Small and Large Intestinal pathology, part 4

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Colonic Adenocarcinoma

- Most common malignancy of the gastrointestinal tract
- Small intestine is uncommonly involved by neoplasia.
- Peak: 60 to 70 years
- 20% under 50 years.
- Developed countries lifestyles and diet.
- **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.

Pathogenesis

- Heterogeneous molecular events.
- Sporadic >>>> familial.
- **Two pathways:**
- **APC/ß-catenin pathway >> increased WNT signaling**
- **Microsatellite instability pathway due to defects in DNA mismatch repair**

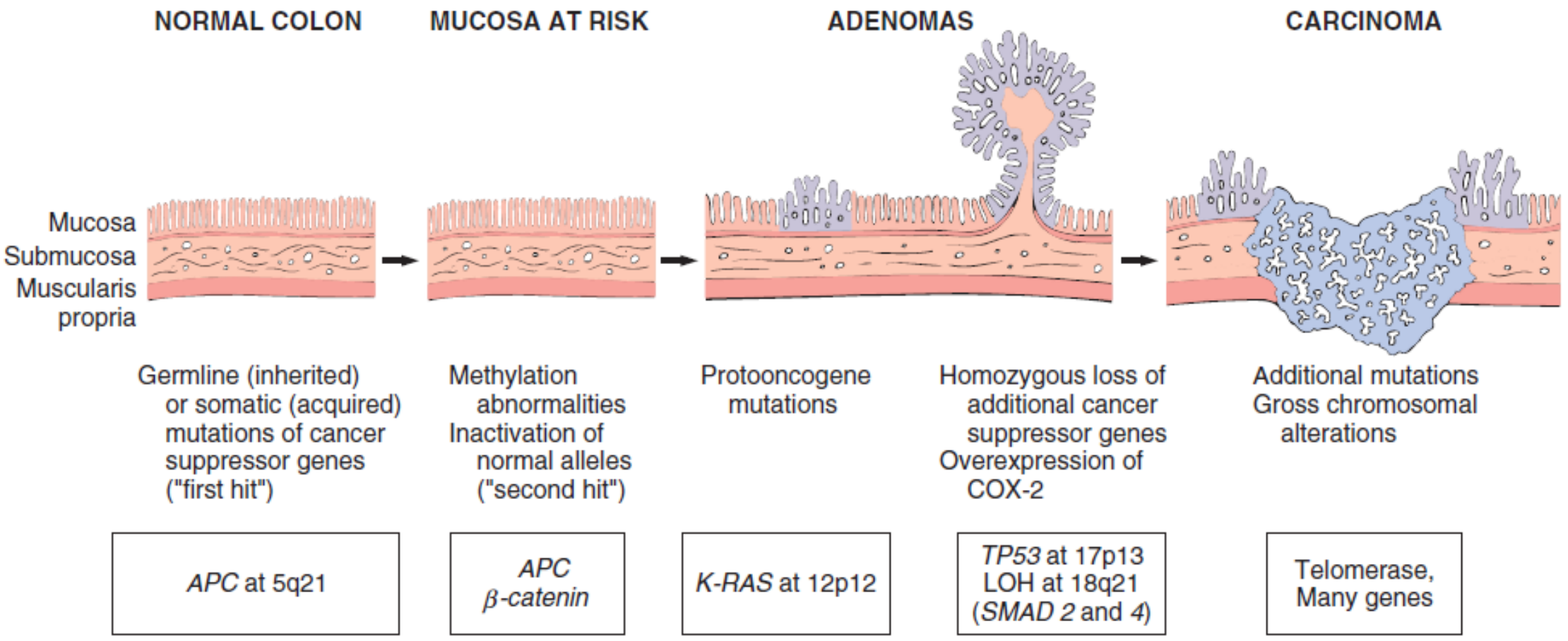
- Stepwise accumulation of multiple mutations

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, a component of the WNT signaling pathway.*
- *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).*

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

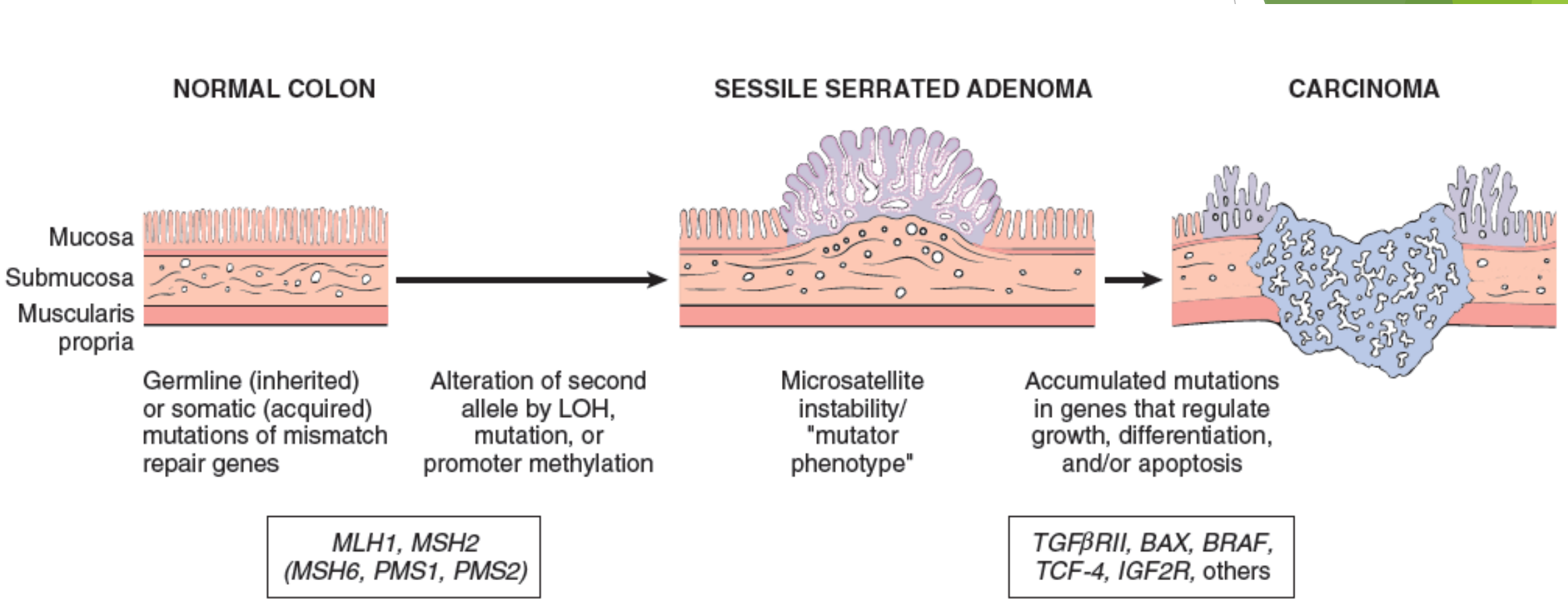
- ***TP53* is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)**
- TP53 inactivation mutation
- Expression of telomerase also increases as the tumor advances.


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
APC
β-catenin
K-RAS at 12p12
TP53 at 17p13
LOH at 18q21
(SMAD 2 and 4)
Telomerase,
Many genes

The microsatellite instability pathway

- 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)


NORMAL COLON
SESSILE SERRATED ADENOMA
CARCINOMA
Mucosa
Submucosa
Muscularis propria
Germline (inherited) or somatic (acquired) mutations of mismatch repair genes
Alteration of second allele by LOH, mutation, or promoter methylation
Microsatellite instability/ "mutator phenotype"
Accumulated mutations in genes that regulate growth, differentiation, and/or apoptosis
MLH1, MSH2 (MSH6, PMS1, PMS2)
TGFβRII, BAX, BRAF, TCF-4, IGF2R, others

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

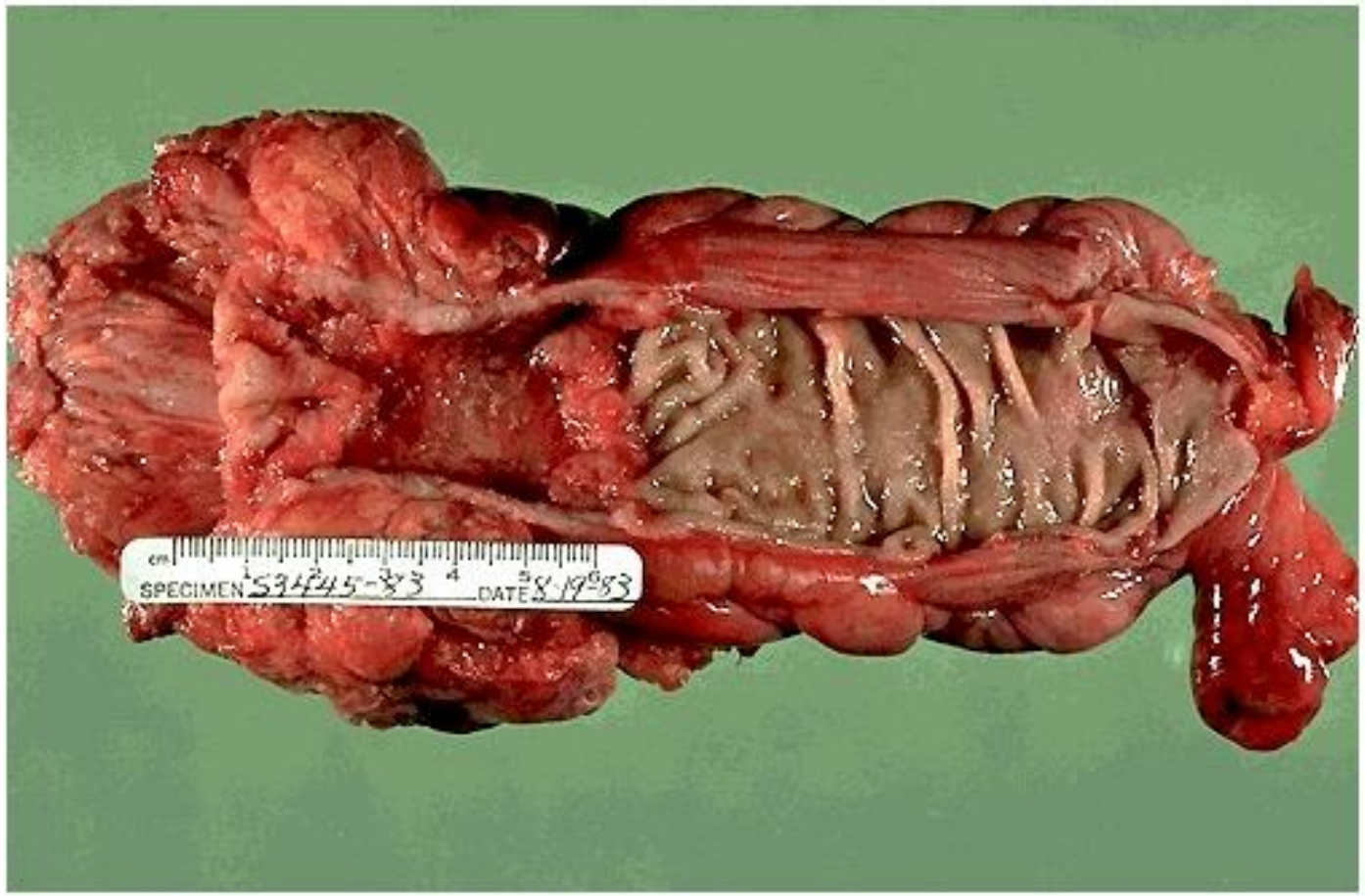
MORPHOLOGY

- Macroscopic:
- Proximal colon tumors: polypoid, exophytic masses
- Proximal colon: rarely cause obstruction.
- Distal colon: annular lesions “napkin ring” constrictions & narrowing

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

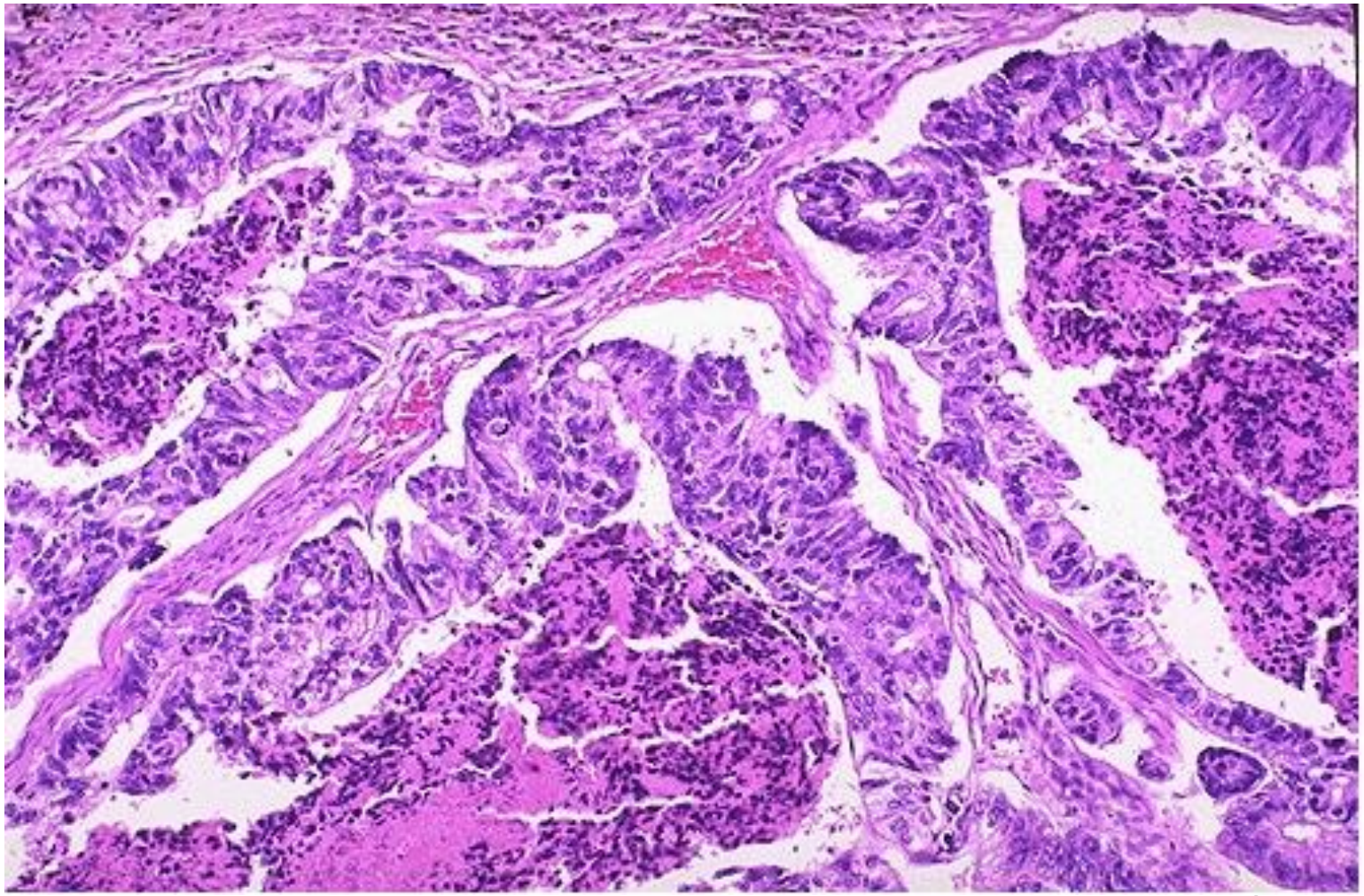
Napkin ring

Rectosigmoid adenocarcinoma, napkin ring

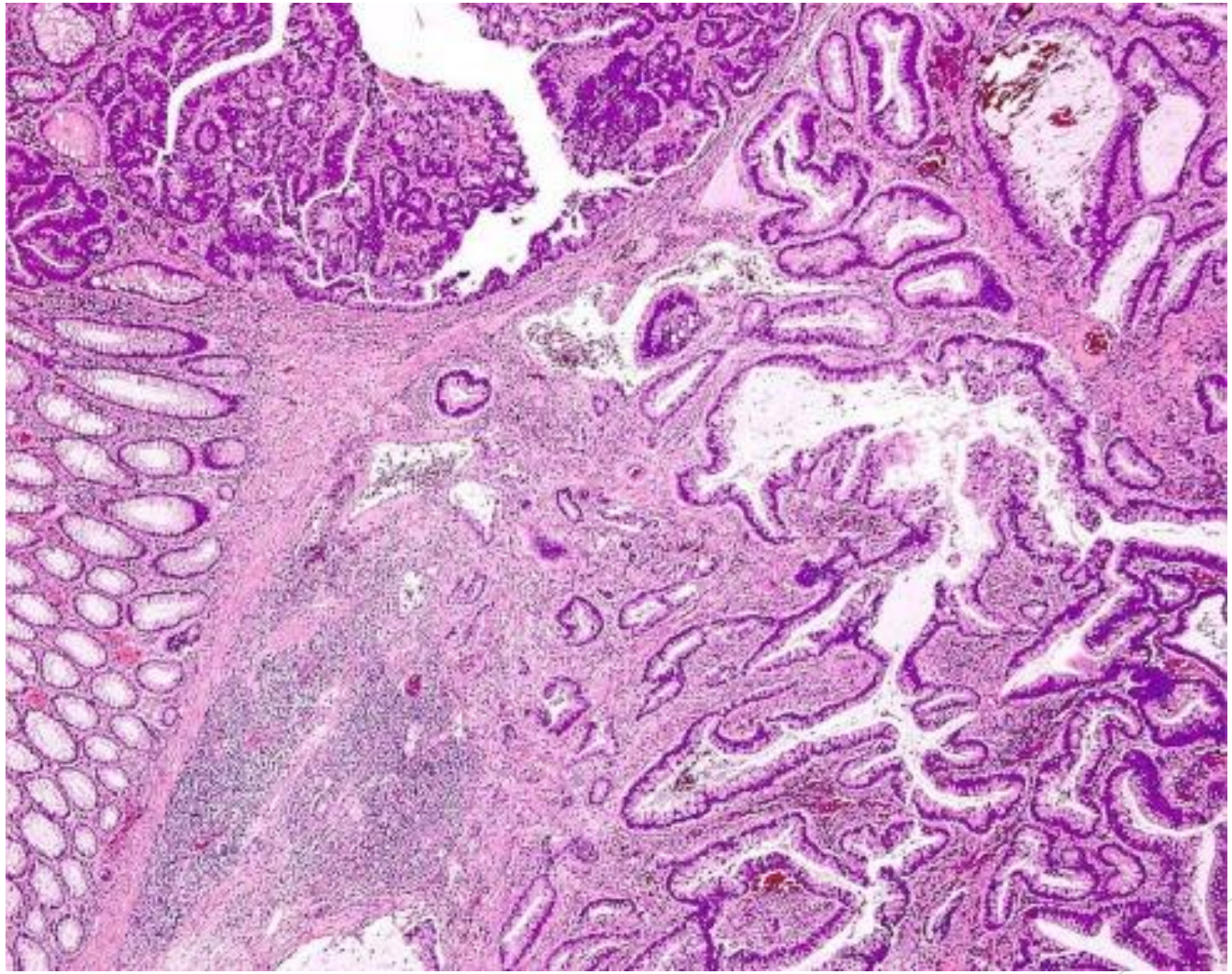


Exophytic adenocarcinoma

Adenocarcinoma with necrosis



Invasive carcinoma



Clinical Features

- 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.**

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

- Poor differentiation and mucinous histology >> poor prognosis

- ***Most important two prognostic factors are***
- ***Depth of invasion***
- ***Lymph node metastasis.***

- *Distant metastases (lung and liver) can be resected.*

Liver metastasis.