Familial Syndromes

Adenomas → Dysplastic polyps which are considered pre-cancer.

- Syndromes associated with colonic polyps and increased rates of colon cancer
- Genetic basis.

They have genetic bases and pattern of inheritance.

- **Familial Adenomatous Polyposis (FAP)**
- **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**

also called Lynch syndrome.

Not true as HNPCC has polyps but there is no polyposis's. Less polyps than FAP.

Familial adenomatous polyposis FAP

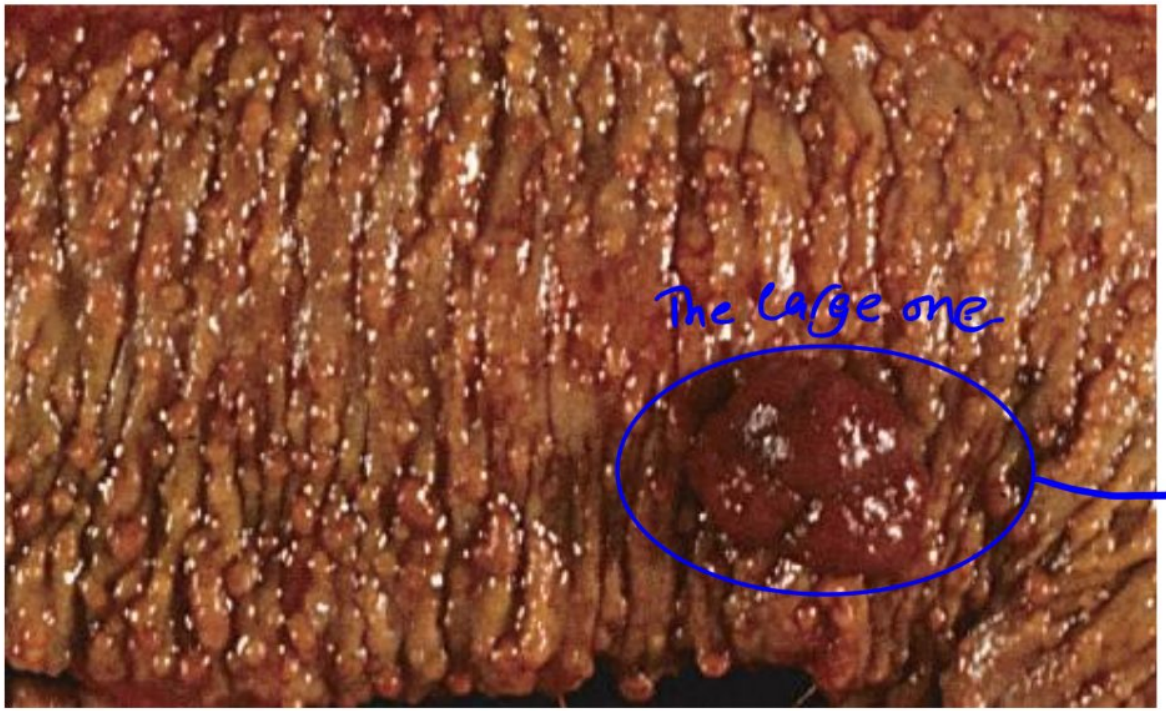
- Autosomal dominant.
- Numerous colorectal adenomas: teenage years. They have more than 100 adenomas.
- Mutation in APC gene.
- At least 100 polyps are necessary for a diagnosis of classic FAP. without 100 polyps we can't say that it's FAP.
- Morphologically similar to sporadic adenomas Adenomas with age.
- 100% of patients develop colorectal carcinoma, IF UNTREATED, often before age of 30.
- Standard therapy: prophylactic colectomy before 20 Year of age.
- Risk for *extraintestinal manifestations*, not just colorectal cancer.

- Variants of FAP: Gardner syndrome and Turcot syndrome.

- **Gardner syndrome**: intestinal polyps + osteomas (mandible, skull, and long bones); epidermal cysts; desmoid and thyroid tumors; and dental abnormalities.
  - → begin bone tumor.
  - ↳ in skin
- **Turcot syndrome**: intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)

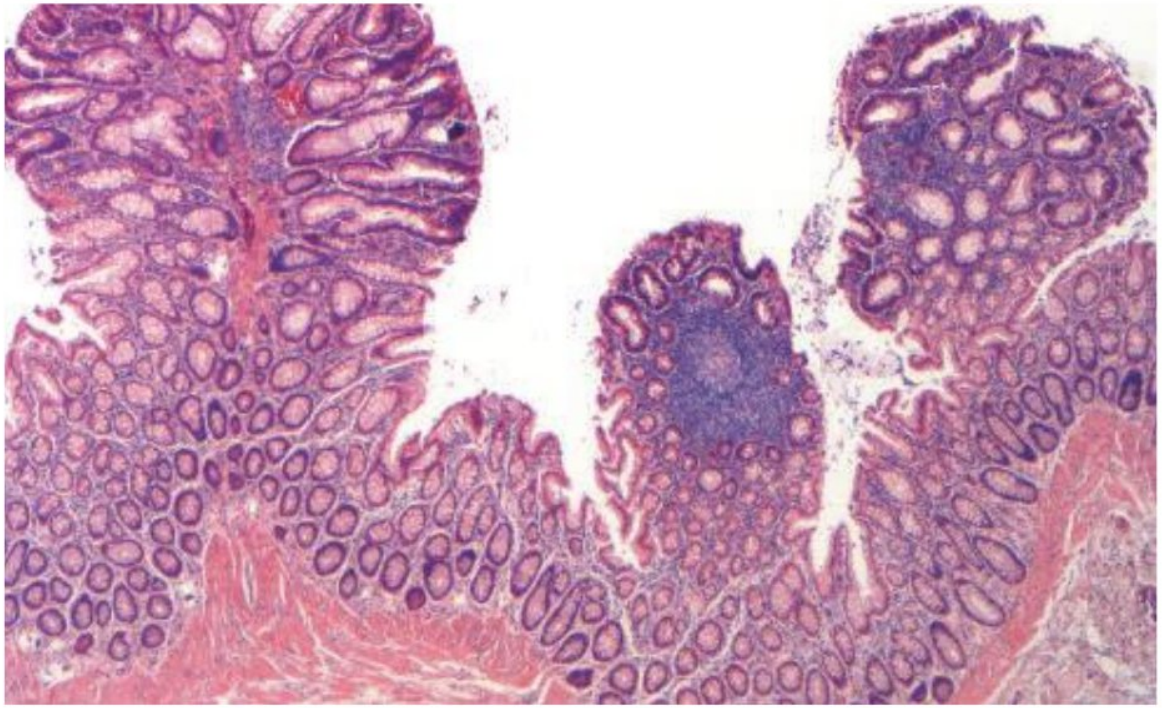
The colon is like it's filled with polyps.

الدكتورة قالت حرفيا بلا polyps



Here there are 100 of small polyps and one large polyp

Polyps project above normal level of mucosa.



Hereditary Nonpolyposis Colorectal Cancer: HN*PCC*, L*ynch syndrome*

- Clustering of tumors: **Colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin**
- Colon cancer at younger age than sporadic cancers
- Right colon with excessive mucin production .
- Adenomas are present, BUT POLYPOSIS IS NOT.

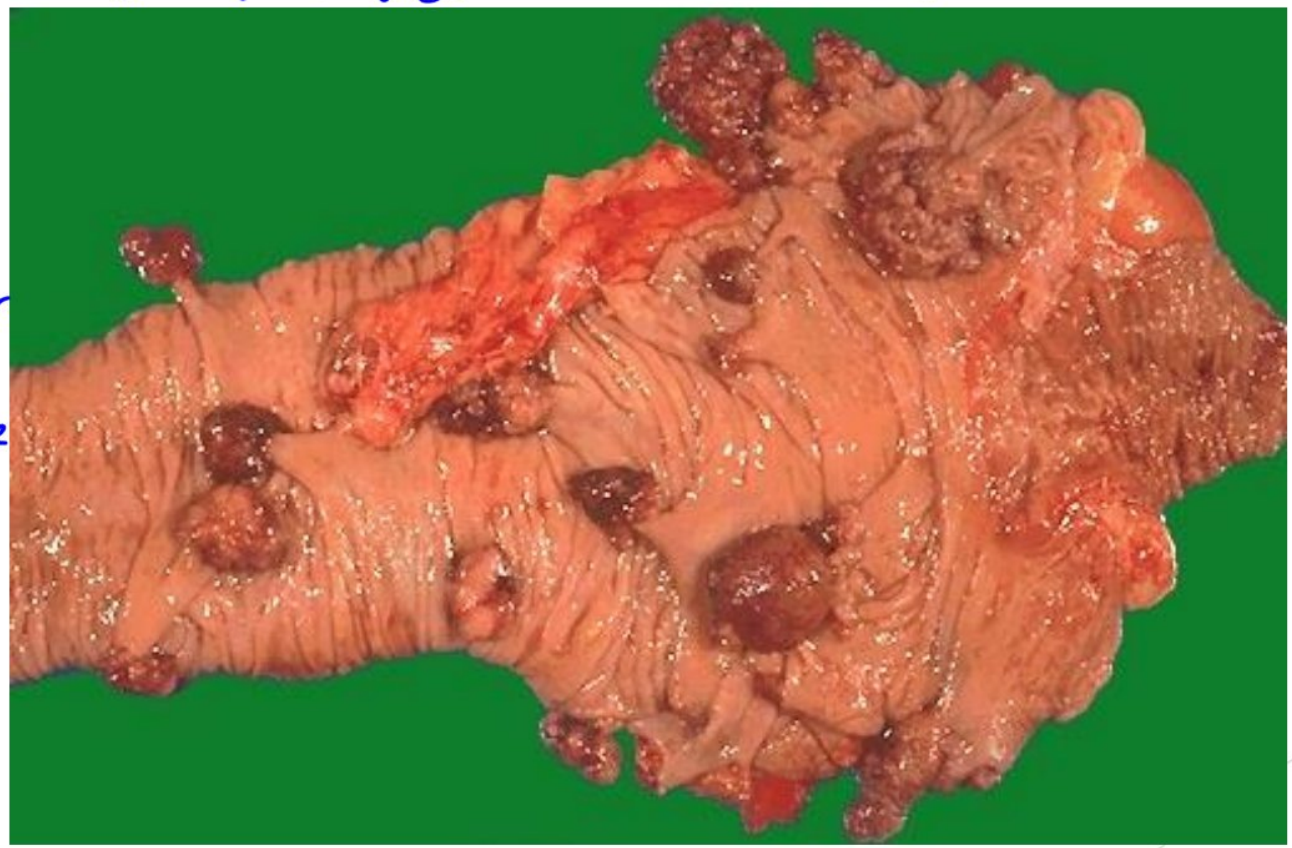
Usually colon cancers are found in old people, so when we see case under 50 years, we should think about familial syndrome.

- **Inherited germ line mutations in DNA mismatch repair genes**
- Accumulation of mutations in *microsatellite DNA (short repeating sequences)*
- Resulting in *microsatellite instability*
- Majority of cases involve either *MSH2* or *MLH1*.

genes that correct any mistake could happen during DNA replication.

Cecal polyps in HNPCC.

you can see multiple polyps, but they are not like the carpet of polyps that found in FAP.



That part is the cecum as it has larger diameter than the rest of the colon.

هذا الجزء يعني من بين عمره بالاربعينات و right colon بشو بتفكر جزيرة؟ HNPCC لتطورين؟

Small and Large Intestinal pathology, part 4

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Colonic Adenocarcinoma

colon cancer are the most common cancers in GI.

- Most common malignancy of the gastrointestinal tract
- Small intestine is uncommonly involved by neoplasia.
- Peak: 60 to 70 years older age group.
- 20% under 50 years. when age is <50 think about hireclitiry → but it can be NOT!
- Developed countries lifestyles and diet. Low vegtebles intake and high carbs. Fat, reed meat diet increases the risk of cancer.
- **Low intake of vegetable fiber and high intake of carbohydrates and fat.**
- Aspirin or other NSAIDs have a protective effect.
- Cyclooxygenase-2 (COX-2) promotes epithelial proliferation.
  - when it's inhibited by NSAIDs or Aspirin, the proliferation will be prevented.

Pathogenesis

- Heterogeneous molecular events. it's Not a single mutation, it is multiple mutation.
- Sporadic >>>> familial.
- **Two pathways:**
- 1st **APC/β-catenin pathway >> increased WNT signaling**
- 2nd **Microsatellite instability pathway due to defects in DNA mismatch repair**

They are the same mutations that happen in familial syndromes. but here they are sporadic.

- Stepwise accumulation of multiple mutations

The APC/B-catenin pathway: chromosomal instability

- Classic *adenoma carcinoma sequence*. begins as adenoma then develops to carcinoma.
- *80%* of sporadic colon tumors
- Mutation of the *APC* tumor suppressor gene: EARLY EVENT
- *APC is a key negative regulator of B-catenin, a component of the WNT signaling pathway.*
- *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).* That takes many time to happen → so it happens at high age.

To be cancer

As it's a tumor suppressor gene it's had to be inactivated, so the mutation is inactivation mutation.

As APC negative regulator for B-catenin ⟹ No APC ⟿ high B-catenin level.

- *Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >>* promote proliferation.
- Additional mutations >> activation of KRAS *oncogene (LATE EVENT)*
- *SMAD2* and *SMAD4 mutations (tumor suppressor genes.)*

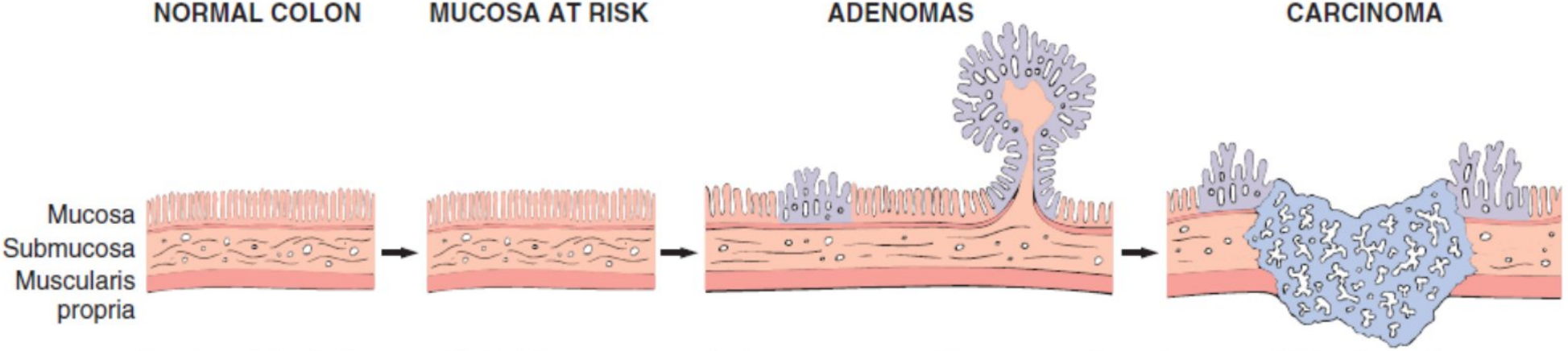
Important!

- ***TP53* is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**
- TP53 inactivation mutation
- Expression of telomerase also increases as the tumor advances.

An enzyme in cells that helps keep them alive by adding DNA to telomeres.

The doc asked if we know telomerase, then she said: mmmm.

بحس كانت تهز الها راسه، جبتها مشانكم ♡

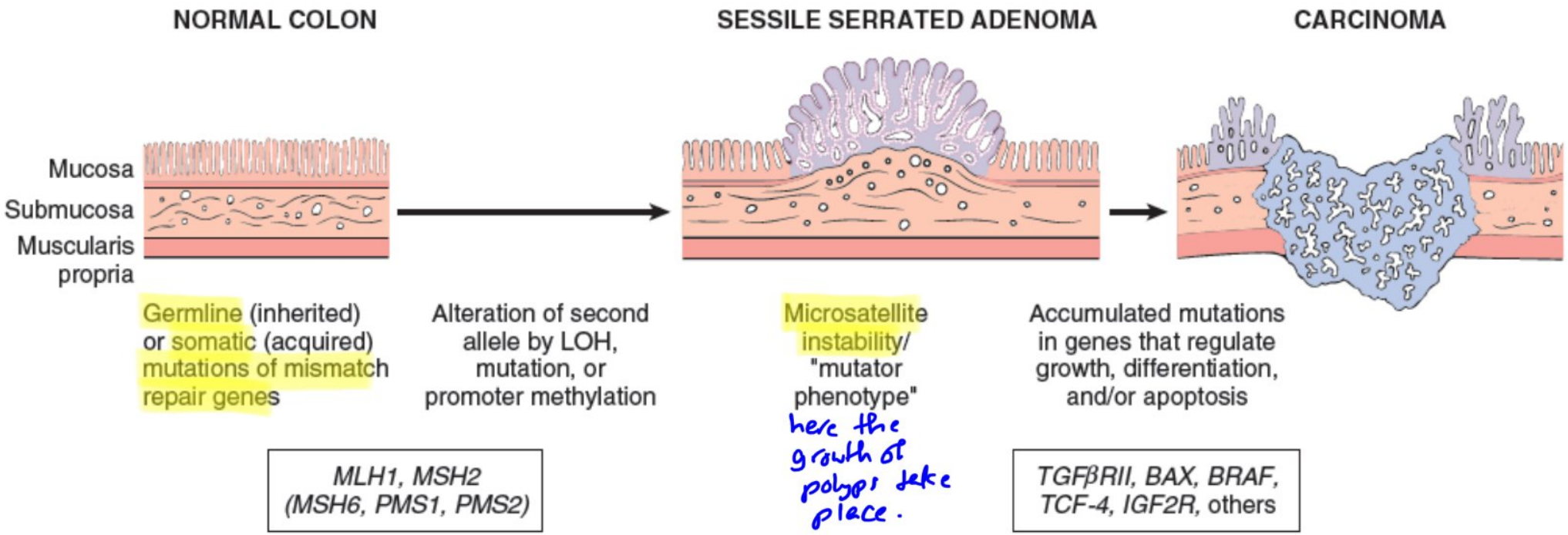

NORMAL COLON
MUCOSA AT RISK
ADENOMAS
CARCINOMA
Mucosa
Submucosa
Muscularis propria
Germline (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")
Methylation abnormalities
Inactivation of normal alleles ("second hit")
Protooncogene mutations
Homozygous loss of additional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

The microsatellite instability pathway

Here we have totally different story.

- DNA mismatch repair deficiency
- Loss of mismatch repair genes
- Mutations accumulate in microsatellite repeats
- *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)



here the growth of polyps take place.

Dr. said: Don't care about the names, Just know that there is mismach repair gene mutation.

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

usually cancers are masses, but they may be ulcer or lesion.

- Macroscopic:
- Proximal colon tumors: polypoid, exophytic masses
- Proximal colon: rarely cause obstruction. as its diameter is large!
- Distal colon: annular lesions "napkin ring" constrictions & narrowing

cecum

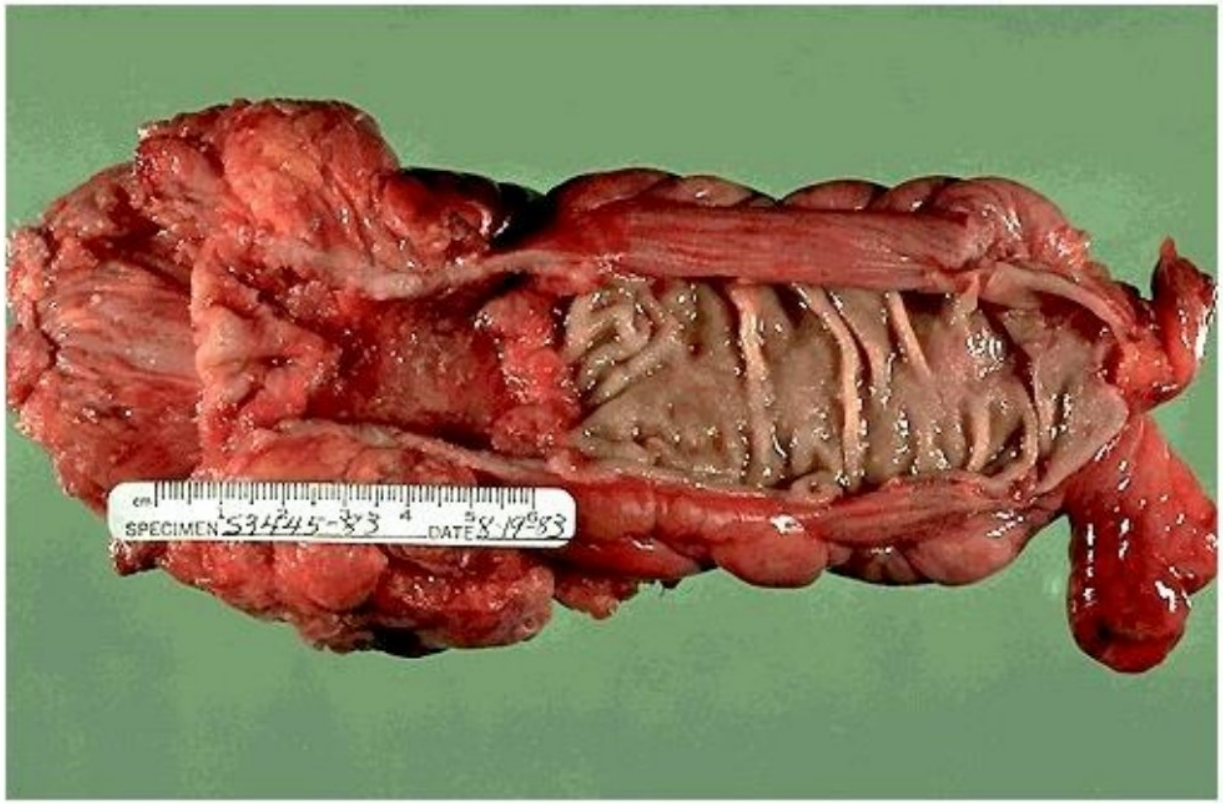
- Microscopic:
- Dysplastic GLANDS with strong desmoplastic response.
- Necrotic debris (dirty necrosis) are typical. necrotic debris = dead cells.
- Some tumors give abundant mucin or form signet ring cells.

Napkin ring

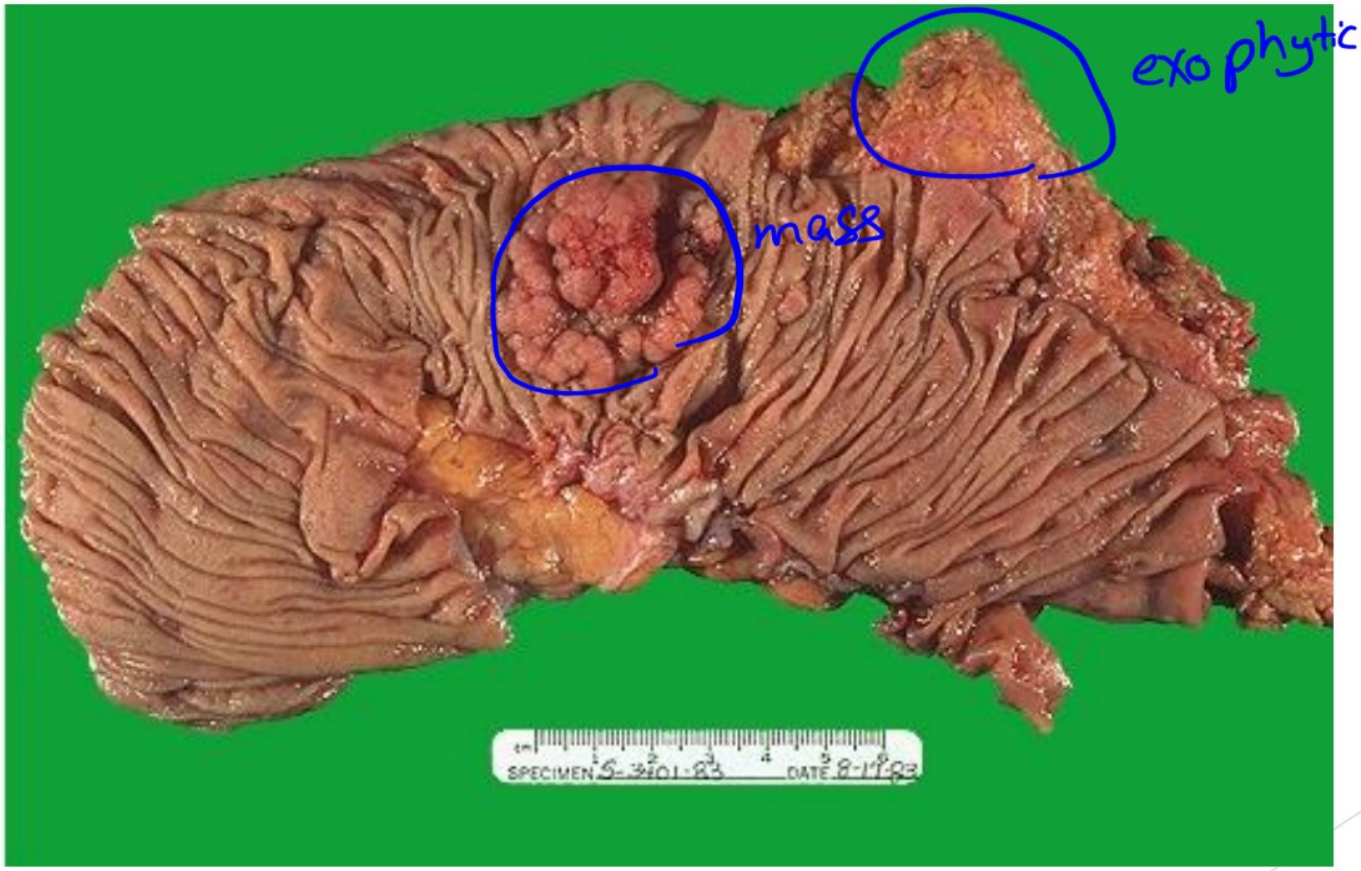
that is the tumor → the narrowing.

طبعًا بتكون بقولولك
مش بالشريط ده

Rectosigmoid adenocarcinoma, napkin ring

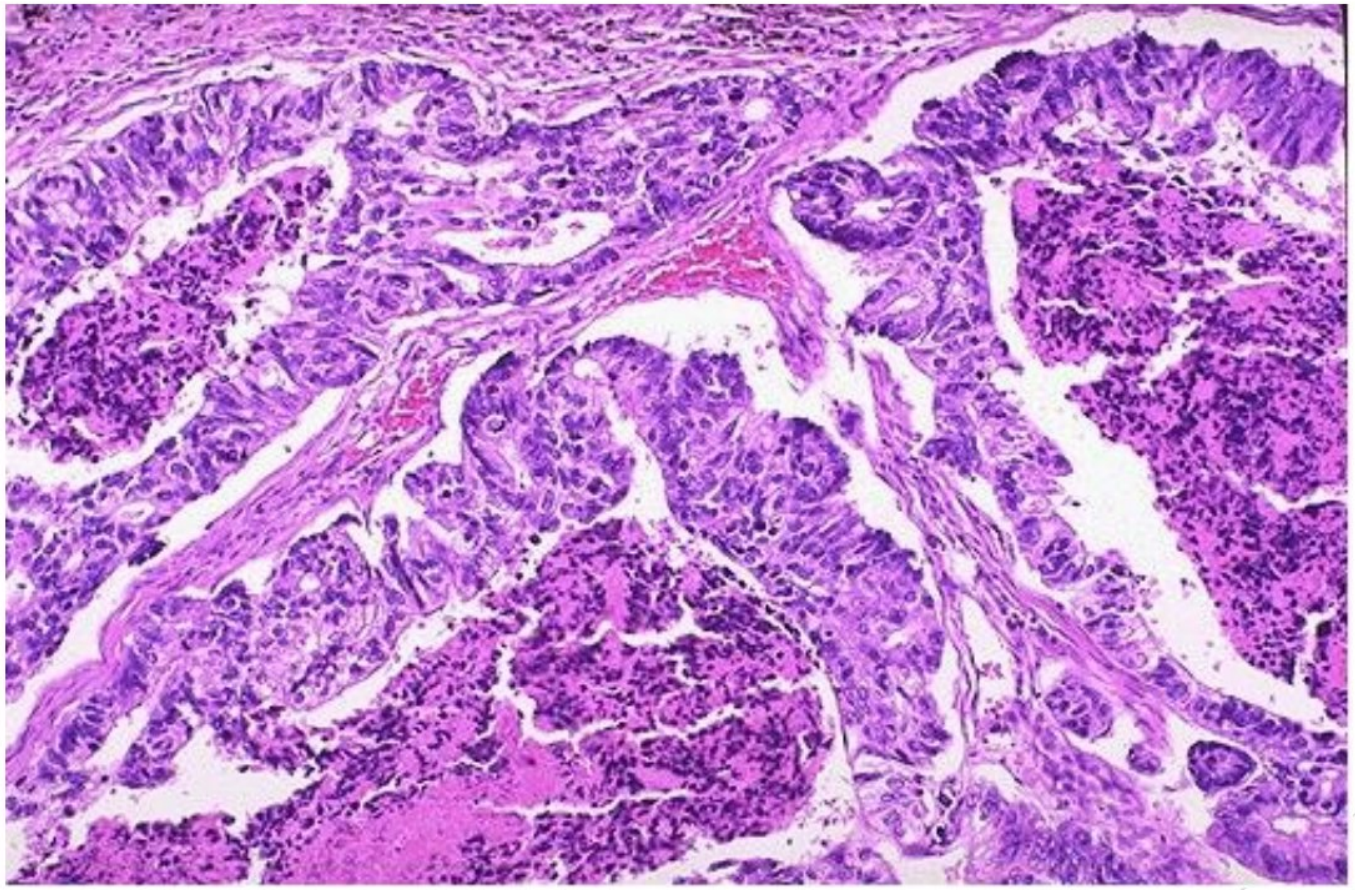


Exophytic adenocarcinoma

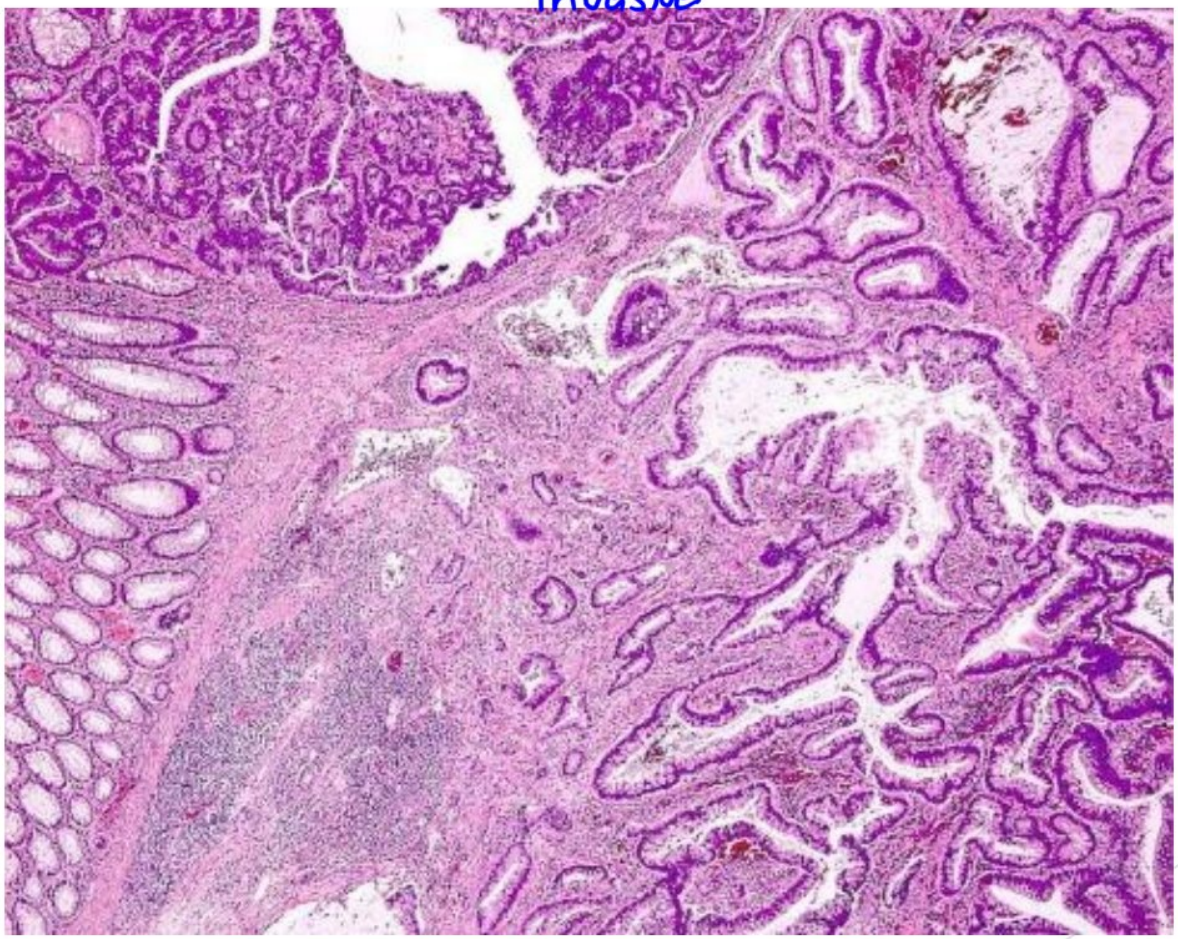


Adenocarcinoma with necrosis

Typically they have necrotic debris.



Invasive carcinoma → to say that is cancer, it have to be invasive



Clinical Features

important as they may be Asymptomatic

- Endoscopic screening >> cancer prevention
- Early cancer is asymptomatic !!!!!!!!
- Cecal and right side cancers: F*atigue and weakness (iron deficiency anemia)*
- **Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.**

50 or above

Colonoscopy is recommended here

- *Left sided carcinomas: occult bleeding, changes in bowel habits*, cramping left lower-quadrant discomfort.

as constipation.

we detect it by stool piopsy.

any patient comes with iron deficiency anemia with change in bowel habits

It is Colorectal cancer until proven otherwise.

[Stool for occult blood test] as there is any change on the color of stool.

What affect prognosis?

- Poor differentiation and mucinous histology >> poor prognosis
  - high grade.
- ***Most important two prognostic factors are:***
- ***Depth of invasion*** (1)
- ***Lymph node metastasis.*** (2)
- *Distant metastases (lung and liver) can be resected.*

Liver metastasis.

Liver with multiple metastatic foci.