Clinical Colon Cancer 2008
Abby Siegel MD

1. EPIDEMIOLOGY

- Colorectal cancer is the third most common cancer in the United States
- About 150,000 new cases/year
- Most cases in people over 50

2007 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>766,860</td>
<td>678,060</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>19%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

2007 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>289,050</td>
<td>270,100</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>
| Liver & intrahepatic bile duct | 4% | 3% Non-Hodgkin lymphoma
| Urinary bladder   | 3%    |       |
| Non-Hodgkin lymphoma | 3%    |       |
| Kidney            | 3%    |       |
| All other sites   | 23%   |       |

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
EPIDEMIOLOGY
- Incidence rates high in U.S., Europe, Australia
- Increasing in Japan
- Low in China, Africa

2. RISK FACTORS:
Protective
- Folic acid
- Exercise
- NSAIDS
- ? Calcium/Vitamin D
- ? Fiber

NSAIDS
1) Cox-1 and Cox-2 inhibition
   - Aspirin, Ibuprofen
   - Bleeding risk
2) Selective Cox-2 inhibition
   - Rofecoxib (Vioxx),
     - Celecoxib (Celebrex)
   - Thrombosis risk

RISK FACTORS:
Increased risk with...
- Advanced age
- Inflammatory bowel disease
- Consumption of high-fat diet and red meat
- Personal or family history of colon cancer
FAMILIAL SYNDROMES

- HNPCC
  - Hereditary non-polyposis colon cancer
- APC
  - Adenomatous polyposis coli
- Both usually autosomal dominant

HNPCC (Lynch Syndrome)
Hereditary Non-Polyposis Colon Cancer
- 2-5% of colon cancers
- Caused by mutations in mismatch repair genes
- Tend to present in the right colon
- Often associated with endometrial cancer in women
- Start screening at age 21

HNPCC Increases the Risk of Colorectal Cancer

HNPCC Increases the Risk of Endometrial Cancer

HNPCC: Cancer Risks

APC
Adenomatous Polyposis Coli
- Less than 1% of colon cancers
- Caused by mutation of APC gene (5q21)
- Also associated with duodenal cancers, desmoid tumors, “CHRPE” (congenital hypertrophy of the retinal pigment)
- Start screening at puberty
3. MANIFESTATIONS

1. Growth of cancer at primary site

2. Metastatic spread

MANIFESTATIONS

1. Growth of cancer at primary site
   a. Asymptomatic/screening
   b. Right sided syndrome
   c. Left sided syndrome
MANIFESTATIONS

1. Growth of cancer at primary site
   i. Asymptomatic
      - Detected by screening test
      - Fecal occult blood
      - Sigmoidoscopy
      - Colonoscopy
      - “Virtual” colonoscopy
      - Molecular techniques

Screening summary

• Average risk: colonoscopy every 10 years over age 50
• Family history: colonoscopy 10 years before index case
• Dysplastic polyps: repeat colonoscopy after 3 years

Screening, continued…

• APC: annual flexible sigmoidoscopy starting at age 11, colectomy when polyps develop
• HNPCC: colonoscopy at age 21, then every 1-2 years
• Inflammatory bowel disease: start 8 years after pancolitis, 12 years after distal disease

1. Right sided syndrome
   a) Ascending colon has thin wall, large diameter, distensible
   b) Liquid fecal stream
   c) Chronic blood loss results in iron deficiency anemia
   d) Obstruction unlikely
MANIFESTATIONS
1. Growth of cancer at primary site
   iii. Left sided syndrome
   a) Descending colon wall thicker, less distensible
   b) More solid fecal stream
   c) Tumors tend to infiltrate
   d) Bright red blood more common
   e) Obstruction more common

“Apple core lesion”

COMPARISON RIGHT AND LEFT SIDED COLON CANCERS

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Occult bleeding</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Gross bleeding</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Abd. Mass</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Change in bowel habits</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Obstruction</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Colorectal Cancer: Staging (AJCC/ Modified Dukes’)

PROGNOSIS
1. Histological features
   - poor differentiation
   -vascular invasion
2. Depth of invasion
3. Nodal involvement
4. Genetic alterations
   -18q LOH (bad), MSI (good)
MANIFESTATIONS
Metastatic Spread
1. Lymphatics
   - Mesenteric nodes
   - Virchow’s node
2. Hematogenous spread
   - Liver via portal circulation

MANIFESTATIONS
LIVER METASTASES
1. Pain (stretching capsule)
2. Hepatomegaly, nodularity
3. Elevated liver function tests

TREATMENTS
4. TREATMENTS
   1. Surgery
      - Localized disease (Stage I, II, III)
      - Try to remove isolated metastases
   2. Radiation therapy
      - Rectal cancer-helps prevent local recurrence
   3. Pharmaceuticals
      - Stage III and IV disease

TREATMENT: Pharmaceuticals
   1. 5-Fluorouracil
      - pyrimidine antimetabolite
   2. Irinotecan
      - topoisomerase inhibitor
      - prevents re-ligation after cleavage of DNA by topoisomerase I
   3. Oxaliplatin
      - alkylating agent, causes formation of bulky DNA adducts
Exciting new biologics…

4. Bevacizumab
   - Antibody against VEGF
   - May block angiogenesis and also stabilize leaky vasculature

5. Cetuximab, Panitumomab
   - Antibody against EGFR
   - Binds to EGF receptor on tumor cells and prevents dimerization and cell signaling

TREATMENT

Pharmaceuticals
1. “Adjuvant” (after surgery)
   - Curative goal in patients after complete resection
2. Palliation in patients with gross metastatic disease
3. “Neoadjuvant” (before surgery)
   - Shrink tumors, then try to resect in limited metastatic disease

TREATMENT: Metastatic disease

- Systemic chemotherapy now has improved survival for those with metastatic disease to about 2 years
- We now sometimes treat neoadjuvantly (before surgery), shrinking metastases and then surgically removing them
- This is important, because some of these “limited metastases” patients are cured!

Trends in the Median Survival of Patients with Advanced Colorectal Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment Status</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmoll et al.</td>
<td>before any chemotherapy</td>
<td>8 mos</td>
</tr>
<tr>
<td>Choong et al.</td>
<td>Fluorouracil, irinotecan</td>
<td>16.2 mos</td>
</tr>
<tr>
<td>Van Cutsem et al.</td>
<td>Fluorouracil, oxaliplatin, irinotecan, cetuximab</td>
<td>19.2 mos</td>
</tr>
<tr>
<td>Golimumab et al.</td>
<td>Fluorouracil, levamisole, cetuximab</td>
<td>19.2 mos</td>
</tr>
<tr>
<td>Hodi et al.</td>
<td>Nivolumab plus ipilimumab &amp; anti-CD137 monoclonal antibody</td>
<td>19.2 mos</td>
</tr>
</tbody>
</table>
Conclusions:

- Know HNPCC and APC—these may help you prevent cancers in others
- Understand how colon cancer commonly presents (right versus left-sided), and common sites of spread
- Think about colon (or other GI) cancer in an older person with iron-deficiency anemia—don’t just give them iron!
- Don’t give up on those with metastatic disease with new treatment options and occasionally cures

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Many thanks to Tom Garrett for many slides!