## **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
  - o Begin screening at 50 y/o
  - Colonoscopy: q10yr, preferred
  - o Flexible sigmoidoscopy: q5yr
  - o Double contrast barium enema: q5yr
  - o FOBT, FIT: annually
  - o CT colonography (virtualy colonoscopy): q5yr
  - Stool DNA test: value currently unknown

\*if any test comes back

abnormal, still need to confirm

with colonoscopy

## **Clinical presentation**

	Right colon	Left colon	Rectum
Pain	III defined	Colicky	Steady, gnawing
Obstruction	Infrequent	Common	Infrequent
Bleeding	Brick red	Red, mixed with stool	Bright red, coating stool
Weakness	Common	Infrequent	Infrequent

## **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**

Stage I & II	High risk stage II:	Stage III	Stage IV – metastatic
<ul> <li>Surgery alone</li> <li>Surveillance: H&amp;P +         CEA q3 months x 2yrs         then q6 months x 5yrs</li> </ul>	<ul> <li>Surgery + adjuvant chemo</li> <li>Options: capecitabine, FOLFOX, or 5FU + leucovorin regimens</li> <li>High risk: bowel obstruction, grade 3 or 4 lesions, indeterminate/positive margins, &lt;12 nodes sampled, venous invasions</li> </ul>	<ul> <li>Surgery</li> <li>Adjuvant chemo: 5FU based regimen x 6 months</li> <li>Regimens: 5FU + LV, FOLFOX4, mFOLFOX6 (standard), capecitabine, CapeOx</li> </ul>	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
  - o Isolated metastases to liver & lung: curative intent possible with resection
- Adjuvant chemotherapy
  - o Systemic (5-FU, capecitabine, irinotecan, oxaliplatin) or regional (if isolated liver metastasis)
- Targeted therapy: monoclonal antibodies
  - VEGF (bevacizumab), EGFR (cetuximab, panatumumab)

## Adjuvant chemotherapy regimens | non-metastatic setting

- 5FU + LV
  - o 5FU bolus + leucovorin
    - Administration: LV 500 mg/m<sup>2</sup> IVPB over 2hrs then 5FU 500 mg/m<sup>2</sup> IVP for 1hr
    - Frequency: weekly x 6 weeks or every 8 weeks for 4 cycles
  - Leucovorin: to ↑efficacy of 5FU
  - o Toxicities: myelosuppression, grade 3/4 diarrhea, grade 1/2 N&V, mucositis
- FOLFOX
  - $\textbf{Fol} = \text{folinic acid/leucovorin} \\ 400 \text{ mg/m}^2 \text{ IV} \\ 400 \text{ mg/m}^2 \text{ IVP day 1, then } 1200 \text{ mg/m}^2/\text{d x 2 days} \\ 85 \text{ mg/m}^2 \text{ over 2 hr day 1}$
  - Frequency: repeat every 2 weeks x 12 cycles, total of 6 months
  - o Oxaliplatin toxicities: acute/delayed neuropathy, moderately emetogenic, hypersensitivity reactions
  - o 5FU infusion toxicities: hand-foot syndrome, less hematologic/GI effects
- Capecitabine: oral prodrug of 5FU
  - O Dose: 1250 mg/m<sup>2</sup> po q12hr x 14 days q21 days  $\rightarrow$  totally dose/day = 2500 mg/m<sup>2</sup>/day
  - o Preferred if patient is >70 y/o or PS ≤2
  - o Renal adjustment: CrCl <50 mL/min
  - Toxicities: hand-foot syndrome, diarrhea, myelosuppression, N/V, photosensitivity
  - o 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)
  - o 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 st progression

- No improvement in functional status
- Best supportive care
- Improvement in functional status
  - · Initial therapy