GI

Pathology

LEC no.

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Intestinal pathology, part 4

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Diseases of the intestines

Are divided into

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

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 affected more than >females, less than >20% of cases are present before the age of 50

> Some of these cancers before the age of 50 are considered familial colon cancer.

- Developed countries lifestyles and diet are considered risk factors for the development of colonic adenocarcinoma
- **Risk factors: Low intake of vegetable fiber and high intake of carbohydrates and fat. Obesity, smoking and alcohol.**

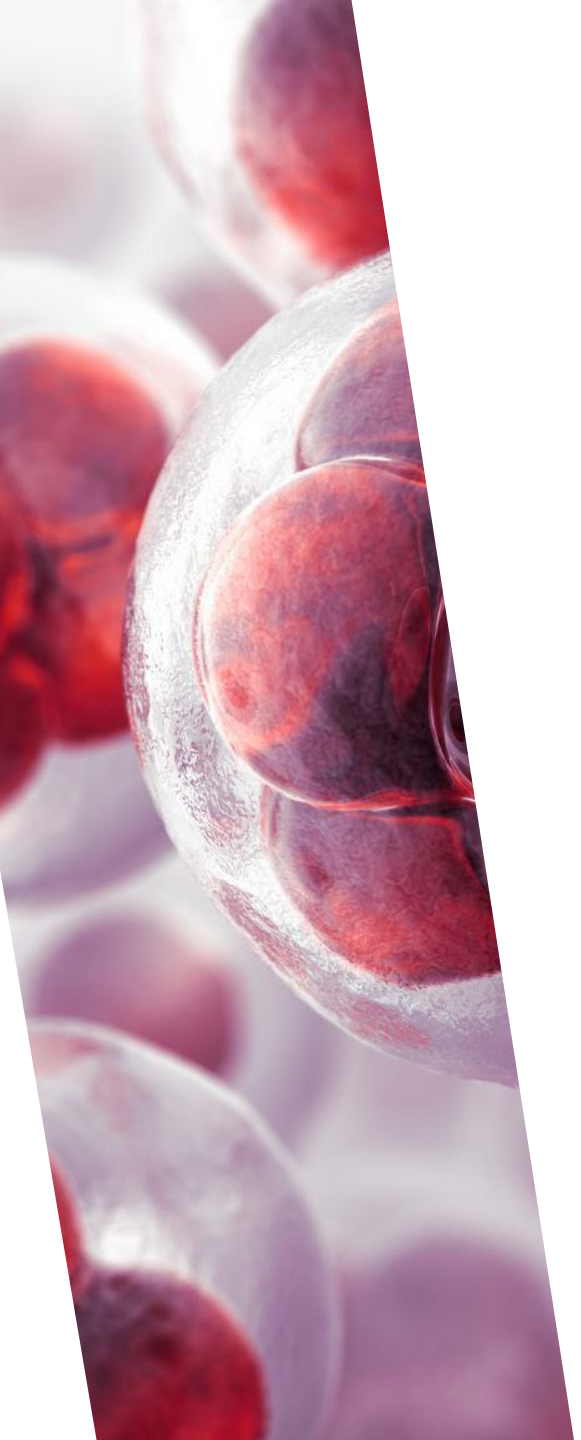
Colonic Adenocarcinoma

- Aspirin or other NSAIDs have a protective effect because they inhibit (Cyclooxygenase-2 (COX-2) pathway which is expressed in 90% of carcinomas, and even it is expressed in adenomas, This enzyme promotes epithelial proliferation).

so inhibition of this enzyme leads to inhibition of this proliferation and increasing the risk or protection against colon cancer

- **Prevention: dietary modification, pharmacologic chemoprevention.**

prevention of colon cancer, if you reduced high risk factors, by the dietary modifications: high in vegetable and fibers and low in carbohydrates and fat, by weight reduction and to stop smoking and alcohol consumption, and by the use of non-steroidal anti-inflammatory drugs and aspirin which in habits the COX-2 enzyme.



Pathogenesis

- Heterogeneous molecular events including (genetic and epigenetic).
- Sporadic >>>> familial.

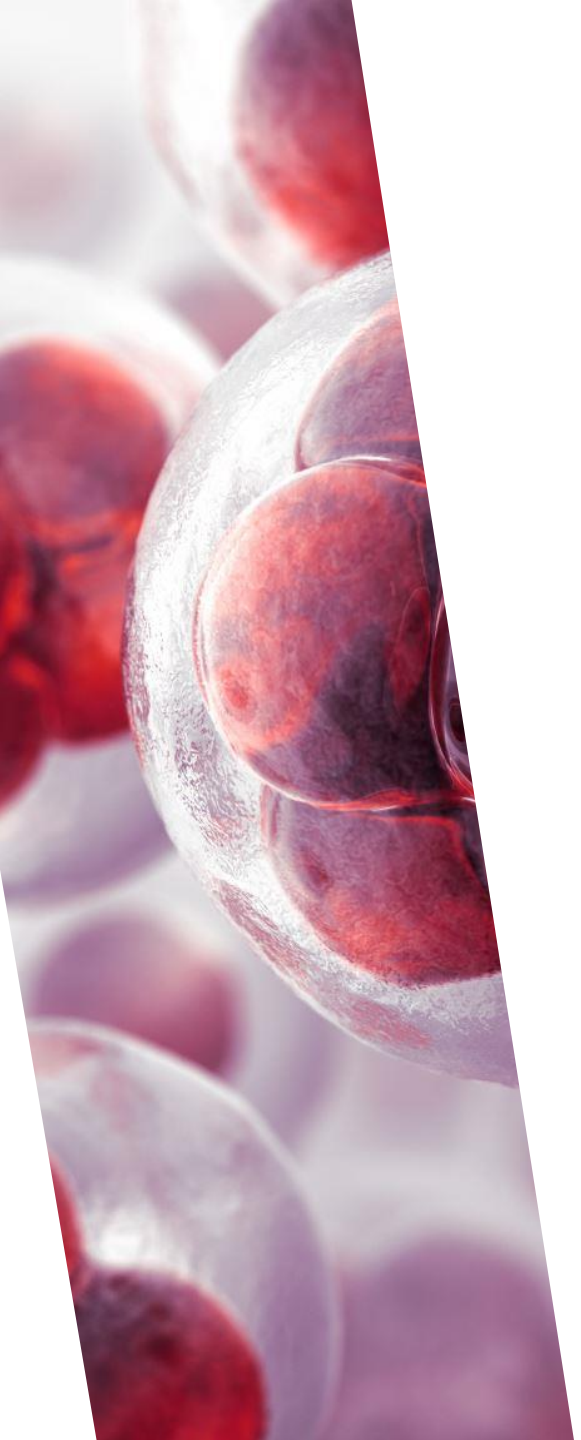
Sporadic colon cancer is much more common than familial colon cancer,

- **Two pathways** of carcinogenesis**:**
- **APC/β-catenin pathway leads to>> increased WNT signaling**
- **Microsatellite instability pathway due to defects in DNA mismatch repair**

APC gene is also involved in FAP syndrome. **Microsatellite instability pathway** is also the same pathway of the hereditary nonpolyposis colon cancer syndrome HNPCC.

- Stepwise accumulation of multiple mutations

So in both of these pathways, there is a sequenced 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 β-catenin degradation), a component of the WNT signaling pathway.*
- *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).*
- ***Chromosomal instability by deletions (hallmark)***

the APC beta-catenin pathway, is also called the chromosomal instability pathway.

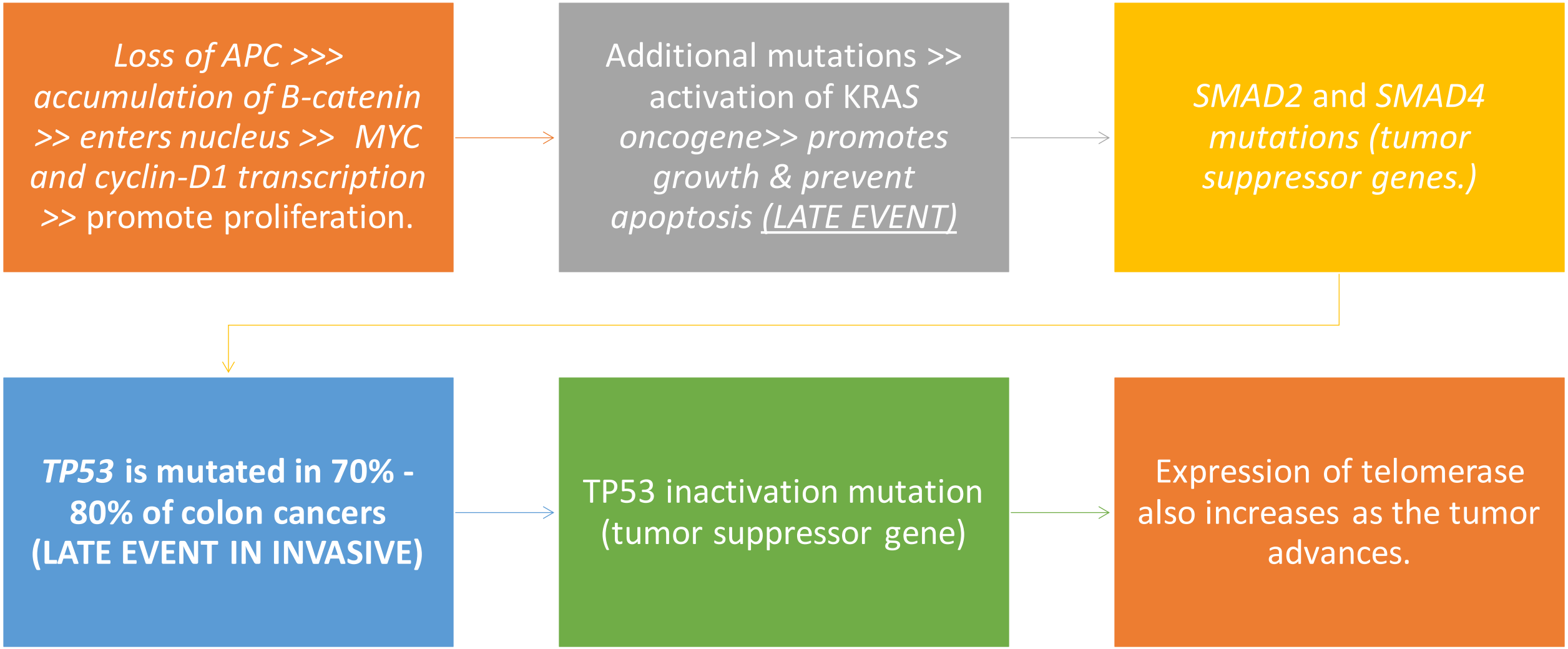
the classic pathway of progression from an adenoma to carcinoma.

Check the next slide.

This pathway is called the chromosomal instability pathway, because we have these mutations by chromosomal deletion

If this negative regulation is lost, this will lead to build up of beta-catenin. Both copies of the APC gene should be inactivated, or mutated, in order for the adenoma to develop, then the adenoma progress to carcinoma.

So for both copies to be mutated, we need a first hit, and a second hit. If the first hit is an inherited, or a germline mutation, then the second hit will occur at an earlier age, or the tumor will present at an earlier age, like what happens in the inherited cancer syndrome.


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.

- The first thing that occurs during this pathway is the loss of the APC gene. This will lead to accumulation of beta-catenin. As we said, the inhibition is lost. The beta-catenin, in turn, enters the enucleus. It activates the MYC and the cyclin D1 genes, and it transcribes them. This will promote proliferation of the cells in the colon. EARLY EVENT

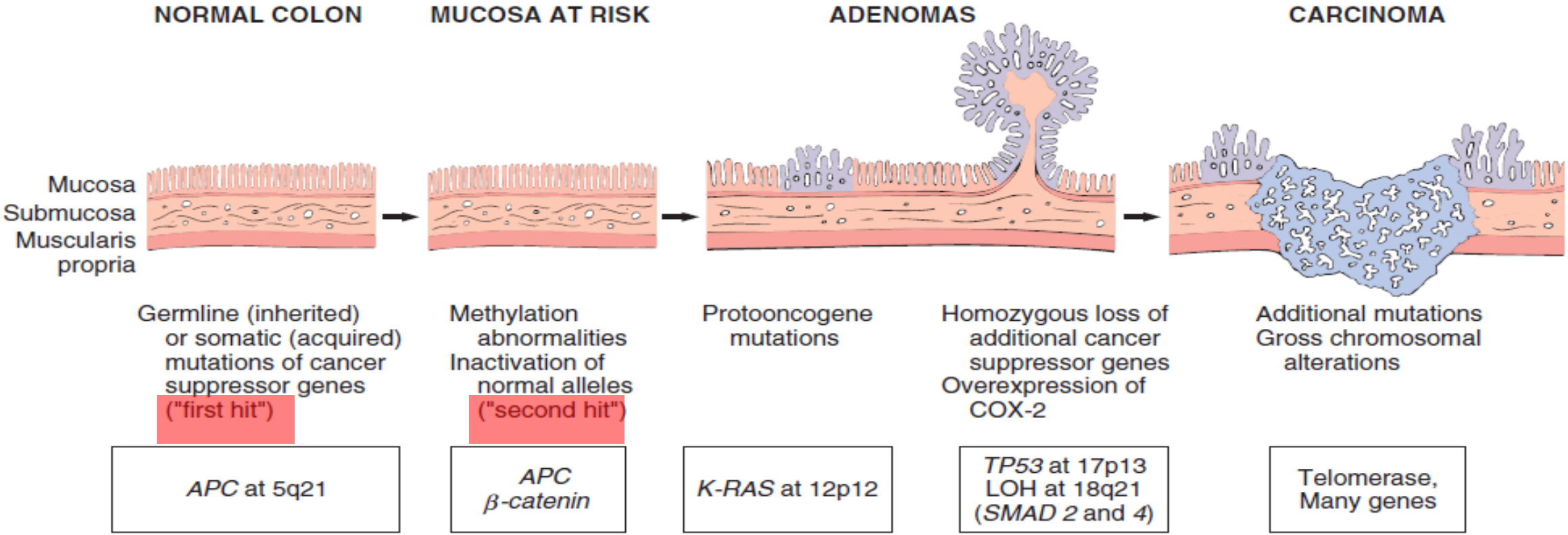
- Cell mutations, by activation of the KRAS oncogen, this will lead to promotion of the growth and prevention of apoptosis LATE EVENT

الكلام الموضح بالأحمر هو إعادة صياغة ليس أكثر لا يوجد معلومات جديدة

The APC mutations are earlier events, and the KRAS mutations are considered late events in carcinogenesis. So, you will find KRAS mutations mostly in the invasive carcinoma, not in the adenoma.

- Then, this acquiring or accumulation of more mutations, like SMAD2 and SMAD4 mutations, which are considered the tumor suppressor genes.

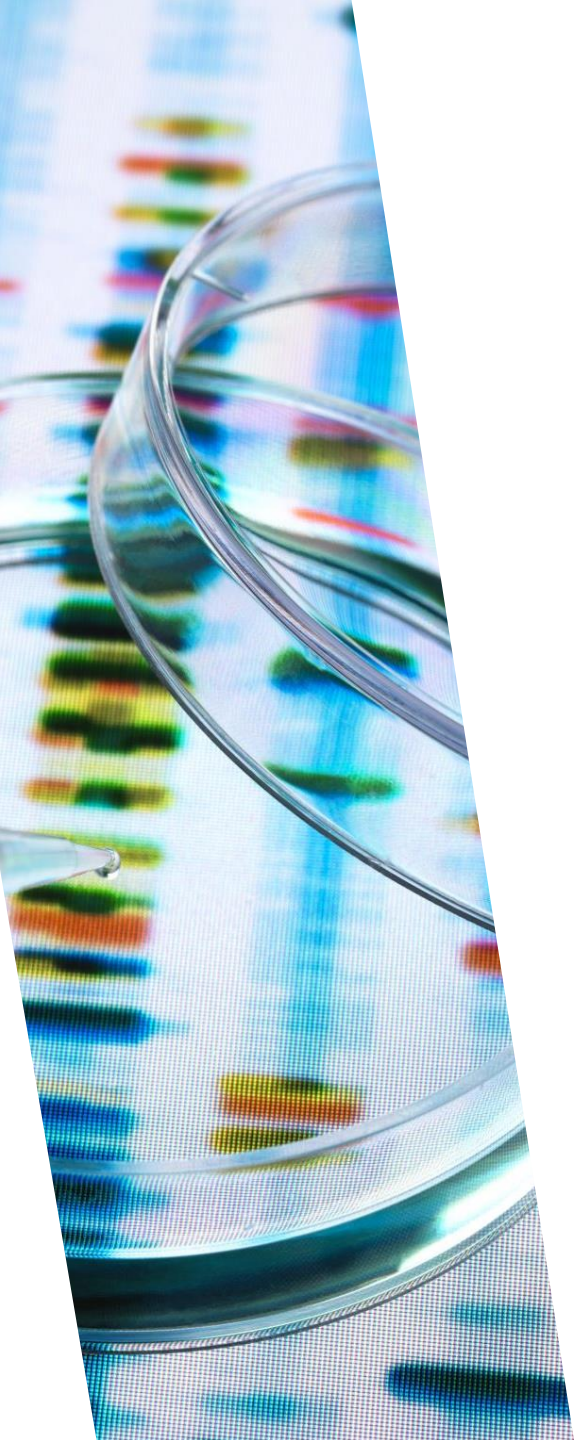
- Then, at a later consequence, the P53 will be mutated, and this occurs in 70 to 80 percent of colon cancer, but it is a late event.it is found in the majority of colon cancers, mainly the invasive cancers, but it is usually not detected in adenomas.
- P53 is considered a tumor suppressor gene, so its inactivation leads to tumor progression.
- Later on, expression of telomerase also increases as the tumor advances.



muscular propria. This is the normal colon, and the patient inherits a germline mutation

overexpression of the cyclooxygenase 2 enzyme. As we said, the use of NSAIDS and aspirin to prevent this enzyme are considered protective.

Additional and additional mutations will accumulate, leading in the end to invasive carcinoma.



The microsatellite instability pathway

- The problem here is in the DNA mismatch repair deficiency (Loss of genes) or loss of the function of these genes
- As a result Mutations accumulate in microsatellite repeats (mostly non-coding)
- Leads to 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 and occur later. However, P53 and KRAS are absent

Not chromosomal instability pathway because of the problem in the micro-satellite repeats of the DNA.

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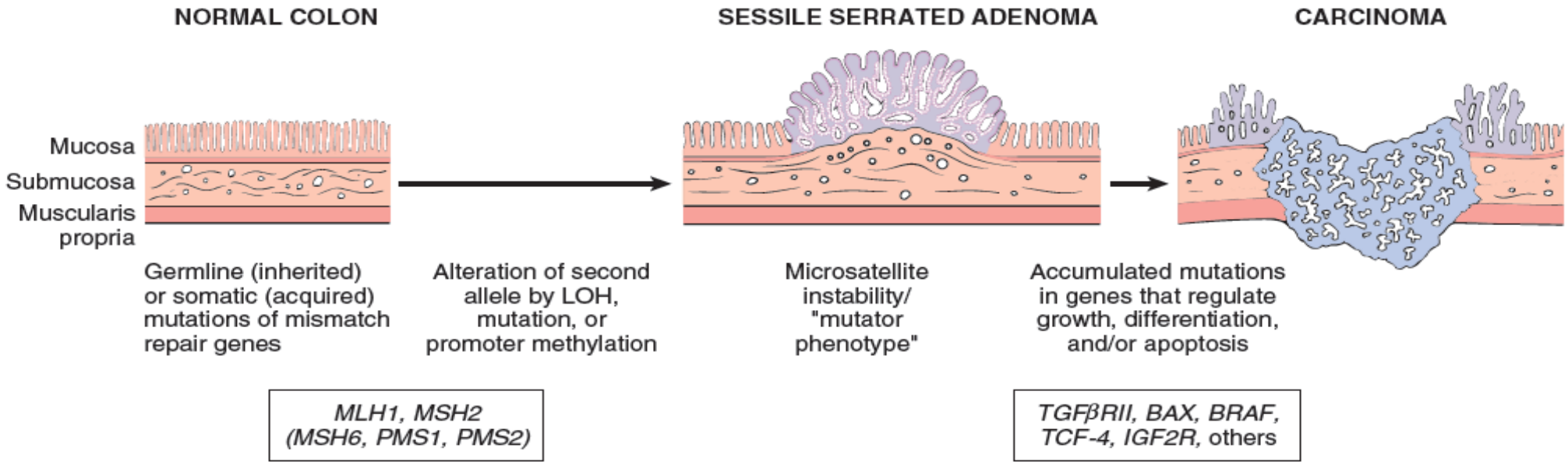
p53 mutations and KRAS mutations, which were described in the chromosomal instability pathway, are absent here.

these micro-satellite repeats are mostly non-coding, so if a mutation occurs in a non-coding region, the result will be silent effect and no effect,

but if the mutation occurs in the coding or the promoter region of some genes, like genes involved in cell growth(TGF-B) and apoptosis (BAX genes) will lead to cell growth and inhibition of apoptosis and the tumor development.



Again, we need both of these genes to be inactivated in order for the tumor to be expressed. The first mutation is called germline mutation as the tumor is inherited, and the second mutation would be a somatic mutation

If the tumor is sporadic, then both of the alleles will be inactivated in a somatic acquired pathway.

RECALL POLYPS LECTURE!!

We are talking here about the mismatch repair genes, like the MLH1 and NSH2, mostly. This will lead to micro-satellite instability and the tumor cellular proliferation and appearance of the precursor lesion for these tumors, which are called the sessile serrated adenoma. As we described in the previous lecture, the sessile serrated adenoma will progress to an invasive carcinoma by acquiring more mutations, like in the BRAF gene.

both of pathways of pathogenesis occur in both the familial and sporadic , most of colon cancer cases are sporadic 80%of cases

Recall
The familial cancer syndromes(FAP & HNPCC), inherited in an AD pathway.
first hit →inherited as a germline mutation,
the second hit-->somatic mutation.
Later on, the age of onset for these cancers will be earlier.

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

These tumors with microsatallite instability, /DNA mismatch repair abnormality/, they tend to occur on the right side of the colon and preceded by the precursor lesion, which is the Sessile serrated adenoma, sometimes with a tendency for mucin production

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” causing constrictions & narrowing of the lumen

Therefore, they present most of the time with obstruction.

MORPHOLOGY

- **Microscopic:**
- Dysplastic GLANDS with strong desmoplastic response (firm).

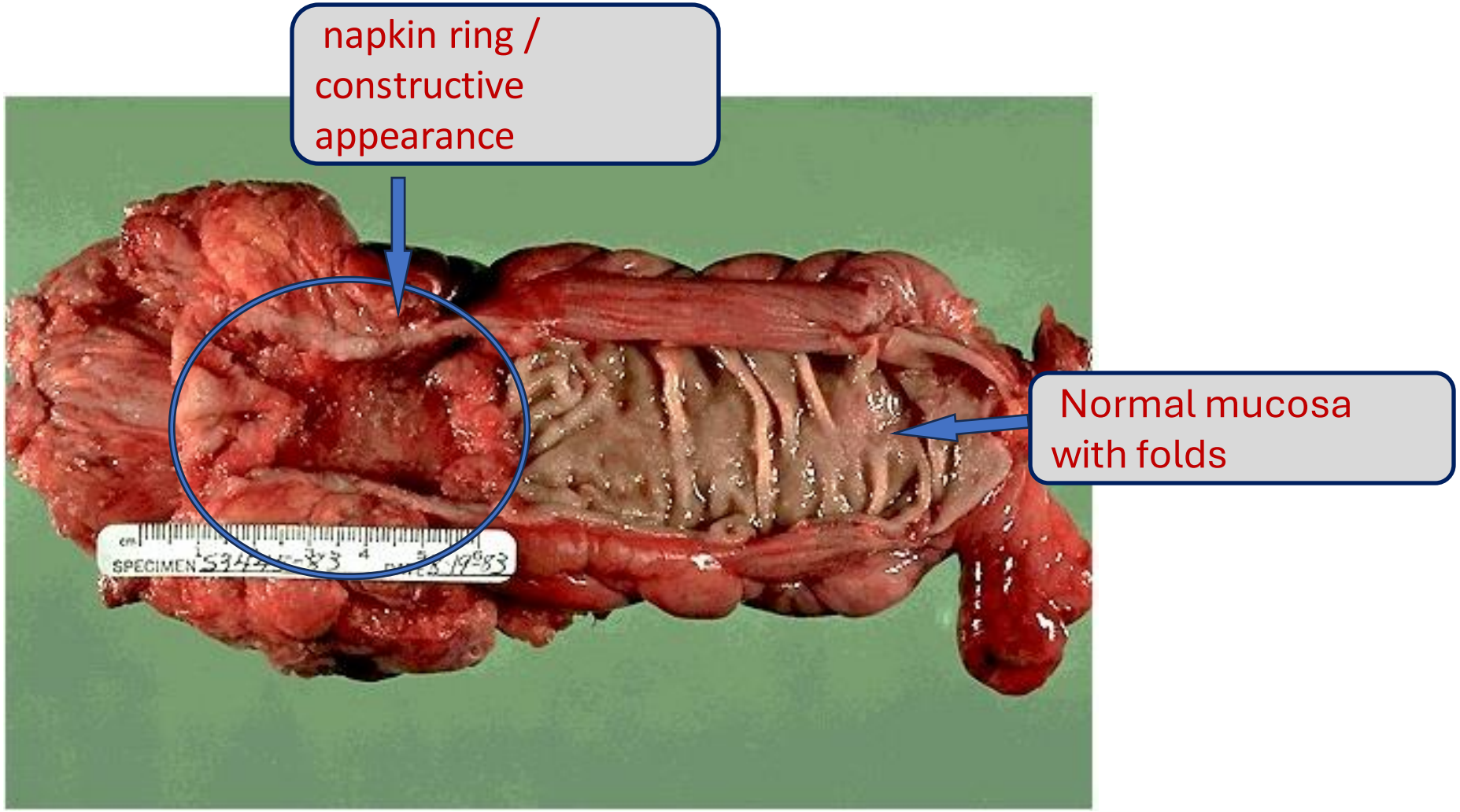
dysplastic implants, displaying hyperchromasia, stratification, high N/C ratio, with a strong dysplastic response around them, or a fibrotic response. That's why these tumors tend to be firm

- Characteristically shows under microscope Necrotic debris (dirty necrosis) are typical.
- Some tumors give abundant mucin this is considered a (poor Px "prognostic sign") or form signet ring cells.

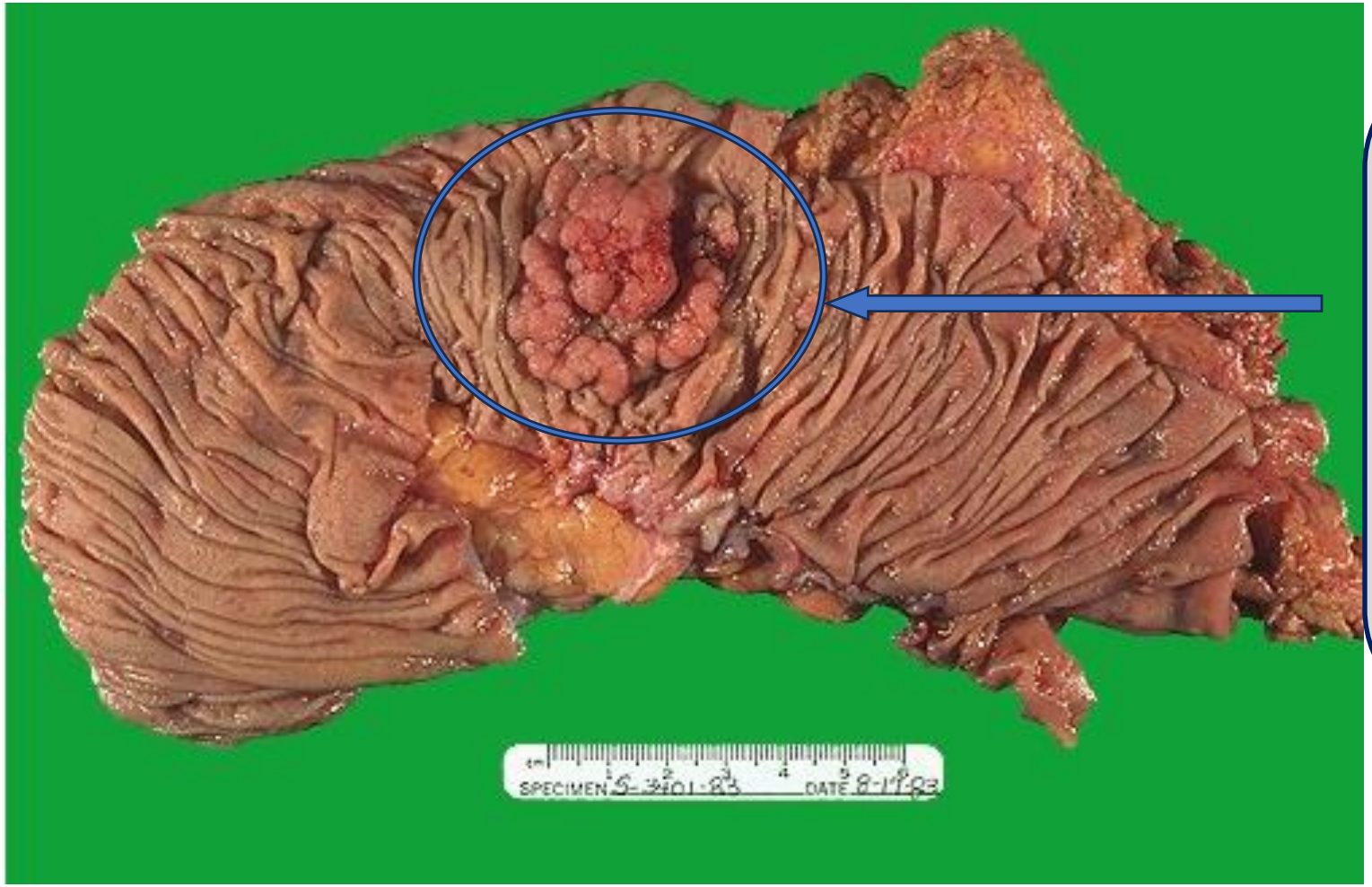
Napkin ring

This is napkin ring appearance which is described for tumours in distal colon that causes narrowing with obstructive symptoms

Recto-sigmoid adenocarcinoma, napkin ring

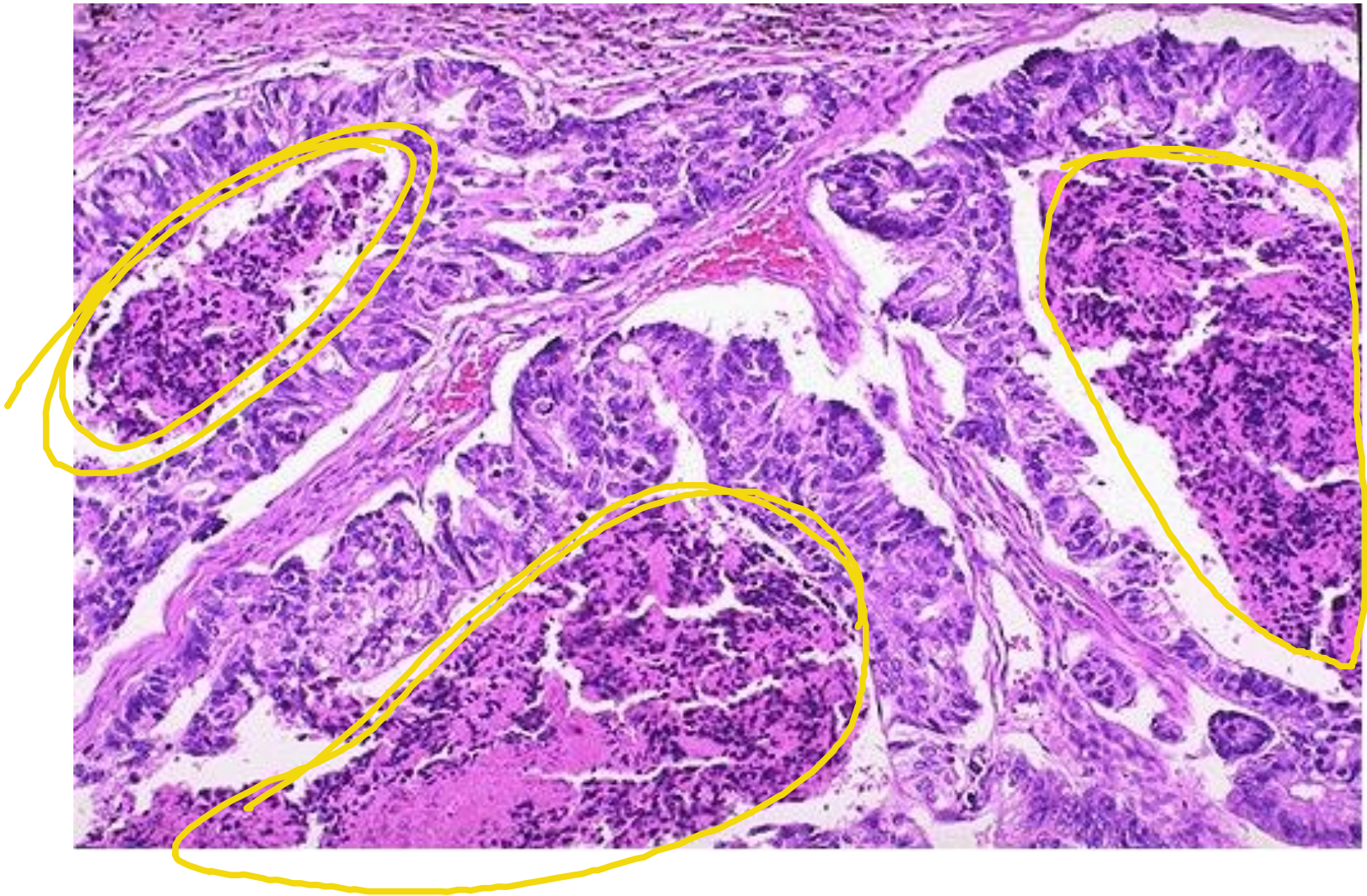


Exophytic adenocarcinoma



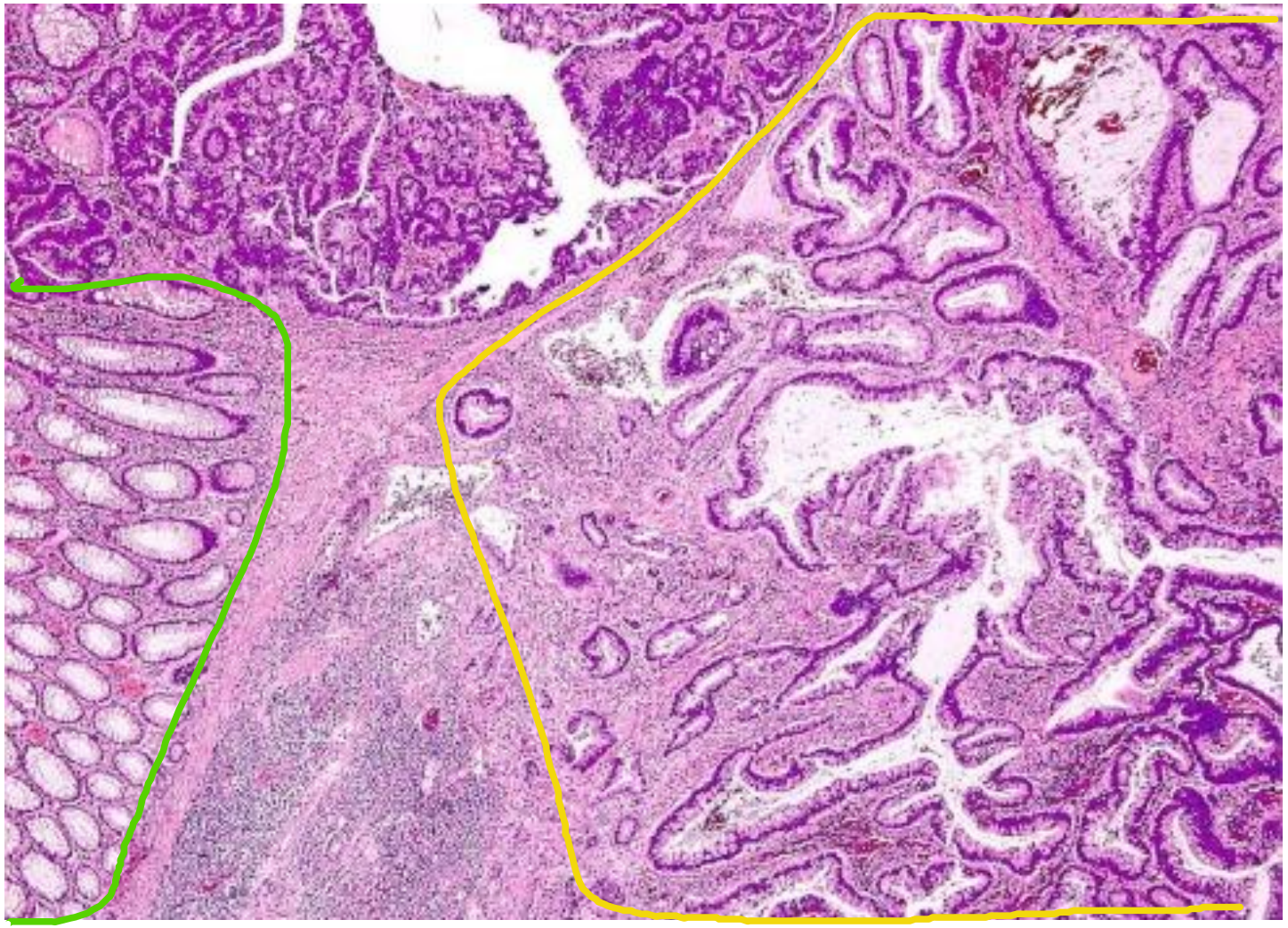
Mass projecting to the lumen of the bowl ,would cause partial obstruction not because mostly they occurs in the vacuum which has large diameter

Adenocarcinoma with necrosis



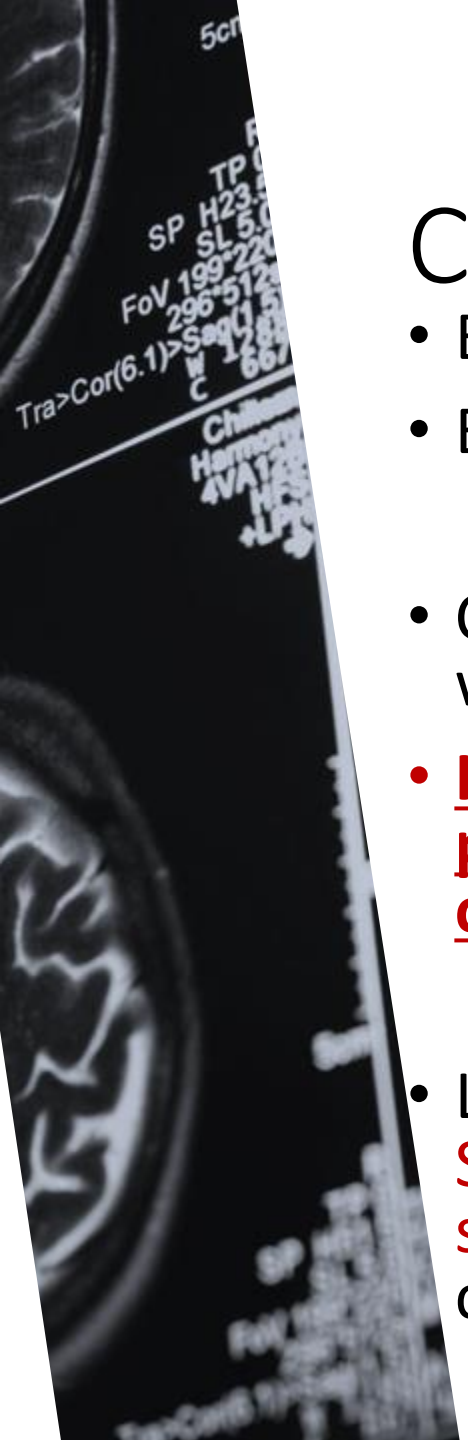
dirty necroses in the center of the dysplastic gland.

Invasive carcinoma



Normal crypts of the colon.

dysplastic invasive component.



Clinical Features

- Endoscopic screening >> cancer prevention
- Early cancer is asymptomatic !!!!!!!!

especially in patients with a family history of colon cancer

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 secret cancers, they present with prolonged blood loss leading to iron deficiency

- Left sided carcinomas: occult bleeding, Sometimes it presents with obstructive symptoms , changes in bowel habits, cramping left lower-quadrant discomfort.

Occulted bleeding is invisible bleeding that the patient will not notice, needs Laboratory investigations, because it is a chronic low volume of blood loss, this can lead also to iron deficiency anemia.

Prognosis:

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

T N M staging classification.
T : to the depth of invasion,
N applies: lymph node metastasis.

Solitary metastases in these sites can be detected by surgery, microsatallite instability is detected by immunohistochemical staining for the DNA mismatch repair gene mutations.

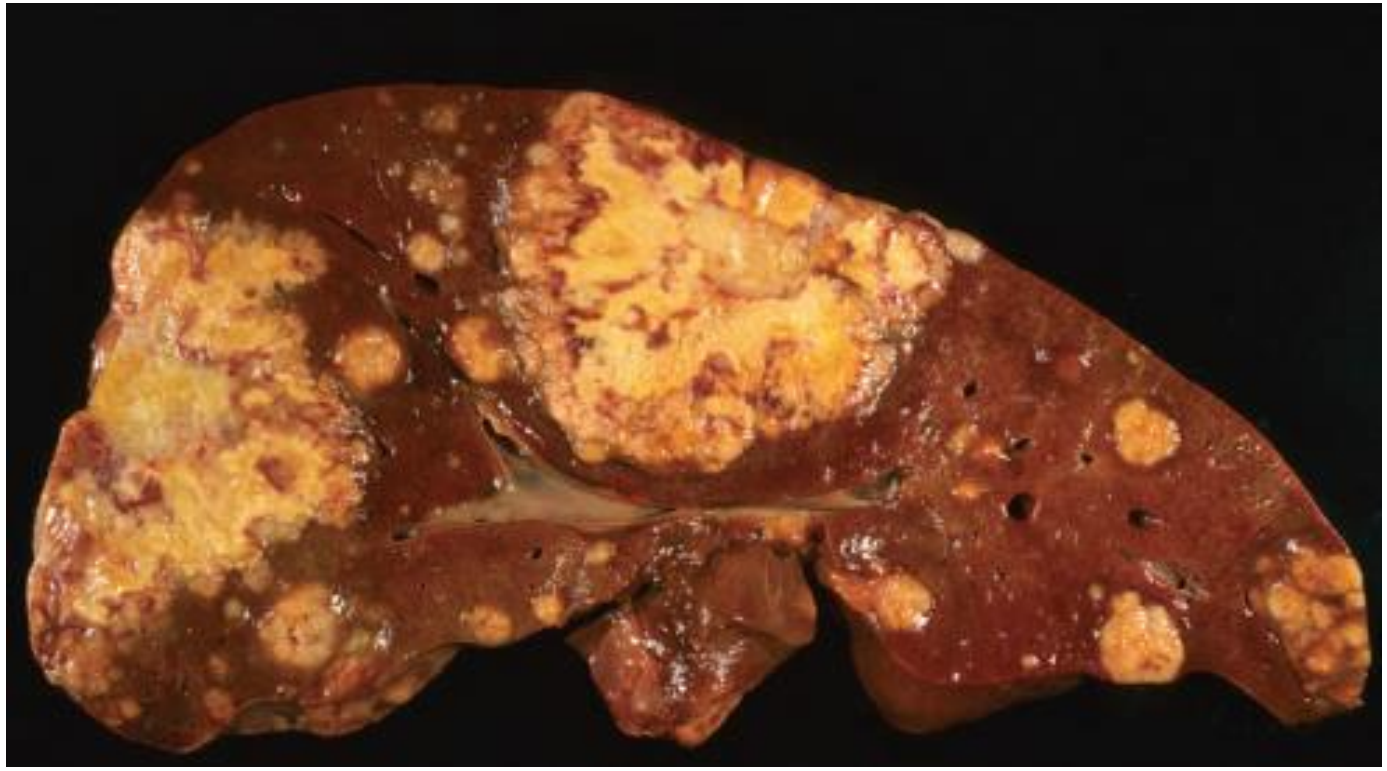
- Poor differentiation under microscope and mucinous histology >> poor prognosis
- ***Most important two prognostic factors are***

1. ***Depth of invasion (mucosa, submucosa, MP*** musculoskeletal propria ***, serosa)***
2. ***Lymph node metastasis*** the second most important prognostic factor***. (needs Rx*** radiotherapy ***and Chemox*** chemotherapy***)***

In addition other factors are important for prognosis***:***

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

Patients that have microsatallite instability or loss of these DNA mismatch repair genes can use immune checkpoint inhibitor therapy, which is considered a targeted therapy.



This is a liver metastasis found to yellow-colored in a patient with colon cancer

Liver metastasis.

Appendix diseases:

- Normal true diverticulum of the cecum

diseases of the appendix.

- ACUTE APPENDICITIS

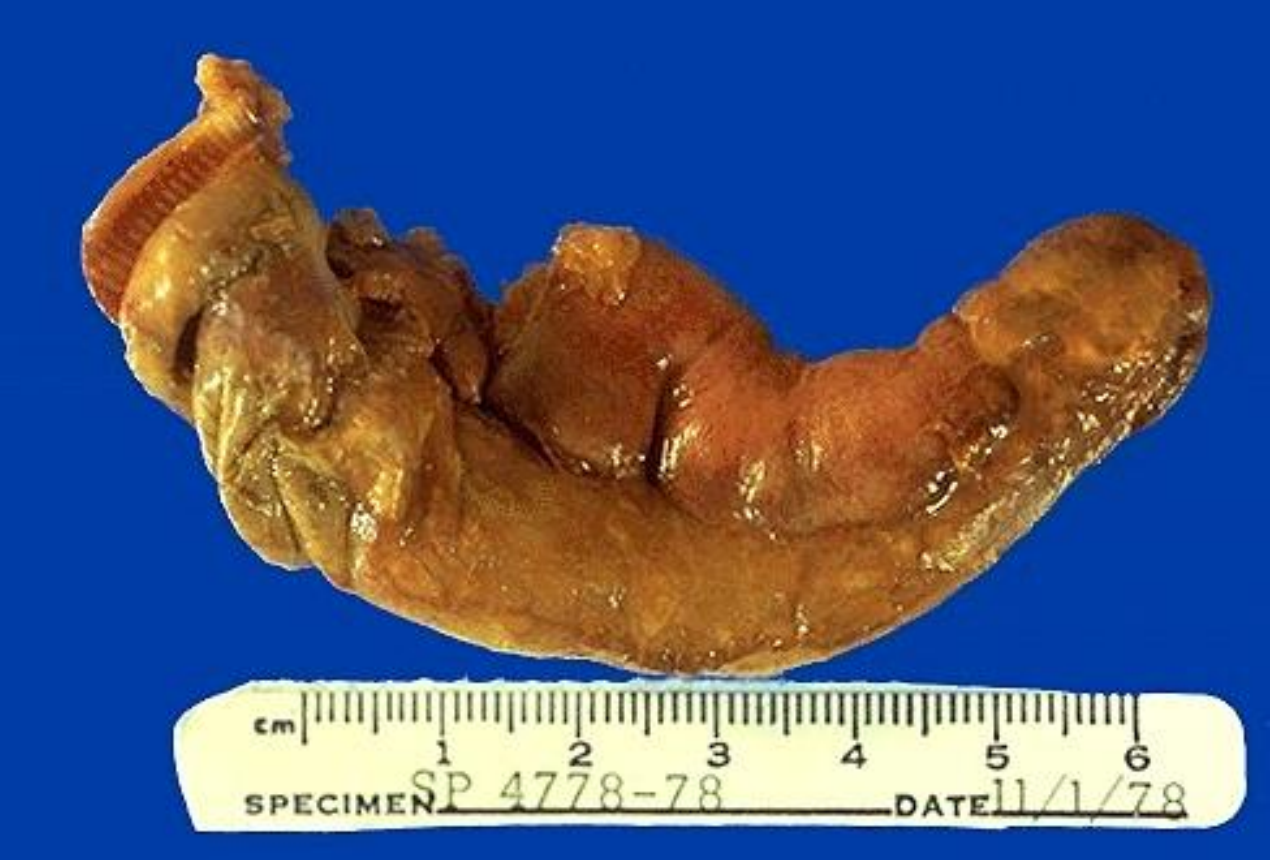
Number one

- TUMORS OF THE APPENDIX

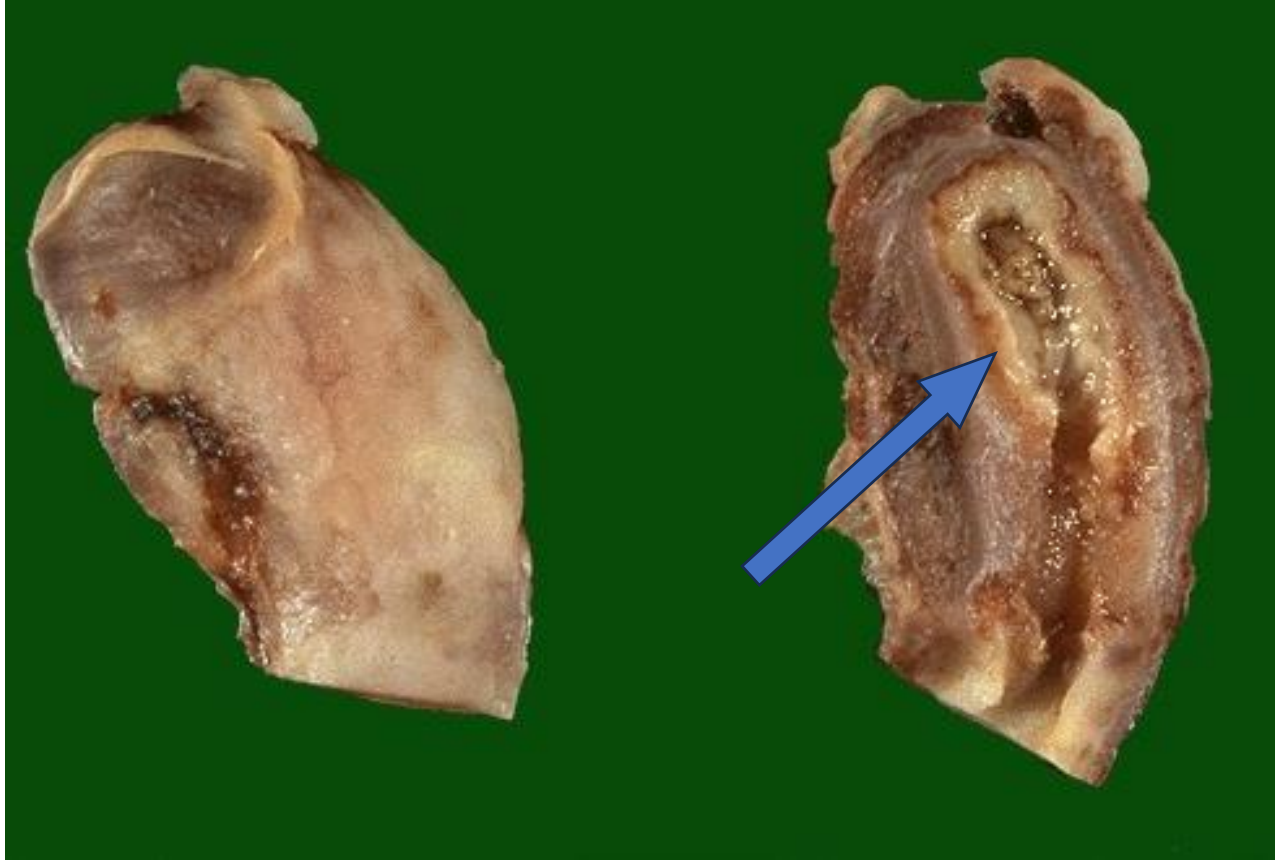
Not common.

ACUTE APPENDICITIS

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

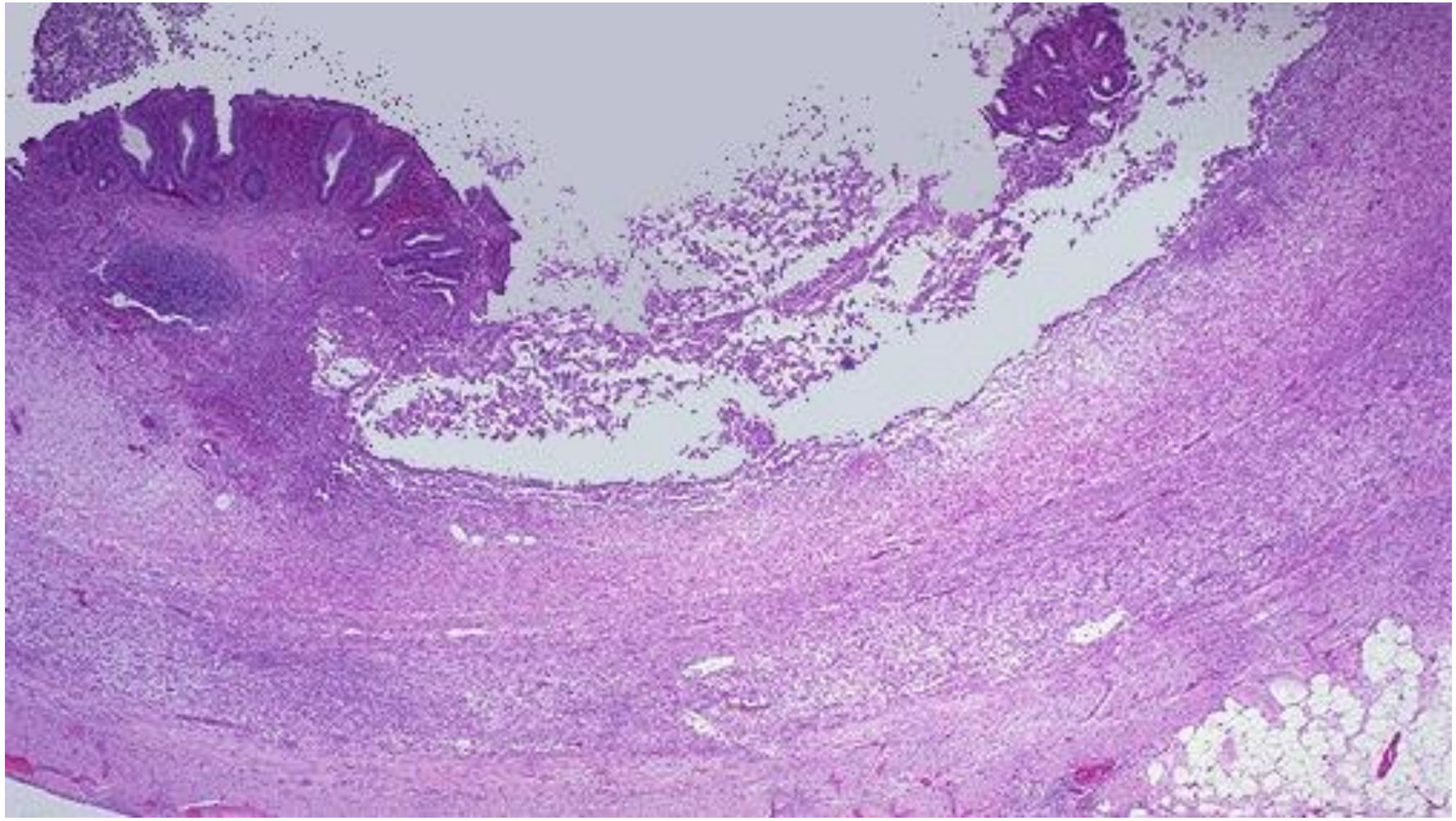


normal appendix with glistening serosal surface



appendix with acute appendicitis. This serosal is dusty and covered by yellowish exudates(left), and even the mucosa here also is covered by a yellowish exudate(right)

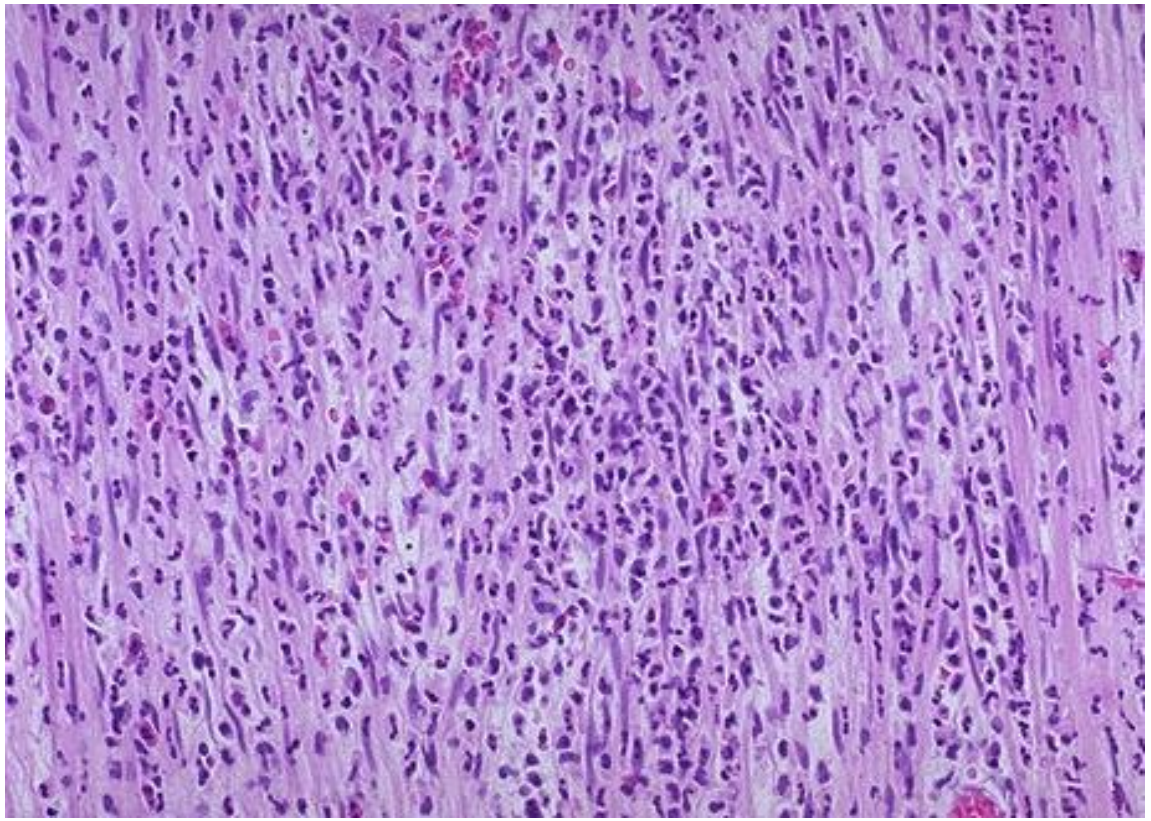
Normal appendix versus acute appendicitis



In order to diagnose appendicitis, we need to confirm histopathological infiltration of the muscle wall or the musculoskeletal propria by a neutrophils

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.

من الطبيعي أحيانا أن تتم عملية استئصال و تكون الزائدة طبيعية و غير ملتهبة ، و هناك نسبة مسموح فيها لحصول هذا الخطأ خاصة و أن التهاب الزائدة خطير فقد تنفجر و ينتشر الالتهاب

DDx of acute appendicitis:

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

When a female patient complained a acute abdominal pain, suspecting acute appendicitis firstly, you should exclude gynecologic causes of abdominal pain..

- Mesenteric lymphadenitis, usually follows an upper respiratory tract infection, children, and females of the 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 the ileocecal valve inflammation

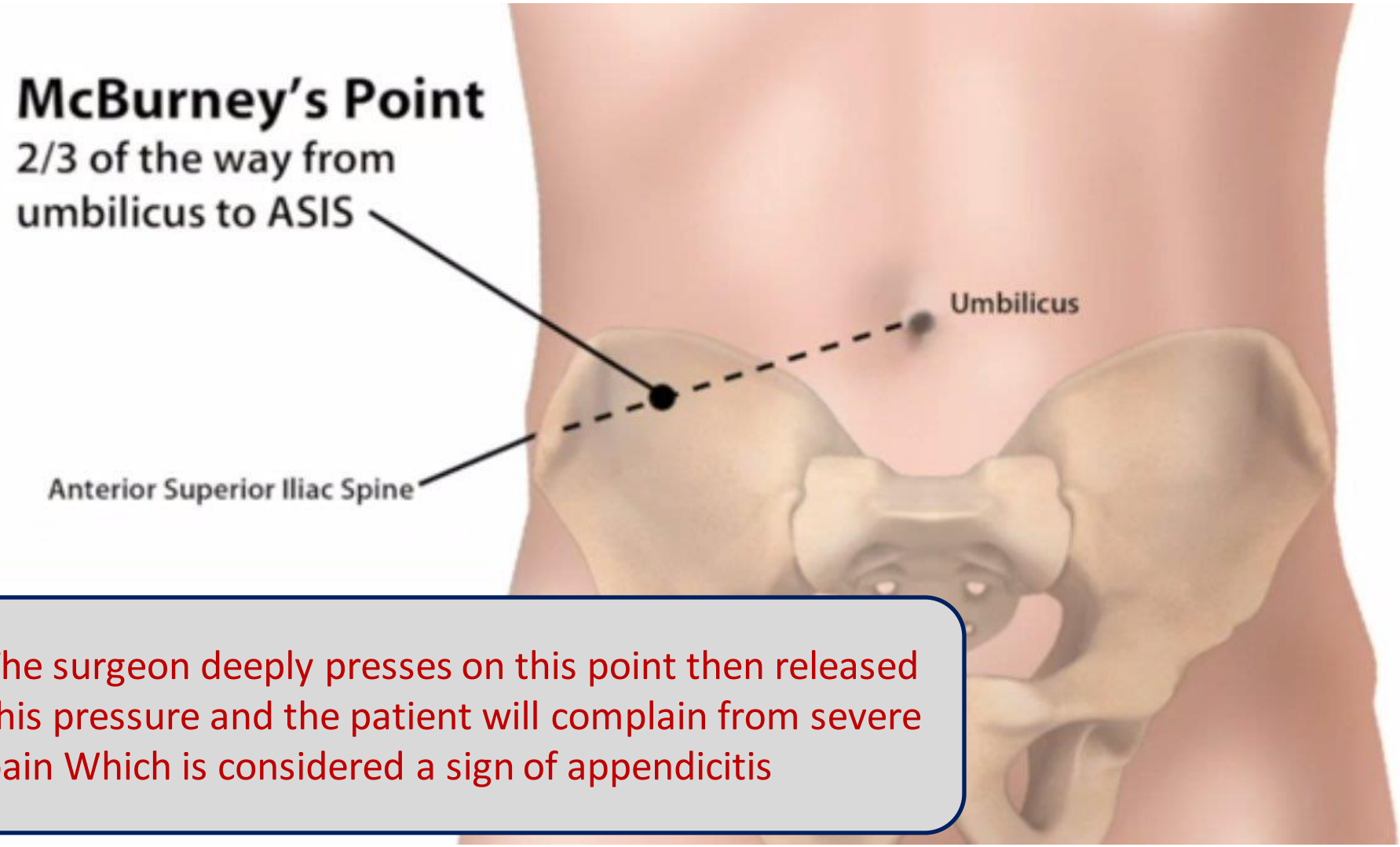
Pathogenesis:

- Increased luminal pressure >> impaired venous drainage >>decreased blood supply >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema of appendiceal wall
- Luminal obstruction in 50-80% of cases by fecalith (small mass-like stone of stool), less commonly caused by: 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 and enteritis.**

Clinical Features

- Early acute appendicitis:comes periumbilical pain which is not specific which is later on disappears then localised in the lower right quadrant
- Later: pain localizes to the right lower quadrant,
- Nausea, vomiting, low-grade fever, mildly leukocytosis elevated white blood cells .
- A classic physical finding is *McBurney's sign* (McBurney's point).
- Signs and symptoms are often absent, creating difficulty in clinical diagnosis.



The surgeon deeply presses on this point then released this pressure and the patient will complain from severe pain Which is considered a sign of appendicitis

TUMORS OF THE APPENDIX

- **The most common tumor: *carcinoid* (neuroendocrine tumor)**

similar to the tumor we talked about in the stomach, which is a neuroendocrine tumor.

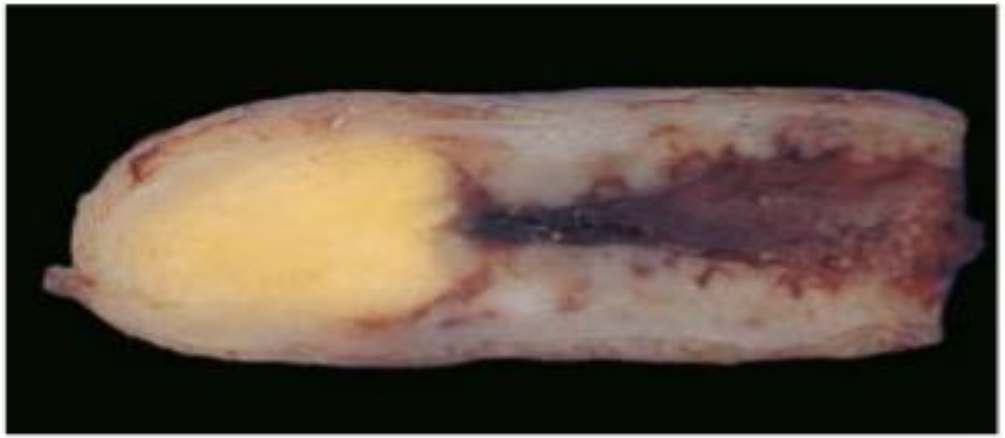
- Incidentally found during surgery or on examination of a resected appendix
- The most common location Distal tip of the appendix

These tumors behave in an indolent fashion with a good Prognosis because

- Nodal metastases & distant spread are rare.

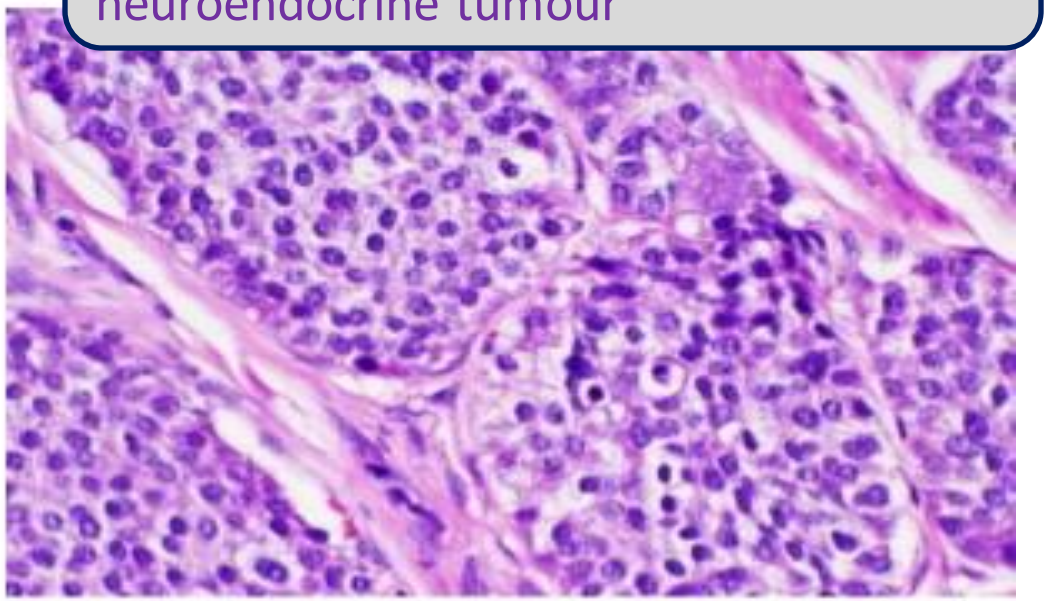
Carcinoid tumor

On the tip of the appendix with yellow discoloration



Gross

This tumour shows Nesting pattern with salt and pepper Chromatin typical for A neuroendocrine tumour



Microscopic

E learning activity

- A 70-year-old previously healthy man notes blood-streaked stool for the past 2 days. On physical examination his stool is positive for blood. There is no abdominal tenderness, and bowel sounds are active. A colonoscopy is performed, and there is an area of obstruction from an encircling mass with superficial ulceration that is located at 20 cm above the anal verge. Which of the following risk factors was most likely to have been present for development of this lesion?
- Celiac disease
- High fat diet
- Diverticulosis
- Human papillomavirus infection

- Answer: high fat diet