Colorectal Cancer

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Incidence

• 4th most common malignancy in the U.S.
• In 2002, est. new cases= 148, 300
• In 2002, it is estimated nearly 56,600 Americans will die from colorectal cancer
• Third most common cause of cancer-related deaths
• More women over the age of 75 die from colorectal cancer than from breast cancer.

Risk Factors

• Race
  – African Americans > Caucasians > Asians > Amer Indian > Hispanics
• Age
  – Risk increases after age 40, median age at diagnosis is 69 years
• Gender
  – Males > females
• Environment
  – Industrial countries are the highest
• Diet
  – A diet high in fat and low in fiber increases your risk.
Risk Factors

- Inactivity
- History of Polyps/Genetics (10-20% of all cases)
  - Hereditary Nonpolyposis Colon Cancer (Lynch Syndrome; HNPCC)- 50% have colon ca. by age 80.
  - Familial Adenomatous Polyposis (FAP)- 100%
  - Gardner’s Syndrome
- History of Inflammatory Bowel Disease
  - Ulcerative Colitis-increases your risk 30x
  - Crohn’s Disease

Risk Factors

- Personal history of colorectal cancer or other cancers
- Other Increased Risk Factors
  - Obesity, EtOH use, tobacco
- Favorable Risk Factors
  - Calcium supplementation, selenium, aspirin, NSAIDS, estrogen supplementation, physical activity

Aspirin and NSAIDS for Prevention

- Celecoxib – indicated for reduction of polyps in FAP; 400 mg BID.
- ASA (81 or 325 mg QD) to prevent colorectal adenomas – moderate benefit, increased episodes of bleeding (NEJM. March 6, 2003).
- Clinical trials to assess whether ASA can decrease frequency/intensity of screening are warranted.
### Signs and Symptoms

- Rectal bleeding or blood in the stool (with corresponding drop in Hgb)
- Change in bowel habits such as diarrhea, constipation or narrowing of the stools
- A feeling of fecal urgency despite defecation
- Cramping or steady abdominal pain, distention
- Decreased appetite
- Weakness, fatigue
- Jaundice

### Natural History of Disease

- Local invasion through lumen of bowel wall, adenoma-carcinoma sequence theory (fig 127-4-DiPiro)
- Metastasis: LLBB-lymph nodes, liver, lungs, brain, bone (sacrum, coccyx, pelvis & lumbar)
- Pathology: 90% are adenocarcinomas
- Liver is the initial site of spread in 30% of cases, and is the only site of spread in 40% of colon cancer cases.

### Pathology: Genetic Model

- Normal Epithelium
- Hyperproliferative Epithelium
- Adenoma Class I
- Adenoma Class II
- Adenoma Class III
- Carcinoma
- Metastasis

- APC/MCC mut.
- Chrom. 5q alteration
- DNA looses methyl group
- K-ras gene mutation
- Chrom. 18q loss (DCC)
- Chrom. 17p loss (p53)
- Other chrom. alterations
Screening

- 1. Fecal occult blood test (FOBT)
- 2. Digital Rectal Exam (DRE)
- 3. Endoscopy
  - a. Flexible Sigmoidoscopy (Flex. Sig.)
  - b. Colonoscopy
- 4. Barium Enema
- 5. Tumor Marker Blood Test
- 6. CT Colonography

FOBT

- Methods: Guaic dye, heme-porphyrin, or immunochemical methods
- False Negatives
  - 1. Samples stored too long before testing
  - 2. Vit C > 250 mg/day
  - 3. Failure to ingest high-residue diet
- False Positives
  - 1. Ingestion of red rare meat, uncooked fruits/veg
  - 2. NSAID/ASA induced bleeding
  - 3. Iron

Causes of Positive Fecal Guaiac Test

<table>
<thead>
<tr>
<th>Foods with Peroxidase Activity</th>
<th>Medications which Interfere with FOBT</th>
<th>Common Causes of Blood in Stool</th>
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<tbody>
<tr>
<td>Broccoli</td>
<td>Steroids</td>
<td>Colorectal CA</td>
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<tr>
<td>Cauliflower</td>
<td>NSAIDs</td>
<td>Colorectal polyps</td>
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<tr>
<td>Turnips</td>
<td>Reserpine</td>
<td>Diverticulitis</td>
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<td>Horseradish</td>
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<td>Hemorrhoids</td>
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<td>Cabbage</td>
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<td>Fissures</td>
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<td>Potatoes</td>
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<td>Proctitis</td>
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<tr>
<td>Cucumbers</td>
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<td>Inflammatory bowel disease</td>
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<td>Mushrooms</td>
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<td>Artichokes</td>
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Note: large amounts of ascorbic acid can cause falsely negative FGT
DRE (Digital Rectal Exam)
- Accounts for the diagnosis of 10% of all cancers that are within 7-10 cm of the anus
- High intra-examiner variability
- Should never be done alone but rather in combination with other tests

Endoscopy
- Sigmoidoscopy
  - Visualizes the lower 35-60% of the bowel
- Colonoscopy
  - Visualizes the bowel up to the cecum and allows for removal of lesions
  - Greater risk and inconvenience, not routinely done for screening purposes.

Barium Enema
- Produces an image of the entire colon
- When combined with a flex. sig., this method can detect 98% of colorectal malignancies
## Tumor Marker

- **CEA:** Often expressed on the surfaces of tumor marker cells
- May be used to monitor response
- CEA is elevated in:
  - 28% of patients with stage A colorectal cancer
  - 45% of patients with stage B colorectal cancer
- False Positives:
  - Alcoholic/chronic hepatitis, diverticulitis, renal failure, cholelithiasis, fibrocystic breast disease, and smoking

## CT Colonography

- Expensive new procedure
- Involves using a colon prep, filling up the GI tract with air and allows for a single image of the colon in 20 seconds, with minimal patient discomfort
- Advantages include little discomfort and can visualize extracolonic abdominal organs
- Disadvantage: Cannot remove lesions!

## “Low Risk” Screening

- Starting at age 50, a yearly FOBT
- Flex sig every 5 years OR
- Colonoscopy every 10 years OR
- Double contrast barium enema q 5-10 years
- DRE performed at every flex. Sig., colonoscopy or barium enema examination
“High Risk” Definition

- High-risk: FAP, HNPCC, h/o colorectal cancer previously, h/o ulcerative colitis or Crohn’s colitis.
- Amsterdam Criteria (high risk):
  - 1. 3 relatives with colon ca (2 must be 1st degree relatives of the third)
  - 2. Colon cancer must span 2 generations
  - 3. 1 case must be diagnosed under age 50

Diagnosis

- Sigmoidoscopy and/or flex. sig.
- Barium enema with air contrast
- Computed Tomography (CT) or ultrasound
- Magnetic Resonance Imaging (MRI)
- CXR: lung mets
- Bone Scan: bone mets
- Laparotomy: open surgery (rare)
<table>
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<tr>
<th>AJCC Classification of Colon and Rectal Cancer</th>
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<tr>
<td><strong>Tumor Size</strong></td>
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<tr>
<td>T1: Involves submucosa</td>
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<td>T2: Involves muscularis propria</td>
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<td>T3: Into subserosa, pericolic or perirectal tissues</td>
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<td>T4: Invades other organs or perforates visceral peritoneum</td>
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<tr>
<td><strong>Lymph Node Involvement</strong></td>
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<tr>
<td>N0: No regional node involvement</td>
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<tr>
<td>N1: 1-3 regional nodes</td>
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<td>N2: 4 or more regional nodes</td>
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<tr>
<td><strong>Metastatic Disease</strong></td>
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<td>M0: No distant metastases</td>
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<td>M1: Distant metastases present</td>
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<th>Staging of Colorectal Cancer</th>
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<td><strong>AJCC Stage</strong></td>
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Treatment: Colon Cancer

1. Surgery
2. Radiation Therapy
3. Chemotherapy
   - A. Combination therapy with 5-FU based regimens
   - B. Capecitabine (Xeloda)
   - C. Hepatic artery infusion
4. Immunotherapy

Surgery

- Mainstay for stages I-III, palliation for stage IV
- Surgery is used alone in localized colon cancer, stages I-II
- Generally involves tumor resection with an appropriate margin of tumor-free bowel and a regional lymphadenectomy.
- A colostomy may be needed and involves making an opening in the abdomen for the removal of fecal material.

Radiation

- External beam vs. Internal beam
- Often administered before surgery to reduce the initial size of the tumor and render it more resectable.
- Can be administered after surgery to limit local recurrence of the neoplasm.
- Radiation is adjuvant therapy and palliation for rectal cancer; palliation for colon cancer
- SE’s: heme, depression, dysuria, diarrhea, proctitis, abdominal cramping
Chemotherapy

• Considered for stage II, standard treatment for stages III and IV.
• 5-FU IVP + Leucovorin
• 5-FU continuous infusion
• Capecitabine (Xeloda)
• Stage IV: irinotecan or oxaliplatin may be added
• Second Line: irinotecan/oxaliplatin
• Hepatic artery infusion: fluorodeoxyuridine (FUDR)

5-FU + Leucovorin Regimens for Colon Cancer (NCCN)

• Starting 3-5 weeks after surgery:
  – 5-FU 425 mg/m² IVP + LV 20 mg/m² IVP on d1-5, repeated every 4-5 weeks x 6 months (Mayo Regimen) OR
  – 5-FU 370-400 mg/m² IVP + LV 200 mg/m² IVP on d1-5, repeated q 5 weeks x 6 months OR
  – 5-FU 500 mg/m² IVP + LV 500mg/m² IVP weekly during 6 of every 8 weeks x 1 year

5-FU Continuous Infusion

• Continuous infusion of 5-FU is one of the most efficacious methods of dose intensification.
  – Max cumulative 5-FU dose given as IVP= 2400-2500 mg/m² as compared to 4000-7500 mg/m² when given as a continuous infusion.
• 24 hour infusions
  – 1000 mg/m²/d for 4 days repeated q 28 days
  – 250-300 mg/m²/d for up to 10 weeks
Treatment: Colon Cancer

- Second line:
  1. Irinotecan (Camptosar®) 125 mg/m² IV x 90 minutes every week x 4 weeks + 5-FU/LV, followed by 2 weeks off
     - Side-effects: neutropenia, diarrhea (early and/or late onset) Saltz, J.B. NEJM, 2000
  2. Irinotecan 350 mg/m² single agent Q 3wks JCO, 2003.
  3. Oxaliplatin (Eloxatin®) 85 mg/m²/2 hours IV q 2 weeks + 5-FU/LV
     - Side-effects: sensory neuropathies (acute and/or persistent), anaphylactic-like reactions

Capecitabine (Xeloda®)

- An oral prodrug of 5-FU
- Capecitabine must be converted to 5-FU by the enzyme thymidine phosphorylase which is found predominately in cancer cells.
- Dose= 2500 mg/m²/d x 14 days every 3 weeks
- May soon be first line in place of 5-FU!!

Oral Xeloda achieves at least equivalent efficacy compared with 5-FU/LV

- Superior (p<0.0001) response rates
- Equivalent time to disease progression
- Equivalent overall survival
Summary of Safety

Compared with 5-FU/LV, oral Xeloda results in:
- Significantly lower incidence of diarrhea, stomatitis, nausea and alopecia
- Superiority in frequency and time to first onset of key grade 3/4 adverse events
- Lower incidence of grade 3/4 neutropenia and stomatitis
- More hand-foot syndrome, but rarely led to hospitalization or withdrawal
- Significantly lower treatment-related hospitalization rate

Capecitabine vs. 5-FU/LV*

- 605 chemo-naïve pts with advanced/metastatic colorectal cancer were randomized to either:
  - Capecitabine 1,250 mg/m² po bid in 3-week cycles
  - 5-FU + LV (Mayo Regimen)
- Treatment was continued until disease progression, unacceptable toxicity or until the scheduled assessment at 30 weeks


Capecitabine vs. 5-FU/LV*

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Conclusions:
- Capecitabine more active than 5-FU in the induction of tumor responses
- Capecitabine and 5-FU had similar duration of response and time to response
- Capecitabine and 5-FU had similar time to disease progression and overall survival
- Capecitabine caused fewer side-effects and was better tolerated

Hepatic Artery Infusion for Colon Cancer

- 5-FU is directly infused into the portal vein, beginning 24 hours post-op and continuing for 14 days as a continuous infusion
- Rationale:
  - Liver is the site of recurrence in approx. 40% of colorectal cancer patients
  - Surgical manipulation may cause microemboli of tumor cells to metastasize to the liver
  - 80% of 5-FU is metabolized by the liver
Hepatic Artery Infusion for Colon Cancer

• Other HAI regimens
  – Alternating Fluorodeoxyuridine (FUDR)/5FU
  – 5FU + Interferon
  – FUDR + Leucovorin
  – FUDR + systemic chemo
  – FUDR alone x 2 weeks
  – FUDR + Mitomycin C

Hepatic Artery Infusion for Colon Cancer

• HAI Colorectal Cancer Indications:
  – Nonresectable regional disease
  – Failed systemic chemotherapy
  – Institutions with clinical expertise and experience
  – Adjuvant setting posthepatic resection or radiofrequency ablation (RFA)

Hepatic Artery Infusion for Colon Cancer

– Per McArdle and colleagues*: A meta-analysis of existing trials indicated that although HAI resulted in higher response rates, the overall pt survival did NOT change. In addition, it was discovered that only 37% of HAI pt’s could tolerate the entire 6 cycles due to catheter-related problems.

Adjuvant Immunotherapy

- Bacillus Calmette-Guerin (BCG)
- Levamisole
- Autologous tumor cell vaccines
- IFN-alpha
- Monoclonal antibodies (e.g., edrecolomab)

Rectal Cancer

- Rectal cancer involves those tumors within the most distal 15 cm of the large bowel
- Rectal cancer has a high rate of both local and distal recurrence
- Tumors in the lower third of the rectum have lower cure rates
- Tumors in the upper third of the rectum are treated like colon cancer

Treatment: Rectal Cancer

- Stage I - surgery alone
- Stage II-III - preoperative bolus 5-FU with or without LV + XRT, postoperative 5-FU + LV x 6 months. Capecitabine, irinotecan, or oxaliplatin also used
- Stage IV - palliation
**Investigational Agents**

- Thymidylate synthase inhibitors - Raltitrexed (Tomudex®)
- Angiogenesis inhibitors – bevacizumab
- Epidermal Growth Factor Receptor inhibitors (EGFR) – IMC-C225
- Oral fluorinated pyrimidines
  - UFT (Ftorafur®)
  - Eniluracil + 5-FU
  - Emitefur

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**Pancreatic Carcinoma**

- 4th most common cause of cancer-related death, peaks in 7th-8th decade of life
- No early warning signs (> 80% present with advanced disease
- Whipple Procedure- removal of head of pancreas, duodenum, part of common bile duct and gall bladder. Remaining portions are rejoined to restore continuity. Mortality rate of procedure < 2%. High rate of recurrence.

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**Pancreatic Carcinoma**

- Goal of treatment is palliative (pain, obstructive jaundice, cachexia, pancreatic insufficiency, gastric outlet obstruction, depression)
- 5-FU
- Gemcitabine – mostly for palliation 800-1500 mg/m² weekly. Myelosuppression = most common adverse event.
- Pancrelipase-contains lipase, amylase, protease to aid digestion of meals.