



HEREDITARY NONPOLYPOSIS
COLORECTAL CANCER
(HNPCC)
LYNCH SYNDROME

Hereditary Non-polyposis colorectal cancer (HNPCC)

- Autosomal dominant disorder.
- Molecular defect - DNA mismatch repair
- Target genes – MSH 2, MLH 1 on chr 2p16, p21
- Cancers at several sites
 - Colorectum
 - Endometrium
 - Stomach
 - Ovary
 - Uterus
 - Brain
 - Small bowel
 - Hepatobiliary
 - Skin



Features of CRC in HNPCC

- Young age
- Right –sided location
- Mucinous features
- Poor differentiation
- Lymphocytic infiltration
- Lack of necrosis

ADENOCARCINOMA

- 3rd most common cancer in both men & women.
- 2nd leading cause of death (1st is lung cancer).

RISK FACTORS :

- *AGE :most CRC occurs in people age of 50 & more.
- *DIET : High risk in red meat , processed meat .
lower risk in fruits , vegetables & fibre.
- *High risk in less physical activity , obesity ,
smoking , alcohol , type -2 Diabetes .

* High risk in IBD

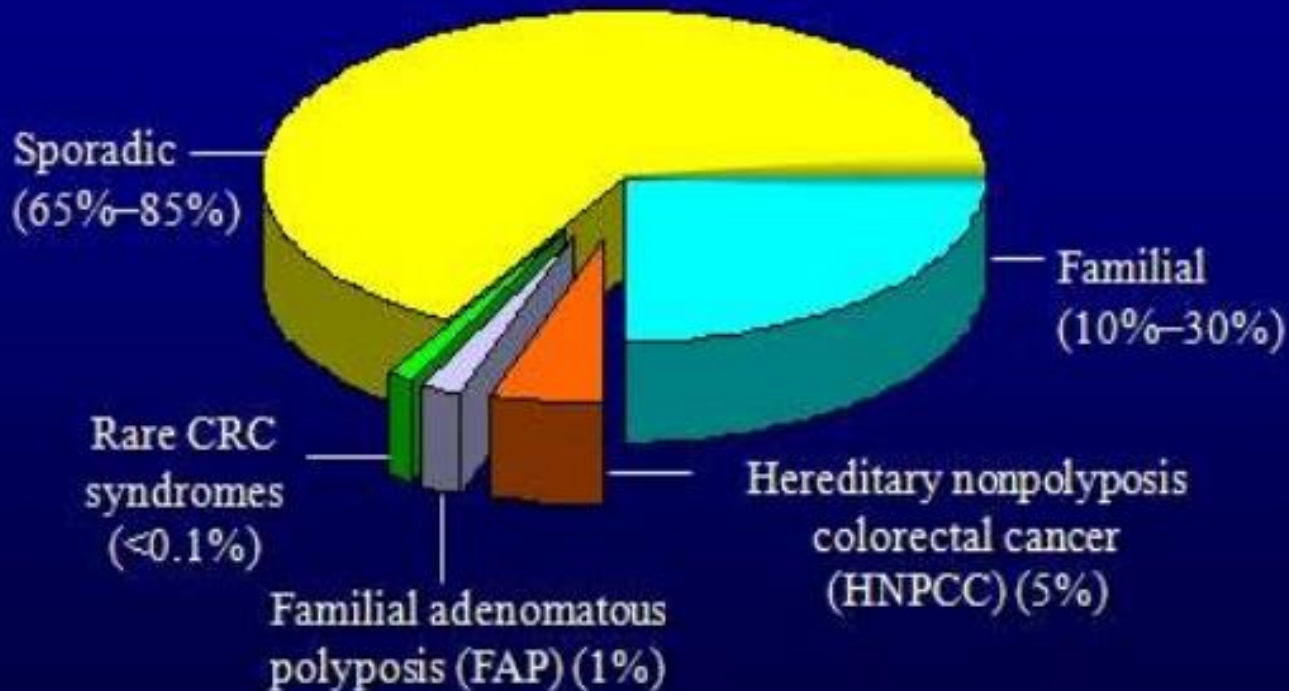
Ulcerative colitis & Crohn's disease
radiation to abdomen

adenomas

FAP

HNPCC

Causes of Hereditary Susceptibility to CRC



Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

PATHOGENESIS :

Two pathways:

1. APC/ β – catenin pathway.
 2. Microsatellite instability pathway.
- APC / β -catenin pathway :
 - classic adenoma-carcinoma sequence.
 - 80% sporadic colon cancer.
 - mutation in APC tumor suppressor gene.
 - both copies of APC gene must be functionally inactive.


- APC is a key negative regulator of β -catenin , a component of WNT signaling pathway.

- with loss of APC, β -catenin accumulates & translocated to nucleus & activates the transcription of gene.

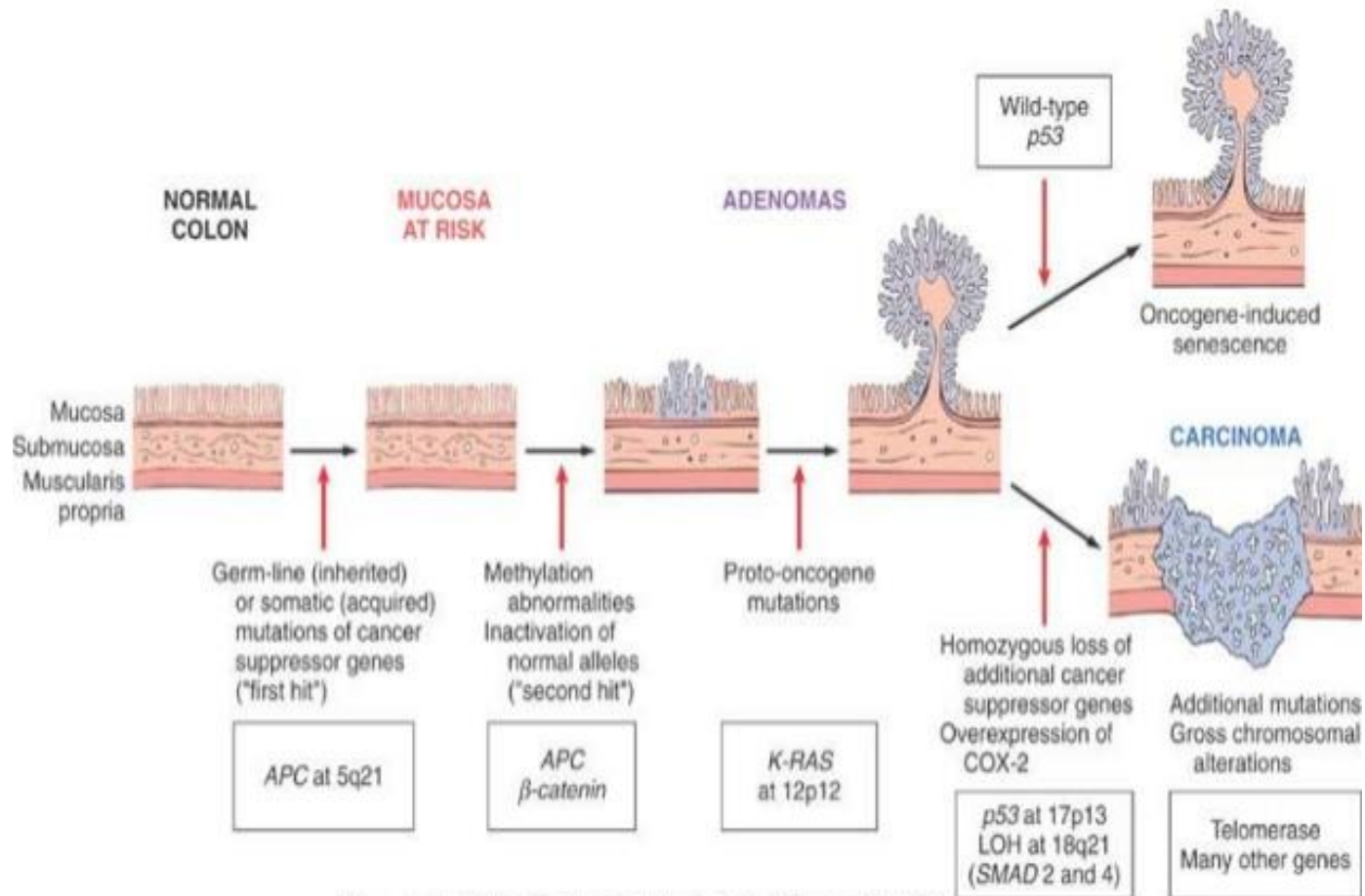
eg.- MYC & Cyclin D encoding genes.

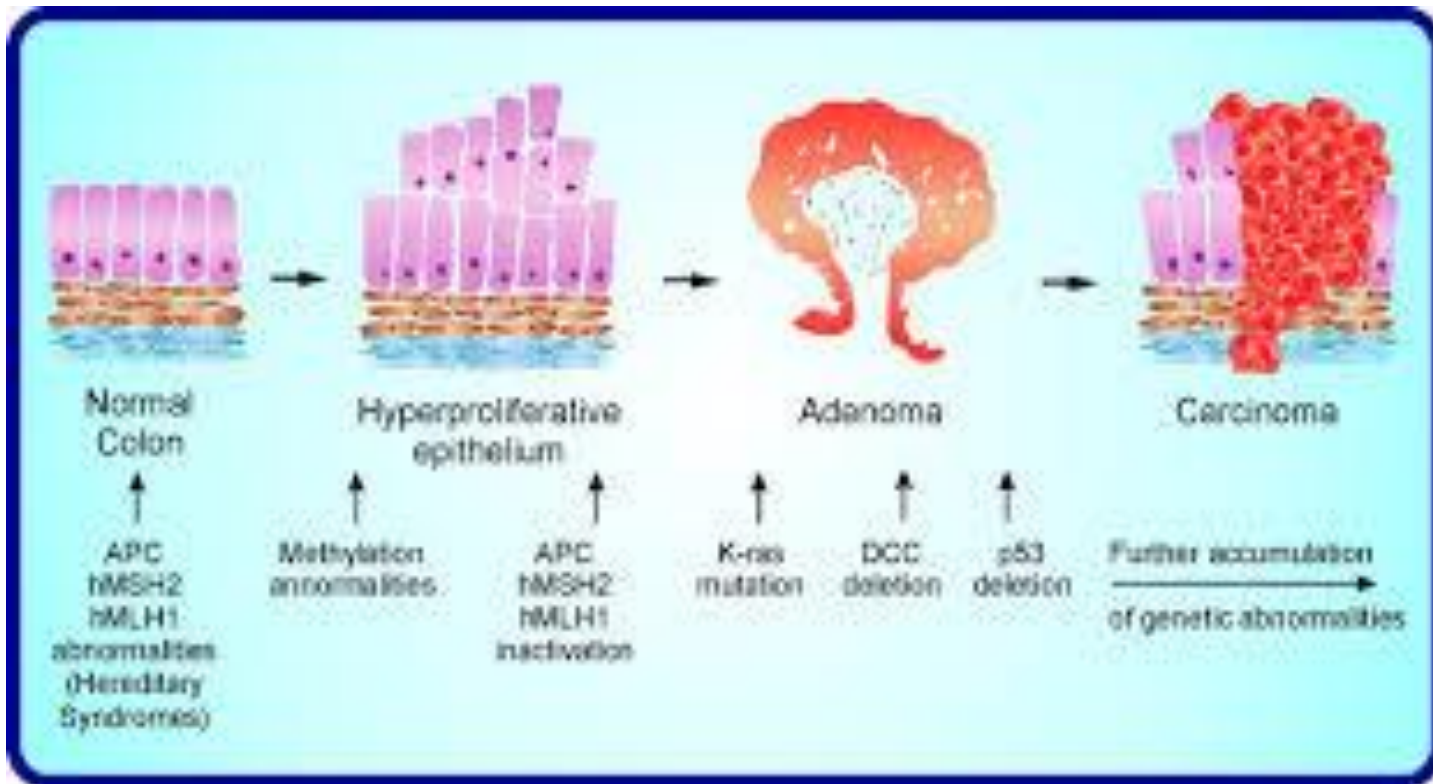
- promotes proliferation.

- K ras mutation follows which promotes growth & prevent apoptosis.

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- Mutation in other tumor suppressor genes like SMAD₂ & SMAD₄ which allows unrestrained cell growth.
 - Loss of function mutation in TP₅₃ genes.


Adenoma-carcinoma sequence



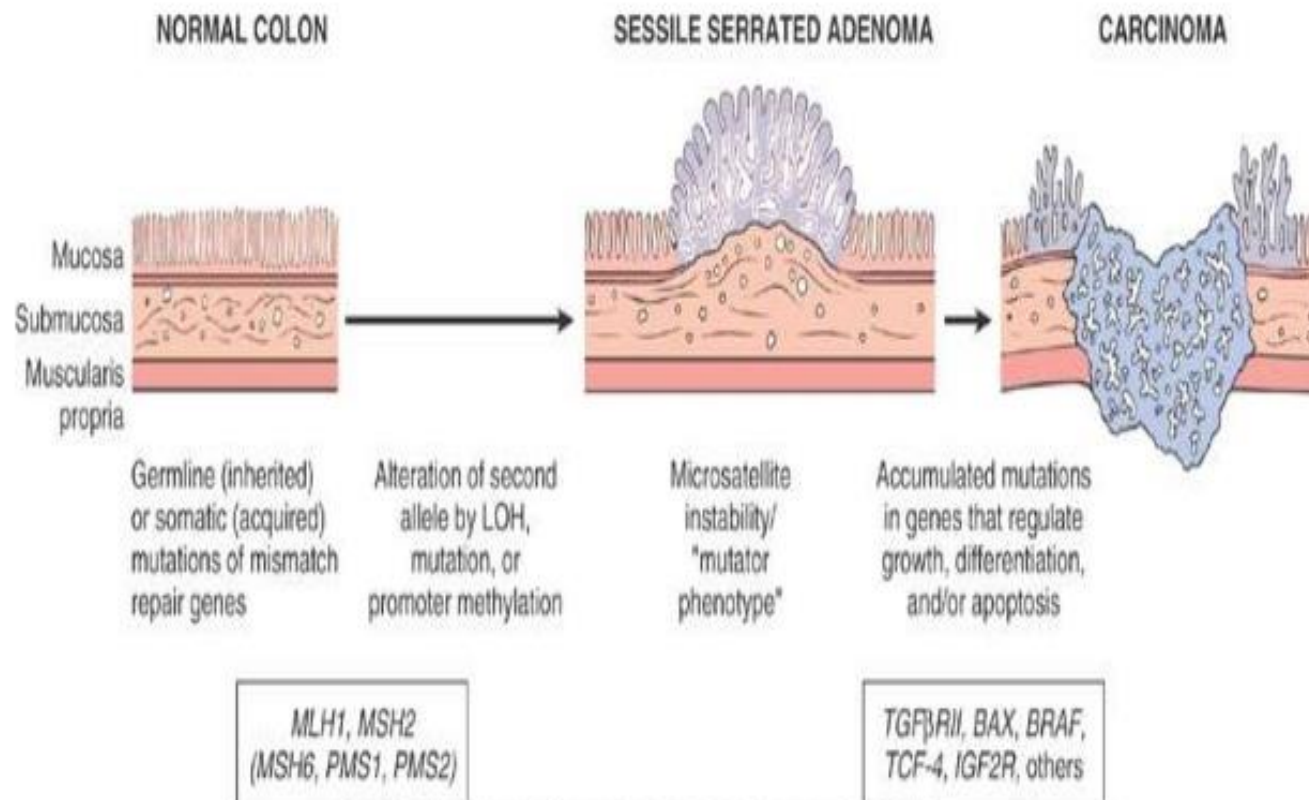


Microsatellite instability pathway:

- DNA mismatch repair deficiency.
- mutation accumulates in microsatellite repeats occurs in coding region of gene involved in cell growth.
- Type II TGF- β & BAX mutation.
- Type II TGF - β leads to uncontrolled proliferation of colonic epithelial cells.

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- Loss of BAX contributes to ↑ed survival & genetically abnormal clones.
 - Mutation in oncogen BRAF also occurs.
 - KRAS & TP53 not mutated.

Microsatellite instability



MOLECULAR PATHOGENESIS

- **TWO** distinct genetic pathways .

1. **APC / β -catenin pathway**

- Associated with **WNT signaling pathway** and the **chromosomal instability pathway**.

2. **Microsatellite instability pathway**

- Associated with **defects in DNA mismatch repair**

To conclude

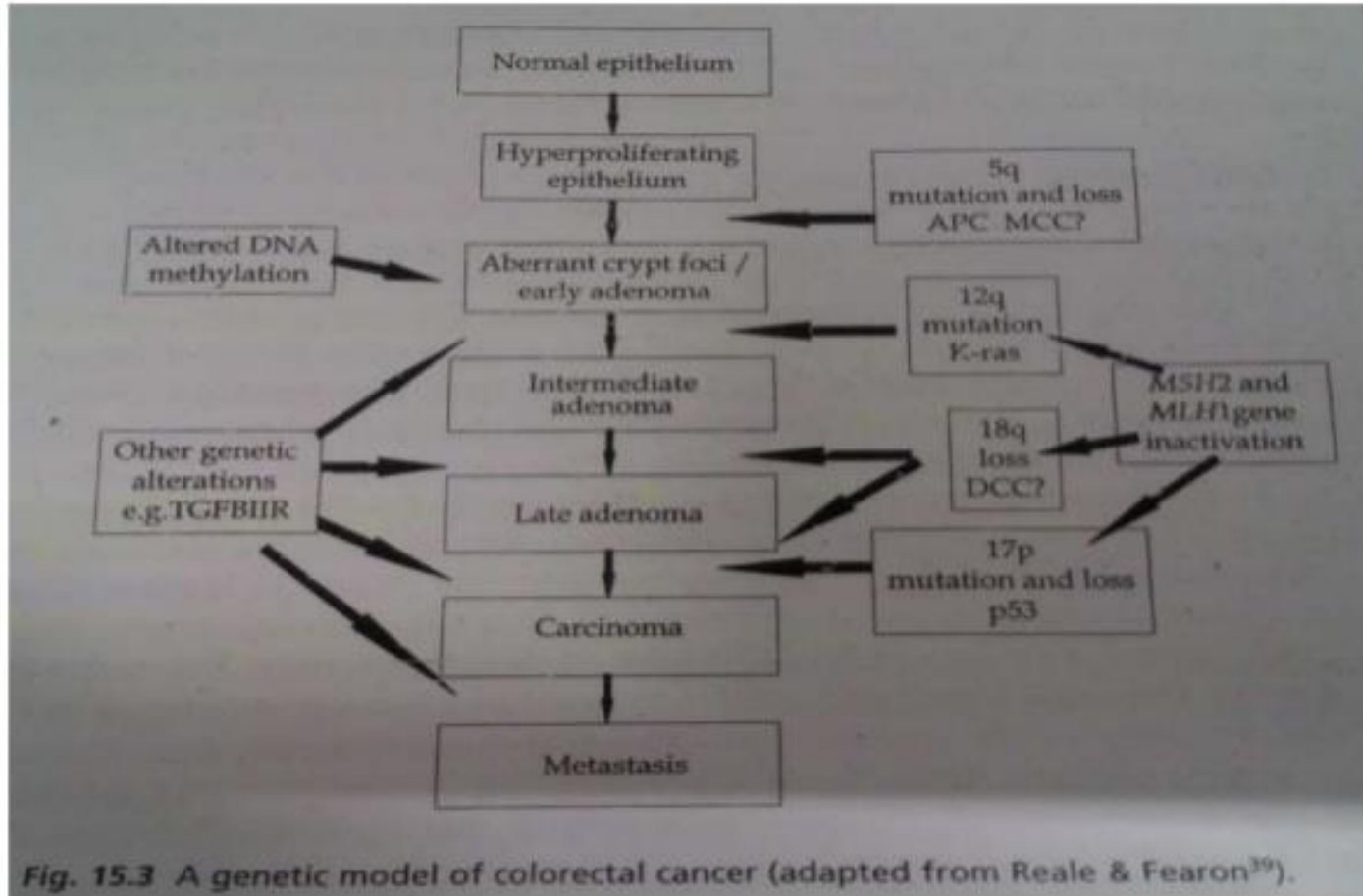
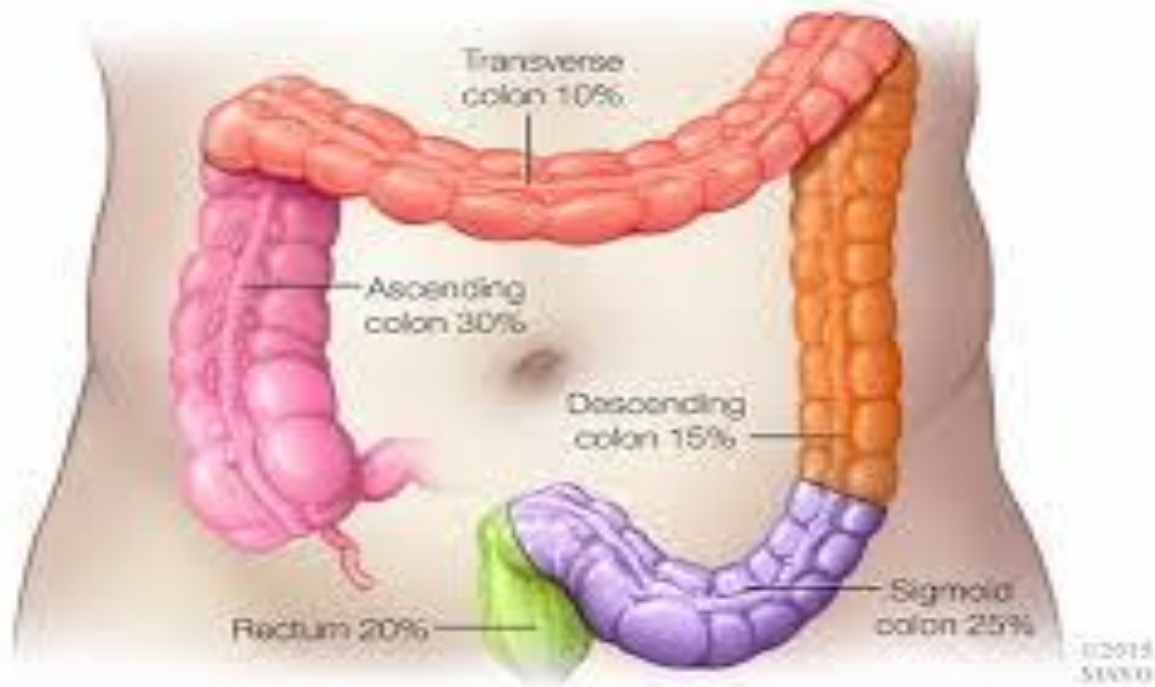


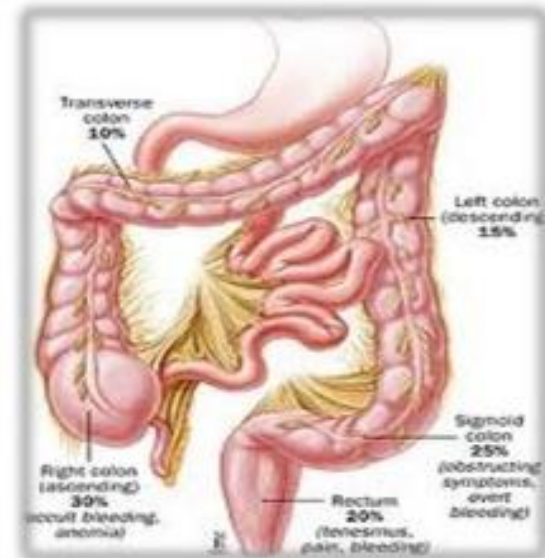
Fig. 15.3 A genetic model of colorectal cancer (adapted from Reale & Fearon³⁹).

Average distribution of colon cancer



MORPHOLOGY

- 50% → rectosigmoid area (involvement of the proximal colon is increasing)
- Right-sided tumors more common in the
 - elderly
 - blacks
 - patients with diverticular disease



GROSS

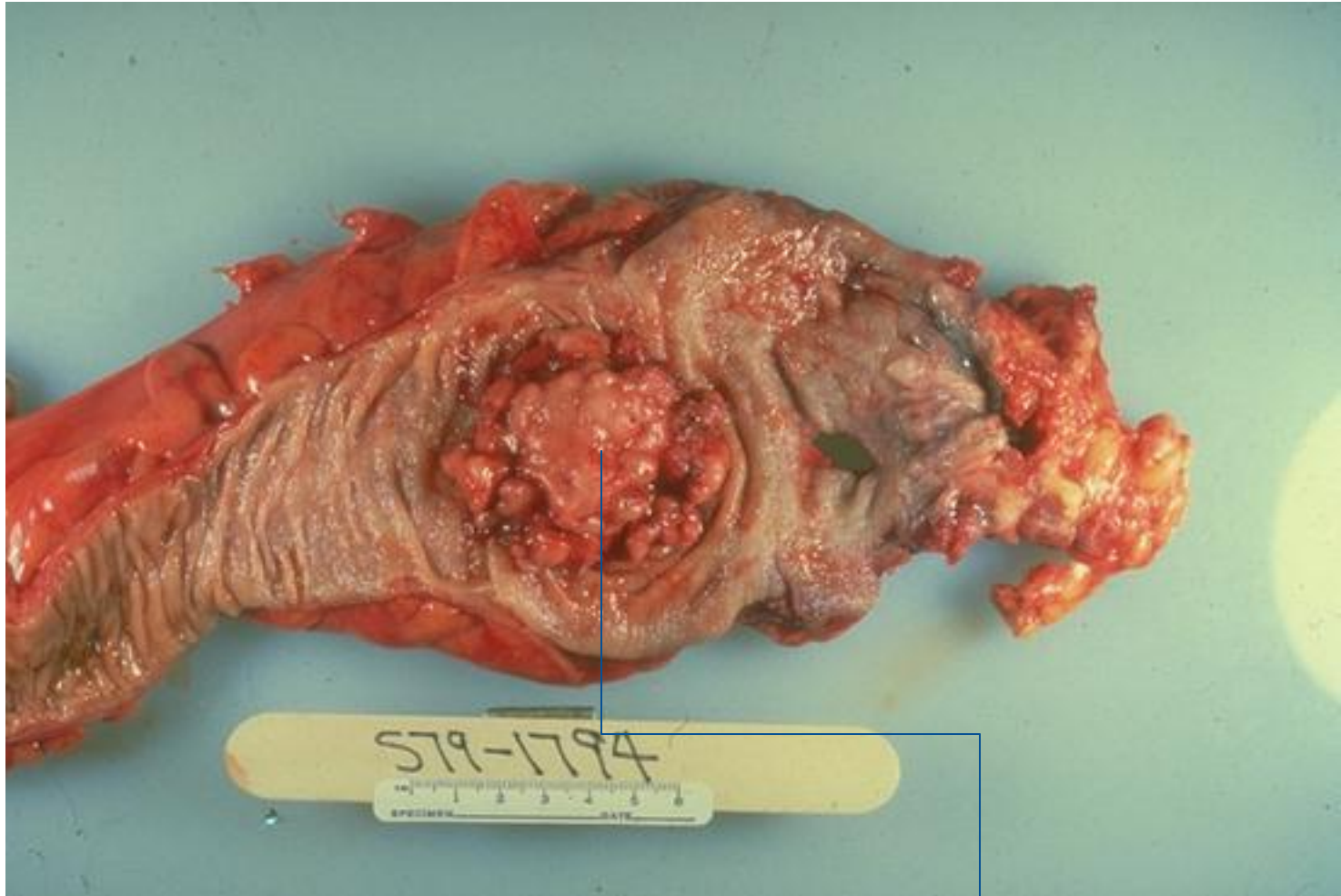
A. PROXIMAL COLON

- **Polypoid:**
 - Bulky mass, well-defined/ rolled margins and a sharp dividing line with the normal bowel.
- **Ulcerative:**
 - Less elevated surface and is centrally ulcerated
- These tumors rarely cause obstruction



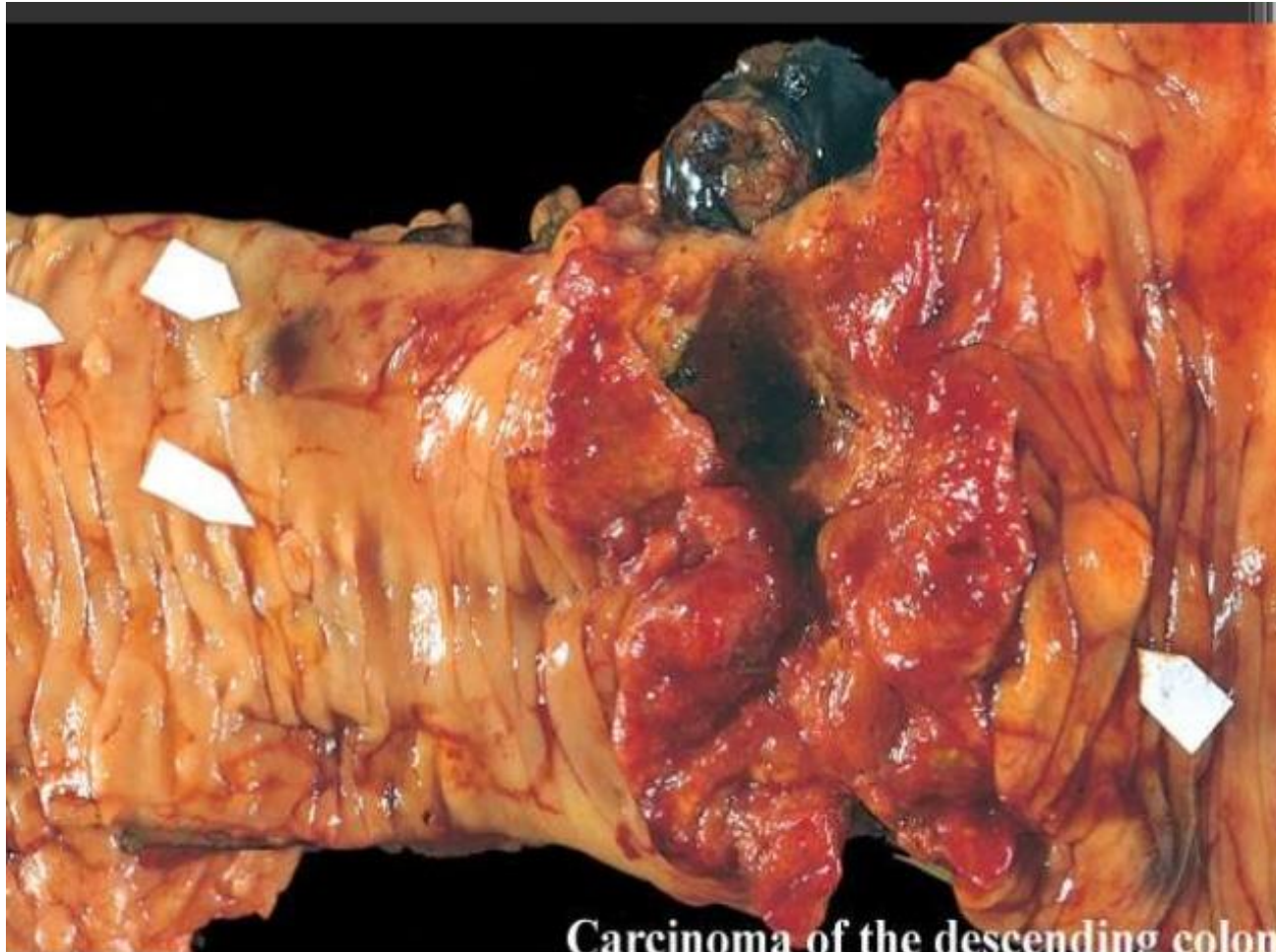
B. DISTAL COLON

- Annular lesions producing “napkin – ring” constrictions and luminal narrowing .
- These tumors can cause obstruction.



579-1794

SPECIMEN DATE



Carcinoma of the descending colon

Both histologically same &

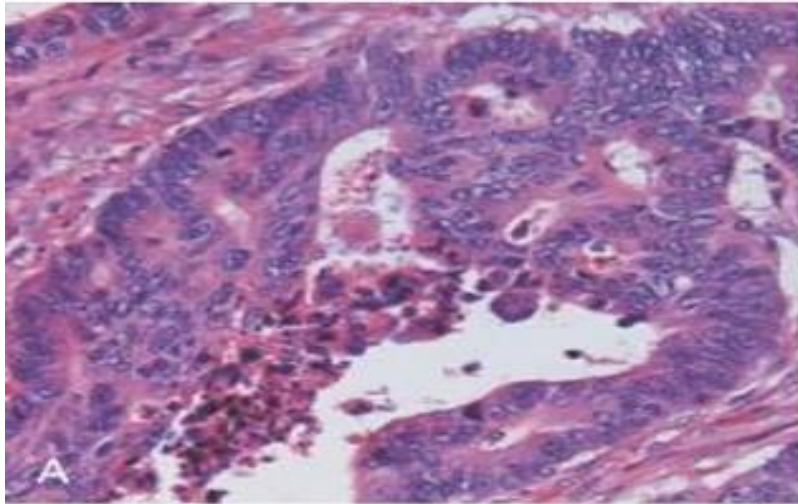
- tall columnar cell composing glands with features of cytologic atypia.
- Desmoplastic reaction ,so firm
- Mucin may or may not be present
- Signet ring carcinoma may be present.



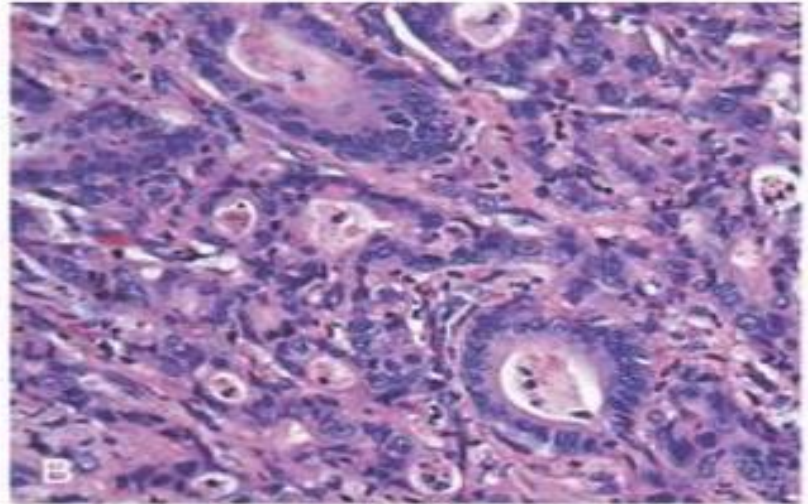
Microscopically, colorectal carcinoma can be graded into

- I – well differentiated
- II- moderately differentiated
- III- poorly differentiated

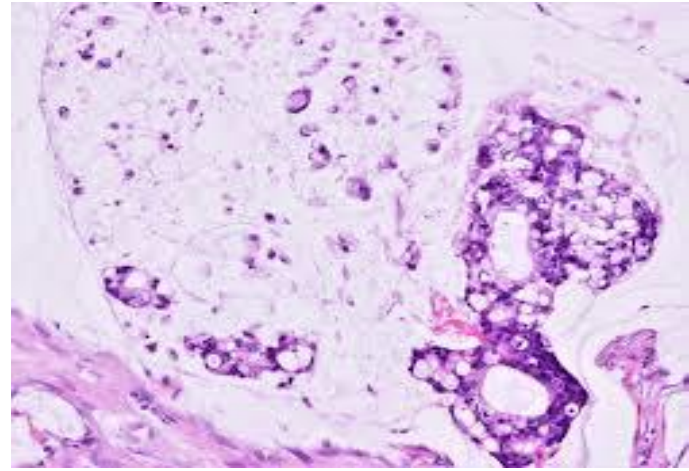
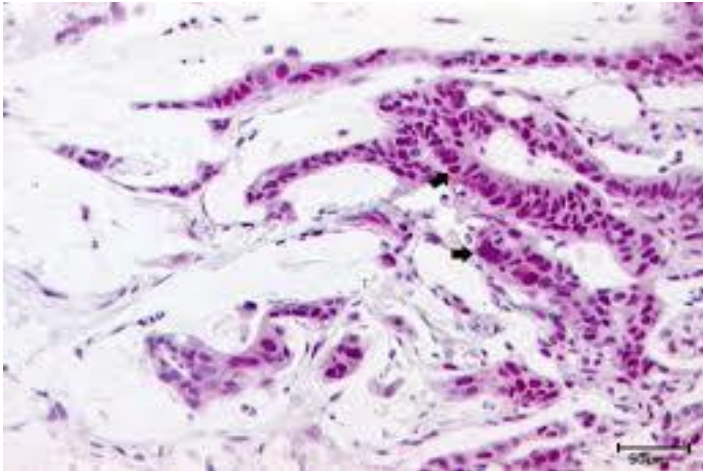
Well - differentiated



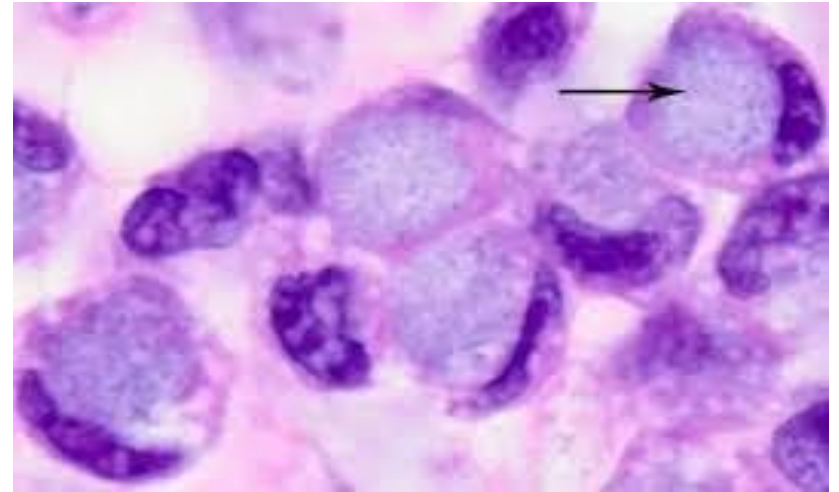
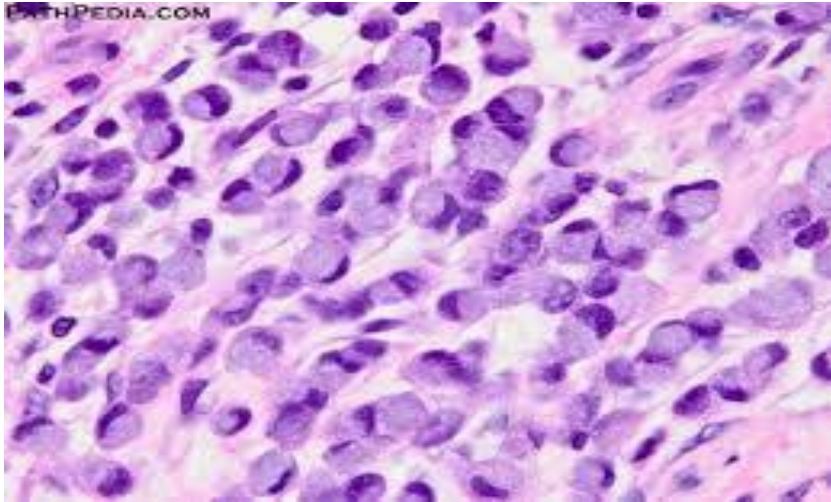
Poorly differentiated



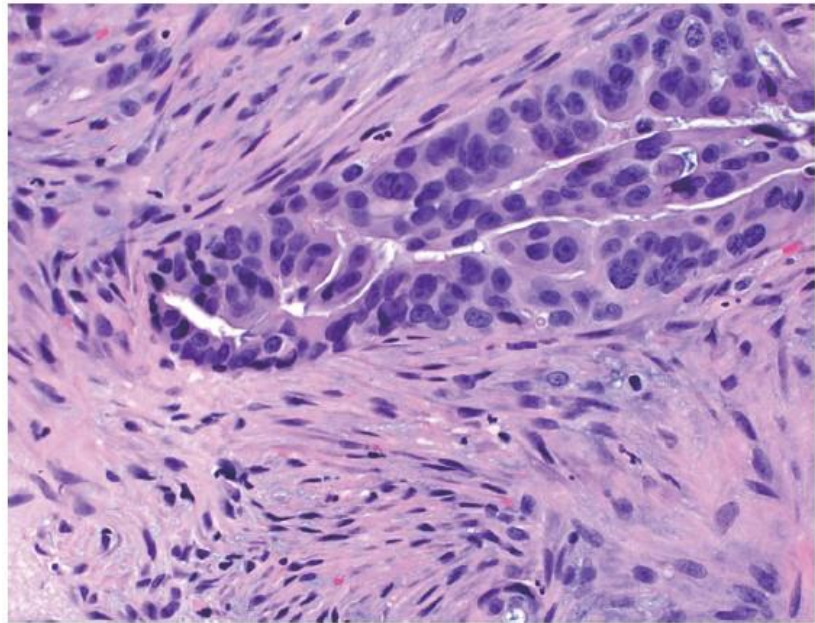
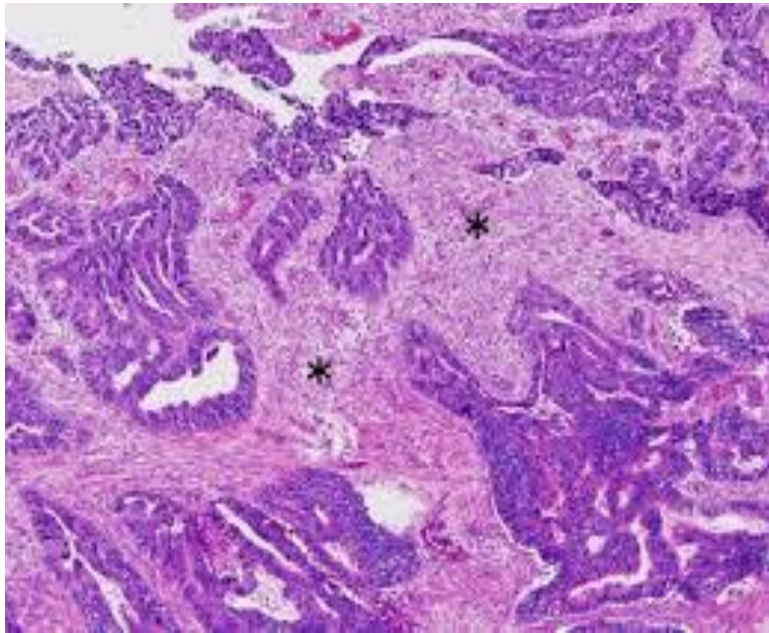
Mucinous carcinoma :



Signet ring carcinoma :

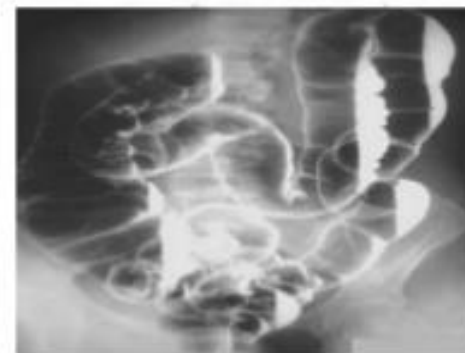


Desmoplastic reaction Carcinoma Colon :



Various screening modalities

- Colonoscopy
- Sigmoidoscopy
- Fecal occult blood test
- Double contrast barium enema
- Digital rectal examination




Biopsy

- There is a need of POSITIVE BIOPSY before radical surgery for CRC.
- In large lesions, several biopsies should be taken from diverse areas.
- Biopsy from center → only granulation tissue
- Biopsy from the very periphery → only hyperplastic colonic epithelium

CLINICAL FEATURES :


- Insidious onset.
- Iron deficiency anemia may be presenting symptom.(when in elderly people always sought for CRC)
- Occult blood in stool
- Altered bowel habits.
- cramping lower abdominal pain.
- depth of invasion & lymph node metastases – two important prognostic factors.

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- poorly differentiated carcinoma & mucinous carcinoma --- poor prognosis.
 - TNM classification & staging AJCC.

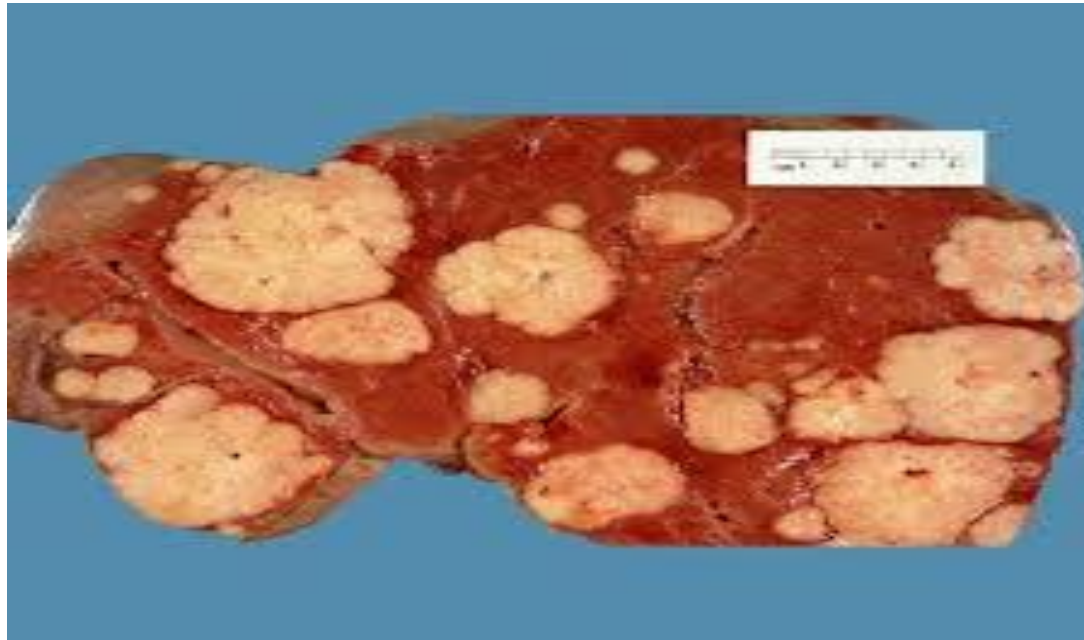


Spread and Metastasis

- Common sites
 - Regional lymph nodes
 - Liver

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- Other relatively common metastatic sites include
 - peritoneum
 - lung
 - ovaries.

Liver metasis of carcinoma colon :





THANK YOU

Dr. Rajul Shah