COLORECTAL CANCER SCREENING
SOUTHEAST REGIONAL ONCOLOGY SYMPOSIUM

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Gastroenterology
Objectives

• Epidemiology of colorectal cancer (CRC)

• Pathogenesis of CRC

• Who to screen

• Screening modalities and tiered recommendations for CRC screening
ADENOCARCINOMA
>95% of all colon cancers

Incidence:

• 1 in 22 (4.5%) will develop colorectal cancer in a lifetime

• 1 in 50 (2%) will die from colorectal cancer

CDC, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. BRFSS Prevalence & Trends Data, online.
CRC Incidence/Mortality, USA (2018)

- CRC is 3\textsuperscript{rd} leading cause of cancer in males/females
- CRC is 3\textsuperscript{rd} leading cause of cancer related death in males/females
Men have higher incidence and mortality than women

African American men and women have higher incidence and mortality than white men and women
U.S. Trends in CRC Incidence and Mortality

Decline in mortality:
• Improved treatment (12%)
• Changing patterns in CRC risk factors (32%)
• Increased Screening (53%)
## Cancer Screening and Risk Factor Prevalence

<table>
<thead>
<tr>
<th>Cancer Screening</th>
<th>Tennessee</th>
<th>National Rank</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography, women 40 years and older, 2016</td>
<td>71.2%</td>
<td>30</td>
<td>72.4%</td>
</tr>
<tr>
<td>Stool test/endoscopy, 50 years and older, 2016</td>
<td>68.2%</td>
<td>27</td>
<td>68.9%</td>
</tr>
<tr>
<td>Pap/HPV test, women 21 to 65 years, 2016</td>
<td>84.4%</td>
<td>21</td>
<td>84.2%</td>
</tr>
</tbody>
</table>
Screening Goals

80% by 2018

NATIONAL SCREENING RATE – BRFSS
Percentage of U.S. Adults Age 50-75 years Up-to-Date with CRC Screening, Behavioral Risk Factor Surveillance System

- 65.2% in 2012
- 66.2% in 2014
- 67.3% in 2016

American Cancer Society, Colorectal Cancer Facts and Figures 2017-2019, online.
Colon Polyps, Precursor to CRC

Cancerous Polyps
- Serrated Lesion
- Conventional Adenoma

Benign Polyps
- Hyperplastic
- Inflammatory
- Hamartomatous
- Juvenile
Pathogenesis

A. Chromosomal Instability (CIN) Pathway

- APC loss
- K-ras and other oncogenes
- 18q LOH
- TP53 inactivation
- Normal Epithelium → Early Adenoma → Late Adenoma → Cancer

B. Microsatellite Instability (MSI) Pathway

- APC loss
- Failure of MMR genes
- MLH1, MLH2, MLH6, PMS2
- Adenoma → Cancer

C. Serrated Pathway

- BRAF mutation
- DNA methylation
- TP53, p16 inactivation, LOH
- Normal Epithelium → Serrated Adenoma → Cancer

Lynch Syndrome

- ~3-5%
- Fast growing

MLH1, MLH2, MLH6

~25-30%
- Can be fast growing
- Can be hard to see

~65-70%
- Slow growing

~25-30%
- ~25-30%

Colorectal cancer screening

Goal:

• Reduce CRC incidence and mortality

Definition:

• Method used to detect early stage CRC or precancerous polyps in asymptomatic people with no prior history of colon cancer or precancerous polyps – Average Risk
Colorectal cancer screening

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• Reduce CRC incidence and mortality

Definition:
• Method used to detect early stage CRC or precancerous polyps in asymptomatic people with no prior history of colon cancer or precancerous polyps – Average Risk

Incorrect use of Average Risk Screening Guidelines:
• Persons with high risk family history of colorectal cancer or advanced polyps
• Surveillance – Interval follow up of previously found colorectal cancer or precancerous polyps
• Diagnostic – Evaluation of symptoms
Who to screen for colorectal cancer (Average Risk):

Adults 50 to 75 yo
• Start at age **50** (Grade A evidence)
• African Americans start at age 45

Adults 76-85
• Stop screening if age >75 with **up to date** negative prior screen (particularly colonoscopy)
• Screen up to age 85 if no prior screen
• Individualized
All individuals should begin colorectal cancer screening at age 45

Colorectal Cancer Incidence Patterns in the United States, 1974–2013


<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stool Based Tests:</strong></td>
<td></td>
</tr>
<tr>
<td>gFOBT/FIT</td>
<td>Every year</td>
</tr>
<tr>
<td>FIT DNA (Cologuard)</td>
<td>Every 3 years</td>
</tr>
<tr>
<td><strong>Direct Visualization:</strong></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>Every 5 years</td>
</tr>
<tr>
<td>Flex Sig with FIT</td>
<td>FS every 10 years &amp; FIT yearly</td>
</tr>
<tr>
<td>CT Colography</td>
<td>Every 5 years</td>
</tr>
</tbody>
</table>

*JAMA. 2016;315(23):2564-2575*
FOBT Screening and CRC Mortality:

*RCT shows 33% reduction in CRC mortality for yearly FOBT testing

Shaukat et al. NEJM 2013; 369:1106-14
Fecal Immunochemical Test (FIT):

- Detects antibodies against human Hgb
  - More sensitive than gFOBT
- Annual home test, non-invasive, no prep or diet restrictions
- Lowest Cost (~$20)
- ~73-88% sensitivity for CRC
- ~30% sensitivity for advanced adenoma (villous, HGD, lesion >1cm)
- ~96% specificity for CRC
- Poor to no sensitivity for serrated class polyp
FIT Fecal DNA (Cologuard):

- Combination of FIT plus markers for abnormal DNA
- Home test every 3 years, non invasive, no prep or diet restrictions
- Cost: ~$500 (Medicare)
- ~92% sensitivity for CRC
- ~42% sensitivity for advanced adenoma (including serrated polyps >1cm)
- ~86% specificity for CRC (decreased with age, 83% specificity in age >65)
- False positive confusion (anxiety, higher cost compared to FIT)
CT Colography:

- Test every 5 years
- Visualizes entire colon through images
- Sensitivity:
  - ~84% for CRC
  - 82-92% for adenomas >1cm
  - ~57% for adenomas <10mm
- Specificity ~88% for CRC
- Flat polyps can be missed
- Aggressive bowel preparation
- “Non invasive”
- Radiation exposure
- Extra-colonic findings (additional tests recommended in 6-24% of screening CTCs)
Flexible Sigmoidoscopy:

**CRC Incidence and Mortality reduction with FS: 23-40%**

Flexible Sigmoidoscopy:

- Test every 5 years or every 10 years (plus yearly FIT)
- Direct Visualization of left colon
- No Sedation
- Less aggressive bowel regimen than colonoscopy
- Lower cost than colonoscopy
- Will miss right sided colon cancer
- Invasive – risks (<1 in 1000)
- Unpopular in United States, essentially disappeared in opportunistic screening

## Colonoscopy Effectiveness – US Studies Colonoscopy and CRC Mortality

*CRC Reduction of Mortality: 55-68%*

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Overall</th>
<th>Left Colon</th>
<th>Right Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahl</td>
<td>Veteran Affairs</td>
<td>0.45</td>
<td>0.32</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.42, 0.48)</td>
<td>(0.29, 0.35)</td>
<td>(0.40, 0.63)</td>
</tr>
<tr>
<td>Baxter</td>
<td>SEER-Medicare</td>
<td>0.40</td>
<td>0.24</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.37, 0.43)</td>
<td>(0.21, 0.27)</td>
<td>(0.53, 0.64)</td>
</tr>
<tr>
<td>Nishiara</td>
<td>Nurses &amp; Physician Health</td>
<td>0.32</td>
<td>0.18</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Studies</td>
<td>(0.24, 0.48)</td>
<td>(0.10, 0.31)</td>
<td>(0.29, 0.76)</td>
</tr>
<tr>
<td>Doubeni</td>
<td>Kaiser Permanente</td>
<td>0.33</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.21, 0.52)</td>
<td>(0.12, 0.53)</td>
<td>(0.18, 0.65)</td>
</tr>
</tbody>
</table>

Nishihara R, et al. NEJM 2013; 369;1095-1105
Courtesy of C Schmitt, MD
Colonoscopy:

- Test every 10 years (longest interval)
- Direct visualization
- Single session detect and remove polyps
- Highest sensitivity (>95% for lesions >6mm)
- Specificity >90% for CRC
- Higher cost
- Invasive – risks (1 in 1000)
- Bowel Regimen
- Operator dependent
  - Adenoma detection rate (ADR) needs to be >25% overall

Colonoscopy Quality
Adenoma Detection Rate Variability

Adenoma detection rate target:

- >25% overall
  - Males: 30%
  - Females 20%

# Summary: CRC Screening Options (1)

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>• Highest sensitivity for cancer and <strong>all classes</strong> of precancerous polyps</td>
<td>• Bowel Preparation&lt;br&gt;• Invasive Risks&lt;br&gt;• Operator dependent quality</td>
</tr>
<tr>
<td></td>
<td>• Single session diagnosis and treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Long interval between screens</td>
<td></td>
</tr>
<tr>
<td>FIT</td>
<td>• Noninvasive&lt;br&gt;• 1 time sensitivity for CRC 79%</td>
<td>• Annual test&lt;br&gt;• Poor to no sensitivity for sessile serrated polyps</td>
</tr>
<tr>
<td></td>
<td>• Fair sensitivity for advanced adenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td></td>
</tr>
<tr>
<td>FIT-fecal DNA</td>
<td>• Noninvasive&lt;br&gt;• 1 time sensitivity for CRC 92%</td>
<td>• Decreased specificity&lt;br&gt;• Higher cost compared to FIT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>CT Colonography</td>
<td>• Sensitive to adenomas &gt;1cm</td>
<td>• Bowel Preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poor detection of flat sessile polyps or polyps&lt;1cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Incidental findings discovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiation exposure</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>• RCTs confirm reduction in CRC</td>
<td>• No protection of right sided CRC</td>
</tr>
<tr>
<td></td>
<td>• Lower Cost</td>
<td>• Poor patient satisfaction</td>
</tr>
<tr>
<td></td>
<td>• Limited Bowel Prep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No sedation</td>
<td></td>
</tr>
</tbody>
</table>
U. S. Multi-Society Task Force on Colorectal Cancer, 2017

Recommended Screening for CRC

**Sequential Approach:**

- Give first preferred option, if patient declines, a second test is offered, etc.
- Options tiered from best to worst based on performance and cost.
Recommended Screening for CRC

**Tier 1**
- Colonoscopy every 10 years
- Annual FIT

*Sequential Approach: Give first preferred option, if patient declines, a second test is offered, etc.*
U. S. Multi-Society Task Force on Colorectal Cancer, 2017
Recommended Screening for CRC

Sequential Approach: Give first preferred option, if patient declines, a second test is offered, etc.

Tier 1
• Colonoscopy every 10 years
• Annual FIT

Tier 2
• CT Colonography every 5 years
• FIT-fecal-DNA every 3 years
• Flex Sig every 5 years or every 10 years (+ yearly FIT)
U. S. Multi-Society Task For on Colorectal Cancer, 2017

Recommended Screening for CRC

Sequential Approach: Give first preferred option, if patient declines, a second test is offered, etc.

Tier 1
- Colonoscopy every 10 years
- Annual FIT

Tier 2
- CT Colonography every 5 years
- FIT-fecal-DNA every 3 years
- Flex Sig every 5 years or every 10 years (+ yearly FIT)

Tier 3
- Capsule colonoscopy every 5 years
Conclusions:

• Screening has contributed to the declining incidence and mortality of colorectal cancer in the United States

• Colonoscopy is the most effective screening method to detect and remove precancerous lesions

• With multiple screening options, a sequential approach maximizes efficacy and adherence

• With rising incidence of CRC in young population, do not ignore symptoms
“The best test is the one that gets done”

<table>
<thead>
<tr>
<th>Screening Method and Frequency</th>
<th>Model Estimates, CRC Deaths Averted per 1000 Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 5 y</td>
<td>20</td>
</tr>
<tr>
<td>FIT-DNA every 3 y</td>
<td>20</td>
</tr>
<tr>
<td>FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>HSgFOBT every year</td>
<td>22</td>
</tr>
<tr>
<td>CT colonography every 5 y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy every 10 y plus FIT every year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
</tr>
<tr>
<td>FIT-DNA every year</td>
<td>23</td>
</tr>
<tr>
<td>Colonoscopy every 10 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
</tr>
</tbody>
</table>

![Bar chart showing CRC deaths averted per 1000 screened for different screening methods.](image)
THANK YOU