Gastrointestinal Malignancies:
A Focus on Colorectal Cancer

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Case Study

- Mr. W is a 76 yo Caucasian male with past medical history remarkable for 2 prior cancers – papillary thyroid carcinoma and prostate cancer.
- In July 2004, he presented for screening colonoscopy, and a sessile polyp was discovered, with polypectomy performed.
Case Study

- The polyp was found to be a tubular adenoma, 4mm in size.
- In March 2006, he presented for routine physical examination by his PCP, and was found to be markedly anemic.
- Repeat colonoscopy was recommended.
Case Study

- On colonoscopy, there was evidence of a villous, infiltrative, ulcerative partially-obstructing mass, involving 2/3 of the lumen.
- The lesion appeared to be located at the distal ascending colon around the hepatic flexure, measuring 3cm in length.
- Biopsy was positive for moderately-differentiated adenocarcinoma, and the pt was referred for surgical evaluation.
Epidemiology

- An estimated 145,290 new cases of CRC are diagnosed each year (104,950 colon and 40,340 rectal).
- An estimated 56,290 deaths from CRC in 2005 alone.
- About 6% of Americans will be diagnosed with CRC during their lifetime.
- 3rd most common malignancy and 2nd leading cause of cancer death in US men and women.
Epidemiology

- Affects men and women about equally through age 50, then more cases in men.
- Incidence in blacks greater than whites.
- Recent decrease in incidence attributed to better screening techniques.
Large Intestine Anatomy
Large Intestine Anatomy

- Approximately 1.5 meters long.
- Extends from the ileocecal valve to the anus.
- Large refers to the diameter in comparison to the small intestine.
Pathophysiology

The colon has 4 tissue layers evolving from the internal lumen outward:

- Mucosal layer
- Submucosa
- Thick muscle
- Serosa

The extent of invasion into these layers helps to define the stage of CRC.
Histology

- Adenocarcinoma is the most common histologic type of CRC (approx. 90%).
- Squamous cell carcinoma is rare, and may indicate chronic exposure to carcinogens.
- Also rarely can see other types of large bowel cancer (lymphoma, carcinoid, signet ring, adeno-squamous).
Polyps - what are they?

- Tissue growth/outpouchings of the colon wall, varying in size and appearance, that may project on a stalk.
Polyps – what are they?

- Often they are benign, however, certain polyps are precancerous, and confer an increased risk of CRC development:
  - Villous, tubulovillous, tubular
  - 2-5% will progress to malignancy
  - The larger the polyp, the more likely it will become malignant (>2mm)
  - Can be detected on colonoscopy and removed by polypectomy
Polyps – what are they?

Small Polyp with Snare
Risk Factors

- Modifiable
  - Dietary – low fiber, high fat
  - Lifestyle – heavy alcohol, tobacco, sedentary, chronic exposures (asbestos, radiation, printing supplies, etc)
Risk Factors

- Non-modifiable
  - Advanced age – increased after 40, but worsens 50-60s
  - First degree relative with CRC
  - Relative with CRC at young age
  - Personal/family history of adenomatous polyps or CRC
  - IBD (inflammatory bowel disease)
Genetic Factors

- Genetic mutations may also play a role in the development of CRC.
- Two hereditary syndromes account for about 5% of CRC cases:
  - FAP (Familial Adenomatous Polyposis)
  - HNPCC (Hereditary Non-polyposis CRC)
Signs and Symptoms

- Vary depending on the location of the tumor and can include any of the following:
  - Vague, dull abdominal pain
  - Weight loss
  - Abdominal fullness
  - Rectal bleeding
  - Alternating constipation/diarrhea
  - Change in stool diameter
  - Rectal pain
How do we screen?

- **Average risk:**
  - Beginning at age 50, both men and women should have 1 of the following 5:
    - FOBT or FIT yearly
    - Flex sigmoidoscopy every 5 years
    - Yearly FOBT/FIT plus flex sig every 5 years
    - DCBE every 5 years
    - Colonoscopy every 10 years
How do we screen?

- **High-risk:**
  - Includes patients with family/personal history of CRC/adenomas, FAP, HNPCC, Inflammatory bowel disease:
    - Those with family history should have colonoscopy at 40, or 10 years younger than the family member’s age of diagnosis
    - FAP families should undergo flex sig/colonoscopy beginning at 12 yo
    - HNPCC families should begin colonoscopy at 20 yo every 1-2 years
Staging: TNM vs. Duke

- **TNM:**
  - **Tumor-**
    - **Tis:** Carcinoma in situ, intraepithelial or invasion of the lamina propria
    - **T1:** Tumor invades submucosa
    - **T2:** Tumor invades muscularis propria
    - **T3:** Tumor invades through the muscularis propria into the subserosa, or into the pericolic or perirectal tissues
    - **T4:** Tumor directly invades other organs or structures, and/or perforates
  - **Node-**
    - **N0:** No regional lymph node metastasis
    - **N1:** Metastasis in 1 to 3 regional (pericolic or perirectal) lymph nodes
    - **N2:** Metastasis in 4 or more regional lymph nodes
  - **Metastasis-**
    - **MX:** Distant metastasis cannot be assessed
    - **M0:** No distant metastasis
    - **M1:** Distant metastasis present
Staging: TMN vs. Duke

- **TMN cont’d**
  - **Stage I** – T1N0M0, T2N0M0
    - Cancer has begun to spread, but is still in the inner lining.
  - **Stage II** – T3N0M0, T4N0M0
    - Cancer has spread to other tissues near the colon or rectum, but is not reached the lymph nodes.
  - **Stage III** – any T, N1-2, M0
    - Cancer has spread to the lymph nodes, but has not been carried to distant parts of the body.
  - **Stage IV** – any T, any N, M1
    - Cancer has been carried through the lymph system to distant parts of the body. The most likely organs to experience metastatic disease from CRC are liver and lungs.
Staging: TNM vs. Duke

- Prognosis (5-year survival rates) based on staging:
  - Stage I – 93%
  - Stage IIA – 85%
  - Stage IIB – 72%
  - Stage IIIA – 83%
  - Stage IIIB – 64%
  - Stage IIIC – 44%
  - Stage IV – 8%
Staging: TNM vs. Duke

- Modified Duke staging system:
  - Duke A – The tumor penetrates into the mucosa of the bowel wall, but no further.
  - Duke B – B1: The tumor penetrates, but not through, the muscularis propria of the bowel wall. B2: The tumor penetrates into and through the muscularis propria.
  - Duke C – C1: The tumor penetrates into, but not through the muscularis propria, but evidence of cancer in lymph nodes. C2: The tumor penetrates into and through the muscularis propria, and evidence of cancer in lymph nodes.
  - Duke D – The tumor has spread beyond the confines of the lymph nodes, to liver, lung, or bone.
On April 10, 2006, the patient had right hemicolectomy with final pathology below:

- **RIGHT COLON**
  - Case #: S06-12522

- **ILEUM, APPENDIX, AND COLON, RIGHT HEMICOLECTOMY:**
  - MODERATELY DIFFERENTIATED MUCINOUS ADENOCARCINOMA OF THE ASCENDING COLON, 7.0 CM
  - THE TUMOR INVADES THROUGH THE INTESTINAL WALL AND IS PRESENT AT THE SEROSAL SURFACE
  - LYMPHOVASCULAR INVASION IS IDENTIFIED
  - NO PERINEURAL INVASION IS IDENTIFIED
  - THE TUMOR HAS A PUSHING BOARDER, AND ELICITS A MILD INFLAMMATORY RESPONSE
  - PROXIMAL AND DISTAL RESECTION MARGINS ARE NEGATIVE FOR CARCINOMA
  - TWENTY EIGHT LYMPH NODES NEGATIVE FOR CARCINOMA (0/28)
  - PATHOLOGIC STAGING (AJCC, 2002): T4 N0 MX, STAGE IIB
Prognostic Factors

- How likely is the cancer to come back?
  - Stage is the most important factor.
  - Histologic features (well-differentiated better than poorly-differentiated; lymphovascular or perineural invasion worse).
  - Anatomic location of tumor (rectal, transverse, and descending worse).
  - Bowel obstruction or perforation at presentation.
  - Genetic mutations.
Early Stage CRC

- Surgery is the *only* curative treatment.
- Type of resection depends on location of tumor:
  - Right or left hemicolecctomy
  - Transverse colectomy
  - Low anterior resection (for sigmoid or proximal rectal tumors)
  - Total mesorectal excision (TME) for rectal tumors
  - Abdominoperineal resection (APR) is a more radical resection of rectal tumors
Early Stage CRC

- Adjuvant therapy (after surgery)
  - Stage I – surgery only
  - Stage II – “gray area”, adjuvant therapy not currently recommended, but trending that direction
  - Stage III – adjuvant therapy recommended
Early Stage CRC

- Adjuvant treatment options:
  - Fluorouracil (with/without leucovorin)
    - Bolus, infusional, oral (capecitabine)
  - Oxaliplatin
  - Irinotecan
    - Not usually, unless contraindication to oxaliplatin

*Common regimens include FOLFOX, FOLFIRI, XELOX*
The liver is the primary and most common site of metastases from CRC.

About 25% of patients have liver mets at the time of diagnosis.

Chemotherapy has been shown to increase survival in this setting, however, adding more agents usually adds more toxicity.

Targeted therapies are usually ideal, given that the toxicity profile is less, and doesn’t overlap with that of chemotherapy.
Abnormal CT scans
Advanced CRC

- Newer chemotherapy options:
  - Irinotecan, Oxaliplatin, Capecitabine

- Liver-directed therapies:
  - Hepatic resection
  - RFA (radiofrequency ablation)
  - Cryoablation or cyrosurgery
  - Chemoembolization
  - Hepatic arterial infusion (HAI)

- Targeted therapies:
  - Bevacizumab (Avastin)
  - Cetuximab (Erbitux/C225)
Complications of Advanced CRC

- Jaundice
- Ascites
- Bowel obstruction
- Dyspnea
Complications of Advanced CRC

- Jaundice = accumulation of bilirubin in tissues, usually when total bilirubin > 3.0mg/dL.
- “Tea-colored” urine usually first sign observed by patient.
- Conjugated bilirubin usually collects in high elastin tissues such as sclerae, mucous membranes.
Complications of Advanced CRC

What do you ask the patient?
- What is the color of your urine?
- What is the color of your stool?
- Are you itchy?
- Have you had abdominal pain?
- Have you noticed yellowing of your eyes or skin?
Complications of Advanced CRC

- Management of jaundice:
  - ERCP (endoscopic retrograde cholangiopancreatography)
  - External biliary drainage
  - Removal of stones
Complications of Advanced CRC

- Ascites = fluid in the peritoneal cavity.
- Liver is fibrotic and lymph cannot effectively drain and leaks outward.

What do you ask the patient?
- Have you clothes become tight across your middle?
- Do you feel full after eating only small amounts?
- Weight gain or abdominal pain?
Complications of Advanced CRC

- Management of ascites:
  - Therapeutic or diagnostic paracentesis
  - Limit salt intake
  - Diuretics
  - Pain management
Complications of Advanced CRC

- Bowel obstruction = failure of intestinal materials to move forward in the normal manner.
- GI tract secretes normally 7-8 liters/d.
- 90% are SBO (small bowel obstruction).
- Altered bowel motility.
- Causes include adhesions, hernia, malignancy, inflammation, impaction, drug-induced, radiation-induced.
- Treatment includes surgical repair vs. supportive measures including NPO, NGT, replace fluids, pain management.
Complications of Advanced CRC

- Dyspnea = shortness of breath.
- May be secondary to several factors including metastatic disease involving lungs/bronchi, pleural effusion, pulmonary embolus, anemia.
- Consider pulmonary consult, PFTs, V/Q vs. high-resolution chest CT.
- Management may include morphine, inhalers, pRBC transfusion, Denver catheter drainage, other supportive care.
Abnormal CT scans
Abnormal CT scans
To summarize, Mr. W is a 76 yo male with history of adenomatous polyps, who presented with anemia, and was found to have a large, fungating mass on colonoscopy in March 2006, requiring right hemicolecotomy.

Final pathology confirmed a T4N0Mx, stage IIIB CRC, with evidence of lymphovascular invasion.
Chemotherapy was recommended, with FOLFOX-6 (Oxaliplatin, Leucovorin, 5-FU) for a total of six months.

The patient admitted to having 2 sons, ages 43 and 45, who had not yet had colonoscopy.

Genetic testing was also recommended.
Clinical Trials at Yale for GI Cancers

- **Pending - HIC 060100100, Dr. Edward Chu** – “XELOX-A-DVS”: A Randomized Study of Intermittent Capecitabine in Combination with Oxalplatin (XELOX q3w) and Bevacizumab vs. Intermittent Capecitabine in Combination with Oxaliplatin (XELOX q2w) and Bevacizumab as 1st line for pts with metastatic CRC.

- **HIC 0602001069, Dr. Wasif Saif** – Phase II clinical trial of Genexol-PM in patients with advanced pancreatic cancer.

- **HIC 0512000895, Dr. Wasif Saif** – A Phase I/II, Multicenter, Open-Label, Dose-Escalation, Safety and Efficacy Study of PHY906 Plus Capecitabine in Patients With Advanced, Unresectable Hepatocellular Carcinoma.

- **HIC 0509000643, Dr. Wasif Saif** – A Phase I, Open-label Study Evaluating the Pharmacokinetics of Components of S-1 in Patients with Varying Degrees of Renal function.

- **HIC 0509000642, Dr. Wasif Saif** – A Phase I, Open-label Study Evaluating the Pharmacokinetics of Components of S-1 in Patients with Impaired Hepatic function.
Final Points

- CRC is 2nd leading cause of cancer-related death in the U.S.
- It is the 3rd most common malignancy.
- Screening is very important, especially in high-risk individuals.
- Prognosis most often depends on stage of disease.
- Early stage usually entails surgery followed by chemo (+/- radiation for rectal).
- Advanced disease usually includes mets to liver.
- Chemotherapy and targeted therapy are mainstay of treatment.
- Clinical trials for adjuvant and advanced dz should be considered.

QUESTIONS?
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