Update on the Prevention and Treatment for Colorectal Cancer

Christopher Lieu, MD
Director, Colorectal Medical Oncology
University of Colorado Cancer Center

Disclosures

- Consulting
  - Merrimack Pharmaceuticals
  - Merck

- Data Safety Monitoring Board
  - Immune Concepts

Objectives

- Review the risk factors and epidemiology of colorectal cancer
- Discuss the appropriate screening, diagnosis, and work-up of colorectal cancer
- Discuss the standard of care treatment options for early and late-stage colorectal cancer
- Review emerging treatment options for colorectal cancer
Colorectal Cancer 101:
Epidemiology, Risk Factors, Screening

Colon Cancer At-A-Glance*

Colorectal cancer is the second leading cause of cancer-related death in the U.S.
On average, your risk is about 1 in 20, although this varies widely according to individual risk factors.
90% of new cases occur in people 50 or older.
People with a first-degree relative (parent, sibling or offspring) who has colorectal cancer have two to three times the risk of developing this disease.
There are currently more than one million colorectal cancer survivors in the U.S.

Advances in screening


*Source: American Cancer Society
†Source: Surveillance, Epidemiology, and End Results Program: Cancer Statistics Review, 1975–2008
Advances in colorectal cancer

5-year-survival rates (all stages)

<table>
<thead>
<tr>
<th>Period of Diagnosis</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-2016</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>2011-2012</td>
<td>55%</td>
<td>65%</td>
</tr>
<tr>
<td>2012-2013</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>2013-2014</td>
<td>65%</td>
<td>75%</td>
</tr>
<tr>
<td>2014-2015</td>
<td>70%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Risk Factors

• Overweight or Obesity
• Physical Inactivity
• Diet high in red meats, processed meats, and cooking meats at very high temperatures
• Smoking
• Heavy alcohol use
• Family History
  - FAP (1%)
  - Lynch Syndrome 2-4%

Early-Detection Is Critical!

5 Year Survival Rates when diagnosed in

- Early Stage: 90%
- Late Stage: 13%

84% of Late Stage Colorectal Cancer will spread to the Liver

70% of these patients will die from Liver Failure
### United States Preventative Services Task Force Guidelines

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults, beginning at age 50 years and continuing until age 75 years</td>
<td>The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary.</td>
<td>A</td>
</tr>
<tr>
<td>Adults age 76 to 85 years</td>
<td>The USPSTF recommends against routine screening for colorectal cancer in adults 76 to 85 years of age. There may be considerations that support colorectal cancer screening in an individual patient.</td>
<td>C</td>
</tr>
<tr>
<td>Adults older than age 85 years</td>
<td>The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years.</td>
<td>D</td>
</tr>
<tr>
<td>Computed Tomographic Colonography and Fecal DNA testing as screening modality</td>
<td>The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer.</td>
<td>I</td>
</tr>
</tbody>
</table>
American Cancer Society Guidelines

- Flexible sigmoidoscopy every 5 years
- Colonoscopy every 10 years
- Double-contrast barium enema every 5 years
- CT colonography (virtual colonoscopy) every 5 years
- Guaiac-based fecal occult blood test every year
- Fecal immunochemical test (FIT) every year
- Stool DNA test every 3 years

**TAKE HOME POINT:**

Everybody should start screening at age 50

Or 10 years before the youngest case in the immediate family

Patients 76 – 85? No good evidence.

Colonoscopy is the GOLD standard

Colorectal Cancer:
*Presentation, Work-up, Early-Stage Management*
History and Physical Examination

- Hematochezia – 58%
- Abdominal Pain – 52%
- Unexplained Iron Deficiency Anemia – 57%
- Weight Loss – 39%
- Altered Stools – 25%
- Obstruction – 4%

Diagnosis/Staging

- Labs
  - CBC, CMP, CEA
- Procedures
  - Colonoscopy with biopsy
  - Flexible sigmoidoscopy with biopsy
- Radiology
  - CT scan
  - Chest/Abdomen/Pelvis (Chest is controversial)
  - PET/CT (?)
  - Liver MRI (?)

Distribution of Colorectal Cancer
Factors Influencing Treatment Selection

- Tumor
  - Resectability
  - Biology
  - Symptoms

- Patient
  - Age
  - General Health
  - Other Diseases
  - Preference

- Treatment
  - Efficacy
  - Toxicity
  - Availability

Surgical Resection:
*Treatment of choice for early-stage colorectal cancer*

Radiation Therapy:
*Used prior to surgery or sometimes to treat metastases*
**Limited Stage Colon Cancer**

- Stage I through III Colon Cancer (no distant metastases)
  - Surgical Resection First

- Adjuvant Chemotherapy – 6 months of chemotherapy
  - High-Risk stage II
    - Poorly differentiated, T4 tumor, Obstruction/Perforation, Vascular invasion, < 12 Lymph Nodes removed
  - Stage III (any lymph node involvement)
    - FOLFOX (5-fluorouracil and oxaliplatin)

**Limited Stage Rectal Cancer**

- Stage I
  - Surgical Resection First

- Stage II or higher
  - “Neoadjuvant” chemotherapy and radiation (chemoXRT)
  - 5-FU/leucovorin or capecitabine combined with radiation therapy (5 weeks)

**Neoadjuvant Treatment – Rectal Cancer**

- ChemoXRT (5 weeks)
  - 5-FU or Cape

- Surgery

- Chemotherapy (4 months)
  - FOLFOX
Colorectal Cancer:  
*Management of late-stage disease*

General Themes of Treatment

- Some patients with stage IV disease are cured using multi-disciplinary approaches (surgery, chemo, etc)
- Combination therapy is generally well-tolerated
- Biologics have added incremental (and somewhat disappointing) benefit
- Era of personalized therapy began with KRAS

**11 FDA Approved Drugs for Colorectal Cancer**

<table>
<thead>
<tr>
<th>“Cytotoxics”</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 5-Fluorouracil (5-FU)</td>
<td>pyrimidine analog</td>
</tr>
<tr>
<td>2. capecitabine</td>
<td>oral 5-FU pro-drug</td>
</tr>
<tr>
<td>3. TAS-102</td>
<td>5-FU drug with metabolism inhibitor</td>
</tr>
<tr>
<td>4. irinotecan</td>
<td>topoisomerase I inhibitor</td>
</tr>
<tr>
<td>5. oxaliplatin</td>
<td>3rd generation platinum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Biologics/Targeted”</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. cetuximab</td>
<td>antibody against EGFR</td>
</tr>
<tr>
<td>2. panitumumab</td>
<td>antibody against EGFR</td>
</tr>
<tr>
<td>3. bevacizumab</td>
<td>antibody against VEGF</td>
</tr>
<tr>
<td>4. ziv-aflibercept</td>
<td>VEGF trap</td>
</tr>
<tr>
<td>5. regorafenib</td>
<td>tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>6. ramucirumab</td>
<td>antibody against VEGFR2</td>
</tr>
</tbody>
</table>
### Colorectal Cancer is Expensive

- 5-FU (500 mg/m²) $6
- Leucovorin (500 mg/m²) $85
- Capcitabine (2000 mg/m²/day) $3,250
- Irinotecan (180 mg/m²) / generic $2,360 / $480
- Oxaliplatin (85 mg/m²) / generic $4,190 / $590
- Bevacizumab (5 mg/kg) $2,560
- Cetuximab (250 mg/m²) $5,120
- Panitumumab (6 mg/kg) $4,360
- Aflibercept (4 mg/kg) $5,380
- Regorafenib (160 mg, 3/1) $5,650

1997: 6 months of 5-FU/LV costs ~$500
2016: 30 months of therapy with combinations costs >$400,000

### Surgical Resection of Liver Tumors

- High frequency alternating current
- Ionic vibration & heat generation
- 45°C Protein denaturation
- 70°C Thermal coagulation
- 100°C Tissue desiccation

### Radiofrequency Ablation (RFA)

**mCRC Outcomes Have Improved With the Evolution of Treatment Options**

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>Cetuximab, BSC, Irinotecan, 5-FU, Oxaliplatin, Bevacizumab</td>
</tr>
<tr>
<td>1990s</td>
<td>CAPECITABINE, OXALIPLATIN, BEVACIZUMAB</td>
</tr>
<tr>
<td>2000s</td>
<td>AFLIBERCEPT, REGORAFENIB</td>
</tr>
</tbody>
</table>

---

**Overview of EGFR and VEGFR Growth Signaling Pathways**

- **EGFR**: epidermal growth factor receptor
- **VEGFR**: vascular endothelial growth factor receptor

**Targeted by cetuximab and panitumumab**

**Targeted by bevacizumab and aflibercept**

**VEGF**

**Recent “progress” in colorectal cancer**

- **On average, patients lived for 6 weeks longer**

---

**References**


---

**Abbreviations**

- **BSC**: best supportive care
- **5-FU**: fluorouracil
- **CAPECITABINE**: capecitabine
- **OXALIPLATIN**: oxaliplatin
- **BEVACIZUMAB**: bevacizumab
- **AFLIBERCEPT**: aflibercept
- **REGORAFENIB**: regorafenib
Current Cancer Treatment Strategy: One-size-fits-all

Where are we going?
The future of Colorectal Cancer Therapy

BRAF inhibition in Melanoma
BRAF Inhibition in Melanoma

Cancer signaling is complex!
Advances in Understanding the Genetic Landscape of Cancer

- On average, there are 50-70 genes mutated per cancer
- However, < 20 pathways will actually drive cancer development
- Most mutations are harmless

Roadmap of Precision Oncology

- ImmunoHerapy 101
Hallmarks of Cancer

Types of Immune Therapy

PD-1 and PD-L1 Function as Immune Checkpoints: Prevents Activation
Number of mutations vary by cancer

Clinical Activity of Anti-PD-1 Therapy: Melanoma
Baseline: April 13, 2012  April 9, 2013
72-yr-old male with symptomatic progression after biochemotherapy, HD IL-2, and ipilimumab

Clinical Activity of Anti-PD-1 Therapy: Lung Cancer
Lung cancer response to anti-PD-1 (4 prior treatments)
Pembrolizumab Antitumor Activity

Change From Baseline in Sum of Largest Diameter of Target Lesions (%)

Melanoma (N = 411)  
KEYNOTE-001

NSCLC (N = 262)  
KEYNOTE-001

HNSCC (N = 61)  
KEYNOTE-012

Urothelial Cancer (N = 33)  
KEYNOTE-012

Gastric Cancer (N = 39)  
KEYNOTE-012

TNBC (N = 32)  
KEYNOTE-012

cHL (N = 29)  
KEYNOTE-013

Microsatellite Unstable CRC

MSI-high

The Importance of Mismatch Repair
Microsatellite High Colorectal Cancer

• **Germline (Hereditary):**
  - HNPCC or Lynch Syndrome
  - Due to mutations in one of the mismatch repair (MMR) genes
  - MLH1, MSH2, MSH6, PMS2, and/or EPCAM
  - Increased lifetime risk of colorectal, endometrial, stomach, ovarian, urothelial, and other cancers

• **Acquired MSI**
  - Most due to hypermethylation of the MLH1 promoter and epigenetic silencing of MLH1
  - Can also have “double somatic” MSI caused by mutations in MMR genes

• **Two methods for testing**
  - PCR – identify variation in genomic repeats
  - IHC – loss of expression of one or more MMR proteins

MSI-high tumors have more mutations

MSI-high Cancers Have Tumor Infiltrating T-cells (which can help kill cancer)
MSI-H in Colon Cancer: Prevalence and Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prevalence</th>
<th>Prognosis Compared to MSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>15%-20%</td>
<td>excellent</td>
</tr>
<tr>
<td>III</td>
<td>8%-10%</td>
<td>same</td>
</tr>
<tr>
<td>IV</td>
<td>4%-5%</td>
<td>same or worse</td>
</tr>
</tbody>
</table>

- Hypermutated cancers too "deranged" to metastasize
- Immune system can prevent spread
- But once a metastatic clone has been selected, same or worse prognosis than microsatellite stable CRC

PD-1 Pathway and Pembrolizumab

- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function
- PD-L1 expression on tumor cells and macrophages suppresses immune surveillance, permitting neoplastic growth
- Pembrolizumab is a humanized, IgG4 monoclonal antibody that
  - Binds to PD-1 with high affinity, preventing PD-1 from binding to PD-L1 and PD-L2
  - Has demonstrated robust antitumor activity and manageable toxicity in multiple advanced cancers

Study Design

<table>
<thead>
<tr>
<th>Colorectal Cancers</th>
<th>Non-Colorectal Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A</td>
<td>Cohort B</td>
</tr>
<tr>
<td>Deficient in Mismatch Repair (n=26)</td>
<td>Proficient in Mismatch Repair (n=25)</td>
</tr>
<tr>
<td></td>
<td>Cohort C</td>
</tr>
<tr>
<td></td>
<td>Deficient in Mismatch Repair (n=21)</td>
</tr>
</tbody>
</table>

- Anti-PD1 (Pembrolizumab) = 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability
### Objective Responses

<table>
<thead>
<tr>
<th></th>
<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
<th>MMR-deficient non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
</tr>
</tbody>
</table>

### Responses in MSI-high CRC

#### A Biochemical Response

- Mismatch repair-proficient colorectal cancer
- Mismatch repair-deficient colorectal cancer
- Mismatch repair-deficient noncolorectal cancer

#### B Radiographic Response

- 20% increase (progressive disease)
- 40% decrease (partial response)
**Marck Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for KEYTRUDA® (pembrolizumab) in Advanced Colorectal Cancer**

Designation based on results in patients with metastatic colorectal cancer with high levels of microsatellite instability

- Intended to expedite the development and review of a drug where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies

---

**Keynote-164**

**Patients**
- Locally advanced, unresectable, or metastatic MSI-high CRC
- ≥ 2 prior treatments with standard therapy

**Pembrolizumab**
- 200mg every 3 weeks
- Complete Response
- Organ shrinkagePrimary Response
- Partial Response or Stable Progression
- Progression
- Discontinue

**Treatment of CRC**

- The revolution of genetic information on tumors over the last 5 years has greatly increased understanding of tumor biology
- But… this has not yet translated into the clinic, since surgery is still the mainstay of curing solid tumors like colorectal cancer
- Ignorance (lack of research) is costly and deadly; without knowledge of KRAS/NRAS, for instance, we would be spending >$800,000,000 per year harming patients
- Knowledge of relevant biomarkers is critical in caring for colorectal cancer patients; however, important to use markers that have been validated/qualified across multiple studies
Questions