CRC Screening Methods: Now and the Future

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www.cc.nih.gov/drd/summers.html
1.5 cm rectosigmoid polyp
Overview

- Clinical background
- Virtual colonoscopy
- Clinical Trials
- Current Status
- Computer-aided detection
Clinical background
Overview

- Cancer
- Staging
- Polyps
- Screening
Colon Cancer in Americans

- 2nd leading cause of cancer death
- 131,000 diagnosed annually
- 55,000 annual mortality
- 6% will develop colon cancer during their lifetime (40% die)

Risk Factors

- Increased mortality risk
  - Men (35%)
  - African American (40%)
  - Obesity
  - Smoking
  - Moderate alcohol intake (>= 4 drinks/week)

- Decreased risk
  - Regular physical activity (50%)

American Cancer Society 2005
Dietary Factors

- Increased risk
  - Fat
  - Red meat

- Decreased risk
  - Calcium
  - Folate
  - HRT
  - Vegetable and fruit
Chemoprevention

- 30-50% decrease in cancer and adenomas
  - Aspirin (at least 325 mg twice weekly)
  - NSAID’s
  - COX-2 inhibitors
- Side effects
  - GI bleeding
  - Stroke
  - M.I.

Current Medical Diagnosis and Treatment 2005
Introduction - Colon Cancer

- Risk categories
  - Average (75%)
    - No risk factors
  - Moderate (15 – 20%)
    - Family hx
  - High (5 – 10%)
    - FAP, HNPCC, IBD

APC gene at 5q21
FAP

- Autosomal dominant
- 1:10,000 people
- > 100 colonic adenomatous polyps
- Mutation of APC gene at 5q21 (300 different reported mutations)
- Normal APC regulates cell adhesion and apoptosis
- 25% spontaneous (not inherited)

Current Medical Diagnosis and Treatment 2005
HNPCC – “Lynch Syndrome”

- Autosomal dominant
- 4-6% of all colorectal cancer
- Develop only a few polyps but these progress rapidly
- Mutation of DNA mismatch repair leading to microsatellite instability
- Associated with other cancers, particularly endometrial

Current Medical Diagnosis and Treatment 2005; OMIM 2009
Genomics

• Of ~80 mutations in a tumor, ~15 likely to be important
• Gene mutation “mountains” & “hills” reflect frequency of mutations found in a series of CRC tumors

L. Wood et al., Science 2007
Colon Cancer Prognosis

- Presenting stage determines long-term survival
  - I, > 90%
  - II, > 70%
  - III, < 4 + lymph nodes, 67%
  - III, > 4 + lymph nodes, 33%
  - IV, < 5%
- Rectal cancers have worse prognosis

Current Medical Diagnosis and Treatment 2005
Colon Cancer Prognosis

American Cancer Society 2005
<table>
<thead>
<tr>
<th>Joint Committee Classification</th>
<th>TNM</th>
<th>Dukes Class¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>Tis N0 M 0</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor invades submucosa</td>
<td>T1 N0 M Dukes 0 A</td>
<td></td>
</tr>
<tr>
<td>Tumor invades muscularis propria</td>
<td>T2 N0 M Dukes 0 B₁</td>
<td></td>
</tr>
</tbody>
</table>

Source: Current Medical Diagnosis and Treatment 2005
Joint Committee Classification

Stage II

- Tumor invades into subserosa or into nonperitonealized pericolic or perirectal tissues
  
  - Tumor perforates the visceral peritoneum or directly invades other organs or structures

TNM  Dukes

- T3  N0  M  Dukes
  0  B₁ or B₂

- T4  N0  M  Dukes
  0  B₂
## Joint Committee Classification

<table>
<thead>
<tr>
<th>Stage III</th>
<th>TNM</th>
<th>Dukes Class</th>
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<tbody>
<tr>
<td>Any degree of bowel wall perforation with lymph node metastasis</td>
<td>Any T N1 M</td>
<td>Dukes C1</td>
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<tr>
<td>One to three pericolic or perirectal lymph nodes involved</td>
<td>Any T N1 M</td>
<td>Dukes C1</td>
</tr>
<tr>
<td>Four or more pericolic or perirectal lymph nodes involved</td>
<td>Any T N2 M</td>
<td>Dukes C2</td>
</tr>
<tr>
<td>Metastasis to lymph nodes along a vascular trunk</td>
<td>Any T N3 M</td>
<td>Dukes C3</td>
</tr>
</tbody>
</table>

1.5 cm rectosigmoid polyp
### Joint Committee Classification

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<tr>
<th>TNM</th>
<th>Dukes Class$^1$</th>
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<tr>
<td>Any</td>
<td>M Dukes</td>
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<tr>
<td>T</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>D</td>
</tr>
</tbody>
</table>

**Stage IV**

Presence of distant metastasis

$^1$Gastrointestinal Tumor Study Group modification of Dukes classification (Astler-Coller system).
Introduction - Colon Cancer

• Colonic polyps
  • Precursor to colon cancer
  • Grow slowly
  • Usually present several years before becoming cancerous
  • Removal curative
Polyp Types

- Adenocarcinoma
- Adenoma
  - Villous
  - Tubulovillous
  - Tubular
- Benign polyps
  - Hyperplastic
  - Leiomyoma
  - Lipoma

c/o PJ Pickhardt, W Schindler
What We Have Learned

• Removal of adenomas prevents progression to adenocarcinoma
• Frequency of recurrence is high after polyp removal
  • Invasive cancer (6%)
  • Nonadenomatous polyps (9%)
  • Adenomatous polyps (29%)
What We Have Learned

• Greater cancer risk
  • Larger polyp size
  • Villous component
  • High grade dysplasia
  • Multiple adenomas
Screening for Colon Cancer

- Screening reduces incidence
- Only 39% of Americans > 50 y.o. screened
- Tremendous variability by state (DC 68%, WY 38%), education level, insurance availability

NHIS 2000, CDC 2001-2
ACS Screening Recommendations

• Average risk patients
  • Begin screening at age 50
ACS Screening Recommendations

- One of 7 methods:
  - Sigmoidoscopy every 5 yrs
  - Colonoscopy every 10 yrs
  - Double contrast barium enema every 5 yrs
  - CT colonography every 5 yrs
  - gFOBT every year
  - Fecal immunochemical test (FIT) every year
  - Fecal DNA every ? yrs
Screening test sensitivities, polyps and cancers > 1 cm

- FOBT
  - 25 – 90% for cancer
  - < 10% for polyps
  - Specificity 90%
  - 33% decrease in cancer mortality

Photo: Aetna InteliHealth web site
Screening test sensitivities, polyps and cancers > 1 cm

- FIT – fecal immunochemical test
  - Some have higher sensitivity than Hemoccult II
  - 61 – 91% for ca
  - 27 – 67% for advanced neoplasia or large adenomas
  - Some have similar specificity to Hemoccult II
  - Specificity 97-98%

Whitlock et al., Ann Int Med 2008 for USPSTF
Screening test sensitivities, polyps and cancers > 1 cm

- Fecal DNA test
  - Only 1 major study
  - 51.6% for ca
  - 15.1% for advanced adenoma
  - Specificity 94.4%

Imperiale et al., NEJM 2004
Screening test sensitivities, polyps and cancers > 1 cm

• Barium enema
  • 45 - 83%
Screening test sensitivities, polyps and cancers > 1 cm

• Sigmoidoscopy
  • 30 - 65% depending on length of scope
  • 60 - 80% decrease in rectosigmoid cancer

• 0.34 serious complications per 1000 patients (0.034%)

Complications data:
Whitlock et al., Ann Int Med 2008 for USPSTF
Screening test sensitivities, polyps and cancers > 1 cm

- Colonoscopy
  - 87 - 95%
  - Incomplete in 5 – 10% of patients
  - 0.1% perforation risk
Screening test sensitivities, polyps and cancers > 1 cm

- Colonoscopy
  - Insufficient data to determine sensitivity in community setting
  - 2.8 serious complications per 1000 patients (0.28%)

Whitlock et al., Ann Int Med 2008 for USPSTF
For patients with no adenomas at baseline colonoscopy, 5-year risks of:

- CRC extremely low (0 – 0.24%)  
- Any adenoma (16.0%)  
- Advanced adenomas (1.3%)  
- Adenomas greater in men  

Data supports 5 year rescreening interval  

Imperiale et al., NEJM 2008
Colonoscopy – Flat Polyps

- May be more common than currently appreciated
- May be associated with CRC or HGD more often
- 2.5 X more frequent in surveillance patients

Soetikno et al., JAMA 2008
Colonoscopy – Quality

- Cecal intubation rate
- Scope withdrawal time (>6 min desirable)
- Interexaminer differences

Barclay et al., NEJM 2006
U.S. Endoscopic Capacity

- 1800 physician practices offer endoscopy
- 3M flex sigs, 14M colonoscopies (2002)
- Capacity for 7M more FS, 8M OC
- 41.8M unscreened average risk patients 50 y.o. or older (60%)
- Sufficient capacity if FOBT precedes OC
- If FS or OC are primary screen, could take 10 years to screen all U.S. adults

CDC SECAP/Gastroenterology 2004
Virtual Colonoscopy
Overview

• History
• Bowel Prep
• Scanning
• Performance
• Interpretation
Virtual Colonoscopy

- Proposed in 1994
- Detects polyps noninvasively
- Sensitivity and specificity 50 - 90% (polyps > 1 cm)
What’s in a Name?

- Virtual colonoscopy
- CT colography
- “Fly-throughs”
- CT colonography
VC Timeline

- 1995 – Present: How to Scan
- 1996 – Present: How to Interpret
- 1996 – Present: Patient Preparation
- 2000 – Present: Faster Scanners
- 2001 – Present: Large Clinical Trials
- 2004 – Present: Multi-center Clinical Trials
ISI WOS through 9/8/2005
Patient Preparation

- Bowel cleansing similar to B.E. and colonoscopy
- Magnesium citrate or polyethylene glycol (GoLytely)
- Sodium Phosphate (Fleet’s Phosphasoda)
  - Significantly less retained fluid than GoLytely (Macari et al., Radiology 2001)
Virtual Colonoscopy Examination

- Colon filled with air or CO₂
- CT scan abdomen & pelvis
Virtual Colonoscopy Examination

- Multi-detector helical CT
- Slice thickness ≤ 2.5 mm
- Reconstruction interval ≤ 1.25 mm
- Single 15 – 20 sec. breathhold
- Supine and prone
- IV contrast, sedation, glucagon unnecessary
- Scan duration 15 – 20 min.
Virtual Colonoscopy Examination

- Addition of prone scanning increases sensitivity 13 to 15%

Fletcher et al., Radiology 2000
Carcinoma

• 100% sensitivity
• Occlusive cancers
• Synchronous cancers and polyps
Incomplete Conventional Colonoscopy

- Unrevealed proximal colon successfully examined in 90% of 40 subjects in which cecum not reached
- Slightly better than B.E. at revealing proximal colon

Morrin et al., AJR 1999
Other Colonic Disorders

- Inflammatory Bowel Disease
- Insufficient data
Interpretation Pitfalls

- Residual stool
- Impacted diverticuli
- Papillary and labial type ileocecal valves
- Extrinsic compression
  - Liver, spleen, kidneys
  - Other bowel loops
  - Psoas muscle
  - Aorta

Macari and Megibow, AJR 2001
Extracolonic Findings

- 11% have “highly important” findings
  - Masses, AAA, pulmonary nodule, adrenal nodule, hernia, PTX
- 7% undergo further examination
- 6 of 264 consecutive patients underwent surgery based on VC finding

Hara et al., Radiology 2000
Laxative-free Prep

- Feasibility shown in a small study
- Dilute oral contrast material given over 24 – 48 hrs prior to VC
- Labels stool
- Clear liquid diet
- Avoid fiber-containing foods

Callstrom et al., Radiology 2001
Laxative-free Prep

• Wake Forest Univ. Trial
  • 205 patients
  • Oral contrast
  • Patients with lesions >=10mm
    • Sensitivity: 90%
    • Specificity: 94.6%

Source: Pineau et al., Gastroenterology 2003
Role of IV Contrast

- May improve sensitivity, esp. in suboptimally prepared colons
- Increases cost and risk
- Not desirable for screening
Many patients prefer VC
Conflicting survey results
68/111 patients expressed a preference, 82% chose VC (less painful, less difficult)
• Svensson et al., Radiology 2002
MR Colonography
Clinical Trials
Overview

• DOD
• MUSC (Cotton)
• Mayo Clinic
• Duke (Rockey)
Clinical Trials

- DOD Screening Trial
  - 1233 patients
  - 3-center trial
  - Uniform performance across centers
  - Equivalent sensitivity to OC
  - 2 cancers, one missed by OC
  - 1 in 13 patients referred for OC

Source: Pickhardt et al., NEJM 2003
## Adenoma Detection per Patient

<table>
<thead>
<tr>
<th>Size threshold</th>
<th>≥ 6 mm</th>
<th>≥ 8 mm</th>
<th>≥ 10 mm</th>
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<tbody>
<tr>
<td><strong>VC Se</strong></td>
<td>88.7%</td>
<td>93.9%</td>
<td>93.8%</td>
</tr>
<tr>
<td></td>
<td>(168)</td>
<td>(82)</td>
<td>(48)</td>
</tr>
<tr>
<td><strong>VC Sp</strong></td>
<td>79.6%</td>
<td>92.2%</td>
<td>96.0%</td>
</tr>
<tr>
<td></td>
<td>(1065)</td>
<td>(1151)</td>
<td>(1185)</td>
</tr>
<tr>
<td><strong>OC Se</strong></td>
<td>92.3%</td>
<td>91.5%</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>(168)</td>
<td>(82)</td>
<td>(48)</td>
</tr>
</tbody>
</table>

Source: Pickhardt et al., NEJM 2003
Clinical Trials

- Cotton (MUSC) Clinic Trial
  - 615 patients, symptomatic or family history
  - Sensitivity: 55%
  - Specificity: 96%
  - Primary 2-D reading, poor training, 5 mm slice
  - One center did well, others did poorly
    - 82% at institution enrolling 30% of patients
  - “Techniques and training need to be improved”

Source: Cotton et al., JAMA 2004
Clinical Trials

- Mayo Clinic Trial
  - 705 patients, asymptomatic, > average risk
  - 5% prevalence adenomas >= 1 cm
  - 70% proximal to descending colon
  - Sensitivity: 63%
  - Specificity: 95%
  - Large inter-observer variability

Source: Johnson et al., Gastroenterology 2003
Clinical Trials

- Rockey Clinical Trial
  - 614 patients, symptomatic or family history
  - 63 patients had polyps >= 1 cm

<table>
<thead>
<tr>
<th></th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>59%</td>
<td>96%</td>
</tr>
<tr>
<td>ACBE</td>
<td>48%</td>
<td>90%</td>
</tr>
<tr>
<td>OC</td>
<td>98%</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

Source: Rockey et al., Lancet 2005
Meta-Analysis 1

• Mulhall et al., Ann. Int. Med. 2005
• 6393 patients, 33 studies
• $\geq 1$ cm:
  • Se 85% [CI, 79% to 91%]
  • Sp 97% [CI, 96% to 97%]
• 6 – 9 mm:
  • Se 70% [CI, 55% to 84%]
  • Sp 93% [CI, 91% to 95%]
• Concern: Consistency of performance, technical variability
• Halligan et al., Radiology 2005
• 2610 patients, 24 studies
• ≥ 1 cm:
  • Se 93% [CI, 73% to 98%]
  • Sp 97% [CI, 95% to 99%]
• ≥ 6 mm:
  • Se 86% [CI, 75% to 93%]
  • Sp 86% [CI, 76% to 93%]
• Cancer: Se 95.9% [CI: 91.4%, 98.5%]
• Very sensitive for cancer; poor study reporting
CTC Complication Rate

- Phosphosoda (renal failure)
- Perforation (~0.06 to 0.08% vs 0.35% for OC)

Burling et al., Radiology 2006
CTC - Quality

- C-RADS
- Training
- Automated insufflators
- QA of distention & residual fluid

Van Uitert et al., AJR 2008
Current Clinical Trials

• ACRIN
• SIGGAR 1 (U.K., 4500 pts, 2007)
• IMPACT (Italy)
• Munich
• U. Wisconsin
ACRIN Trial

- Planned in 2003, data accrued 2006
- 2531 screening patients
- 15 institutions
- Oral contrast, cathartic, glucagon
- 16-slice helical CT, 1-2 mm ST, 1-1.25 mm RI
- Same day OC
- All patients with polyps ≥ 7 mm
ACRIN Trial – Final Results

- 12% potential referral to same day OC
- 1/2 of readers underwent additional training before passing certification exam
- 374 adenomas including 7 cancers
- Sensitivity 90%, specificity 86%, polyps $\geq 10$ mm
- Per-polyp sensitivity 84%

Johnson et al., NEJM 2008
U. Wisconsin Experience

- CTC versus OC screening in over 3100 adults
- Similar detection rates for advanced neoplasia in both groups (about 3%)
- Only 7.9% of CTC patients referred for OC
- 1/4 as many polypectomies in the CTC group
- 7 colonic perforations in OC group, none in CTC group
- 8 extra colonic cancers found at CTC

Source: Kim et al., NEJM 2007
Current Clinical Status

- Offered to general public by a few community radiologists and university medical centers
- Commercial software available
- Training seminars proliferating
Reimbursement

- Screening is Fee-for-Service: Reimbursible by private insurance in some states
- Diagnostic: reimbursable for incomplete OC or obstructing colonic mass in many states
Reimbursement - Medicare

- Local Coverage Determinations (LCD’s)
- Varies by state
- National Coverage rejected (May, 2009)
  - Benefit to Medicare beneficiaries unproven
  - Risk of EC finding workup and radiation require clarification
  - USPSTF did not recommend VC (insufficient evidence; November 2008)
Effect on Gastroenterologists

- Still too early
- Referrals for polypectomy
- Shift to therapeutic colonoscopy
- Increased awareness of colon cancer screening
- Net increase in examinations
Cost Effectiveness

- Analyses depend on many variables having uncertain values
  - Sensitivity, specificity (Target lesion size)
  - Charges for colonoscopy, VC
  - Exam frequency
  - Compliance
  - Effect on mortality
Cost Effectiveness

- VC dominant over OC if:
  - OC costs > 1.6 x VC
  - VC q 5 yrs
  - VC Se > 83% for polyps ≥ 1 cm

V.A. Health Services Research, Am J. Gastro. 2007
Cost Effectiveness

- Extracolonic findings
  - Workup ↑ cost $28 - $34 per VC
Cost-effectiveness

• Economic analyses suggest CTC is very cost-effective CRC screening test, particularly if diminutive polyps ignored

Pickhardt et al., Cancer 2007
Ionizing Radiation

- CTC is relatively low radiation dose test (about 5 mSv or 0.5 rem)
- Less frequent screening interval
- Probability of cancer induction thought much lower than lifetime risk of CRC (0.14% vs 6%)
CTC Screening Paradigm

- Only pts with + CTC get OC if polyp $\geq 1$ cm
- 6 – 9 mm polyps go to surveillance
Rationale for Computer-aided Detection (CAD)

- High cost
- High interobserver variability
- Time consuming interpretation

Source: Johnson CD, Dachman AH. Radiology 2000
Virtual Colonoscopy CAD

R.M. Summers, Abd Imaging 2002
Multi-Institutional CAD Trial

- DOD Screening Trial
  - Pickhardt et al., NEJM 2003
- 1186 patients enrolled from 3 centers
- 2 cancers, one missed by OC
- 178 adenomas 6 mm or larger
- Patients divided into training and test sets

RM Summers, et al. Gastroenterology 2005
### Sensitivity Per Patient and FP Rate

<table>
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<tr>
<th>Size threshold</th>
<th>$\geq 8$ mm</th>
<th>$\geq 10$ mm</th>
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<tbody>
<tr>
<td>CAD</td>
<td>85.4% (41/48)</td>
<td>89.3% (25/28)</td>
</tr>
<tr>
<td>OC</td>
<td>89.6% (43/48)</td>
<td>85.7% (24/28)</td>
</tr>
<tr>
<td>CAD FP rate</td>
<td>6.7</td>
<td>2.1</td>
</tr>
</tbody>
</table>

RM Summers, et al. Gastroenterology 2005
0.6 cm polyp in transverse colon found by CAD

RM Summers, et al. Gastroenterology 2005
CAD as 2nd Reader

7 mm TA in rectum found by 3 readers with CAD

Petrick et al. Radiology 2008
Summary

• FOBT & colonoscopy firmly established
• CTC a rising star
• Fecal DNA a more distant prospect
• Quality assessment & improvement urgently needed
• Unknown impact of healthcare restructuring
To Learn More …

www.cc.nih.gov/drd/summers.html

Acknowledgment:
Viatronix provided V3D visualization software