Adenocarcinoma of the Colon and Rectum

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Colorectal CA

- 3\textsuperscript{rd} most commonly diagnosed CA
- 2\textsuperscript{nd} most common fatal CA
- Overall incidence and mortality decreasing since 1980s
- More common in African-Americans, men and distal colon
Colorectal CA

- Vast majority worldwide are sporadic
- 5% associated with genetic syndromes in US
Genetics

• Accumulation of mutations in tumor suppressor genes and proto-oncogenes
• DNA hyper- or hypo-methylation
• Inactivation of APC gene
Microsatellite Instability

• Alternative pathway to genomic instability and subsequent carcinogenesis

• Arises from defects in mismatch repair genes

• In HNPCC – hMLH1 and hMSH2 genes

• Sporadic – hMLH1
HNPPCC

- Most common genetic syndrome
- Accounts for majority of patients with familial CRC
- MSI is characteristic finding
- Diagnosed clinically on basis of Amsterdam Criteria
Risk Factors

- Family history of CA or adenomatous polyps
- Familial CRC syndromes
- IBD (lifetime risk of 3.7%)
- Dietary and lifestyle factors
Risk

- 1<sup>st</sup> degree relative – 2.25
- > 1 relative – 4.25
- Dx before age 45 – 3.87
- 1<sup>st</sup> degree relative with adenomatous polyps – 1.74 (4.36 ≥ age 50)
Lifestyle

- Lower levels of physical activity
- Increased body mass
- Western-style diet (high in calories and fat, low in fiber)
- Increased dietary Ca$^{+2}$ – protective?
Early is Better

- Diagnosis at a pre-symptomatic stage is vital for improving survival
- Detection of adenomatous polyps prior to development of invasive CA is focus
- Important for high-risk as well as average-risk patients
Modalities

- Colonoscopy
- Flexible sigmoidoscopy
- DCBE
- Virtual colonoscopy
- FOBT and stool DNA testing
Utility

- Sigmoidoscopy has been shown to decrease both incidence and mortality
- Colonoscopy better in asymptomatic patients
- **ONLY** FOBT consistently been shown to decrease mortality in randomized trials
Virtual Colonoscopy

- Uses high resolution CT scan
- Sens/spec: 89% and 80% for polyps > 6 mm and 94% and 96% for > 10 mm
- Still require colonoscopy for Tx or tissue Dx
Guidelines

- Average risk patients
  - Screening begin at 50
  - Colonoscopy at 10-year intervals

- Unwilling or unable
  - FOBT yearly
  - Flex sig q 5 years
  - Yearly FOBT and flex sig q 5 years
  - DCBE q 5 years
  - CT colonoscopy q 5 years
Guidelines

- High-risk patients
  - Earlier screening
  - Age 40 or 10 years younger than age of affected 1st degree relative
  - 5-year intervals
Clinical Evaluation
Presentation

- Patients often asymptomatic at Dx
- Can present with occult GIB and anemia
- Often do not exhibit symptoms until late in the course of disease
- BRBPR, abdominal or back pain, change in bowel habits or stool caliber, fatigue, weight loss, nausea, vomiting, obstruction, perforation
Staging

- Important for determining prognosis and need for adjuvant therapy
- TNM classification
- Depth of bowel wall penetration (T), presence and # of involved mesenteric nodes (N) and distant mets (M)
<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
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<tbody>
<tr>
<td><strong>T0</strong>  No evidence of primary tumor</td>
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<tr>
<td><strong>Tis</strong>  Carcinoma in situ, intraepithelial or invasion of lamina propria</td>
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<tr>
<td><strong>T1</strong>  Tumor invades submucosa</td>
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<td><strong>T2</strong>  Tumor invades muscularis propria</td>
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<td><strong>T3</strong>  Tumor invades through muscularis propria</td>
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<td><strong>T4</strong>  Tumor invades other organs or perforates visceral peritoneum</td>
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<th>Regional lymph nodes (N)</th>
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<tr>
<td><strong>N0</strong>  No regional lymph node metastases</td>
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<tr>
<td><strong>N1</strong>  Metastases in 1 to 3 regional lymph nodes</td>
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<td><strong>N2</strong>  Metastases in 4 or more regional lymph nodes</td>
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<th>Distant metastasis (M)</th>
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<tr>
<td><strong>M0</strong>  No distant metastasis</td>
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<tr>
<td><strong>M1</strong>  Distant metastasis</td>
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<td>Stage</td>
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Clinical Staging

- Based on H&P, endoscopic findings and biopsy results
- If colonoscopy cannot be completed, air-contrast BE needed
- Imaging studies (plain films, CT, MRI, PET)
Pathologic Staging

- Occurs after surgical exploration and examination of resected specimen
- Final stage is based on TNM system
- Degree of lymphatic invasion and extent of vascular invasion, certain histologic types (signet ring and mucinous)
Management
Surgical Therapy

- R0 resection (leaving no gross or micro disease) with wide margins along bowel wall + regional lymphadenectomy

- Arterial vessels supplying bowel segment excised at their origins

- Minimum margin of 5 cm
Extent of Resection

• Cecum and ascending colon
  - Right hemicolecctomy
  - Right branch of middle colic artery

• Hepatic flexure
  - Extended right colectomy
  - Include entire middle colic artery

• Transverse colon
  - Extended right or left colectomy
  - Transverse colectomy
Extent of Resection

- Splenic flexure
  - Left hemicolecotomy

- Sigmoid
  - Sigmoid colectomy
Surgical Staging

• Use of adjuvant therapy relies heavily on accurate staging

• Minimum of 12 nodes to confirm node negativity

• SLN
Special Situations
Perforated CA

- Occurs either via direct erosion through colon wall or secondary to obstruction
- Associated with poor prognosis and increased morbidity
- ELAP, washout, resection, diversion
Obstructing CA

- Usually treated with resection + anastomosis (right-sided)
- Diversion ± resection (left-sided)
- Associated with poor prognosis and increased morbidity
- Stents
Significant progress has been made in past 20 to 30 years.

5-year survival rate is inversely correlated with pathologic stage.

5-FU-based regimens + oxaliplatin
Adjuvant Therapy

- Standard of care for those with Stage III
- High-risk Stage II
  - Obstruction
  - Perforation
  - High-grade or lymphovascular invasion
  - < 12 LNs in resected specimen
Rectal Cancer
Management

- Local recurrence after resection
- 16.2% after LAR
- 19.3% after APR
- Multimodality therapy (radiation, chemo or both) in combination with appropriate operative therapy can significantly reduce local recurrence rates
Surgical Therapy

- Extent of resection
- Sphincter preservation
- LAR
- APR
- Preop chemoradiation used to downstage
Local Excision

- Transanal
- Transssphincteric
- Transcoccygeal
- Transanal endoscopic microsurgery (TEM)
- Reserved for early-stage lesions
Local Excision

• Patient selection is critical
• EUS
• Endorectal coil MRI
• Depth of tissue invasion and presence of nodal disease
• CT to r/o distant disease
Transanal Excision

- Lesion no > 3 cm in diameter
- Encompass no > 30% of rectal circumference
- < 8 cm from anal verge
- With advent of TEM, higher lesions
Margins

- 2 to 5 cm for distal margin
- With interest in sphincter preservation, some have considered smaller distal margins
- No higher recurrence rates or reduced survival
- Radial margins < 2mm – increased local recurrence
Adjuvant and Neoadjuvant

- Focused on locoregional control of disease and treatment of systemic disease
- Preoperative therapy can potentially induce tumor regression prior to resection
- Improves chances of clear radial and distal margins
- Higher sphincter preservation rates
Metastatic Disease

• Seen in as many as 20% of CRC patients
• In symptomatic pts with unresectable met disease, resection or diversion
• In those with resectable met disease, curative resection may be undertaken
• In asymptomatic pts with unresectable met disease, role of surgical resection of the primary lesion is controversial
Follow Up
Recurrence

• Goal is to detect any recurrences or metachronous lesions that are potentially curable

• As many as 80% occur within the first 2 years and 90% within the first 4 years

• Incidence of 2\textsuperscript{nd} primary in those with resected stage II and III is 1.5% at 5 years
Recommendations

• CEA q 2 to 3 months for 2 years, then q 3 to 6 months for 3 years, then annually

• Clinical exam q 3 to 6 months for 3 years, then annually

• Colonoscopy perioperatively, then q 3 to 5 years if pt remains free of polyps and CA

• CT of chest and abdomen for 3 years; pelvic CT for rectal CA
Primary aim is detection of treatable recurrences or met disease

Most common met sites = liver and peritoneal cavity

Surgery is only potentially curative option for recurrent CRC
Amsterdam Criteria (1991)

- \( \geq 3 \) relatives (2 1\textsuperscript{st} degree) with CRC
- CA occurring across \( \geq 2 \) generations
- \( \geq 1 \) CA diagnosed before age 50
- FAP excluded
Bethesda Guidelines (1997)

- Meet Amsterdam Criteria
- 2 HNPCC-related cancers
- CRC + 1st degree relative with
  - CRC before age 45 or
  - HNPCC-related extracolonic disease < 45 or
  - Colorectal adenoma before 40
- CRC or endometrial CA before age 45
Bethesda Guidelines (1997)

- Proximal colon CA of undifferentiated type or histopathology before 45
- Signet-ring CRC before age 45
- Colorectal adenomas before age 40