Colorectal Cancer Update - 2017

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Financial Disclosures

• none
CRC Epidemiology

• 4th most common malignancy in US (136,000 cases/yr)
• 2nd most common cause of cancer death (50,000 cases/yr)
• Cumulative lifetime risk of CRC is 6%
• Slight male predominance
• Average age of diagnosis: 65 yo
• 80% of cases occur in people without identifiable risk factors
• Prognosis is directly related to stage of disease
Colon cancer arises from a defined precursor lesion

Tubular adenoma  Tubulovillous Adenoma  High grade dysplasia (Carcinoma-in-situ)  Invasive cancer

Time → 7-10 yrs
National Polyp Study: *polypectomy reduces the incidence of CRC*

Winawer, NEJM, 1993
National Polyp Study: *polypectomy reduces the mortality from CRC*

A Zauber, NEJM, 2012
Colorectal cancer screening

1. Who to screen?
   - Average risk 75%
   - Moderate risk 20%
   - High risk 5%

2. How and how often to screen?
   - FOBT/FIT
   - Flexible sigmoidoscopy
   - Colonoscopy
   - Virtual colonoscopy
   - Molecular/genetic testing
Decrease in risk of CRC mortality due to FOBT

- Mandel (1993), US
- Hardcastle (1996), UK
- Kronberg (1996), Sweden
- Kewenter (1996), Germany

TOTAL = 329,642 individuals

RR = 0.77

From Towler, BMJ, 1998
## Screening Colonoscopy Trials

<table>
<thead>
<tr>
<th></th>
<th>VA 380</th>
<th>CONCeRN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>3195 (M)</td>
<td>1463 (F)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>50-75 yrs</td>
<td>40-79 yrs</td>
</tr>
<tr>
<td><strong>Adenomas</strong></td>
<td>37%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Advanced adenoma/CA</strong></td>
<td>10%</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>% of proximal advanced adenomas without distal adenoma</strong></td>
<td>50%</td>
<td>65%</td>
</tr>
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From Schoenfeld, NEJM, 2005
Caveats: post-colonoscopy CRCs ("interval CRCs")

• Among 12,487 CRC diagnoses in Ontario, 2-6% arose in context of colonoscopy in prior 3 years

• Risk factors: older age, diverticular disease, right-sided or transverse CRC, internist/FP, non-hospital colonoscopy

Colonoscopy offers greater protection against death from **left-sided** colon cancer

<table>
<thead>
<tr>
<th>Colonoscopy</th>
<th>Right CRC</th>
<th>Left CRC</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Complete exam</td>
<td>0.99*</td>
<td>0.33*</td>
</tr>
<tr>
<td></td>
<td>0.47**</td>
<td>0.18**</td>
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</tbody>
</table>

*Baxter N, Ann Int Med, 2009
**Nishihara R, NEJM, 2013
Quality parameters for colonoscopy

• Adenoma detection rate
• ? withdrawal time
• Bowel prep quality -- Split preps
UK Flex Sig Trial

- One time Flexible Sigmoidoscopy between ages 55 and 64
- 33% reduction in incidence of CRC
- 50% reduction in incidence of distal CRC
- 43% reduction in CRC mortality

PLCO Trial (U.S.)

• 154,900 men and women randomized to screening flexible sigmoidoscopy (with 3-5 year repeat) or usual care

• Median followup: 11.9 years

• Results: 21% reduction in CRC incidence
  (29% in distal colon, 14% in proximal colon)

  26% reduction in CRC mortality
  (50% in distal colon, none in proximal colon)

R. Schoen, NEJM, 2012
## Virtual colonoscopy: performance characteristics

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<tbody>
<tr>
<td>≥ 10 mm</td>
<td>94%</td>
<td>55%</td>
<td>59%</td>
<td>91%</td>
</tr>
<tr>
<td>≥ 6 mm</td>
<td>89-94%</td>
<td>39%</td>
<td>51%</td>
<td>59%</td>
</tr>
<tr>
<td>(No. subjects)</td>
<td>(1233)</td>
<td>(600)</td>
<td>(614)</td>
<td>(605)</td>
</tr>
</tbody>
</table>

*Laxative free exams
CT Colonography: limitations

- No therapeutic capabilities: Those with lesions identified will then need optical colonoscopy. Is there a cut-off size?
- Patient satisfaction: Not uniformly preferred over optical colonoscopy. Air insufflation.
- Pre-procedure cathartic preparation: new data indicate this may not be necessary
- Not reimbursed by insurance
- Radiation exposure (MR-colonography now available)
Immunochemical tests for fecal hemoglobin (FIT)

• More sensitive than guaiac based assays
  – Pooled sensitivity of 79% for cancer (Spec = 94%)
  – Sensitivity between 6-56% for advanced adenoma
• No dietary restrictions necessary, only one stool sample required
• More expensive than FOBT
• Variable performance depending upon kit, storage conditions, and cut-off values
Stool DNA testing

• Based upon principle that tumor cells are shed into the stool.
  – Tumor DNA can be isolated from stool
  – Tumor-specific gene mutations can then be detected
• “Cologuard”: fecal DNA + FIT
• Now covered by Medicare q 3 years.
### Prospective evaluation of fecal DNA testing

N = 9989 subjects referred for screening colonoscopy

<table>
<thead>
<tr>
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<th>Sensitivity (CRC)</th>
<th>Sensitivity (Advanced Adenoma)</th>
<th>Specificity</th>
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<tbody>
<tr>
<td><strong>Fecal DNA</strong></td>
<td>92.3%</td>
<td>42.4%</td>
<td>86.6%</td>
</tr>
<tr>
<td><strong>FIT</strong></td>
<td>73.8%</td>
<td>23.8%</td>
<td>94.9%</td>
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from Imperiale, NEJM, 2014
CRC Screening: Average risk patient

• Men and women over age 50
• No symptoms (bleeding), no positive FOBT
• No risk factors for CRC (Fam Hx, IBD, adenoma)

Tests that detect adenomas and cancer (** preferred)
  - Flex Sig q 5 yrs
  - Colonoscopy q 10 yrs
  - CTC q 5yrs
  - DCBE q 5 yrs

Tests that primarily detect cancer
  - FOBT annually
  - FIT annually
  - stool DNA q 3 yrs

CRC Screening: *Moderate risk patient*

History of adenomas

- Previous history of adenomatous polyps, particularly if large (>1 cm) or multiple:
  
  *Follow-up colonoscopy in 3 years.*

  *Follow-up colonoscopy in 5 years*
  
  *if only 1-2 adenomas < 1 cm.*

- Subsequent exams dependent upon findings
CRC Screening: *Moderate risk patient*

History of CRC

- Personal history of resected colon cancer:
  
  *Full colonoscopy within 1 year of surgery*

  – If negative, follow-up colonoscopy in 3 years, thereafter every 5 years
CRC Screening: *Moderate risk patient*  
Inflammatory Bowel Disease

- 8 years of pan-ulcerative colitis or 15 years of left-sided colitis:  
  
  *Colonoscopy every 1-2 years*

- No data to indicate this reduces CRC mortality

- Crohn’s colitis
RISK OF CRC AMONG 1ST DEGREE RELATIVES OF PATIENTS WITH CRC

Control               One                 > Two             Age < 45
Relative           Relatives

Relative risk of CRC

- Fuchs, 1994
- St. John, 1993
CRC Screening: *Moderate Risk Patient*

Family History of CRC/adenomas

- CRC or adenomas in 1st degree relative < 60 or two 1st degree relatives of any age:
  
  Colonoscopy at age 40, or 10 yrs before youngest case. Then every 5 years.

- CRC or adenomas in 1st degree relative > 60 or two 2nd degree relatives of any age:
  
  Average risk recommendations, but start screening at age 40
CRC Screening: Moderate Risk Patient

In the future, quantitative algorithms may be used to better define the “moderate risk” patient

**Incorporation of multiple variables:**

- age
- family history
- tobacco use
- sex
- prior adenoma
- obesity
When to stop screening?

US Preventive Services Task Force (USPSTF):

* Recommends screening until age 75 yrs
* Advises against screening age 76-85 yrs, but this should be individualized
* Recommends against screening after age 85 yrs

These guidelines do not apply to:
* Surveillance
* High risk individuals

USPSTF, Ann Int Med, 2008
What about “sessile serrated polyps”?

- Sessile serrated polyps/adenomas are pre-cancerous and should be managed like tubular adenomas.
- More common in right colon and in elderly patients
- Likely responsible for “interval cancers”
High-risk patients: Hereditary Colon Cancer families

- Lynch syndrome
- Autosomal dominant inheritance
- CRC: 80% lifetime risk
  - early age of onset (40’s)
  - multiple primary tumors
- Few adenomas (often “flat”)
- Strong association with endometrial cancer
  - (50-60% lifetime risk)
- Genetic testing available (MSH2, MLH1, MSH6, PMS2, EPCAM genes)
Amsterdam Criteria for Lynch Syndrome

- ≥ 3 CRC cases
- 2 or more generations
- One case a first degree relative of the other two
- One case before age 50
Lynch: Screening guidelines

- Colorectal cancer
  Colonoscopy q1-2 yrs from age 25
  Colonoscopy q1 yr from age 40

- Endometrial cancer
  Endometrial aspirate +/- transvaginal ultrasound q1 yr from age 25-35

- Other tumors (ovarian, gastric, renal, brain)
  guided by family history
When to suspect Hereditary Colon Cancer

- Colon cancer in 2 or more family members
- Colon cancer before age 50, adenoma before age 45
- More than 10 cumulative adenomas
- Colon cancer in conjunction with specific extra-colonic cancers: uterine
Participation with CRC screening guidelines

Overall rate of participation: 65%
CRC incidence (and mortality) rates are falling

SEER Observed Incidence, SEER Delay Adjusted Incidence and US Death Rates
Cancer of the Colon and Rectum, by Race and Sex

White Male

Rate per 100,000
SEER Incidence APCs
Delay Adj, 2008-11 = -4.5*
Observed, 2008-11 = -5.0*

Black Male

Rate per 100,000
SEER Incidence APCs
Delay Adj, 2003-11 = -3.4*
Observed, 2003-11 = -3.7*

White Female

Rate per 100,000
SEER Incidence APCs
Delay Adj, 2008-11 = -4.5*
Observed, 2008-11 = -5.0*

Black Female

Rate per 100,000
SEER Incidence APCs
Delay Adj, 2005-11 = -4.2*
Observed, 2005-11 = -4.6*

* Source: SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC).
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines and APCs are calculated using the Joinpoint Regression Program Version 4.1.0, April 2014, National Cancer Institute.
The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.
* The APC is significantly different from zero (p < 0.05).
A healthy 65 year old woman had a sessile serrated polyp (11 mm) removed from the right colon during a full colonoscopy. The prep was reported as good. Which follow-up plan would you recommend?

A. Colonoscopy within 1 year.
B. Colonoscopy in 3 years.
C. Colonoscopy in 5 years.
D. Fecal occult blood testing in 1 year.
When taking a family history to assess colon cancer risk, the least important question to ask is:

A. First or second degree relatives with colon cancer?
B. Ages that relatives were diagnosed with colon cancer?
C. First or second degree relatives with endometrial cancer?
D. Family history of IBD?
E. Family history of colon adenomas?
Key points

- Everyone requires colon cancer screening
- There are many options for CRC screening
- Accurate risk stratification is key, and this depends upon a careful family history
- High quality screening exams are essential, and surveillance intervals may be adjusted if exams are suboptimal
- Refer high-risk families for genetic evaluation