Medical Management of Colon and Rectal Cancer: An Overview

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Outline / Learning Objectives

- Epidemiology and Statistics
- Metastatic colon and rectal cancer (CRC)
  - Stage IV
- Locally advanced colon cancer
  - Post-operative (adjuvant) therapy for Stage III (and II)
- Locally advanced rectal cancer
  - Pre-operative (neo-adjuvant) and post-operative therapy for Stage II and III

How common is colon cancer?

Lifetime Risk is 4.8%
1.1 million Americans living with colon cancer
Worldwide: 1.3 million cases and 700,000 deaths annually


Common presenting symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>Median Duration, Wk (20–76%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal occult blood test positive</td>
<td>149 (77)</td>
<td>2 (1–7)</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>113 (59)</td>
<td>8 (3–15)</td>
</tr>
<tr>
<td>Anemia*</td>
<td>110 (57)</td>
<td>2 (1–15)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>100 (52)</td>
<td>8 (3–20)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>76 (39)</td>
<td>27 (9–62)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>53 (27)</td>
<td>9 (4–20)</td>
</tr>
<tr>
<td>Constipation</td>
<td>53 (27)</td>
<td>16 (1–30)</td>
</tr>
<tr>
<td>Altered stools</td>
<td>48 (25)</td>
<td>14 (1–27)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49 (25)</td>
<td>14 (1–27)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43 (22)</td>
<td>5 (3–15)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>42 (22)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>16 (8)</td>
<td>5 (4–21)</td>
</tr>
<tr>
<td>Muscle in stool</td>
<td>10 (5)</td>
<td>12 (6–28)</td>
</tr>
<tr>
<td>Rectal pain</td>
<td>5 (5)</td>
<td>14 (10–22)</td>
</tr>
<tr>
<td>Obstruction</td>
<td>5 (5)</td>
<td>1 (1–4)</td>
</tr>
</tbody>
</table>

Majumdar SR, Am J Gastro, PMID: 10529666

Colorectal cancer is a disease of older patients

Colorectal cancer deaths are preventable with screening

- Colonoscopy starting at age 50y in average risk patients
- FOBT every 1-2y
- 30-50% don’t get screened - who are we missing?
  - Poor
  - Less educated

More organ dysfunction and comorbidities


Work up and staging of colon cancer patients

- Colonoscopy with biopsy
- CT chest-abdomen-pelvis
- PET or dedicated liver imaging in selected cases
- Rectal cancer only: MRI or endoscopic US
- Depth of invasion
- Identify suspicious lymph nodes
- Labs:
  - CBC, renal function, liver function
  - CEA tumor marker
- Molecular testing of tumor in certain situations
  - Microsatellite instability testing
  - Ras mutation status if considering EGFR mAbs

Colorectal Cancer Staging

- Depth of Invasion
  - T1-T4b
- Number of Nodes
  - N0: 0
  - N1: 1-3
  - N1c: Deposits
  - N2: ≥ 4
- Metastases
  - M0 - M1 (a = 1 site)
  - M1b: > 1 site, peritoneum

Localized colon and rectal tumors: Biologically similar, treated differently

- Colon cancers have low risk of local recurrence
- Rectal cancers have high risk of local recurrence
- Sterilize rectum and surrounding pelvic structures by including radiation therapy

Metastatic colorectal cancer (CRC)

- Liver most common
  - 1/3 liver only
  - 2/3 liver and other organs
- Lung
- Peritoneum
- Extent of metastasis influences therapy and cure rate

Stage at diagnosis and 5 year survival

Most patients present with locoregional disease
Metastatic disease accounts for most deaths

Treatment Overview

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Colon</th>
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</tr>
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<tr>
<td>I</td>
<td>T1-2 N0M0</td>
<td>Surgery</td>
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<td>Surgery +/- Chemo</td>
<td>Neoadjuvant Chemo\XRT then Surgery</td>
</tr>
<tr>
<td>III</td>
<td>Tx N1-2 M0</td>
<td>Surgery + Chemo</td>
<td>then Surgery then Chemo</td>
</tr>
<tr>
<td>IV</td>
<td>Tx Nx M1</td>
<td>Chemo +/- Surgery</td>
<td>Chemo +/- Surgery &amp; XRT</td>
</tr>
</tbody>
</table>

Surgery is an essential component of treatment for most colorectal patients
Treatment of colorectal cancer by stage: Working backwards!

- Once disease spreads distantly, it is treated the same regardless of location of primary tumor in colon or rectum
  - Resectable = potentially curable
  - 10-20% of patients
  - Unresectable = incurable
  - 80% of patients

- Experience in metastatic disease setting guides treatment of earlier stage disease

http://www.cancer.gov/cancertopics/pdq/treatment/colon/Patient/page2#Keypoint14

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Year Approved</th>
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<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>Adrucil</td>
<td>1962</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>Wellcovorin</td>
<td>1990s</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Camptosar</td>
<td>1996</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Xeloda</td>
<td>2001</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Eloxatin</td>
<td>2004</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>2004</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>2004</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
<td>2006</td>
</tr>
<tr>
<td>Ziv-Aflibercept</td>
<td>Zaltrap</td>
<td>2012</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Stivarga</td>
<td>2012</td>
</tr>
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</table>

Fluorouracil (5FU) modestly increases overall survival in metastatic CRC

- IV 5FU or modulated 5FU (+LV) tested in 80s and 90s
  - Response rate 10-30%
  - Overall survival benefit ~ 4 months
- Oral 5FU (capecitabine) equivalent to IV 5FU with less toxicity
  - 1000-1250mg/m2 BID 14 of 21 days

5FU still used as single agent but more important as backbone of multidrug regimens

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Combination therapies: Oxaliplatin and 5FU

- Oxaliplatin is a platinum compound that interferes with DNA replication
- No single agent activity in CRC
- Combination with 5FU very effective
  - Doubles response rate to 50%
  - PFS 9.0 months
- FOLFOX:
  - Oxaliplatin 85mg/m2 q2 weeks
  - 5FU bolus then 46h CI q2 weeks
- Dose limiting toxicity is peripheral neuropathy that is sometimes permanent

Treatment options for metastatic CRC

- CYTOTOXIC CHEMOTHERAPY REGIMENS
  - 5FU/LV PFS 4.2 m
  - Capcitabine PFS 4.3 m
  - FOLFIRI PFS 7.2 m
  - FOLFOX PFS 9.0 m

- CYTOTOXIC + VEGF Inhibitor REGIMENS
  - 5FU/LV + bevacizumab PFS 8.8 m
  - Capcitabine + bevacizumab PFS 8.5 m
  - FOLFIRI + bevacizumab PFS 9.2 m
  - FOLFOXIRI + bevacizumab PFS 12.2 m

Targeting the EGF pathway in colorectal cancer

- Monoclonal antibodies block EGF receptor and inhibit cell growth
  - Cetuximab
  - Panitumumab

- Effective as single agents or in combination with other chemotherapy
  - Given IV every 1-2 weeks
  - 4 month PFS as 2nd line

- Side effects
  - Rash
  - Infusion reactions
  - Diarrhea

Anti-angiogenic agents improve efficacy of chemotherapy

- Tumors depend on blood supply to grow
- No benefit as single agents
- Exactly how these agents work in colorectal cancer is not clear

- Combining bevacizumab with chemotherapy modestly improves efficacy
  - FOLFOX + Bev
  - FOLFIRI + Bev
  - Capcitabine + Bev
  - Bevacizumab adds 1-4 months survival compared to regimens without bevacizumab
  - Bevacizumab can be continued at progression
    - Improved delivery of chemotherapy to tumor?

COMMON SIDE EFFECTS: Hypertension Proteinuria Neutropenia

BLACK BOX WARNINGS:
GI Perforation in 2.4% Wound Healing Problems Bleeding
Arterial Thromboembolic Events (ATE) in older patients and/or history of ATE
Ras Mutations and Benefit from EGFR Inhibitors

*Wild-type ras* when EGF binds EGFR, WT ras signals cell proliferation

*Mutated ras* continuously active

Cell Proliferation

EGFR Signaling Pathway

CETUXIMAB/PANITUMUMAB DO NOT BENEFIT RAS MUTANT

ALL METASTATIC TUMORS NEED RAS TESTING

Regorafenib

• “Multikinase inhibitor”
  - VEGF (angiogenesis)
  - PDGF
  - MAPK
  - c-Kit (GIST)
  - FGF
  - BRAF

• Tested in patients refractory to other therapies – CORRECT Study
  - BSC vs. Regorafenib 160mg qd 21 of 28 days
  - 1.4m benefit in survival (6.4 vs. 5 months)

• Very toxic drug in these heavily pretreated pts
  - 93% had adverse events
  - 76% required dose modifications
    - 50%: Hand-Foot syndrome, Fatigue
    - 30%: Diarrhea, Rash
    - 10%: Liver dysfunction

Few patients can tolerate this drug so its role is very limited

Grothey, Lancet 2013: PMID 23177514

Treatment options for metastatic CRC

• CYTOTOXIC CHEMOTHERAPY REGIMENS
  - 5FU/LV: PFS 4.2 m
  - Capecitabine: PFS 4.3 m
  - FOLFIRI: PFS 7.2 m
  - FOLFOX: PFS 9.0 m

• CYTOTOXIC + VEGF Inhibitor REGIMENS
  - 5FU/LV + bevacizumab: PFS 8.8 m
  - Capecitabine + bevacizumab: PFS 8.5 m
  - FOLFOX + bevacizumab: PFS 9.4 m
  - FOLFIRI + bevacizumab: PFS 10.6 m
  - FOLFOXIRI + bevacizumab: PFS 12.2 m

• TARGETED AGENTS
  - Cetuximab or panitumumab +/- Irinotecan (RAS WT)
  - Regorafenib

Decisions, Decisions!

THE RIGHT TREATMENT FOR THE RIGHT PATIENT

BALANCE EFFICACY WITH TOXICITY

EXPOSURE TO ALL AGENTS MORE IMPORTANT THAN SPECIFIC SEQUENCE

<table>
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<th>POTENTIAL FOR CURE?</th>
<th>EXTENDING SURVIVAL?</th>
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Limited metastatic disease can be cured with chemotherapy and surgery

• What is considered resectable?
  - Limited liver or lung involvement
  - Ask your surgeon!

• ~40% alive 5 years and 20% at 10 years – cure?
  - Highly selected patients

• Typically given active chemotherapy regimen for 2+ months prior to surgery
  - FOLFOX, FOLFIRI, FOLFOXIRI +/- bevacizumab
  - May separate aggressive tumors from more indolent
  - More chemo is not always better
  - Prolonged treatment can complicate surgery

• Additional chemotherapy given post-op
Triplets and quadruplets are highly active and highly toxic

- Generally reserved for potentially curable patients who need disease response
  - "Conversion Therapy" – from unrespectable to resectable

- May be useful for very poor prognosis patients (BRAF mut)
  - FOLFOXIRI + / - bevacizumab
    - Response rate boosted to 65%
    - Improved R0 resection rate
    - But at the expense of severe diarrhea, stomatitis, neutropenia, neuropathy
  - FOLFOX or FOLFIRI + cetuximab / panitumumab
    - Conflicting data – used more sparingly

- DON’T COMBINE EGFR mAb WITH BEV – LIKELY HARMFUL

Balancing efficacy and toxicity in incurable metastatic colorectal cancer:
The role of maintenance therapy

- Intensive First Line Chemo
- Maintenance Chemo
- Intensive Chemo

TOXICITIES
QUALITY OF LIFE

- Maintenance does not compromise survival
  - OPTIMOX1
  - CAIRO-3

STANDARD APPROACH
FOLFOX+Bev > 3m > Cap+Bev > FOLFOX+Bev at progression

Medical management of metastatic Colorectal Cancer: Summary

- One size DOES NOT fit all!
- Most patients will receive 3+ lines of therapy
- Get to know major toxicities of each drug/regimen
  - Oxaliplatin = Neuropathy
  - Irinotecan = Diarrhea
  - Capecitabin = Hand-Foot Syndrome
  - Cetuximab/panitumumab = Rash
  - Bevacizumab = bleeding, clotting

- Balance toxicity with goals of care
  - Save most toxic treatments for excellent performance status and/or potentially curable patients
  - “Stop and Go” lowers toxicity but still very effective

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Surgery is an essential component of treatment for most colorectal patients

5 year survival for non-metastatic CRC

- Stage I: Surgery Only
- Stage II: Consider post-op chemo

Gunderson L et al. JCO 2010;28:264-271
**Post-operative (adjuvant) therapy for high risk disease**

- Risk factors for recurrence
  - Higher T stage
  - Nodal involvement
  - Tumor Grade
- After surgery, recurrence rate of node positive (stage III) disease is 50-80%
- Chemotherapy clearly benefits patients with metastatic disease
- Can chemotherapy decrease the risk of recurrence for resected patients?

**Early studies of adjuvant therapy show clear benefit for stage III patients**

- First generation of trials looked at a variety of 5FU-based regimens
- 6 months of treatment after surgery
- Tolerable regimen with most patients completing all planned chemotherapy
  - 30% with significant side effects
  - Diarrhea, cytopenias, asthenia
- Reduces mortality by ~30%

**Adjuvant therapy with oxaliplatin combinations are superior to 5FU/LV**

- Randomized trials:
  - MOSAIC and NSABP C-07
  - 5FU/LV +/- Oxaliplatin q2 weeks x 12 cycles
  - FOLFOX significantly more toxic
  - Peripheral Neuropathy is biggest concern
    - 92% of patients; 15% long term
  - Cytopenias, nausea, vomiting, diarrhea
- Consistent 3-5% benefit in survival
  - OS at 6 years: 72.9 vs. 68.7
  - DFS at 5 years: 66.4 vs. 58.9

**Additional adjuvant therapy pearls**

- FOLFOX clearly benefits patients
  - ...but FOLFIRI, EGFR mAbs, bevacizumab DO NOT work for adjuvant therapy
- Oral capecitabine can be substituted for IV 5FU
- Older patients (>65-70) have small if any benefit of FOLFOX over 5FU/LV
- Ongoing trials are testing shorter durations of chemotherapy (3 months vs 6 months FOLFOX)

**STANDARD OF CARE:**
- 6 months of FOLFOX
- Older, sicker, poor PS: 6 months of capecitabine or 5FU/LV

**What about stage II patients?**

- Highly controversial
- Patients do very well with surgery alone
  - ~80% cured
- Small benefits of chemotherapy rarely outweigh the side effects, cost, and inconvenience
- Often recommended for selected group of "high risk Stage II" patients
  - T4 lesions, obstruction, perforation
  - Inadequate lymph node sampling
  - Oxaliplatin likely adds very little to 5FU/LV

**Adjuvant therapy for colon cancer: Summary**

- Most Stage III patients:
  - FOLFOX q2w for 6 months
  - If poorly tolerated, drop oxaliplatin
- Older, sicker, poor PS stage III patients:
  - Capecitabine d1-14 of 21d, for 6 months
  - IV 5FU/LV if compliance/toxicity concerns
- Most Stage II patients should not get chemo
  - Drop chemo with any toxicity in Stage II
Locally advanced rectal cancer: Use of radiation to minimize local recurrence

- Rectal cancer has a higher risk of local recurrence
  - Close proximity to other organs
  - Lack of serosa
  - Technical issues related to surgery
- Avoid colostomy if possible

Localized radiation can effectively sterilize the rectal area
Recommended for all patients with stage II or III rectal cancer

Use of radiation in rectal cancer: Take home points

- Pre-op radiation better than post-op
- Radiation has long term toxicities
  - Bowel dysfunction, urinary issues, sexual issues
- Addition of chemotherapy enhances the effects of radiation
  - SFU is standard (continuous infusion or oral)
  - FOLFOX adds toxicity but not efficacy – DON’T USE
- Long term results of chemoradiation:
  - Effectively downstages tumors (60% RR, 20% CR)
  - Lowers chance of local recurrence
  - DOES NOT impact survival
  - Probably doesn’t impact sphincter preservation

Post-op chemotherapy in rectal cancer

- Adjuvant full dose chemo for ~4 months
- Clinical trials show conflicting evidence of benefit
- Extrapolation of data from colon cancer
  - SFU alone – generally capecitabine
  - FOLFOX – higher risk patients (T4, N+)

5-10 week break
5.5 weeks of chemoradiation
Surgery
4 week break
4 months total treatment duration
4 months of adjuvant chemotherapy

Future Directions:
- Full dose chemo up front > see if some can avoid radiation
- Shorter course radiation to minimize toxicities (common in Europe already)

The importance of managing toxicities during treatment for cancer

- Oncology Nurses are critical to...
  - Anticipate
  - Prevent
  - Recognize
  - Treat
  - Know when “enough is enough”

Highly Recommended Articles:

CHEMOTHERAPY FOR METASTATIC COLON CANCER

<table>
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<tr>
<th>Drug</th>
<th>Most Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>Diarrhea, N/V, Stomatitis, Cytopenias</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Diarrhea, Cytopenias</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Hand-Foot Syndrome, Diarrhea</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Neuropathy, Neutropenia, GI side effects</td>
</tr>
<tr>
<td>VEGF</td>
<td>Hypertension, Proteinuria, Vascular events</td>
</tr>
<tr>
<td>EGFR</td>
<td>Rash, Diarrhea</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Fatigue, Hand Foot Syndrome, GI side effects, liver dysfunction</td>
</tr>
</tbody>
</table>

Table 1. Treatment Options for Patients With Colorectal Cancer: Grade 3 or 4 Toxicities in Phase III Clinical Trials

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>EARLY MORTALITY (%)</th>
<th>LATE MORTALITY (%)</th>
<th>ACUTE TOXICITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CapOx</td>
<td>11-15</td>
<td>5-7</td>
<td>3-10</td>
</tr>
<tr>
<td>CaVe</td>
<td>13-15</td>
<td>5-7</td>
<td>3-20</td>
</tr>
<tr>
<td>Ca5FU</td>
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<td>5-12</td>
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</tr>
<tr>
<td>1,3</td>
<td>23-29</td>
<td>46-54</td>
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</tr>
<tr>
<td>1,35FOX</td>
<td>7-11</td>
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</tr>
<tr>
<td>45</td>
<td>18</td>
<td>27</td>
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CapOx – capcitabine and oxaliplatin, CaVe – Capecitabine and irinotecan, Ca5FU – infusional 5-FU and irinotecan, FOX – oxaliplatin and irinotecan, FOXOx – oxaliplatin and oxaliplatin, 1,3 – fluorouracil and irinotecan, 1,35FOX – oxaliplatin and fluorouracil, 45 – infusional 5-FU.
NCCN Guidelines

- Excellent source of up to date information
- Flow diagrams
- Detailed regimen information
- In depth discussions
- Exhaustive references

Acknowledgements

- American Cancer Society

[Find An Event](#)

[RelayForLife.Org](#)