Colorectal Cancer: A Panel of Experts

EPIDEMIOLOGY

Second leading cause of cancer death in U.S (15% of cancer deaths)
- Mortality is declining due to increased vigilance and dietary changes
- Lifetime mortality is 1/3

Lifetime incidence is 5%
- > 90% of cases occur at age > 50 yrs

> 95% of cancers are adenocarcinomas, and thus are preventable

RFs *for* COLORECTAL CARCINOMA

- Age > 50 yrs
- Male gender
- FHx of colorectal cancer (in first or second-degree relative)
- FHx of large *or* numerous benign polyps
- Hereditary Syndromes
  - FAP: Perhaps the strongest risk factor
  - HNPCC : A very strong, but not absolute, risk factor
- DM Type II
- Smoking
- Increased dietary (animal) fat intake
- Decreased dietary fruit intake
- Adult-onset weight gain and Obesity
- Ethnic: highest rate amongst African Americans
- IBD: UC (L-sided disease or pancolitis) and CD (> 1/3 of colon involved)
- Radiation Injury

PFs for COLORECTAL CARCINOMA

- Adequate fruit intake
- NSAIDs : prevents development of polyps and adenomas, BUT no clear effect on malignant transformation
- Multivitamins (including Folate, A, C, E)

FACTORS *of* UNDETERMINED SIGNIFICANCE

- Dietary Fiber
- Dietary vegetables
- Cryptic lifestyle factors unique to North America

SCREENING

Requires > 10 yrs for transformation from adenomatous polyp → overt invasive carcinoma
Incidence is declining by 2% per year in U.S due to colonoscopy

DETECTION OF CANCERS

gFOBT : annual
This is an insensitive and non-specific assay. Requires three sequential samples. The single-sample sensitivity is only 24%
iFOBT : annual
Increased sensitivity and specificity.
Stool DNA
A standardized molecular panel; analyzes for certain genomic changes

DETECTION OF PRECURSOR POLYPS and CANCERS (in GENERAL POPULATION)

Flexible Sigmoidoscopy (FlexSig) : q 5 yrs
This is gradually being replaced by total colonoscopy due to increased incidence of R-sided lesions
Barium Enema : q 5 yrs
Low sensitivity without any reduction in rates of CRC incidence and mortality
CT Colonography : q 5 yrs
Test characteristic for large and advanced adenomas are similar to those of colonoscopy
Colonoscopy : q 10 yrs
The is the diagnostic test of choice and gold standard for screening

FOLLOW-UP SCREENING after **REMOVAL OF ADENOMA**

1 – 2 lesions < 10 mm : repeat colonoscopy in 5 yrs
Advanced lesions > 10 mm OR severe dysplasia : repeat in 3 yrs
Large Sessile Adenoma with Subtotal Resection : repeat in 3 – 6 mos.

INTENSIVE SCREENING for **RISK GROUPS**

FDR < 60 yrs with CRC OR two FDR (any age) with CRC : begin screening at youngest of: age 40 OR 10 years younger than affected relative
FAP : FlexSig at 10 – 12 yrs; prophylactic colectomy
HNPCC : Colonoscopy q 1 – 2 yrs beginning at 20 – 25 yrs, then annually > 40 yrs
UC or CD : Colonoscopy and extensive Bx for dysplasia at 7 yrs post-Dx
If **benign** + extensive colitis : repeat q. 1 – 2 yrs x 2; then q. 1 -3 yrs if lesions are stable
If **benign** + proctosigmoiditis (< 35 cm): no additional screening

THE HEREDITARY SYDROMES

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

- FAP results in < 1% of all CRC
  - But CRC is essentially guaranteed
- AD inheritance: mutation in APC
- Adenomatous polyps begin to develop at 15 – 20 yrs, and can be exceedingly numerous
- Onset of CRC at 30 – 50 yrs (mean is 39 yrs)
- Screen with FlexSig beginning at 10 – 12 yrs
- TX: prophylactic total colectomy with discovery of first adenoma

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

- HNPCC results in < 10% of all CRC
  - The lifetime risk of CRC is 80%
- AD inheritance: mutations in the MLH1 and MLH2 MMR genes
  - This results in accelerated conversion of benign polyps to adenocarcinoma
  - Transformation occurs within 2 – 3 yrs
- *R-sided predominance*
- Associated with extracolonic malignancy: uterine and ovarian cancers
- Suspect HNPCC with the following Hx
  - R/P FAP
  - Three (3) relatives with HNPCC-associated malignancy, including CRC
  - At least two (2) generations involved
    - ≥ 1 must be a FDR of any other affected individual
  - At least a single (1) person Dx < 50 yrs
- TX: subtotal or total colectomy with highly dysplastic adenoma or CRC

CLINICAL FEATURES *of* CRC

Most cancer is Dx during the asymptomatic stage, due to rigorous screening
In total, the majority of CRC is actually subclinical until late stages of the disease

Colon-Predominant

The main triad: abdominal pain, change in bowel habits, hematochezia

- Cecum and R colon : occult GI bleeding, chronic anemia, iron deficiency
- Sigmoid and L colon : *obstructive symptoms predominate*: abdominal pain, diarrhea, constipation

Rectum-Predominant

- Rectal bleeding
- Decreased stool caliber
- Tenesmus with advanced tumors : this can be relatively debilitating
- Invasion of the sacral plexus and radicular pain

MOLECULAR PATHOGENESIS *of* CRC

CRC develops from a series of conserved mutations and epigenetic modifications. The sequence may vary, but most tumors contain the following abnormalities. A minority of primary malignancies can arise due to sporadic non-APC mutations.

There are three **underlying mechanisms** of neoplastic transformation:

THE APC – β-catenin WNT PATHWAY

80% of sporadic (non-hereditary) CRC. This is the precursor mutation that leads to formation of early adenoma with signs of dysplasia

Normal → [methylation abnormalities] → hyperplasia → [APC] →early dysplasia and adenoma → [K-ras] → low-risk adenoma → [ΔDCC region] → high-risk adenoma → [p53] → adenocarcinoma

Tumor Suppressors: APC, DCC, p53
Proto-Oncogenes : K-ras

DNA Mismatch Repair (MMR) PATHWAY: Results in microsatellite instability

Increased CpG island methylation PATHWAY : occurs in absence of microsatellite instability

HISTOPATHOLOGY *of* CRC

BENIGN POLYPS

These are all **genetically normal**

Juvenile: dilated glands, stromal fibrosis, background of *inflammation*

Inflammatory: identical to Juvenile Polyps; hamartomas (benign cells with positional anaplasia).

Mutiple hamartomas with mucocutaneous hyperpigmentation: **Peutz-Jegher Syndrome**.

Hyperplastic: benign; sawtooth frond pattern. Due to decreased epithelial shedding. They usually occur in the colonic sigmoid.

ADENOMATOUS POLYPS

These have incurred some **genetic or epigenetic damage**

Tubular: Requires > 75% of the glands to be tubular

Villous: Requires > 50% of the glands to be villous

Tubulo-Villous: 25 – 50% of the gland is villous

Malignancy increases with the following characteristics

Larger size (> 4 cm)
Villous morphology
Sessile attachment (relative to pedunculated masses)
Severe dysplasia (high-grade)

Most villous adenomas are sessile and display high-grade dysplasia → the most volatile pre-malignant lesion type

In terms of malignancy: villous adenoma > mixed > tubular pedunculated

ADENOCARCINOMA

38% in cecum and ascending colon (R-sided)
35% in sigmoid colon
18% in transverse colon
9% in descending colon

Proximal: tends to be exophytic and **hemorrhagic** (usually there is more extensive local invasion due to anatomic freedom of the R colon)
Distal : tends to be annular and obstructive

STAGING *of* CRC

Before attempting any staging assessment, some baseline studies must be done

Serum carcinoembryonic antigen (CEA)
Abdominal and Pelvic CT + CXR
Evaluation of liver and lungs for metastatic disease; nodal involvement
Trans-Rectal Ultrasound (TRUS)
Determine rectal tumor depth and nodal involvement

T: Tumor Extent

T1: Invasion of the submucosa
T2: Invasion of the muscularis propria (outer muscle layer)
T3: Invasion of subserosa or into pericolic mesentery
T4: Direct invasion of adjacent tissue OR free perforation

N: Nodal Disease

N0: None
N1: Mets in 1 – 3 regional nodes
N2: Mets in ≥ 4 regional nodes

M: Metastasis

M1: Distant

GENERAL STAGING GUIDLINES

Stage I : **T1 or T2** without nodal disease (**N0**) or distant metastasis
(Disease is localized to the mucosa and external muscularis layers)
Stage II : **T3 or T4** without nodal disease (**N0**) or distant metastasis
(Disease is localized and non-nodal, but involves serosa and pericolic tissue)
Stage III : Any **T** with **any N**
(Nodal disease)
Stage IV : Any T, any N, **M1**
(Metastatic disease)

ROUTES of **MESTASTASIS**

Colon Carcinoma: intramucosal (horizontal) extension, direct invasion, lymphatic, hematogenous, **intraperitoneal**

Rectal Carcincoma: same as above, but NO intraperitoneal spread (the rectum is inferior to the peritoneal refection)

Direct invasion into the mesorectum and peri-rectal soft tissue is causes extreme morbidity and is likely to recur if not excised *en bloc*

Colon, Upper/Mid Rectum → inferior mesenteric vein → portal system → liver mets
Mid/Lower Rectum → hypogastric venous plexus → caval system → (isolated) lung mets

DISTANT RECURRENCE is more likely in colon carcinoma
LOCAL RECURRENCE is more likely in rectal carcinoma, due to direct extension into the pelvis

TREATMENT *of* LOCAL DISEASE

COLON

GENERAL TREATMENT STRATEGY

Elective or obligate adjuvant (post-op) chemotherapy is provided for patients in Stage II or III
XRT is typically not employed in treatment

SURGERY

Stage II : surgical resection + elective adjuvant ChemoRx
Stage III: surgical resection + **adjuvant ChemoRx** (5-FU + LV + Oxaliplatin; **FOLFOX**)

All local resection in done *en bloc*

The primary tumor is resected along with all draining blood vessels, lymphatics, and infiltrated nodes
Laproscopic resection is equivalent to open surgery

CHEMOTHERAPY

The goal is sterilization of nodal disease
Appropriate for Stage II and III local disease and **adjuvant** to surgical resection

Stage II: 5-FU + capectibine
5-FU + LV + Oxaliplatin (FOLFOX regime)
Stage III: 5-FU + LV
Capectibine monotherapy
FOLFOX

RADIATION

XRT is generally *not* done

RECTUM

GENERAL TREATMENT STRATEGY

There TWO MAIN MODES of therapy are governed by stage
Chemoradiation is given in patients with ≥ STAGE II Disease

STAGES II and III

Surgery + Adjuvant Chemoradiation

Surgery reveals extent of disease and is prognostic of response to chemoradiation

Thus, it spares unnecessary chemoradiation for patient with N0 and T1 – T2 disease (incorrectly diagnosed STAGE I)

There is a higher morbidity

Neoadjuvant Chemoradiation + Surgery

This is the preferred approach in most institutions
It is recommended for T3 – T4 OR N1 – N2 (STAGE II and III)
TRUS identifies patients with N ≥ 1 AND T ≥ 3

SURGERY

The extent of disease can be clearly defined with TRUS

Stage II and III: **pre-operative** (neoadjuvant) chemoradiation + **TME**

The surgical approach is dictated by the location of the tumor in the rectum
In almost all procedures, Total Mesorectal Excision (**TME**) is practiced

The rectum is dissected along with attached mesorectal tissue

Low Anterior Resection (LAR)

Upper 1/3 : elective TME + wide local resection (low distal margin)
Lower 2/3 : obligate TME + adequate distal margin

Abdominoperianal Resection (APR)

Recurrent of Low Tumors : removal of the rectum and anal canal requires permanent colostomy

Transanal Excision

Early Anal Tumors : full-thickness curettage of anal wall without node dissection

CHEMOTHERAPY

Appropriate for patients with > STAGE I disease

T3 and T4 and **any N** OR
N1 and N2 and **any T**

STAGES II and III

The standard therapy is pre-operative 5-FU + XRT
Alternative: post-operative FOLFOX + XRT

RADIATION

Pre-operative chemoradiation

TREATMENT *of* METASTATIC DISEASE

The goal is **USUALLY** to palliate symptoms with chemotherapy

HOWEVER, metastatic CRC can occasionally be treated with curative intent if there are delayed oligometastases (limited tumors) to the liver and lungs

- The metastatic tumors are resected with cryotherapy or RF ablation
- Large oligomets can be reduced with chemotherapy before excision or ablation

Chemotherapy is appropriate with ECOG PS ≤ 2

- Patient is ambulatory > 50% of waking hours and able to perform most ADL