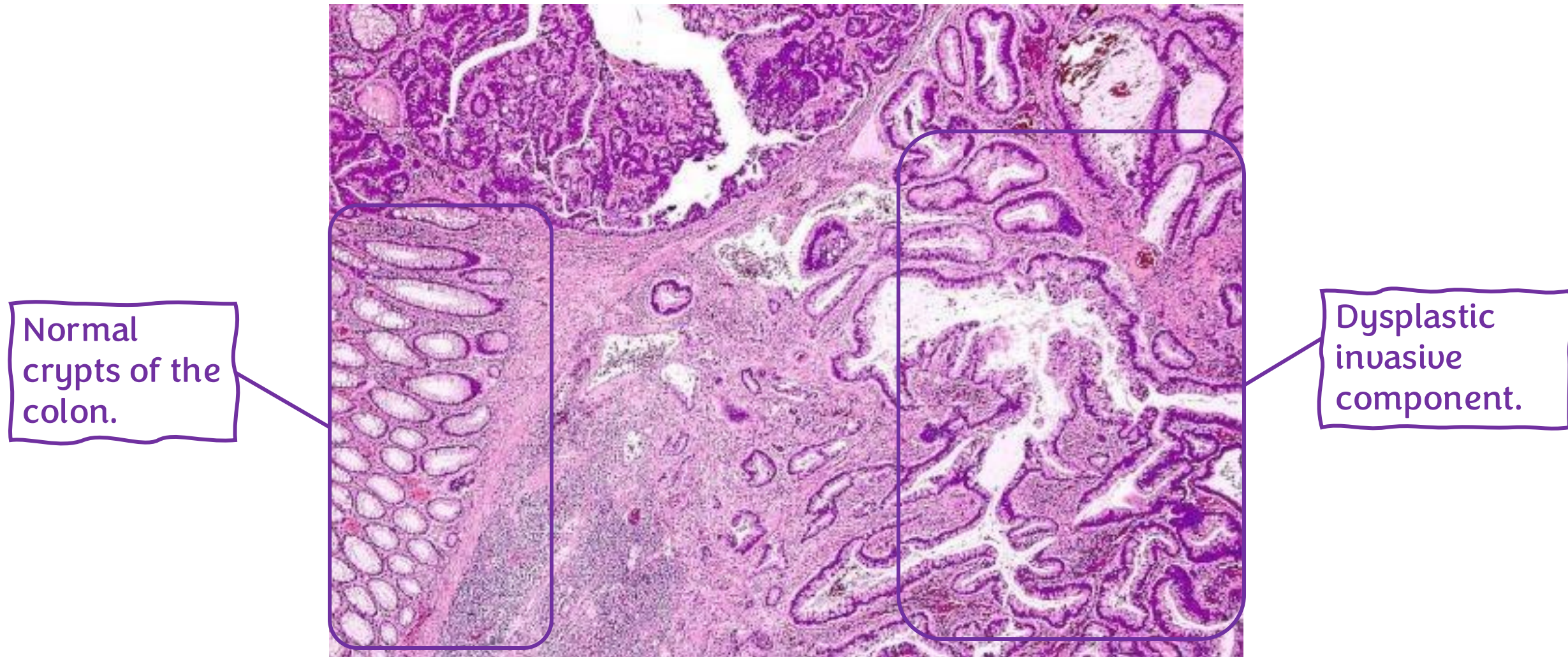
Mass projecting to the lumen of the bowel that can cause **partial** obstruction. Rarely causes complete obstruction due to it occurring mostly in the right side of the colon or cecum which has a large diameter.

Adenocarcinoma with necrosis



Dirty necrosis in the center of the dysplastic gland.

Invasive carcinoma





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.

TNM STAGING SYSTEM

T Tumor

TX:

Primary tumor cannot be measured.

TO:

Primary tumor cannot be found.

T1, T2, T3 or T4:

Primary tumor has been measured. Higher numbers indicate the tumor is larger or has expanded further into nearby tissue.

N Lymph Nodes

NX:

There is no information about the lymph nodes.

NO:

Nearby lymph nodes do not contain cancer.

N1, N2 or N3:

Cancer is present in the lymph nodes. A higher number indicates the cancer has been found in more lymph nodes.

M Metastasis

MX:

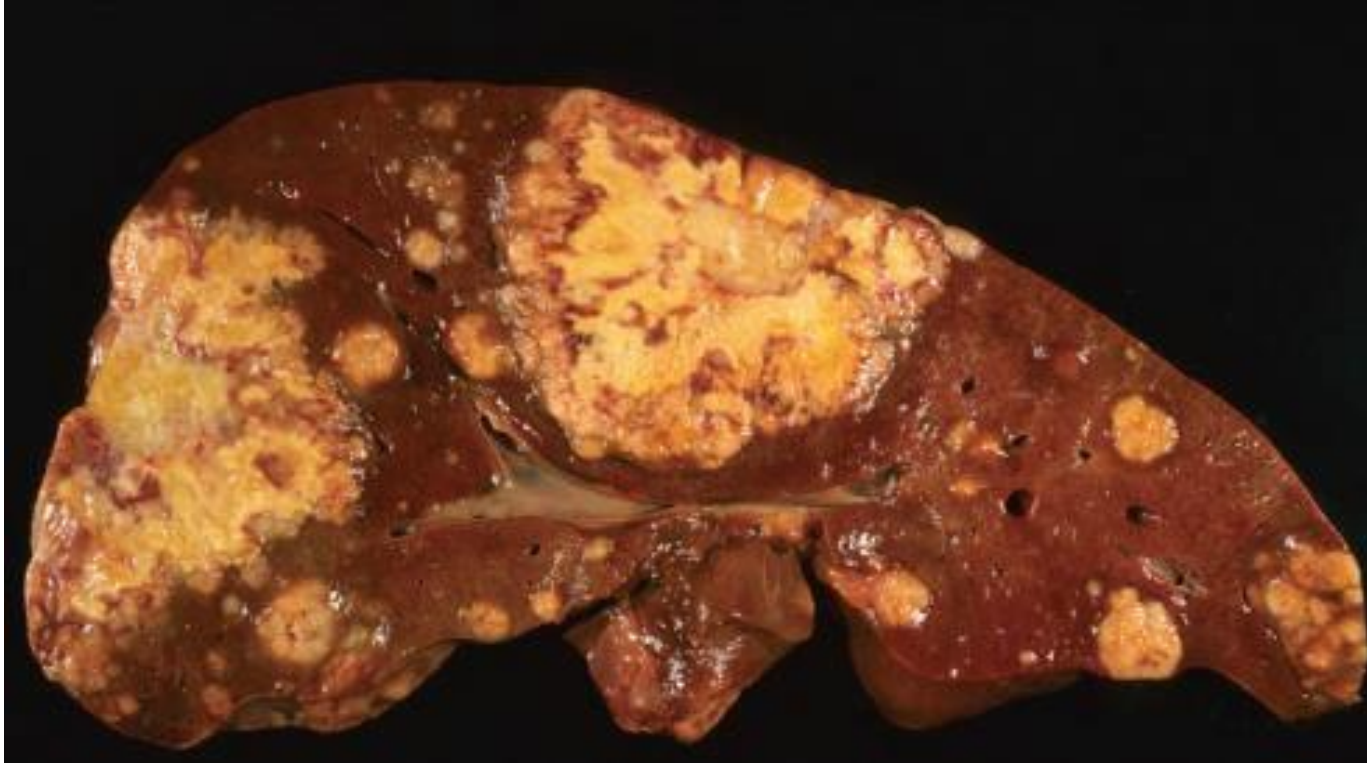
Spread cannot be measured.

MO:

Cancer has not spread to other parts of the body.

M1:

Cancer has spread to other parts of the body.



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

Liver metastasis.

Appendix diseases:

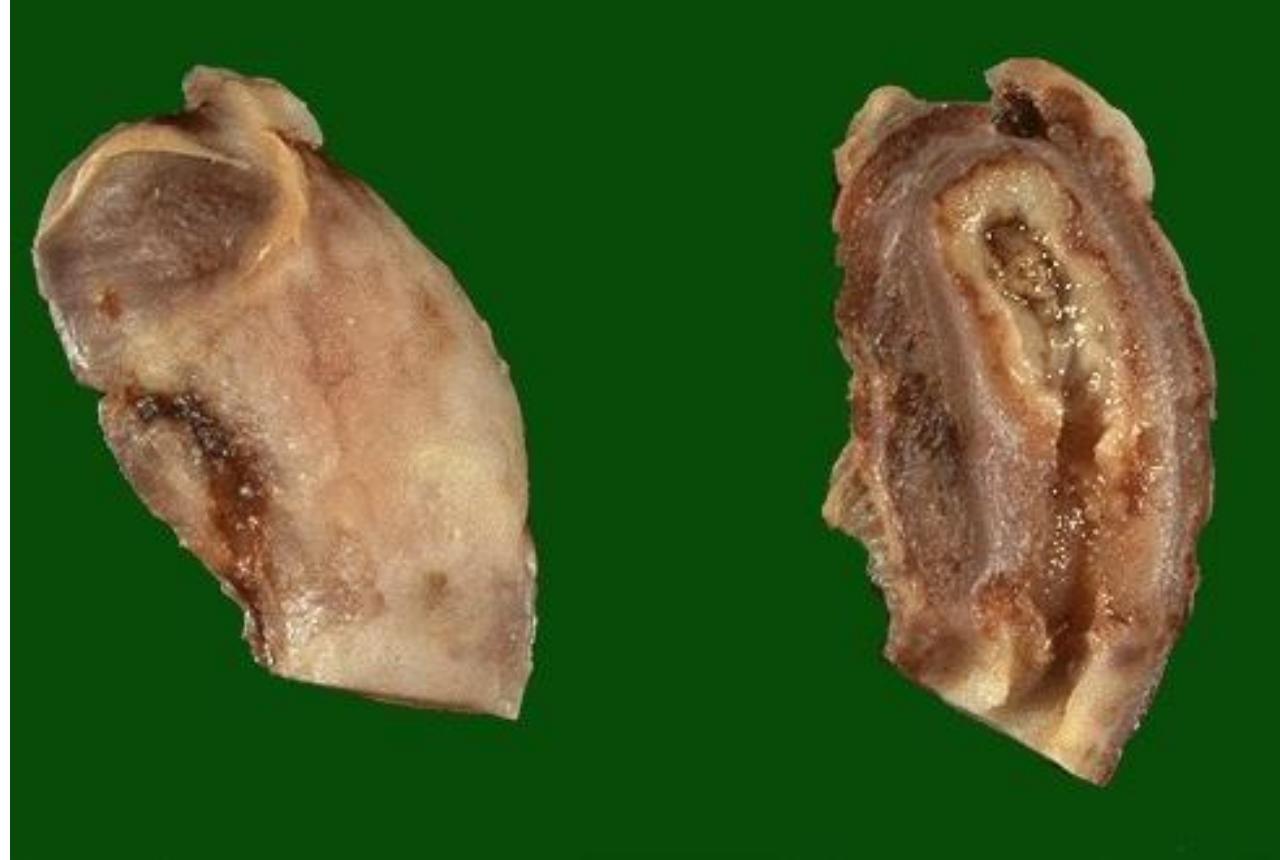
- ▶ Normal true diverticulum of the cecum
- ▶ ACUTE APPENDICITIS → number “1”
- ▶ TUMORS OF THE APPENDIX → not common

ACUTE APPENDICITIS

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

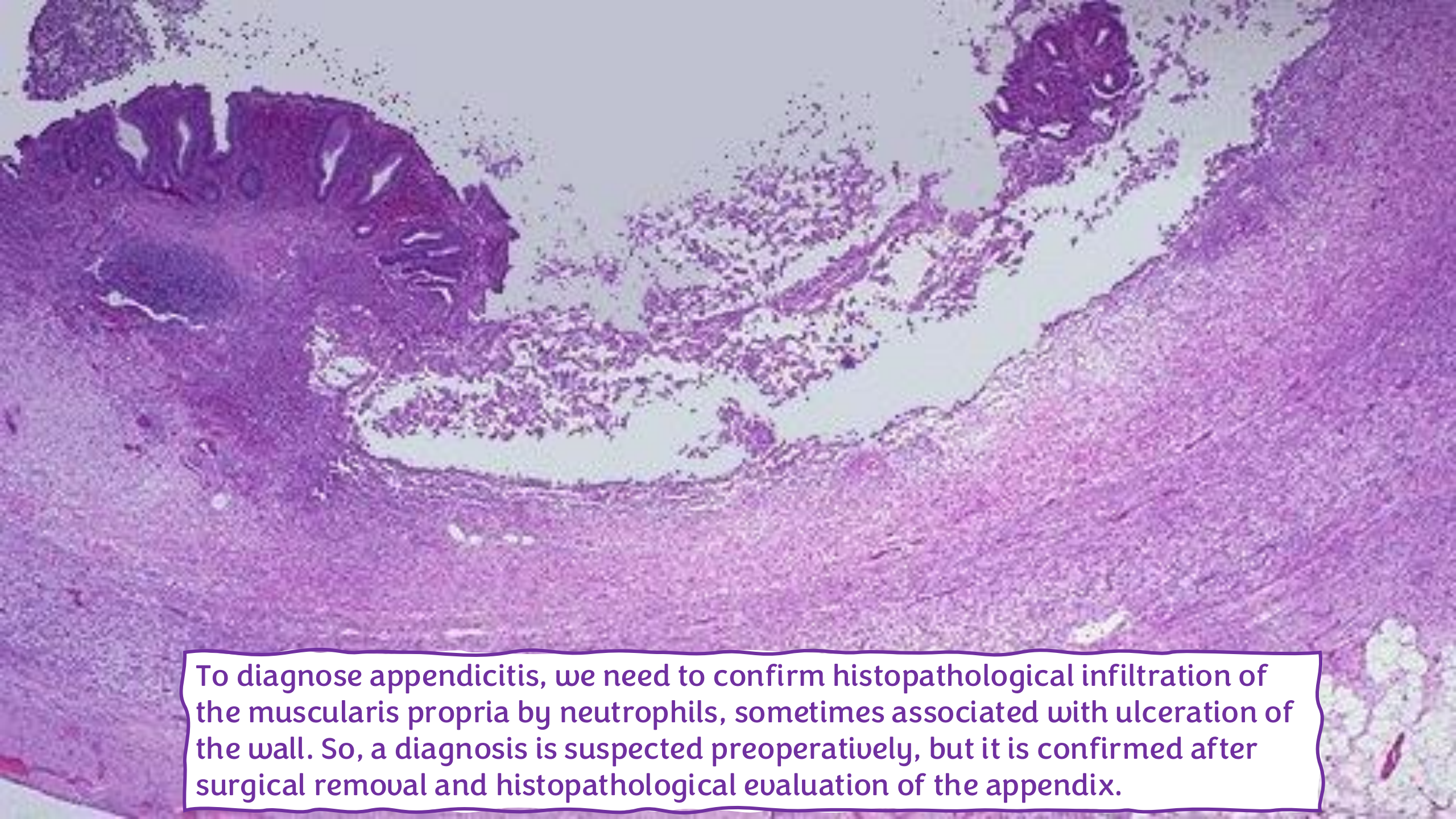


Normal appendix
with glistening
serosal surface.



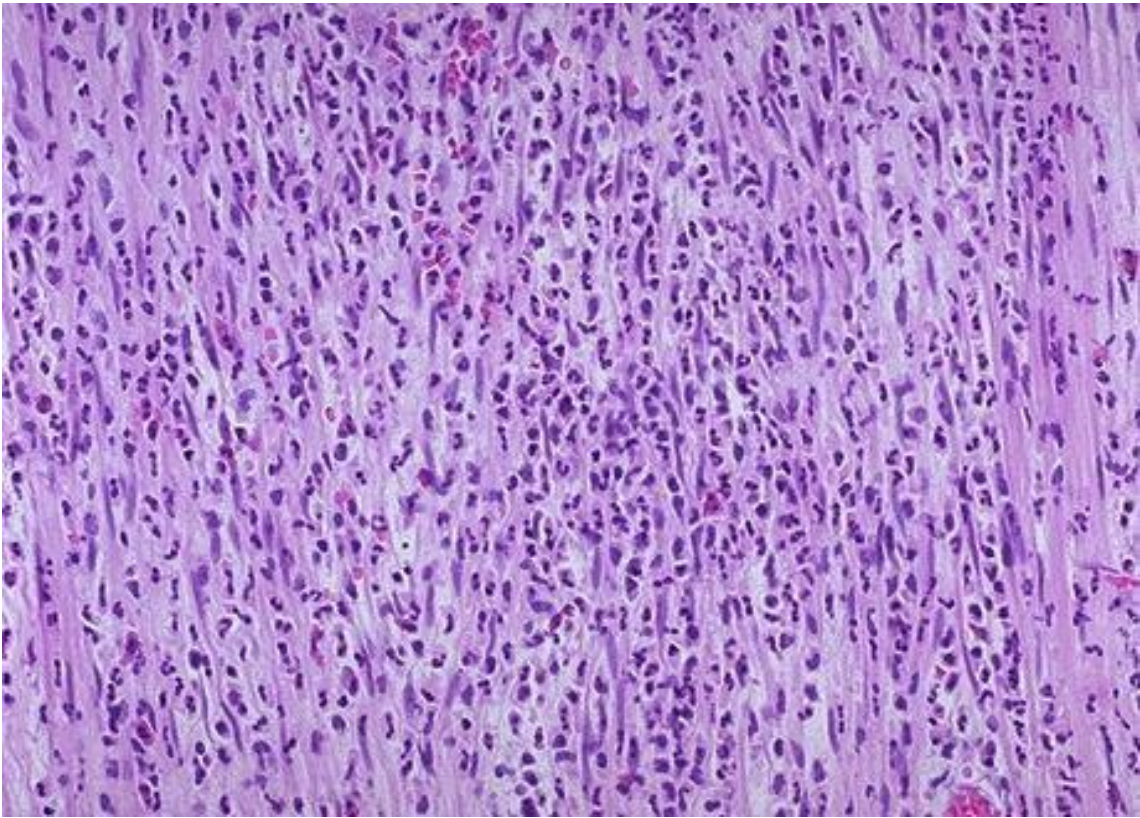
Appendix with acute appendicitis,
serosa is dusky and covered by
yellowish exudates, and the mucosa is
also covered by a yellowish exudate.

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.

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.

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:-

- ▶ 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

Pathogenesis

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.

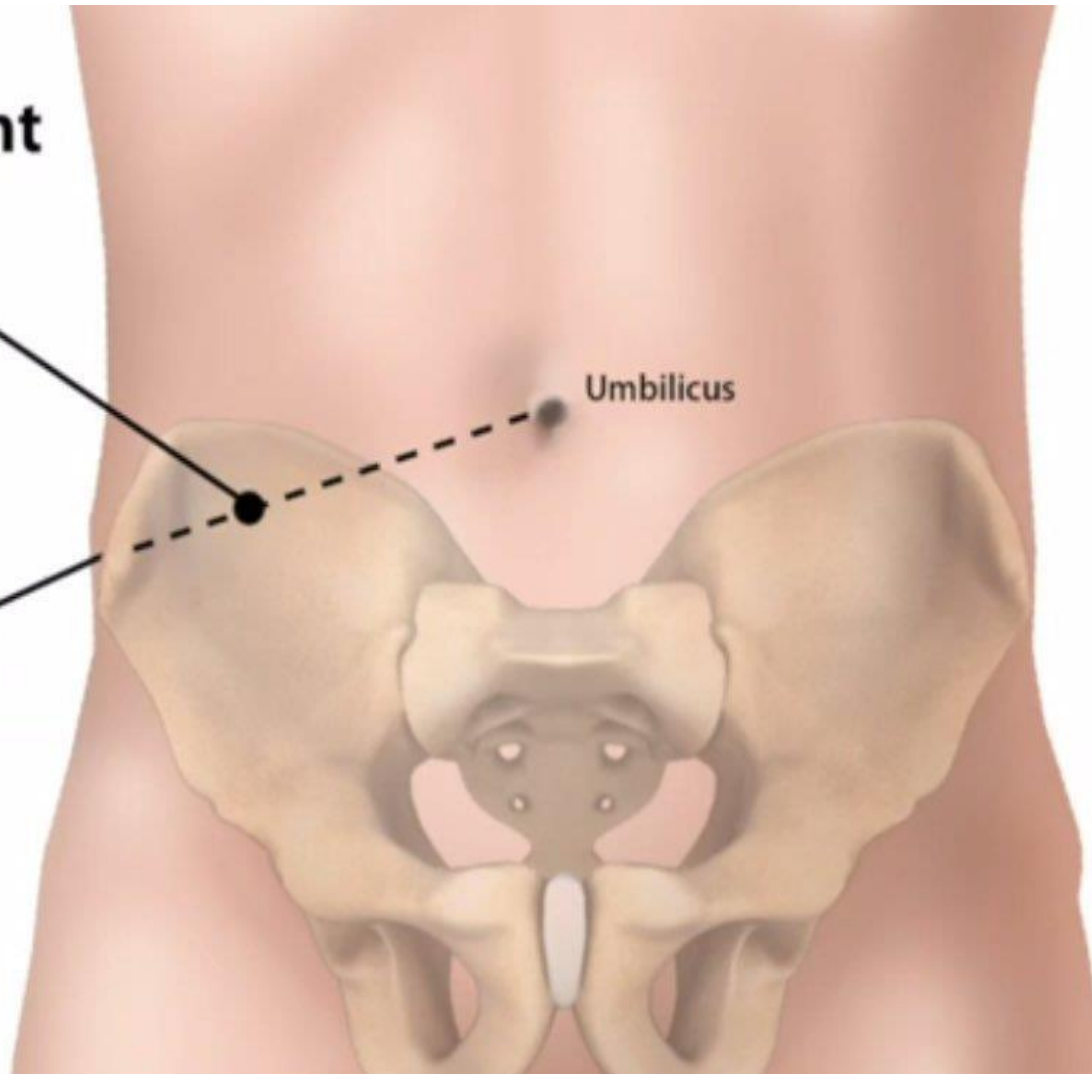
McBurney's sign → rebound tenderness at McBurney's point

McBurney's Point

2/3 of the way from
umbilicus to ASIS

Anterior Superior Iliac Spine

Umbilicus



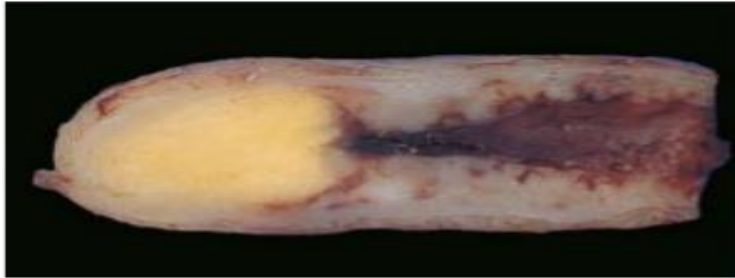
The surgeon deeply presses on the point between the anterior superior iliac spine and the umbilicus one third to the anterior superior iliac spine, then releases pressure. The patient will complain of severe pain which is considered a sign of appendicitis.

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.

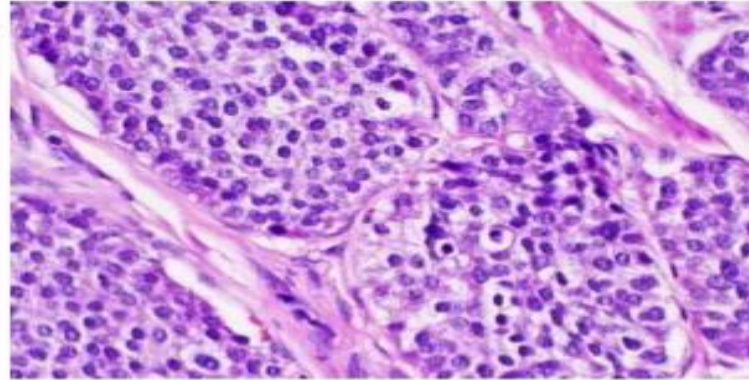
tumors behave in an indolent fashion with a good Prognosis

Carcinoid tumor



Gross

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



Microscopic

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

Test yourself on this lecture!



وآخر دعوانهم أن الحمد لله رب العالمين

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	Slide 4	“ Most of the cases are familial or they present before 50”	Some of the cases present before 50 (<20%) .
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

يقولُ اللهُ تعالى: أنا عِنْدَ ظَنِّ عَبْدِي بِي، وأنا معه إذا ذَكَرَنِي، فإنْ ذَكَرَنِي في نَفْسِهِ ذَكَرْتُهُ في نَفْسِي، وإنْ ذَكَرَنِي في مَلَأٍ ذَكَرْتُهُ في مَلَأٍ خَيْرٍ مِنْهُمْ، وإنْ تَقَرَّبَ إِلَيَّ بِشِبْرٍ تَقَرَّبْتُ إِلَيْهِ ذِرَاعًا، وإنْ تَقَرَّبَ إِلَيَّ ذِرَاعًا تَقَرَّبْتُ إِلَيْهِ باعًا، وإنْ أَتَانِي يَمْشِي أَتَيْتُهُ هَرْوَلَةً.

الراوي: أبو هريرة | خلاصة حكم المحدث: [صحيح [حديث قدسي

{وإذا سألك عبادي عني فإني قريب أجيب دعوة الداع إذا دعان} {البقرة(186):

لا تنسوا اخوانا المسلمين والمستضعفين من دعائكم