A Brief Overview of Screening and Management of Colorectal Cancer

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Disclosures

• Nothing to disclose

Objectives

• Review the epidemiology of colorectal cancer
• Discuss screening, diagnosis, and work-up of colorectal cancer
• Discuss management of early-stage colorectal cancer
• Discuss the standard of care treatment options for advanced / metastatic colorectal cancer
Colorectal Cancer
Epidemiology and Risk Factors

Colorectal Cancer Fast Facts

- Colorectal cancer is the 3rd most common cancer diagnosed in both men and women in the US.
- 2018 ACS estimates:
  - 97,220 new cases of colon cancer
  - 43,030 new case of rectal cancer

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
  - Inherited syndromes: FAP (1%), Lynch Syndrome 2-4%
  - First degree relative

*Source: American Cancer Society
Colorectal Cancer

Screening

The Concept of Screening

Screening is the presumptive identification of unrecognized disease with a feasible strategy that leads to a curative treatment.

Who should get screened and when?

- **Depends on the RISK:**
  - Average risk
  - Higher than average risk
    - A strong family history of colorectal cancer and polyps
    - A personal history of colorectal cancer or certain types of polyps
    - A personal history of inflammatory bowel disease (ulcerative colitis or Crohn's disease)
    - A known family history of a hereditary colorectal cancer syndrome such as familial adenomatous polyposis (FAP) or Lynch syndrome (also known as hereditary nonpolyposis colon cancer)
    - A personal history of radiation to the abdomen (belly) or pelvic area to treat a prior cancer
US Preventative Task Force Guidelines

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults aged 50-75 years</th>
<th>Adults aged 76 to 85 years</th>
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<tbody>
<tr>
<td>Recommendation</td>
<td>Screen for colorectal cancer starting at age 50 years</td>
<td>The decision to screen for colorectal cancer is an individual one</td>
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<tr>
<td>Grade</td>
<td>A</td>
<td>C</td>
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- Methods:
  - Stool-based tests (gFOBT, FIT, and FIT-DNA)
  - Direct visualization tests
    - Flexible sigmoidoscopy (alone or combined with FIT)
    - Colonoscopy
    - CT colonography
  - Serology tests (SEPT9 DNA test)

  “The USPSTF found no head-to-head studies demonstrating that any screening strategy is more effective than others”

USPSTF Screening for Colorectal Cancer. *JAMA* 2016;315(23):2564-2575.

Incidence of colorectal cancer is decreasing

Siegel et al. *JNCI* 2017 109(8).
But increasing in the younger population

The impact of young adult colorectal cancer: incidence and trends in Colorado

American Cancer Society 2018

“Our finding that colorectal cancer risk for millennials has escalated back to the level of those born in the late 1800s is very sobering.”

“People at average risk of colorectal cancer should start regular screening at age 45”
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%

Colon Cancer Diagnosis/Staging

• Labs
  • CBC, CMP, CEA
• Procedures
  • Colonoscopy with biopsy
  • Flexible sigmoidoscopy with biopsy
• Radiology
  • CT scan
  • Chest/Abdomen/Pelvis (Chest is ?)
  • PET/CT (7)
  • Liver MRI (7)
Rectal Cancer (Special Issues)

- Chest CT
  - Venous drainage bypasses the liver
  - Lung metastases
- Rigid sigmoidoscopy
- Transrectal ultrasound
- Pelvic MRI

Colorectal Cancer Staging

Colorectal Cancer Survival by Stage
Colorectal Cancer:
Management Strategies, localized disease

Management of Localized (Early Stage I-II) Colon Cancer
• Surgery is the only curative treatment for colon cancer

5 yr survival rates:

stage I colon cancer: about 92%.
stage II A colon cancer: the 5-year relative survival rate is about 87%.
stage II B cancer: the survival rate is about 65%.
Management of Localized (Early Stage I-II) Colon Cancer

- What about Adjuvant Chemotherapy?
  - Goal is to eradicate microscopic metastasis to increase cure rate
  - Many phase III trials and meta-analyses demonstrate benefit in stage II disease, but absolute survival benefit is small (~3-4% vs observation)
- Regimens used:
  - 5-FU + Leucovorin
  - 5-FU + Leucovorin + Oxaliplatin
  - Capecitabine + Oxaliplatin
- Drugs not used:
  - Irinotecan
  - Biologic targeted therapy (panitumumab, bevacizumab)

Management of Localized Colon Cancer

- Biomarkers and clinical features to predict benefit or non-benefit?
  - dMMR/MSI-H status:
    - ~15-20% of early stage colon cancers
    - A systematic review of 32 studies showed no benefit of adjuvant 5-FU based chemotherapy in stage II dMMR/MSI-H CRC, and a potential for harm (HR for death 1.24, 95% CI 0.72-2.14)
  - BRAF V600E status: unclear
    - Half of dMMR/MSI- in CRCs have BRAF V600E, but similar 5yr OS
    - MSS BRAF V600E tend to do worse
  - Clinical High Risk features:
    - T4, perforation, obstruction, high-grade, poorly differentiated (signet ring, mucinous), LVI, PNI, close margins, less than 13 LNs sampled, very high pre-operative CEA

Management of Localized Rectal Cancer

- Surgery is the only curative treatment for rectal cancer
- Requirements:
  - Negative margins
  - Total mesorectal excision (TME): allows for a wide excision and resection of adjacent lymph nodes within the mesentery
- Transabdominal procedures:
  - low anterior resection (LAR)
  - abdominopерineal resection (APR)
- Anatomical location of the tumor is problematic
- Surgery + Chemotherapy + Radiation
Sequencing of therapies

- Chemotherapy regimens are similar to colon cancer
- Chemo-RT: capecitabine often used (less toxic, more convenient)
- Neoadjuvant vs Adjuvant vs Total Neoadjuvant Therapy (TNT)

Adjuvant Chemotherapy for stage III CRC

- Duration: IDEA trial, 3 vs 6 months of adjuvant chemotherapy

Adjuvant Chemotherapy for stage III CRC

- Negative study, overall statistically. But…
Adjuvant Chemotherapy for stage III CRC

• CAPOX 3 mos if T1-3/N1, 6 mos if T4N2
• If FOLFOX: 6 months

IDEA collaborators, ASCO 2017
Management Principles of Metastatic Colorectal Cancer

• Still multi-disciplinary because of the possibility of cure
• "Oligometastatic" liver only disease
• Systemic therapy:
  • "2018 vs 1980"
  • Biologic / targeted therapy
  • Immunotherapy
  • Predictive biomarkers
    • Mutations
    • TMB
    • Tiledness

Oligometastatic CRC

• Resectable Liver only: 60 study meta-analysis showed 5-year and 10-year survival rates ranging from 16% to 75% (median 38%) and 9% to 69% (median 26%), respectively.
• Ablatable/resectable lung metastasis: data not as strong
• Extrahepatic oligometastatic disease other than lung: limited, weak data

50% of CRC patients will develop liver mets
10% will have liver only
10-20% of CRC patients will develop lung mets
2-4% will have lung only

14 FDA Approved Drugs for Metastatic CRC

<table>
<thead>
<tr>
<th>Cytotoxics</th>
<th>Biologics / Targeted / Immunotherapy</th>
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<tr>
<td>1. 5-FU (pyrimidine analog)</td>
<td>6. Cetuximab (chimeric EGFR antibody)</td>
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<td>2. Capecitabine (oral 5-FU prodrug)</td>
<td>7. Panitumumab (humanized EGFR antibody)</td>
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<td>3. TAS-102 (5-FU w/ metabolism inhibitor)</td>
<td>8. Bevacizumab (VEGF antibody)</td>
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<td>5. Irinotecan (topoisomerase inhibitor)</td>
<td>10. Ramucirumab (VEGFR small molecule inhibitor)</td>
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<td>11. Regorafenib (multi-kinase inhibitor)</td>
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<td>12. Pembroliumab (anti-PD1 inhibitor)</td>
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<td>13. Nivolumab (anti-PD1 antibody)</td>
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<td>14. Ipilimumab (anti-CTLA4 antibody)</td>
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Biomarkers

- Biomarker testing is necessary to tailor treatment and prevent harm
- Mutations
  - KRAS
  - NRAS
  - BRAF
- MSI-H vs MSS

RAS mutations and anti-EGFR therapy

- ~50% of CRCs have RAS mutations (K/Nras)
- RAS mutations confer resistance

MSI-H Immunotherapy

- Hypermutation-antigen probability
- The immune system has the potential to eliminate MSI-H cancers and prevent spread
Sidedness: Right vs Left

- R>L have better prognosis, R CRC don’t respond well to anti-EGFR with 1st line therapy

Therapeutic Fulcrum

Benefit  Harm

Question 1

- 40 year old male presented with hematochezia and was found to have an ascending colon adenocarcinoma on colonoscopic evaluation. He underwent resection and was pathologically staged as pT3pN0 (0/18 LNs). His tumor was found to be MSI-H. There was no LVI, PNI or perforation. What is recommended after the resection?
  1. Adjuvant chemotherapy with FOLFIRI x 6 mo
  2. Adjuvant FOLFOX + bevacizumab x 6 mo
  3. Adjuvant FOLFOX + pembrolizumab
  4. Observation
Question 1

• Answer is 4: observation

This is a low risk stage IIA CRC that is MSI-H. Prognosis is excellent without further chemotherapy in the absence of high risk features. Irinotecan, bevacizumab and pembrolizumab are not used in the adjuvant setting. Potential for harm with 5-FU based regimens in stage II CRCs that are MSI-H.

Question 1.2

• The patient was then lost to follow-up (joined a cult and ultra-cleansed with durian fruit instead of colonoscopic surveillance and genetic counseling). He then presented back with anemia and weight loss and found to a 4cm splenic flexure colon mass with 2 liver hypodensities in segment 6. Biopsy of the liver met showed adenocarcinoma, MSI-H, RAS/RAF wild type. He has re-joined civilization and now wants therapy. What would you treat him with?
  1. FOLFOX + erlotinib
  2. Multi-disciplinary evaluation for resection of primary and liver mets
  3. Ipilimumab and Nivolumab upfront
  4. Probiotics

The End

Questions?