Colon Cancer

Pathogenesis
Normal epithelium → dysplastic ACF → early adenoma → late adenoma → carcinoma → metastatic carcinoma

Adenomas/polyps
- Extra tissue that grows in the colon
- ↑ Polyp size = ↑ cancer risk
- Symptoms: bleeding, irregular bowel (diarrhea, constipation)

Risk factors
- Advanced age: >50 y/o
- Personal or family history: adenomas/polyps, colon cancer, IBD
- Inherited syndromes: familial adenomatous polyposis (FAP), Lynch Syndrome (HNPCC)
- Lifestyle: Western diet, sedentary lifestyle, obesity, heavy alcohol use, smoking

Protective factors
- Lifestyle: diet high in fruits & vegetables, ↑ dietary Ca & Vit D, regular physical activity
- Regular use of ASA or NSAIDs: ↓ PGE2 levels

Screening
- FOBT | fecal occult blood test: high false neg rate, best if used with other tests, ↓ mortality by 1/3
- DRE | digital rectal exam
- Endoscopy: flexible sigmoidoscopy, examines lower 60% of bowel
- Colonoscopy: examples whole bowel, can remove pre-malignant lesions during procedure
- Recommendations
  - Begin screening at 50 y/o
  - Colonoscopy: q10yr, preferred
  - Flexible sigmoidoscopy: q5yr
  - Double contrast barium enema: q5yr
  - FOBT, FIT: annually
  - CT colonography (virtualy colonoscopy): q5yr
  - Stool DNA test: value currently unknown

Clinical presentation

<table>
<thead>
<tr>
<th></th>
<th>Right colon</th>
<th>Left colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td>Ill defined</td>
<td>Colicky</td>
<td>Steady, gnawing</td>
</tr>
<tr>
<td><strong>Obstruction</strong></td>
<td>Infrequent</td>
<td>Common</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>Brick red</td>
<td>Red, mixed with stool</td>
<td>Bright red, coating stool</td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
<td>Common</td>
<td>Infrequent</td>
<td>Infrequent</td>
</tr>
</tbody>
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Diagnosis
- Biopsy detected lesions
- Staging: CSR, abdominal/pelvic CT scan, CBC, LFTs, UA, CEA level
  - Stage I: cancer grown through mucosa
  - Stage II: cancer grown through wall
  - Stage III: lymph node involvement
  - Stage IV: metastases
### Treatment | overview

<table>
<thead>
<tr>
<th>Stage I &amp; II</th>
<th>High risk stage II:</th>
<th>Stage III</th>
<th>Stage IV – metastatic</th>
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| • Surgery alone  
• Surveillance: H&P + CEA q3 months x 2yrs then q6 months x 5yrs | • Surgery + adjuvant chemo  
• Options: capecitabine, FOLFOX, or 5FU + leucovorin regimens  
• High risk: bowel obstruction, grade 3 or 4 lesions, indeterminate/positive margins, <12 nodes sampled, venous invasions | • Surgery  
• Adjuvant chemo: 5FU based regimen x 6 months  
• Regimens: 5FU + LV, FOLFOX4, mFOLFOX6 (standard), capecitabine, CapeOx | 5FU + LV, irinotecan, capecitabine, oxaliplatin, cetuximab, bevacizumab, panitumumab |

- **Surgery:** 50% cure rate  
  - Stage I-II: curative intent → partial or total colectomy + resection of lymph nodes  
  - Stage III-IV: palliative, de-bulking → ↓bleeding, ↓obstruction, ↑QOL  
  - Isolated metastases to liver & lung: curative intent possible with resection

- **Adjuvant chemotherapy**  
  - Systemic (5-FU, capecitabine, irinotecan, oxaliplatin) or regional (if isolated liver metastasis)

- **Targeted therapy: monoclonal antibodies**  
  - VEGF (bevacizumab), EGFR (cetuximab, panitumumab)

### Adjuvant chemotherapy regimens | non-metastatic setting

- **5FU + LV**  
  - 5FU bolus + leucovorin  
    - Administration: LV 500 mg/m² IVPB over 2hrs then 5FU 500 mg/m² IVP for 1hr  
    - Frequency: weekly x 6 weeks or every 8 weeks for 4 cycles  
  - Leucovorin: to ↑efficacy of 5FU  
  - Toxicities: myelosuppression, grade 3/4 diarrhea, grade 1/2 N&V, mucositis

- **FOLFOX**  
  - Fol = folinic acid/leucovorin  
  - 400 mg/m² IV  
  - 400 mg/m² IVP day 1, then 1200 mg/m²/d x 2 days  
  - Frequency: repeat every 2 weeks x 12 cycles, total of 6 months  
  - Oxaliplatin toxicities: acute/delayed neuropathy, moderately emetogenic, hypersensitivity reactions  
  - 5FU infusion toxicities: hand-foot syndrome, less hematologic/GI effects

- **Capecitabine:** oral prodrug of 5FU  
  - Dose: 1250 mg/m² po q12hr x 14 days q21 days → totally dose/day = 2500 mg/m²/day  
  - Preferred if patient is >70 y/o or PS ≤2  
  - Renal adjustment: CrCl <50 mL/min  
  - Toxicities: hand-foot syndrome, diarrhea, myelosuppression, N/V, photosensitivity  
  - Black box warning: severe drug interaction with warfarin

### Advanced metastatic colon cancer

- **Agents available:** 5-FU + LV, irinotecan, capecitabine, oxaliplatin, cetuximab, bevacizumab, panitumumab

- **K-ras mutation:**  
  - Small protein essential in EGFR signaling cascade  
  - Mutation confers resistance to EGFR monoclonal antibodies (cetuximab, panitumumab)  
  - Need to screen genotype in stage IV disease: don’t waste patients time, health, or money

- **Anti-EGFR monoclonal antibodies:** cetuximab, panitumumab  
  - Cetuximab: chimeric → hypersensitivity reactions  
  - Dosing: cetuximab LD followed by qweek, panitumumab q2weeks  
  - Comparative efficacy not established or studied  
  - Not recommended to switch to the other after failure  
  - Toxicities between both: acne-form rash (surrogate for efficacy), hypomagnesemia

- **Anti-VEGF monoclonal antibody:** bevacizumab  
  - Anti-VEGF + anti-EGFR combination not recommended by NCCN
MCRC: Intensive Therapy

Initial Therapy
- FOLFOX ± (BEV or panitumumab*)
- FOLFIRI + BEV
- FOLFIRI ± (cetuximab* or panitumumab*)
- CapeOX ± BEV
- (5FU/LV or capecitabine) ± BEV

Progression After First Therapy
- FOLFOX, FOLFIRI or CapeOX
- FOLFIRI + (cetuximab* or panitumumab*)
- Irinotecan ± oxaliplatin (IROX)
- Irinotecan + (cetuximab* or panitumumab*)
- Cetuximab or panitumumab*

Progression after second Therapy
- (Cetuximab* or panitumumab*) ± irinotecan

Chemotherapy for Patient Not Appropriate for Intensive Therapy

Initial Therapy
- Capecitabine or infusional 5FU/LV ± bevacizumab
- Cetuximab
- Panitumumab

Therapy after 1st progression
- No improvement in functional status
- Best supportive care
- Improvement in functional status
- Initial therapy