Colon Carcinoma: Diagnostic approach

Introduction

- Colon carcinoma is a common GI cancer.
- Early and accurate diagnosis is key to better outcomes.
- Often asymptomatic in early stages.

Why Diagnosis Matters

- Survival is highly stage-dependent.

- Early-stage: >90% 5-year survival.

- Late-stage: Often metastatic with poor prognosis.

When to Suspect Colon Carcinoma

- Change in bowel habits (constipation or diarrhea).
- Rectal bleeding or occult blood.
- Iron-deficiency anemia in older adults.
- Unexplained weight loss, fatigue.

Step-by-Step Diagnostic Approach

▶ Start with history, physical exam, CBC.

▶ Fecal testing (FIT or gFOBT).

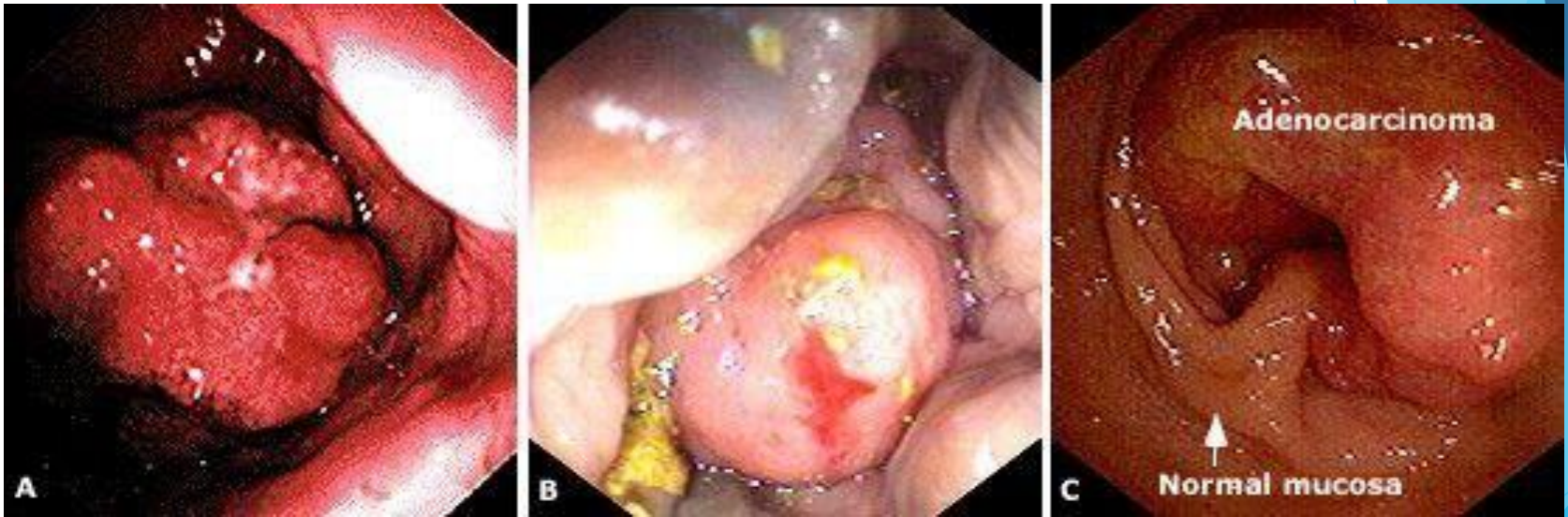▶ Colonoscopy for confirmation.

▶ Imaging for staging (CT, MRI).

Fecal Tests

- FIT: Detects human hemoglobin; more specific.

- gFOBT: Older test, affected by diet.

- Positive tests → Colonoscopy.

Colonoscopy – The Gold Standard

- Direct visualization and biopsy.
- Can remove polyps during the procedure.
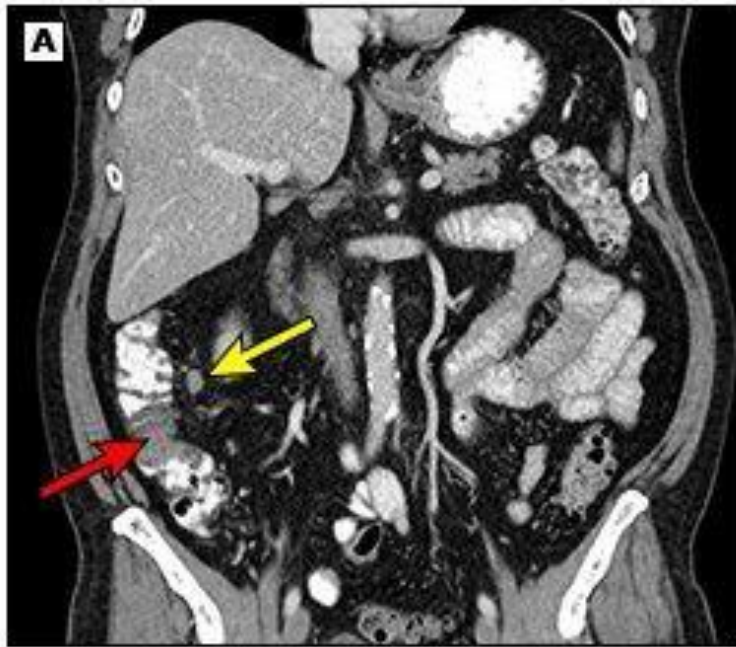- Requires bowel prep and sedation.

Colon adenocarcinoma endoscopy

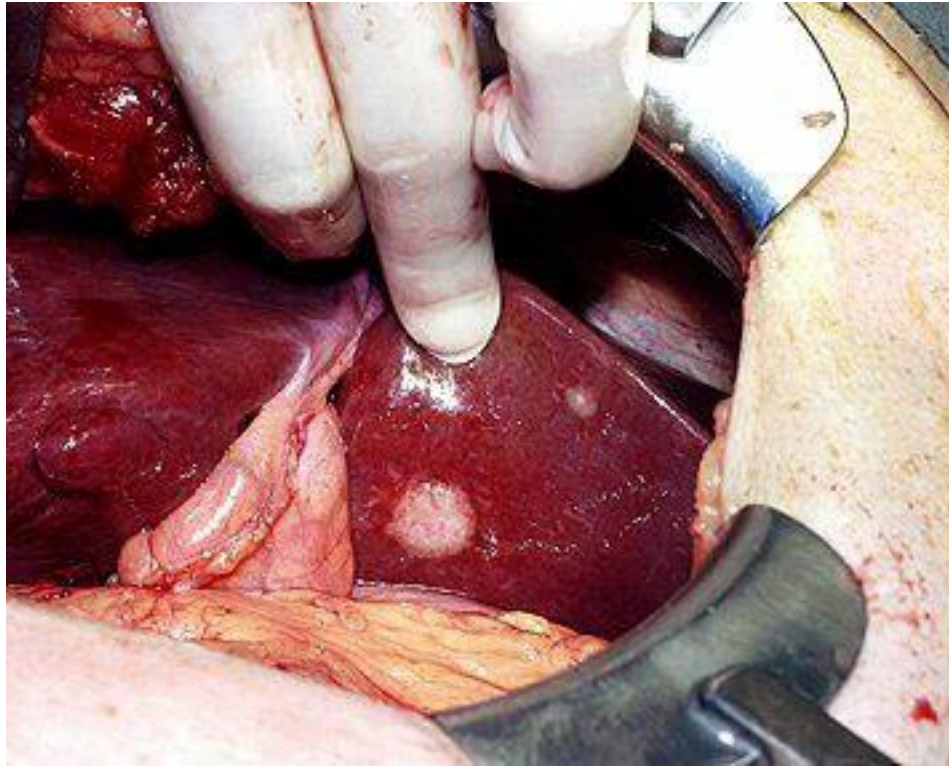# Imaging & Staging

- CT Abdomen/Pelvis for metastasis.
- MRI or endorectal US for rectal cancer.
- TNM staging guides treatment decisions.

Colon cancer on CT & colonoscopy

Liver metastasis of colon cancer on gross view

Tumor Marker – CEA

- Used for monitoring, not screening.
- Helps assess prognosis and recurrence.
- Low sensitivity for early-stage cancer.

Screening Guidelines (Brief)

- Start at age 45–50, earlier if high risk.
- Colonoscopy every 10 years.
- FIT annually, stool DNA every 3 years.

Comparison of Diagnostic Methods

Method	Purpose	Invasiveness	Sensitivity/Specificity	Advantages	Limitations
FIT	Screening	Non-invasive	Moderate / High	Easy, no dietary limits	May miss non-bleeding tumors
gFOBT	Screening	Non-invasive	Lower than FIT	Inexpensive	False positives, dietary limits
Stool DNA	Screening	Non-invasive	High / High	Detects mutations + blood	Expensive
Colonoscopy	Diagnosis + Screening	Invasive	High / High	Gold standard, polyp removal	Sedation, prep, risk of perforation
Sigmoidoscopy	Screening (partial)	Minimally invasive	Moderate / High	No sedation	Misses right-sided lesions
CT Colonography	Alternative visualization	Minimally invasive	High / Moderate	Non-invasive	No biopsy, radiation
CT Abdomen/Pelvis	Staging	Non-invasive	-	Detects metastases	Can't detect small lesions
CEA	Monitoring	Blood test	Low / Low	Used in follow-up	Not for early diagnosis

Summary

- Colon cancer diagnosis starts with suspicion.
- Screening (e.g., FIT, colonoscopy) saves lives.
- Colonoscopy remains the gold standard.
- Imaging and CEA are used for staging and follow-up.

Genetics of Colorectal Cancer

Introduction

- Colorectal cancer (CRC) arises from both environmental and genetic factors.

- Three presentation patterns:

- - Sporadic (~70%)

- - Inherited (≤10%)

- - Familial (~25%)

Molecular Pathogenesis

▶ CRC progresses via a multistep mutation accumulation model.

▶ Fearon & Vogelstein model: APC → KRAS → TP53

▶ Two mutation types: Germline (inherited) & Somatic (acquired)

Key Genetic Pathways

- 1. Chromosomal Instability (CIN) Pathway - FAP and sporadic CRC

- 2. Mismatch Repair (MMR) Pathway - Lynch syndrome & MSI-H tumors

- 3. Serrated/CIMP+ Pathway - Methylation & BRAF mutation, from serrated polyps

Major Gene Mutations

- APC: Early event, Wnt pathway dysregulation

- KRAS/NRAS: 50% CRCs, drives proliferation

- TP53: Late event, genome stability loss

- DCC, SMAD2/4: Tumor suppressors on 18q

- MUTYH: Biallelic mutations cause MAP

Clinical Implications

- Genetic testing identifies high-risk patients (FAP, Lynch, MAP)

- Stool DNA tests include KRAS & methylation markers

- RAS mutations → no benefit from anti-EGFR therapy

- MSI-H tumors → respond to immunotherapy

Pathway	Key Genes	Mutation Type	Syndrome/Condition	Clinical Relevance
Chromosomal Instability (CIN)	APC, TP53, DCC, SMAD2/4	Somatic (mostly)	Familial Adenomatous Polyposis (FAP)	Early event (APC); EGFR therapies ineffective if downstream mutations present
Mismatch Repair (MMR)	MLH1, MSH2, MSH6, PMS2	Germline (in Lynch); Epigenetic in sporadic	Lynch Syndrome	MSI-H tumors; good prognosis; responsive to immunotherapy
Serrated / CIMP+ Pathway	MLH1 (methylation), BRAF (V600E)	Epigenetic + Somatic	Sporadic CRC (esp. in smokers, right-sided)	MSI-H, BRAF+ tumors; poor prognosis if BRAF mutated
Oncogene Activation	KRAS, NRAS, BRAF	Somatic (point mutations)	Sporadic CRC	KRAS/BRAF mutations drive proliferation; anti-EGFR therapy ineffective if mutated
Tumor Suppressor Inactivation	TP53, APC, SMAD4, DCC	Germline (FAP); Somatic	Sporadic and familial cases	Loss of cell cycle control and apoptosis; late events in tumor progression
Base Excision Repair (BER)	MUTYH	Germline (biallelic)	MUTYH-Associated Polyposis (MAP)	Autosomal recessive; increased polyp burden; high lifetime CRC risk
Modifier Genes / Others	COX-2, PPAR, TGFBR2	Varies (epigenetic/somatic)	Sporadic CRC	Influence polyp formation, inflammation, and tumor microenvironment

Conclusion

- Genetic understanding improves screening, prevention, and personalized therapy.
- CRC is a model for studying genetic mechanisms in cancer.