Clinical Colorectal Cancer

Abby Siegel MD, MS
COLON CANCER

1. Epidemiology
2. Risk factors
3. Manifestations
4. Treatment
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
Colorectal Cancer Incidence, 2008

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>25%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,690</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>77,250</td>
<td>10%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>51,230</td>
<td>7%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,450</td>
<td>5%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>34,950</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>33,130</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,310</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,180</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>745,180</td>
<td>100%</td>
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</tbody>
</table>
Colorectal Cancer Deaths, 2009

### Estimated New Cases*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>182,460</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,690</td>
<td>100,330</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>77,250</td>
<td>71,560</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>51,230</td>
<td>40,100</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,450</td>
<td>30,670</td>
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<tr>
<td>Melanoma of the skin</td>
<td>34,950</td>
<td>28,410</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>33,130</td>
<td>27,530</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,310</td>
<td>21,650</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,180</td>
<td>21,260</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>19,090</td>
</tr>
<tr>
<td>All Sites</td>
<td>745,180</td>
<td>692,000</td>
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### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>90,810</td>
<td>71,030</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,660</td>
<td>40,480</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>24,260</td>
<td>25,700</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17,500</td>
<td>16,790</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,570</td>
<td>15,520</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,460</td>
<td>9,370</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,250</td>
<td>9,250</td>
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<tr>
<td>Urinary bladder</td>
<td>9,950</td>
<td>7,470</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,790</td>
<td>5,840</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,100</td>
<td>5,650</td>
</tr>
<tr>
<td>All Sites</td>
<td>294,120</td>
<td>271,530</td>
</tr>
</tbody>
</table>

*Per 100,000, age-adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.


American Cancer Society, Surveillance Research, 2006

*Per 100,000, age-adjusted to the 2000 US standard population. †Uterus cancer death rates are for uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.


American Cancer Society, Surveillance Research, 2006
EPIDEMIOLOGY

- Incidence rates high in U.S., Europe, Australia
- Increasing in Japan
- Low in China, Africa
EPIDEMIOLOGY

- Changes in incidence rates over time and with migration may indicate role of environmental factors.
2. RISK FACTORS: Protective

- Exercise
- NSAIDS
- ? Calcium/Vitamin D
- ? Fiber
- ? Folic Acid
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
- 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 early 20s
HNPCC Increases the Risk of Colorectal Cancer

By age 50

Population Risk 0.2%
HNPCC Risk >25%

By age 70

Population Risk 2%
HNPCC Risk 80%

Gastroenterology 1996;110:1020-7
Int J Cancer 1999;81:214-8
HNPCC Increases the Risk of Endometrial Cancer

By age 50

Population Risk 0.2%
HNPCC Risk 20%

By age 70

Population Risk 1.5%
HNPCC Risk 60%

Gastroenterology 1996;110:1020-7
Int J Cancer 1999;81:214-8
HNPCC: Cancer Risks

- Colorectal: 78%
- Endometrial: 43%
- Stomach: 19%
- Biliary tract: 18%
- Urinary tract: 10%
- Ovarian: 9%

Aarnio M et al. *Int J Cancer* 64:430, 1995
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 epithelium)
- 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
Virtual Colonoscopy

Pickhardt et al. NEJM, 349 (23): 2191, 2003
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
MANIFESTATIONS

1. Growth of cancer at primary site
   ii. 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
### 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>
Stage 1 Colorectal Cancer

- 23% of colorectal CA
- Cancer has grown through the mucosa and invades the muscularis
- Treatment: surgery to remove the tumor and some surrounding lymph nodes
- Survival: 93%

Adapted from www.plwc.org, 2007
Stage 2 Colorectal Cancer

- 31% of colorectal CA
- Cancer grows beyond the muscularis of the colon or rectum but has not spread to the lymph nodes
- Treatment (colon): surgery +/- adjuvant chemotherapy
- Survival: 72 to 85%
- Treatment (rectal): surgery, radiation and chemo

Adapted from www.plwc.org, 2007
Stage 3 Colorectal Cancer

- 26% of colorectal CA
- Cancer has spread to the regional lymph nodes
- Treatment (colon): surgery and adjuvant chemotherapy
- Survival: 44 to 83%
- Treatment (rectal): surgery, radiation and chemotherapy

Adapted from www.plwc.org, 2007
Stage 4 Colorectal Cancer

- 20% of colorectal CA
- Cancer has spread to other areas of the body
- Treatment: chemotherapy. Consider surgery of primary lesion, especially if symptomatic
- Surgery to remove metastases (liver/lung) in carefully selected patients
- Survival: 8%

Source: UpToDate.com, 2007
PROGNOSIS depends on...

1. Histological features
   - poor differentiation
   - vascular invasion
2. Depth of invasion
3. Nodal involvement
4. Genetic alterations
   - 18q LOH (bad), MSI (good), K-ras mutation
     (limits response to anti-EGFR antibodies)
MANIFESTATIONS

Metastatic Spread

1. Lymphatics
   Mesenteric nodes
   Virchow’s node

2. Hematogenous spread
   Liver via portal circulation
Metastases
LIVER METASTASES

MANIFESTATIONS
1. Pain (stretching capsule)
2. Hepatomegaly, nodularity
3. Elevated liver function tests
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
   - Antibodies against EGFR
   - Binds to EGF receptor on tumor cells, prevents dimerization and cell signaling
Bevacizumab toxicities

- Bleeding
- Thrombosis
- Hypertension
- Wound healing complications
- Half life about 3 weeks; wait at least 2 half-lives before major surgery
EGFR inhibition and rash
Correlating Survival With Skin Rash

* Log-rank $P$ value, grade 0 vs. grades 1-3


Slide courtesy of Josep Tabernero, MD
Original Article

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Eric Van Cutsem, M.D., Ph.D., Claus-Henning Köhne, M.D., Erika Hitre, M.D., Ph.D., Jerzy Zaluski, M.D., Chung-Rong Chang Chien, M.D., Anatoly Makhson, M.D., Ph.D., Geert D'Haens, M.D., Ph.D., Tamás Pintér, M.D., Robert Lim, M.B., Ch.B., György Bodoky, M.D., Ph.D., Jae Kyung Roh, M.D., Ph.D., Gunnar Folprecht, M.D., Paul Ruff, M.D., Christopher Stroh, Ph.D., Sabine Tejpar, M.D., Ph.D., Michael Schlichting, Dipl.-Stat., Johannes Nipppgen, M.D., and Philippe Rougier, M.D., Ph.D.

N Engl J Med
Volume 360(14):1408-1417
April 2, 2009
Molecularly Targeted Therapy in Oncology

Bevacizumab
Cetuximab, Panitumumab

PDGFR, EGFR, VEGFR

Sunitinib, Sorafenib

P13K, AKT, mTOR

Gefitinib, Erlotinib

Ras, Raf, Mek

CCI-779, RAD001

HIF-1α, HIF-1β

Survival/↓Apoptosis

Angiogenesis

Metastases

Transcription Factors

Nucleus

Transcription Factors

Survival/↓Apoptosis

Angiogenesis

Metastases

proliferation

Slide courtesy of Wells Messersmith, MD
Hazard Ratios for Progression-free and Overall Survival and Odds Ratios with Tumor Response, According to the Mutation Status of KRAS in the Tumor

Molecularly Targeted Therapy in Oncology

Cetuximab, Panitumumab

Bevacizumab

Sunitinib
Sorafenib

PDGFR
EGFR
VEGFR

P13K
AKT
mTOR

Gefitinib
Erlotinib

Ras
Raf
Mek

CCI-779
RAD001

HIF-1α
HIF-1β

Survival/
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proliferation

Transcription Factors
Nucleus

Slide courtesy of Wells Messersmith, MD
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>Scheithauer et al.(^8)</td>
<td>Before any active chemotherapy</td>
<td>6 mo</td>
</tr>
<tr>
<td>Cochrane Database(^12)</td>
<td>Fluoropyrimidine only</td>
<td>10–12 mo</td>
</tr>
<tr>
<td>Saltz et al.(^60) and de Gramont et al.(^70)</td>
<td>Fluoropyrimidine and one other active cytotoxic chemotherapeutic agent (irinotecan or oxaliplatin)</td>
<td>14–16 mo</td>
</tr>
<tr>
<td>Goldberg et al.(^77)</td>
<td>Fluoropyrimidine, irinotecan, and oxaliplatin (in combination or as sequential therapy) or Cytotoxic chemotherapy and targeted therapy</td>
<td>&gt;20 mo</td>
</tr>
</tbody>
</table>

Estimated drug costs for eight weeks of treatment for metastatic colorectal cancer

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
• My email:

• aas54@columbia.edu

• Many thanks to Tom Garrett for several slides!