Screening and Treatment of Colon Cancer

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Associate Professor of Medicine
Ohio State University
James Cancer Center

2008 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td></td>
<td>20%</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2008.

2008 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>bile duct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

*ONS=Other nervous system.
Source: American Cancer Society, 2008.

Cancer Death Rates*Among Men, US, 1930-2004

*Age-adjusted to the 2000 US standard population.
**Cancer Death Rates* Among Women, US, 1930-2004**

- Lung & bronchus
- Uterus
- Breast
- Skin
- Breast & skin
- Other & unknown

**Colorectal Cancer Death Rates, * by State, 2005†**

**Colorectal Cancer Incidence Rates, * by State, 2005†**

**Survival by Stage of Detection**

- Local: 91.4%
- Regional: 66.1%
- Distant: 8.5%
FOBT and Effect on Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Screening</th>
<th>Control</th>
<th>RR (Test)</th>
<th>Weight</th>
<th>RR (trend)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith 2002</td>
<td>200/500</td>
<td>1500</td>
<td>1.44</td>
<td>0.20</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Jones 2003</td>
<td>100/1000</td>
<td>2000</td>
<td>1.65</td>
<td>0.30</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Burns 2004</td>
<td>500/2000</td>
<td>3000</td>
<td>1.55</td>
<td>0.45</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Total</td>
<td>1000/5000</td>
<td>7000</td>
<td>1.55</td>
<td>0.08</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors for Colon Cancer

- Personal history of adenomatous polyps
- Advancing age
  - CRC: 90% occur in people aged 50 or older
  - Adenomatous Polyps: 33% at age 50, 70% at age 70
- A family history of CRC or colorectal polyps
- Inflammatory bowel disease
- Certain hereditary syndromes
  - HNPCC, FAP, Uterine/Ovarian cancer in a young patient
- Lack of regular physical activity
- Diet high in saturated fats, such as red meat
- Low fruit and vegetable intake
- A low-fiber and high-fat diet
- Overweight and obesity
- Alcohol consumption
- Tobacco use
- Diabetes
- Pelvic Radiation

Fruits, Vegetables, and Colon Cancer Risk

J Natl Cancer Inst. 2007;99(19):1471-1483
Trends in Consumption of Five or More Recommended Vegetable and Fruit Servings for Cancer Prevention
Adults 18 and Older, US, 1994-2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence (%)</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
<td>24.2</td>
</tr>
<tr>
<td>1996</td>
<td>24.4</td>
</tr>
<tr>
<td>1998</td>
<td>24.1</td>
</tr>
<tr>
<td>2000</td>
<td>24.4</td>
</tr>
<tr>
<td>2003</td>
<td>23.6</td>
</tr>
<tr>
<td>2005</td>
<td>24.3</td>
</tr>
</tbody>
</table>

Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

FOBT: Mortality Reduction

Adherence at Every level: 100%
IF adherence to initial test: 75%
IF adherence to repeat test after (-) test: 67%
IF rate of colonoscopy after (+) test: 75%
Potential Mortality Reduction 40%
< 20%
Effective – but only in a program of repeat testing

FOBT- One-time Testing

- % of patients with cancer who have (+) test: 33- 60%
- % of patients with serious Polyps who have (+) test: 11- 50%

More than 50% of patients with serious polyps will not be detected with one test !!!

CT Colonography

- Inter-observer variability
- Detection of flat polyps
- Bowel Prep
- Radiation
- Extracolonic findings
- Intervals uncertain:
  - After negative exam
  - After exam with small polyps

Low Resolution CTC
Colonoscopy

Evidence: Cohort Studies

Efficacy: Uncertain, but extrapolated from FOBT and Sig studies

Quality in practice: unknown

Program performance: unknown

National colonoscopy study (Winawer)

Risk Factors for CRC

Sporadic/Average Risk 75%

Family History 15-20%

HNPPC 3%

FAP-1%

IBD-1%

Colitis

Chromosomal Instability (CIN)

Familial Adenomatous Polyposis (FAP)

- FAP accounts for 1% of CRC
- Hundreds to thousands of colon polyps
- Penetration is 100% (All polyps will develop cancer)
- Colorectal cancer usually occurs by age 40
- Yearly screening at age 12

Gastrointestinal Lesions
- Gastric adenomas
- Fundic Gland polyps
- Duodenal, Ampullary adenoma
- Jejunoileal adenomas
- Colorectal Cancer

Extraintestinal Features
- Brain Tumors
- Osteomas
- Desmoid Tumors
- Epidermal Cysts
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
Familial Adenomatous Polyposis (FAP)

- Colon Adenomas
- Osteomas
- Duedenal adenoma
- Congenital hypertrophy of the retinal pigment epithelium

Familial adenomatous polyposis (FAP)

- APC gene mutations on chromosome 5q21
- Autosomal dominant disease
- Genetic testing is available
- Counseling and informed consent
- Colectomy in late teens in gene carriers
- Screening to include upper GI tract
- Decreased screening in non carriers
- Attenuated FAP: people have fewer polyps

Microsatellite Instability (MSI)

- 85% CIN
- TSG's lost by LOH: APC, p53, 18q genes
- Lynch Syndrome
- Methylation of hMLH1
- MSI
- Mutations at target genes with microsatellites
- CIMP
- Multiple TSG's lost by methylation: APC, PTEN, HIC-1, p16, MGMT, etc
- Cancer
DNA mismatch repair (MMR)

The modified Amsterdam criteria for Lynch syndrome

Three or more family members
colorectal cancer, or a Lynch syndrome phenotype cancer
(endometrial cancer, gastric cancer, ovarian cancer, cancer of the urinary tract, small intestinal cancer, and brain tumors)

One is a first degree relative of the other two

At least two generations are involved

Familial adenomatous polyposis is excluded

One person with cancer less than 50 years of age

Familial colorectal cancer, syndrome X

lack microsatellite instability (MSI)
lack of mutation in DNA mismatch repair gene

Hereditary Colorectal Cancer Syndromes: HNPCC

- Lynch syndrome: 5% to 10% of all CRC
- Autosomal Dominant Disease
- Mismatch Repair gene mutation
- The risk of CRC
  - 70% to 90%, Average age of 45
  - Proximal Location
- Extraintestinal cancers
- Genetic testing for HNPCC genes is available

Revised Bethesda Criteria
Screen for Microsatellite Instability (MSI)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC in a patient who is ≤ 50 years of age</td>
<td></td>
</tr>
<tr>
<td>Presence of CRC or other Lynch syndrome-associated tumors, regardless of age</td>
<td></td>
</tr>
<tr>
<td>CRC with the MSI-H histology diagnosed in a patient who is ≤ 60 years of age</td>
<td></td>
</tr>
<tr>
<td>CRC in one or more first-degree relatives with an HNPCC-related tumor, one of the cancers diagnosed ≤ 50 years</td>
<td></td>
</tr>
<tr>
<td>CRC in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age</td>
<td></td>
</tr>
</tbody>
</table>
Inheritance in Family with Hereditary Nonpolyposis Colorectal Cancer

Hereditary Colorectal Cancer

Distribution of Polyps and Cancer

ACS Screening Recommendations 2008

- Colonoscopy (Gold Standard) Every 10 years
- Flexible Sigmoidoscopy and FOBT Every 5 years
- CT colonography Every 5 years
- Flexible Sigmoidoscopy Every 5 years
- Double Contrast Barium Enema Every 5 years
- FOBT or FIT Annually
- A stool DNA test Interval uncertain

All positive tests must be followed up with a colonoscopy
ACS Screening Recommendations 2008

- Colonoscopy (Gold Standard) Every 10 years
- Flexible Sigmoidoscopy and FOBT Every 5 years
- CT colonography Every 5 years
- Flexible Sigmoidoscopy Every 5 years
- Double Contrast Barium Enema Every 5 years
- FOBT or FIT Annually
- A stool DNA test Interval uncertain

All positive tests must be followed up with a colonoscopy

Colorectal Cancer Screening Guidelines 2008

Average Risk

- Age ≥ 50
- No History of Adenoma
- No History of IBD
- Negative Family History

Can detect Precancerous polyps and early cancer
Can detect early cancer

Screening at 50 years
- Repeat every 10 years if negative
- Repeat 3-5 years if polyps are found
Colorectal Cancer Screening Guidelines 2008

Increased Risk

I. Personal History
- Adenomatous Polyps
- Cancer
- Endometrial/Ovarian Cancer ≤60
- Inflammatory Bowel Disease

II. Family History
- One 1st degree relative with CRC
- Two 2nd degree relative with CRC
- Clustering of CRC or HNPCC related cancer

Start Screening at age 40 or 10 years prior to the earliest CRC case in the family
Repeat every 5 years
Increased Risk

III. Hereditary
• CRC age ≤ 50
• Multiple HNPCC related cancer
• HNPCC cancer with family history of CRC or HNPCC cancers
• FAP
• Lynch Syndrome
• Other polyposis syndromes

- Early specific Screening
- Upper GI tract screening
- Non GI cancer screening
- Consider genetic testing and counseling

Colorectal Cancer Screening Guidelines 2008
### Self Expandable Metal Stent

![Images of self-expandable metal stents]

### Ablation Therapy

- Argon-plasma-coagulation

### Cost-effectiveness (Cost/Year of Life Saved)

<table>
<thead>
<tr>
<th>Safety Measure</th>
<th>Cost (Year of Life Saved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory motorcycle helmets</td>
<td>$2000.00</td>
</tr>
<tr>
<td>Colorectal cancer screening</td>
<td><strong>$25,000.00</strong></td>
</tr>
<tr>
<td>Breast cancer screening</td>
<td>$35,000.00</td>
</tr>
<tr>
<td>Dual airbags in cars</td>
<td>$120,000.00</td>
</tr>
<tr>
<td>Smoke detectors in homes</td>
<td>$210,000.00</td>
</tr>
<tr>
<td>School bus seat belts</td>
<td>$1,800,000.00</td>
</tr>
</tbody>
</table>
Future Of Screening for CRC

A recent CDC study demonstrated that:

- Approximately 41.8 million average-risk people aged 50 or older have not been screened for colorectal cancer according to national guidelines.
- The U.S. health care system has enough capacity to conduct widespread screening of the unscreened population, using FOBT and diagnostic colonoscopy for those with a positive FOBT.
- Widespread screening with flexible sigmoidoscopy or colonoscopy may take up to 10 years, depending on the proportion of available capacity used for colorectal cancer screening.

Trend in the prevalence of persons 50 and older reported having had a Sigmoidoscopy/Colonoscopy over the past 5 years in Ohio


Behavioral Risk Factor Surveillance System (BRFSS) in the US

ACS Colorectal Cancer Objectives

- By 2015, reduce the age-adjusted incidence rate of colorectal cancer by 40%
- By 2015, reduce the age-adjusted mortality rate of colorectal cancer by 50%
- By 2015, increase to 75% the proportion of people aged 50 and older who have colorectal screening consistent National guidelines
Ohio
Senate Bill 50/House Bill 266
(Cancer Screening Coverage Legislation)

National
Senate Bill 710/House Representative Bill 1520
(Eliminate Colorectal Cancer Act)

Physician Intervention

The positive impact of a doctor’s advice has been demonstrated in studies of cancer screening behavior for several cancers:

1. Having a received a physician’s recommendation for a flexible sigmoidoscopy makes it more likely that an individual will be screened for CRC.
2. More preventive health visits also increase the likelihood of screening.
3. Having seen a physician within the prior year is one of the strongest predictors of receipt of CRC screening.

Strategies to Increase CRC Screening

1. Increase Public Awareness: Increase individual awareness of personal risk and stimulate action.
2. Affect Physician Behavior Change: Reach out to physicians individually and through systems to provide screening advice, support and resources.
3. Advocate for Coverage: Advocate for state and federal policies to increase access to breast and colon cancer screening.
4. Collaboration: Collaborations provide access to large numbers of people, physicians, and policy decision-makers. They include:
   - Physicians
   - Health Plans
   - Employers
   - Health Care Systems
   - Influencers (Trade and Accreditation Orgs.)

Conclusion

“The barrier to reducing the number of death from colorectal cancer is not a lack of scientific data but a lack of organizational, financial, and societal commitment.”

Daniel K. Podolsky, MD (NEJM 7/20/00)
Therapeutic and Surveillance Strategies in Colorectal Cancer

Tanios Bekaii-Saab, MD
Assistant Professor of Medicine and Pharmacology
Ohio State University
James Cancer Hospital

AJCC Staging Guidelines for CRC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease Development</th>
<th>Definition</th>
<th>Usual Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any T, Any N, M0</td>
<td>Involves submucosa (T1) or muscular propria (T2)</td>
<td>Surgery ± chemotherapy</td>
</tr>
<tr>
<td>II</td>
<td>T1, N0, M0</td>
<td>Involves muscular propria (T3) or nonperitonealized pericolic/perirectal tissues (T4)</td>
<td>Surgery ± chemotherapy</td>
</tr>
<tr>
<td>III</td>
<td>T2, N0, M0</td>
<td>Involves other organs or structures/visceral peritoneum (T4)</td>
<td>Surgery ± chemotherapy</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, Any N, M1</td>
<td>Involves distant metastases</td>
<td>Chemotherapy ± surgery</td>
</tr>
</tbody>
</table>

**Leading Sites of New Cancer Cases and Deaths – 2006 Estimates**

- **Male**
  - Estimation: 148,610
  - Estimated Deaths: 55,170
  - Cancers:
    - Lung & bronchus: 26,460 (17.6%)
    - Colon & rectum: 24,800 (16.7%)
    - Breast: 38,340 (25.5%)
    - Prostate: 22,980 (15.5%)
    - Lymphoma: 12,060 (8.0%)
    - Melanoma: 2,540 (1.7%)
    - Other: 26,220 (17.6%)

- **Female**
  - Estimation: 208,430
  - Estimated Deaths: 55,170
  - Cancers:
    - Breast: 24,800 (12.3%)
    - Colon & rectum: 23,240 (11.2%)
    - Lung & bronchus: 14,460 (7.0%)
    - Prostate: 5,280 (2.6%)
    - Lymphoma: 7,880 (3.8%)
    - Melanoma: 1,420 (0.7%)
    - Other: 25,910 (12.7%)

**CRC Stage at Diagnosis**

- Localized (Stage I and II): 38%
- Regional (Stage III): 36%
- Distant (Stage IV): 19%
- Unstaged: 5%

**AJCC Cancer Staging Manual, Sixth Edition**

Stage II and III Colorectal Cancer: A Closer Look

Increasing Negative Lymph Node count in Stage III CRC is independently associated with improved long term outcome

<table>
<thead>
<tr>
<th># Negative Nodes</th>
<th>Stage IIIA</th>
<th>Stage IIB</th>
<th>Stage IICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 nodes</td>
<td>86.5%</td>
<td>56.3%</td>
<td>39.0%</td>
</tr>
<tr>
<td>≥ 13 nodes</td>
<td>87.6%</td>
<td>73.3%</td>
<td>60.8%</td>
</tr>
</tbody>
</table>

MOSAIC Phase III Trial

- Primary end point: disease-free survival (DFS)
- Secondary end points: overall survival (OS), safety

MOSAIC: Summary

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4</th>
<th>LV5FU2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (overall)</td>
<td>1123</td>
<td>1123</td>
<td>--</td>
</tr>
<tr>
<td>5-year DFS (overall)</td>
<td>73.3</td>
<td>67.4</td>
<td>0.003</td>
</tr>
<tr>
<td>n (stage III)</td>
<td>672</td>
<td>675</td>
<td>--</td>
</tr>
<tr>
<td>5-year DFS (stage III)</td>
<td>66.4%</td>
<td>58.9%</td>
<td>.78</td>
</tr>
</tbody>
</table>

LV5FU2 = 5-Fluorouracil + Leucovorin
FOLFOX4 = LV5FU2 + Oxaliplatin

De Gramont et al., ASCO 2007; Abs 4007
Overall Survival: Stage II and Stage III

MOSAIC – Disease-Free Survival: Stage II Patients

ASCO Recommendations: Stage II Disease

- Routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is NOT recommended.
- Subsets of patients in whom adjuvant therapy can be considered include those with:
  - Inadequately sampled lymph nodes
  - Poorly differentiated histology
  - T4 lesions
  - Perforation

Disease-Free Survival: High-Risk Stage II Patients
Stage II Colon Cancer

- Most large cooperative group studies have failed to demonstrate survival benefit due to:
  - Insufficient number of patients in earlier trials
  - Relatively good prognosis in stage II disease
- Many patients needed to detect treatment benefit

<table>
<thead>
<tr>
<th>Survival</th>
<th>ARR*</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 3 years</td>
<td>85%</td>
<td>2.5%</td>
</tr>
<tr>
<td>At 5 years</td>
<td>75%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* ARR: absolute risk reduction

Stage II Colorectal Cancer

- May need to identify subsets of patients who might benefit:
  - Genomic markers - 18q, microsatellite instability (MSI), p53, thymidylate synthase (TS), TGF-β, methylation (CIMP), et al
- New protocols examining stage II role of markers
  - Eastern Cooperative Oncology Group (ECOG): Evaluating role of thymidylate synthase (TS) as indicator of prognosis – need for adjuvant chemotherapy for stage II

Surveillance Strategies in Stage II and III Colorectal Cancers

Patterns of Recurrence

- 85% of colon cancer recurrences are diagnosed in the first 3 years after surgical resection.
- Most of the recurrences involve the liver
### History and Physical

- Lack of outcome data
- Frequency: Every 3-6 months for 3 years, then every 6 months for years 4 and 5 and then yearly.
- Only 20% of all recurrences are found on the basis of a H&P
- 45% of recurrences within the first 3 years occur between visits and tests

### CT Scanning

- Candidates for CT scanning include:
  - High risk patients (T4, N+ ...)
  - Patients who would be candidates for liver resection
- Every year for 3 years after surgery
- 3 metaanalysis showed a survival benefit for patients with “liver” imaging (25% lower mortality)

### Laboratory Data

- Lack of specificity and sensitivity for a routine CBC testing or LFTS
- CEA should be tested every 3 months for at least 3 years from diagnosis.
  - If CEA is elevated, retesting is warranted. If still increasing, then further evaluation needs to be performed.
  - Institution of chemotherapy should never be based on an elevation of CEA.
  - Of note that 20-30% of all asymptomatic recurrences are not associated with CEA elevations
  - Nearly 80% of all colorectal recurrences are found based on an elevated CEA

### Colonoscopy

- At the time of surgery, the patients should have complete visualization of their large bowel to rule out any metachronous lesions.
- Studies are conflicting about the value of periodic examinations.
  - In one study by Juhl et al only 1/56 recurrences was in the anastomotic site whereas another study showed 3/17 to be at the anastomotic site
- Each patient should have a post-operative colonoscopy to document cancer and polyp-free colon.
- Frequency: 1st year after surgery, then at 3 years and finally at 5 years
## Stage IV Colorectal Cancer

## Advances in the Treatment of Colorectal Cancer

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
</tr>
</tbody>
</table>

**Therapeutic concepts**
- Palliative CT
- Adjuvant CT
- Neoadjuvant CT

**Targeted therapies**
- Irinotecan
- Cetuximab
- Bevacizumab
- Panitumumab

## Making More Patients Eligible Candidates for Surgery

### Traditional Thought: “Black and White” Treatment Approach

- **Resectable Disease**
  - Long interval since primary surgery
  - Single liver nodule
  - Surgery

- **Unresectable Disease**
  - Multiple organ metastases
  - CT

### Redefining Unresectable Disease

- Several liver lesions
- Liver + lung metastases

### The Role Of Cytotoxic Therapy
Considerations for Therapeutic Agents

- **Goal:** Expose patients to all active agents over time (Irinotecan, Oxaliplatin and 5FU)
- **Balance efficacy and toxicity, and tailor to patient needs and status**
- **Determine in which patients specific agents would be preferred (considering patient’s co-morbidities, occupation, psychological status, etc.)**
- **Optimal duration of use to extend the line of treatment**

---

**Biological targets for cancer therapy**

- 1. Growth factors and growth-factor receptors
  - HER family, VEGFR, c-kit/SCFR
- 2. Signal transduction pathways
  - Ras, Raf, MAPK, ERK, protein kinase C, PI3K
- 3. Tumour-associated antigens/markers
  - Gangliosides, CEA, MAGE, CD20, CD22
- 4. Proteasome
- 5. Cell-survival pathways
  - Cyclin-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2
- 6. Extracellular matrix/angiogenic pathways
  - MMPs, VEGF, integrins

---

**Median OS Correlates With Availability of all Drugs Effective in Advanced CRC**

- Saltz (2002)
- Douillard (2000)
- Grothey (2002)
- de Gramont (2000)
- Grothey (2002)
- Goldberg (2002)
- Goldberg (2002)
- Giacchetti (2000)
- Tournigand (2001)
- Grothey (2002)

\[ P = 0.035 \]

---

**The Angiogenic Switch and Antiangiogenic Therapy**

- Somatic mutation
- Small avascular tumor
- Tumor secretion of pro-angiogenic factors stimulates angiogenesis
- Rapid tumor growth and metastasis
- Antiangiogenic inhibitors may furnish this process
Anti-VEGF Approaches and Agents: Summary


EPC Recruitment
Migration
Invasion
Proliferation
Survival
Permeability
Migration
Lymphangiogenesis
Vasculogenesis

VEGFR-1
VEGFR-2
VEGFR-3
Sunitinib
Vatalanib
Sorafenib
Vandetanib
Motesanib
Axitinib
AZD2171
Pazopanib

IMC-18F1
Bevacizumab
VEGF-Trap
IMC-1121b

First-Line Bevacizumab in MCRC: Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS (mo)</th>
<th>15.6</th>
<th>17.6</th>
<th>19.9</th>
<th>21.3</th>
<th>23.1</th>
<th>20.7</th>
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<tr>
<td>IFL</td>
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<tr>
<td>IFL + Bev</td>
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<td>27.0</td>
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<tr>
<td>mFOLFOX</td>
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<td></td>
<td></td>
<td>26.0</td>
</tr>
<tr>
<td>CapeOx + Bev</td>
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<td></td>
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<td></td>
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<td>22.9</td>
</tr>
</tbody>
</table>

EGFr Activation Enhances Pathways Important for Tumor Cell Growth

EGFr Activation and Downstream Signaling Pathways

EGFr Activation
Blood Vessel
Angiogenesis
Metastatic Spread

Phases 3 and 2

Phase 3
AVF2107g
NO16966
BICC-C
Phase 2
TREE-2

OS (mo)

P=0.001; P=0.0769; P=0.02 vs mFOLFOX + Bev

**NCIC CTG CO.17: Cetuximab vs. BSC**

**Randomization**

- Register
- Randomize

**Failed or intolerant to all recommended therapies**

- Cetuximab 400 mg/m² IV week 1 then 250 mg/m² IV weekly
- BSC alone

**Disease Progression or Unacceptable Toxicity**

- Cetuximab + BSC
- BSC alone

**Stratification:**

- Centre
- ECOG PS (0 or 1 vs. 2)

**Primary:** Overall Survival

**Secondary:**

- Progression Free Survival
- Objective Response Rate (RECIST criteria)
- Safety
- Quality of Life

**Median OS**

- 1.2 mos vs. 1.8 mos
  - Hazard Ratio: 0.99    p=.96
- 6.1 mos vs. 4.6 mos
  - Hazard Ratio: 0.68   p<0.0001

**Median PFS**

- 4.5 mos vs. 4.6 mos
  - Hazard Ratio: 0.98       p=.89
- 9.5 mos vs. 4.8 mos
  - Hazard Ratio: 0.55      p<0.0001

**Overall Response Rate**

- 117 vs. 113
  - 81 vs. 83

**Panitumumab vs. BSC**

**Patients screened**

- n = 577

**Randomly assigned**

- n = 231
- n = 232

**Patients failed screening**

- n = 469

**Recognized panitumumab under cross-over protocol**

- n = 576


**Introduction to Panitumumab**

**Waterfall plots showing maximum percent decrease in target lesions**

(A) Patients receiving panitumumab, mutant KRAS.

(B) Patients receiving panitumumab, wild-type (WT) KRAS.

(C) Best supportive care (BSC) patients, mutant KRAS.

(D) BSC patients, WT KRAS. Percentages are best response within each KRAS group, excluding missing or nonassessable postbaseline tumor assessments. PR, partial response (gray); SD, stable disease (yellow); PD, progressive disease (blue).
Progression-free survival by treatment within KRAS groups


NOTE: This graph is not meant to represent a comparison of studies.

Treatment Evolution in mCRC and Impact on Median Survival

<table>
<thead>
<tr>
<th>First-/second-line chemotherapy</th>
<th>First-/second-line sequencing</th>
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</thead>
<tbody>
<tr>
<td>No chemotherapy</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>5-FU monotherapy</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Combination chemotherapy</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Combination chemotherapy + targeted agents</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Combination chemotherapy + targeted agents + bevacizumab</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Ongoing studies</td>
<td>Best supportive care</td>
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</table>

Months

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<th>14</th>
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</tr>
</tbody>
</table>

First-/second-line chemotherapy:
- 5-FU monotherapy
- Combination chemotherapy
- Combination chemotherapy + targeted agents
- Combination chemotherapy + targeted agents + bevacizumab

First-/second-line sequencing:
- Best supportive care
- Best supportive care
- Best supportive care
- Best supportive care
- Best supportive care

Ongoing studies:
- Best supportive care

NOTE: This graph is not meant to represent a comparison of studies.