



CRC Screening Methods: Now and the Future

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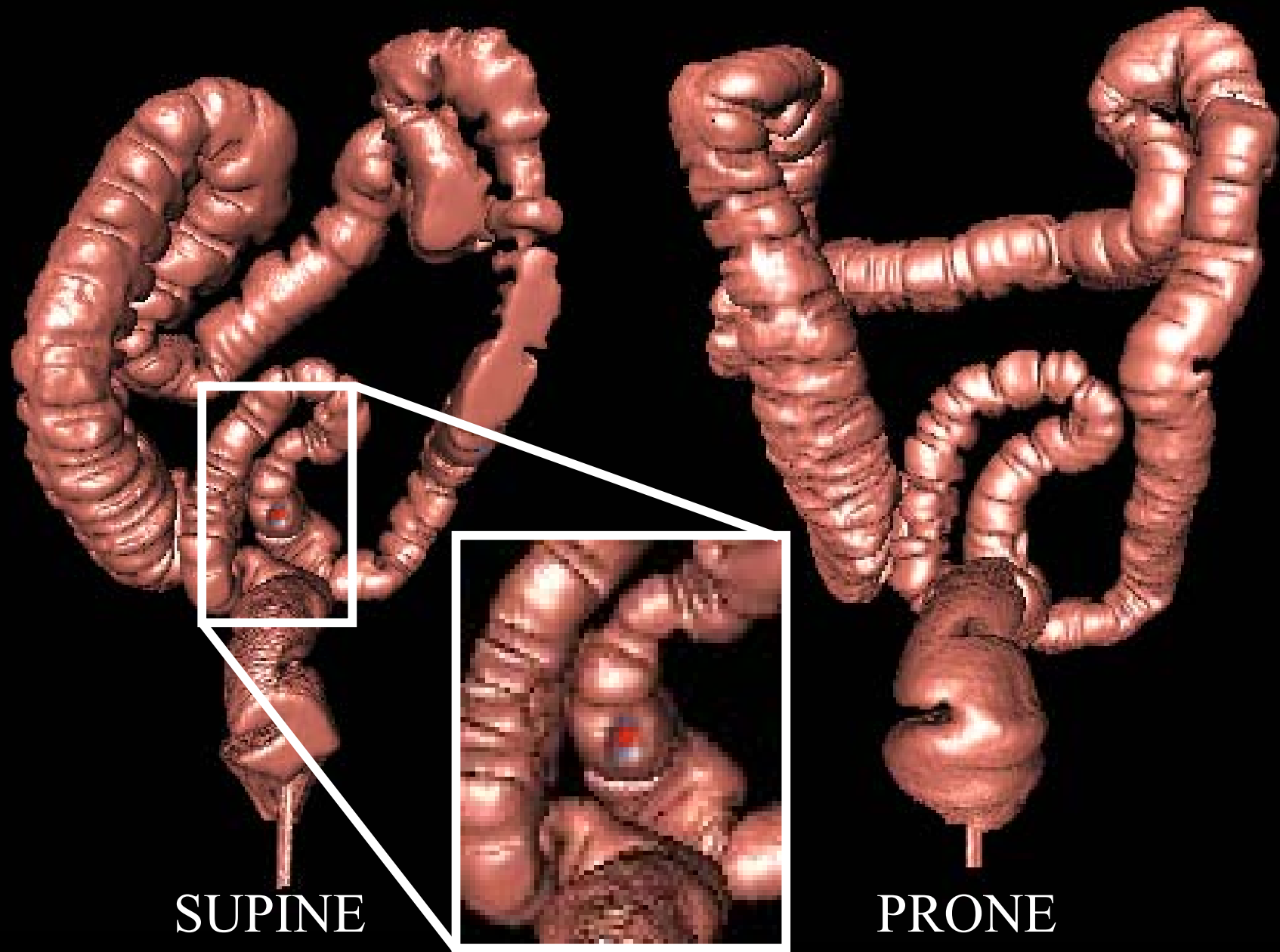
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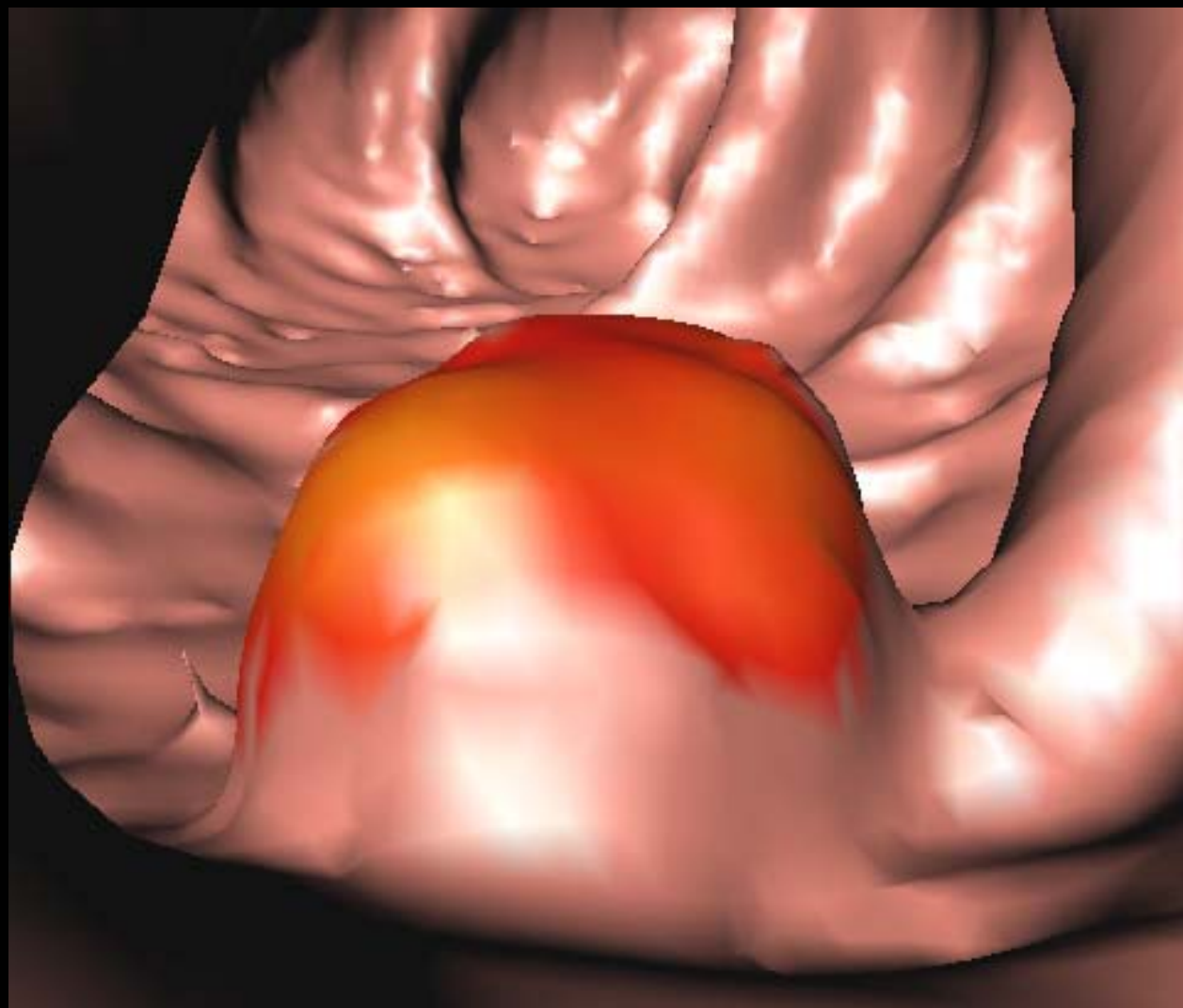
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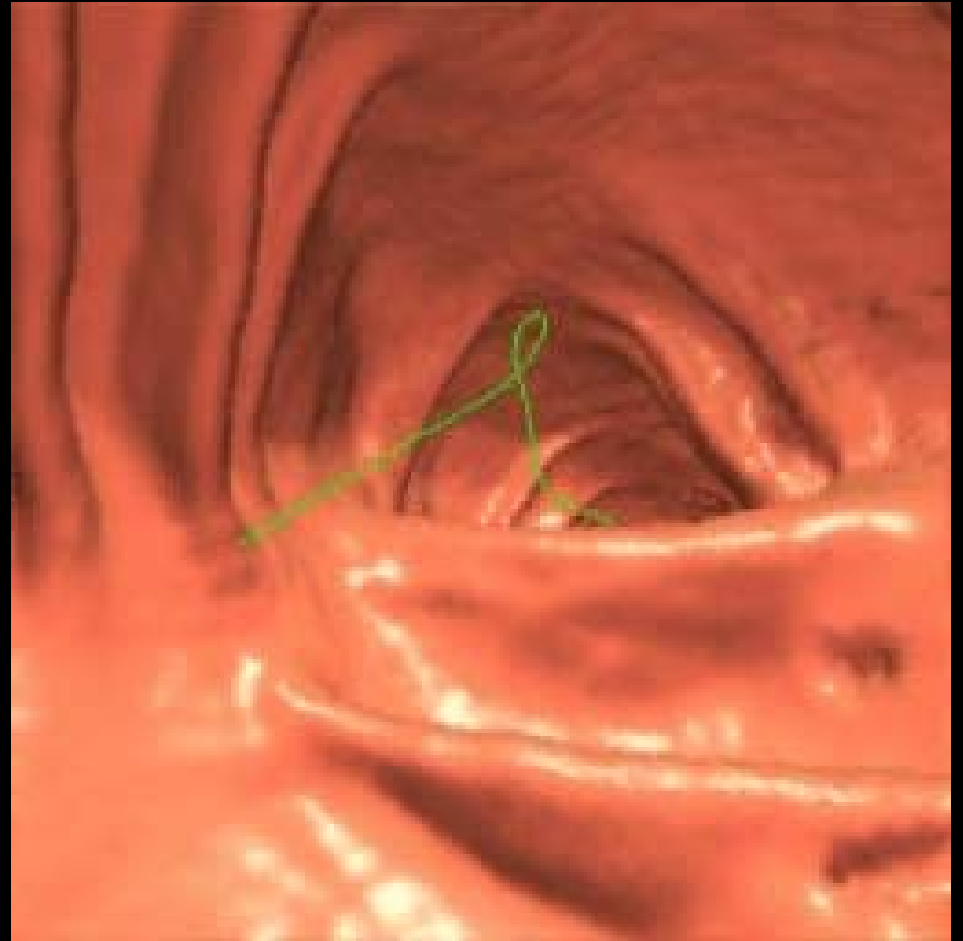




SUPINE

PRONE





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)



Image source: Wikipedia

Risk Factors

- Increased mortality risk
 - Men (35%)
 - African American (40%)
 - Obesity
 - Smoking
 - Moderate alcohol intake (≥ 4 drinks/week)
- Decreased risk
 - Regular physical activity (50%)

Dietary Factors

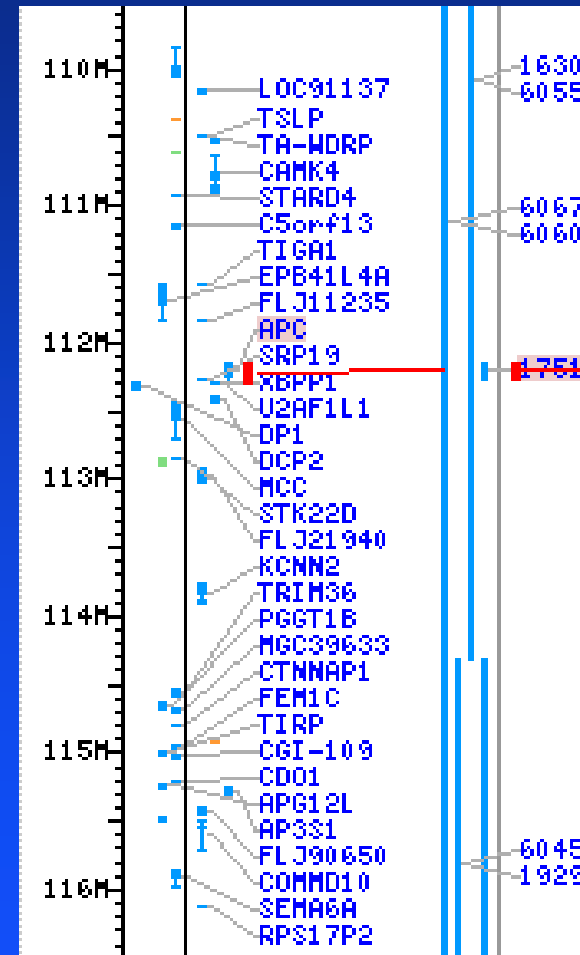
- Increased risk
 - Fat
 - Red meat
- Decreased risk
 - Calcium
 - Folate
 - HRT
 - Vegetable and fruit

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.

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)

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

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

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

Colon Cancer Prognosis

Colon Cancer Staging

Joint Committee Classification

TNM

Dukes Class¹

Stage 0

Carcinoma in situ

Tis N0 M
0

Stage I

Tumor invades submucosa

T1 N0 M Dukes
0 A

Tumor invades muscularis propria

T2 N0 M Dukes
0 B₁

Source: Current Medical Diagnosis and Treatment 2005

Joint Committee Classification

TNM

Dukes Class¹

Stage II

Tumor invades into subserosa or into nonperitonealized pericolic or perirectal tissues

T3 N0 M0 Dukes
B₁ or
B₂

Tumor perforates the visceral peritoneum or directly invades other organs or structures

T4 N0 M0 Dukes
B₂

Joint Committee Classification

TNM

Dukes
Class¹

Stage III

Any degree of bowel wall perforation with lymph node metastasis

One to three pericolic or perirectal lymph nodes involved

Any T N1 M 0 Dukes C₁

Four or more pericolic or perirectal lymph nodes involved

Any T N2 M 0 Dukes C₂

Metastasis to lymph nodes along a vascular trunk

Any T N3 M 0

Joint Committee Classification

TNM

Dukes Class¹

Stage IV

Presence of distant metastasis

Any	Any	M	Dukes
T	N	1	D

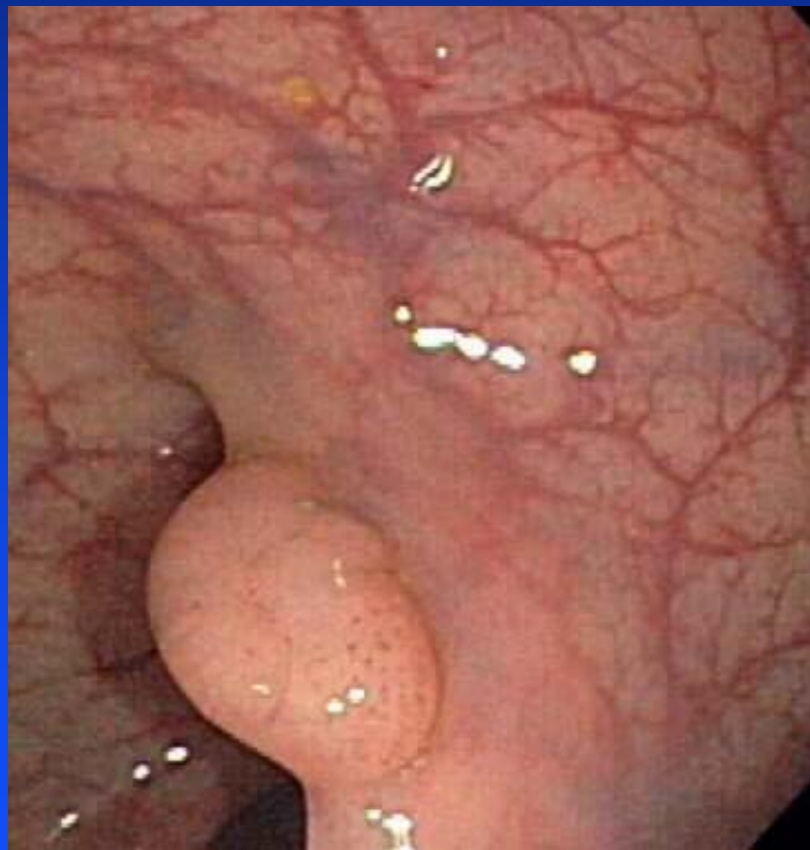
¹Gastrointestinal Tumor Study Group modification of Dukes classification (Astler-Coller system).__

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

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 ca
 - < 10% for polyps
 - Specificity 90%
 - 33% decrease in cancer mortality

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%

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%

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%)

Colonoscopy - Benefits

- 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

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

Colonoscopy – Quality

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

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

Virtual Colonoscopy

Overview

- History
- Bowel Prep
- Scanning
- Performance
- Interpretation

Virtual Colonoscopy

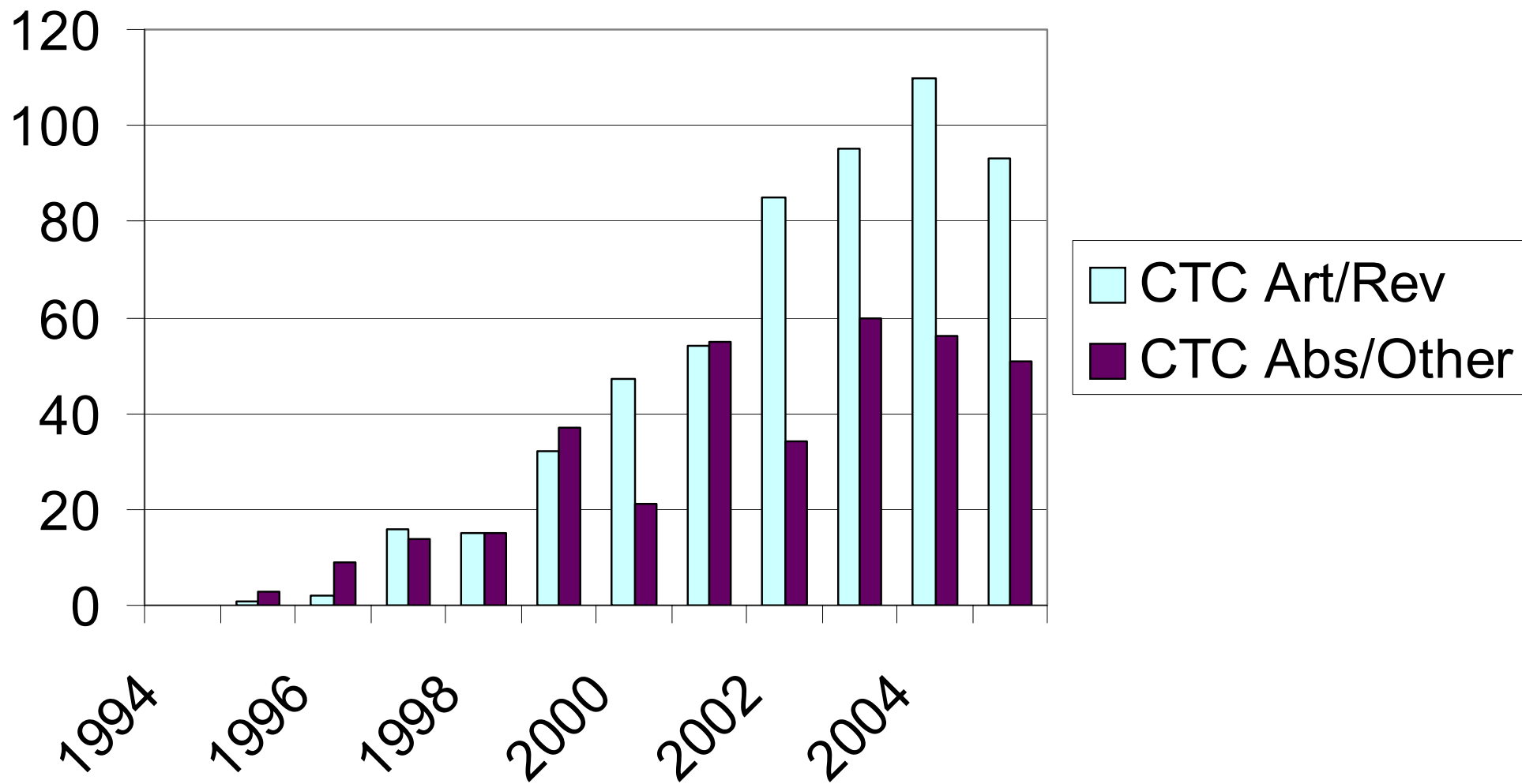
- Proposed in 1994
- Detects polyps noninvasively
- Sensitivity and specificity 50 - 90% (polyps > 1 cm)

What's in a Name?

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

VC Timeline

- 1994 - 1995: Proof of Concept
- 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

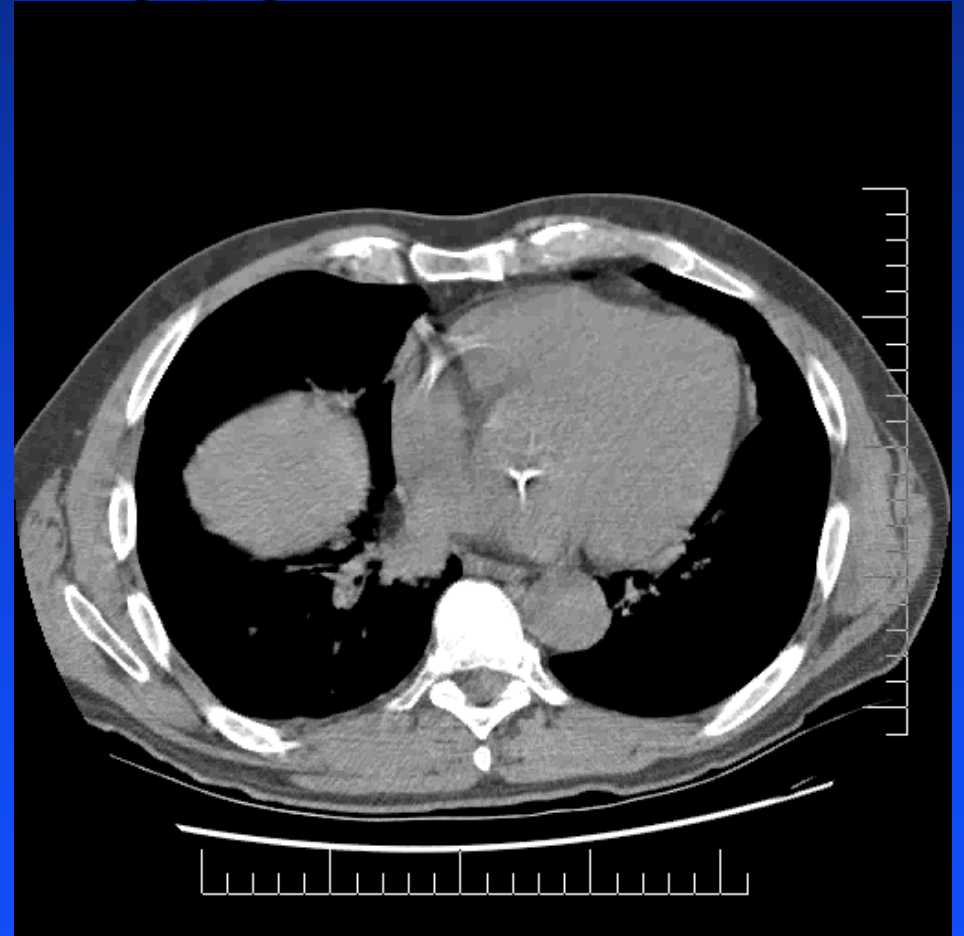


Patient Preparation

- 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

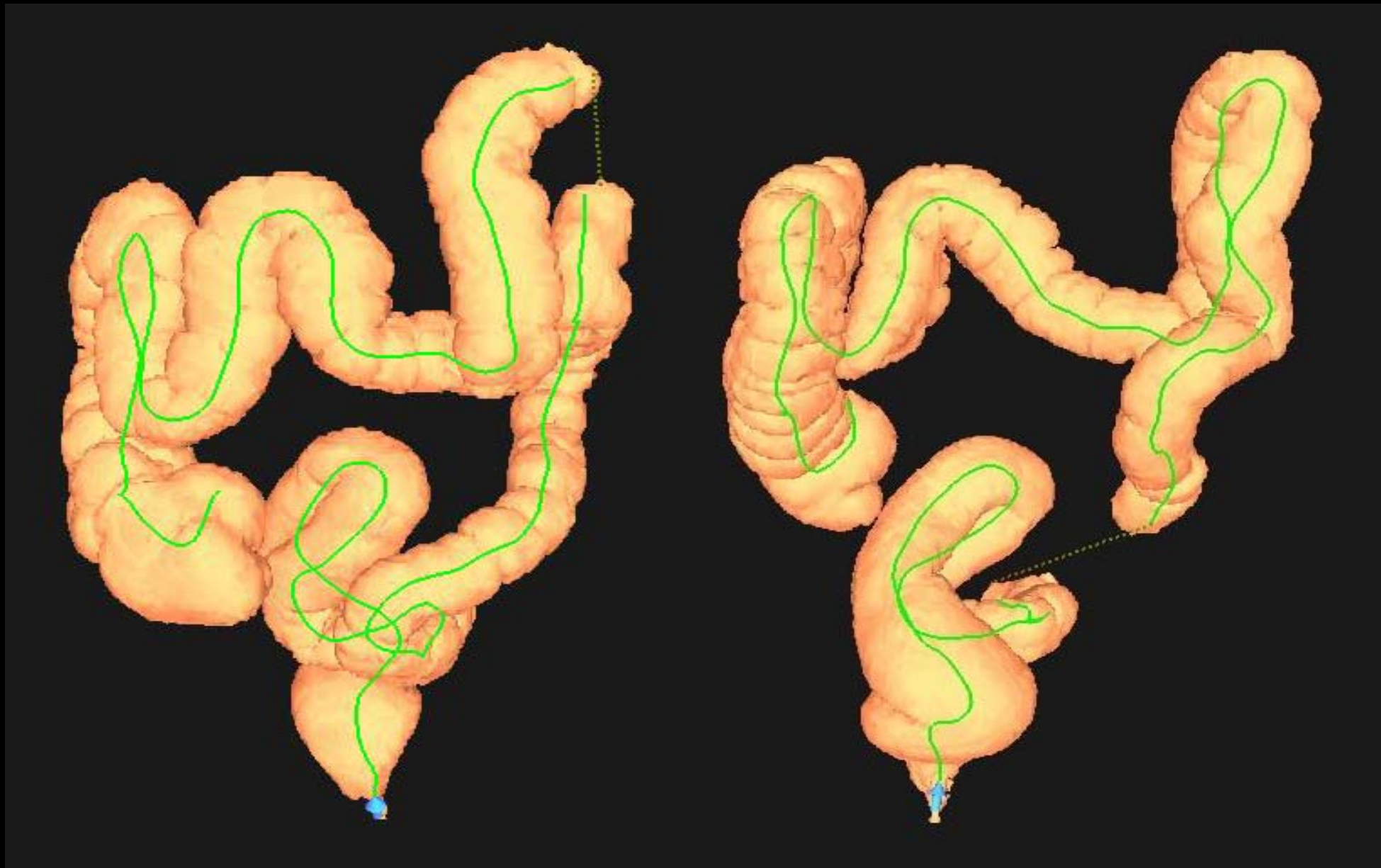
- Multi-detector helical CT
- Slice thickness ≤ 2.5 mm
- Reconstruction interval ≤ 1.25 mm
- Single 15 – 20 sec. breathhold
- Supine and prone
- IV contrast, sedation, glucagon unnecessary
- Scan duration 15 – 20 min.





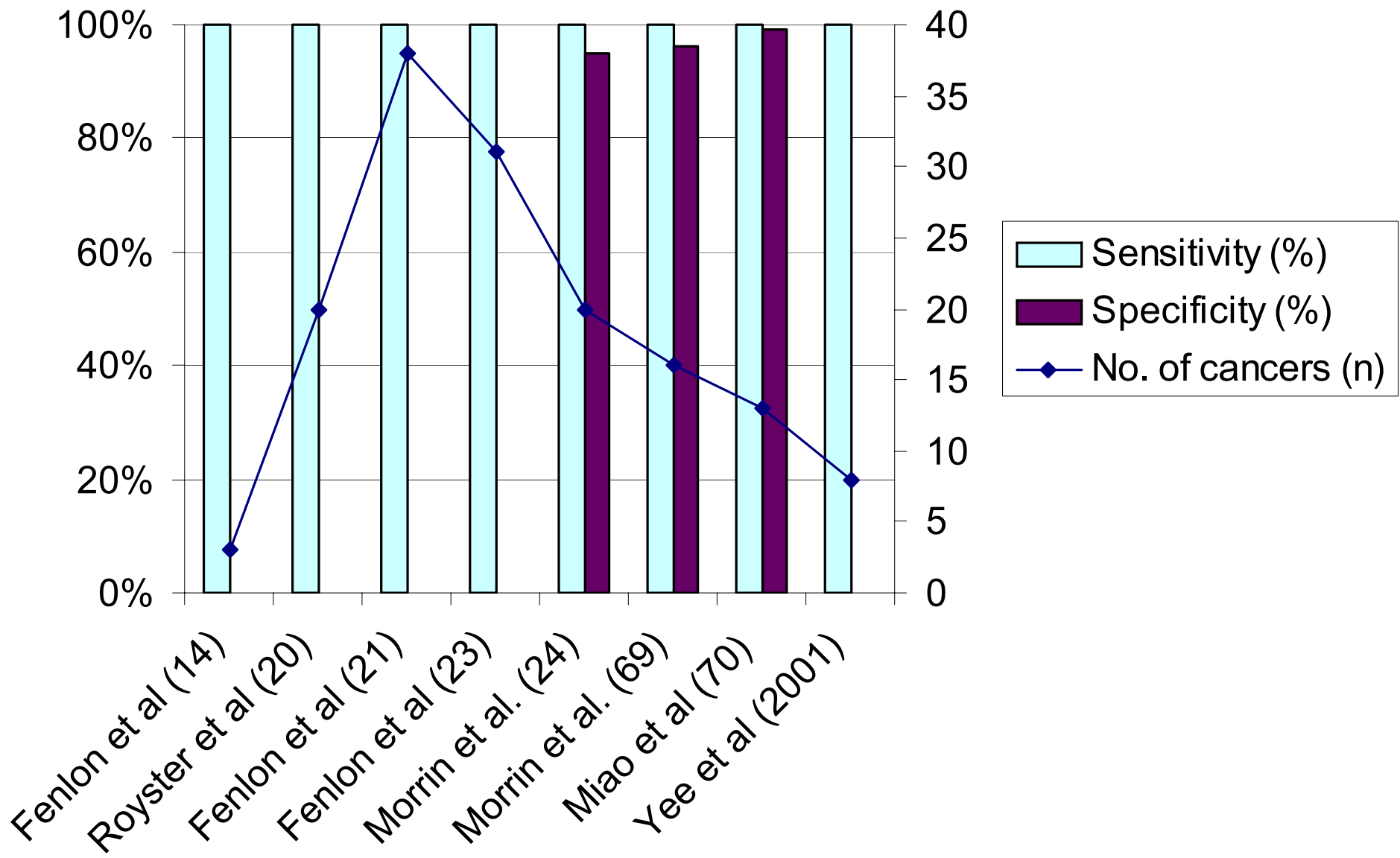
Virtual Colonoscopy Examination

- Addition of prone scanning increases sensitivity 13 to 15%



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

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

Extracolonic Findings

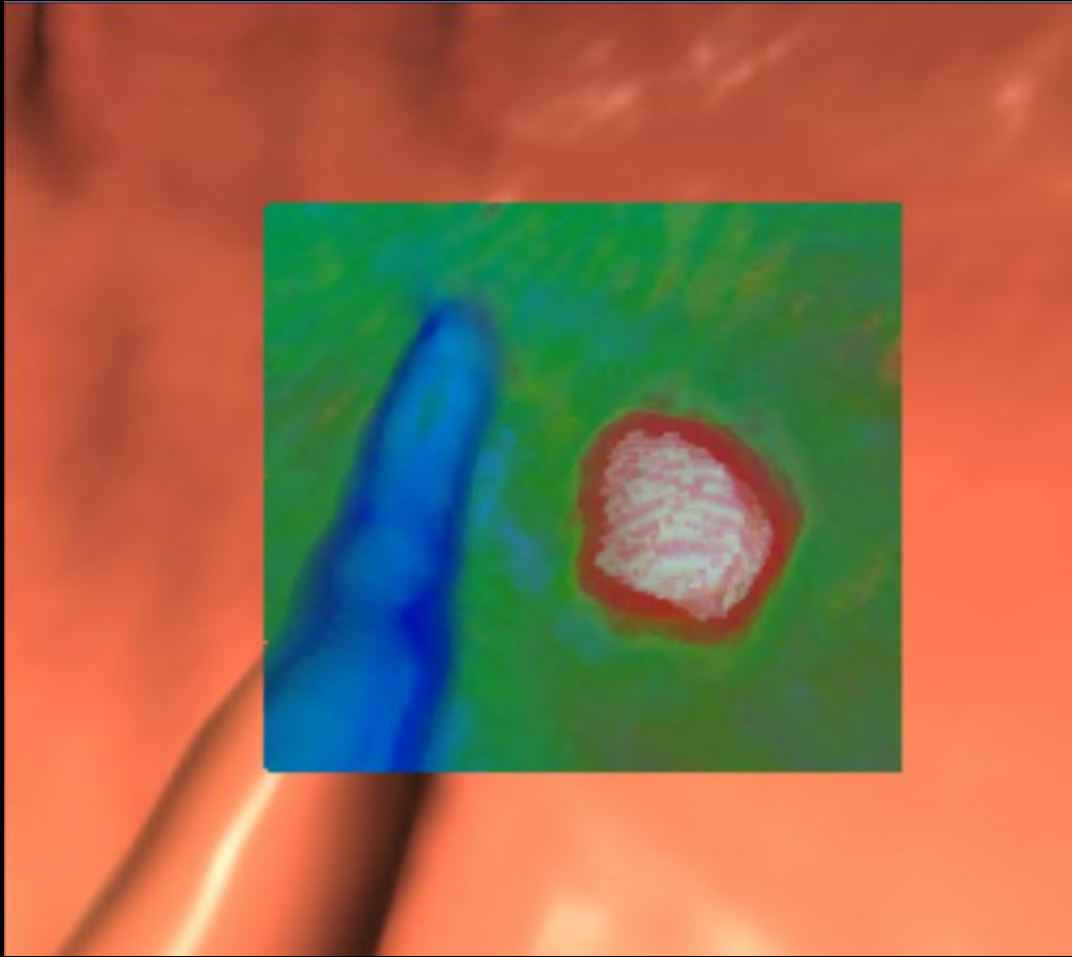
- 11% have “highly important” findings
 - Masses, AAA, pulmonary nodule, adrenal nodule, hernia, PTX
- 7% undergo further examination
- 6 of 264 consecutive patients underwent surgery based on VC finding

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

Laxative-free Prep

- Wake Forest Univ. Trial
 - 205 patients
 - Oral contrast
 - Patients with lesions $\geq 10\text{mm}$
 - Sensitivity: 90%
 - Specificity: 94.6%



Role of IV Contrast

- May improve sensitivity, esp. in suboptimally prepared colons
- Increases cost and risk
- Not desirable for screening

Patient Preference

- 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)

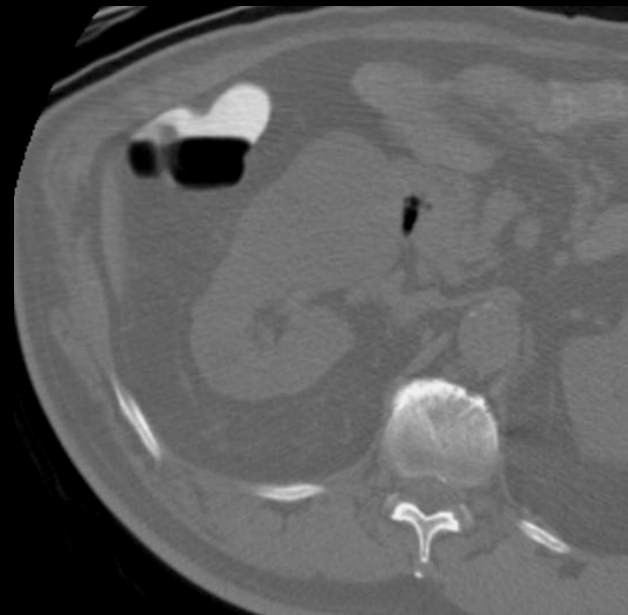
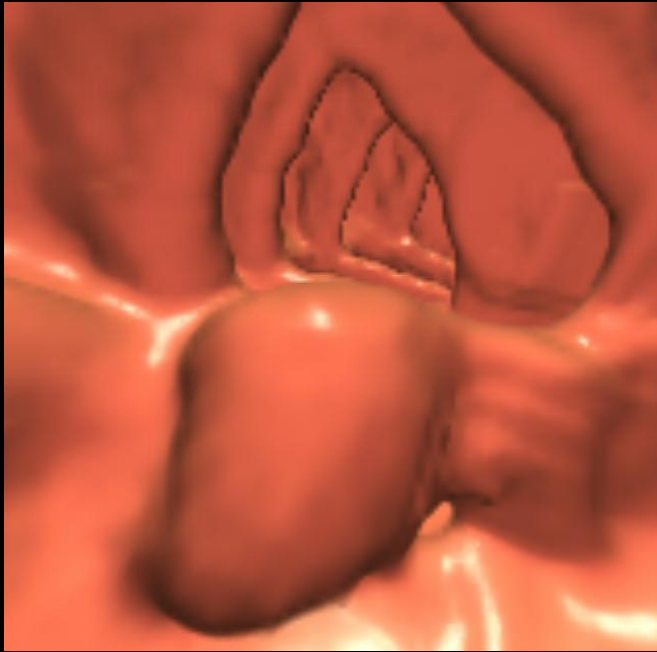
Clinical Trials

- 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

Adenoma Detection per Patient

Size threshold	≥ 6 mm	≥ 8 mm	≥ 10 mm
VC Se	88.7% (168)	93.9% (82)	93.8% (48)
VC Sp	79.6% (1065)	92.2% (1151)	96.0% (1185)
OC Se	92.3% (168)	91.5% (82)	87.5% (48)

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”

Clinical Trials

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

Clinical Trials

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

	Se	Sp
VC	59%	96%
ACBE	48%	90%
OC	98%	99.6%

Source: Rockey et al., Lancet 2005

Meta-Analysis 1

- Mulhall et al., Ann. Int. Med. 2005
- 6393 patients, 33 studies
- ≥ 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

Meta-Analysis 2

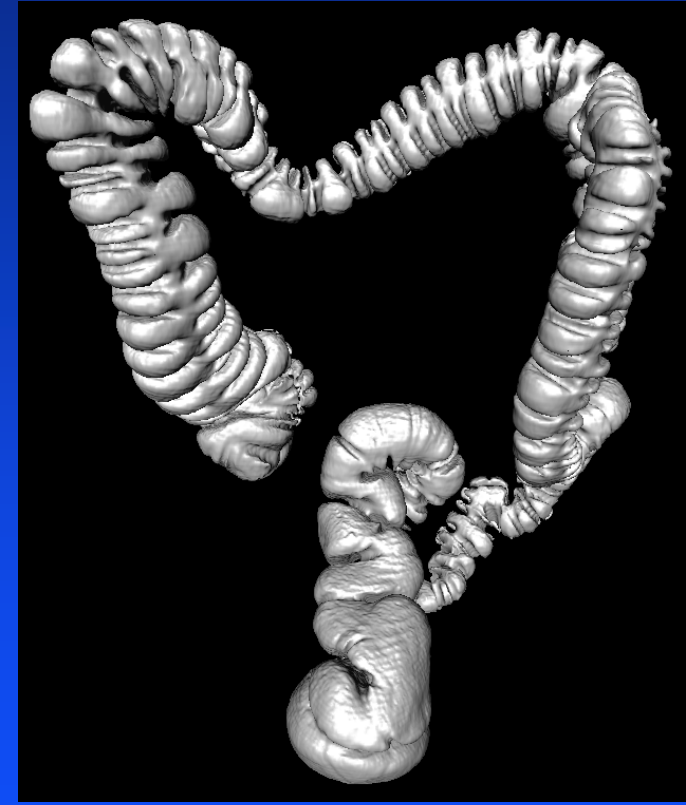
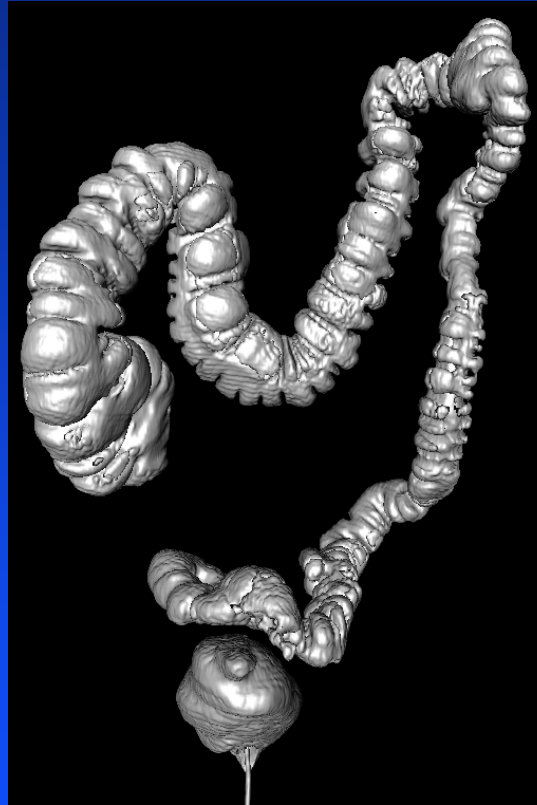
- Halligan et al., Radiology 2005
- 2610 patients, 24 studies
- ≥ 1 cm:
 - Se 93% [CI, 73% to 98%]
 - Sp 97% [CI, 95% to 99%]
- ≥ 6 mm:
 - Se 86% [CI, 75% to 93%]
 - Sp 86% [CI, 76% to 93%]
- Cancer: Se 95.9% [CI: 91.4%, 98.5%]
- Very sensitive for cancer; poor study reporting

CTC Complication Rate

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

CTC - Quality

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



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%

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

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 $> 1.6 \times$ VC
 - VC q 5 yrs
 - VC Se $> 83\%$ for polyps ≥ 1 cm

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

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%)

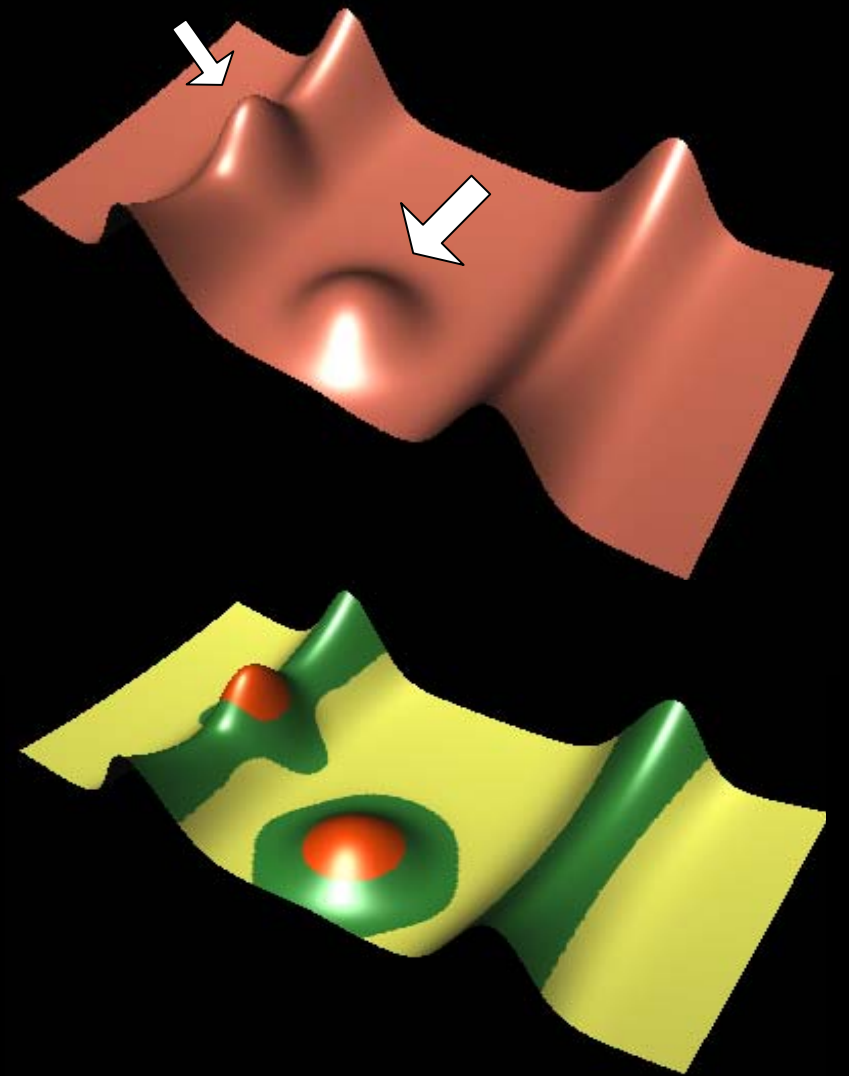
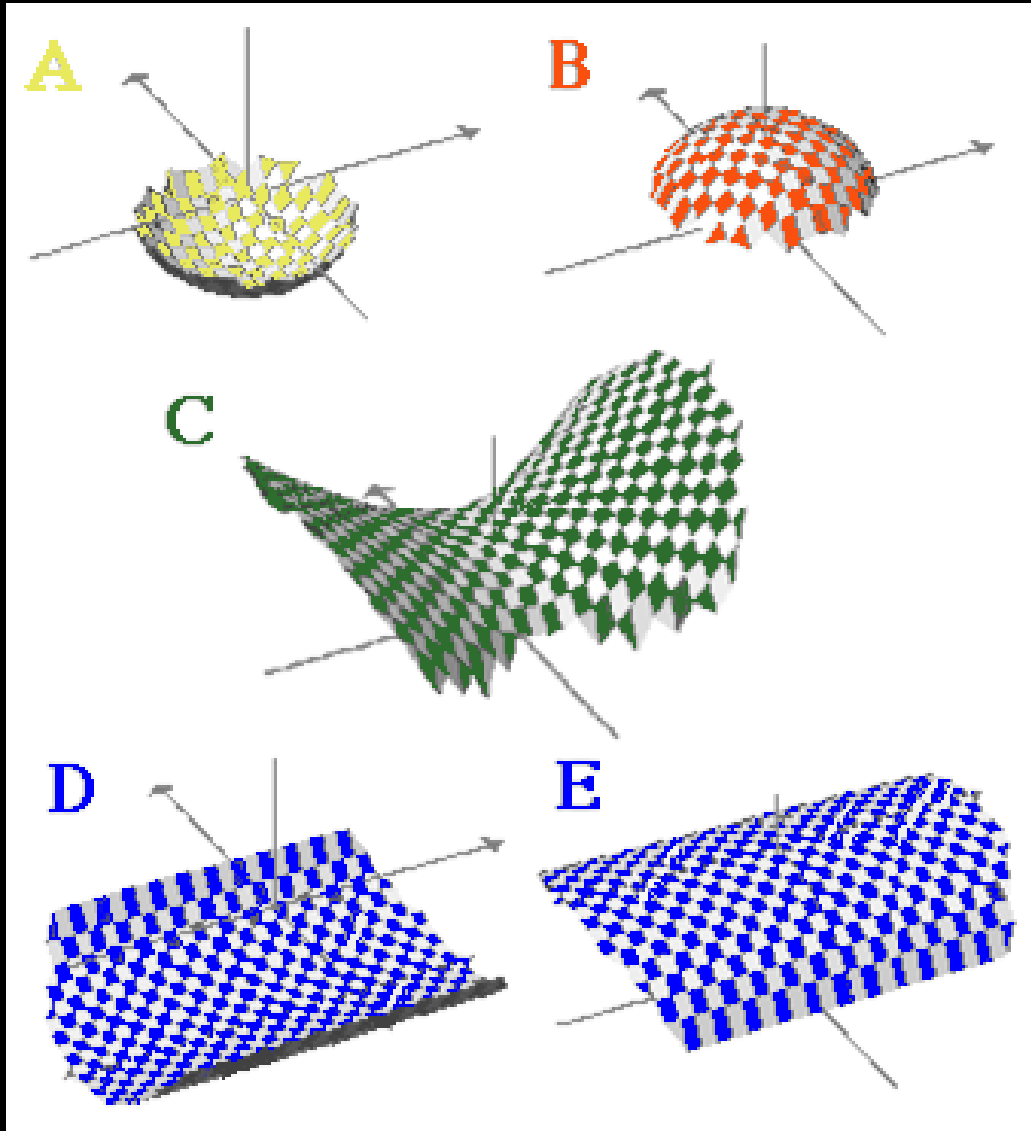
CTC Screening Paradigm

- Only pts with + CTC get OC if polyp ≥ 1 cm
- 6 – 9 mm polyps go to surveillance

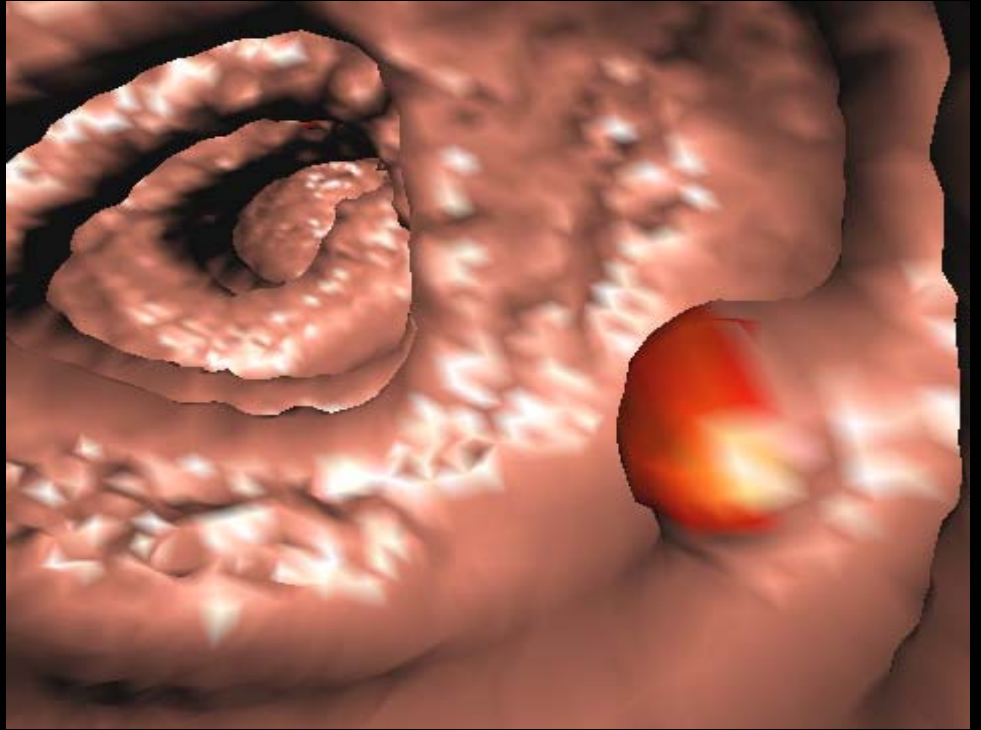
CAD

Rationale for Computer-aided Detection (CAD)

- High cost
- High interobserver variability
- Time consuming interpretation



Virtual Colonoscopy CAD

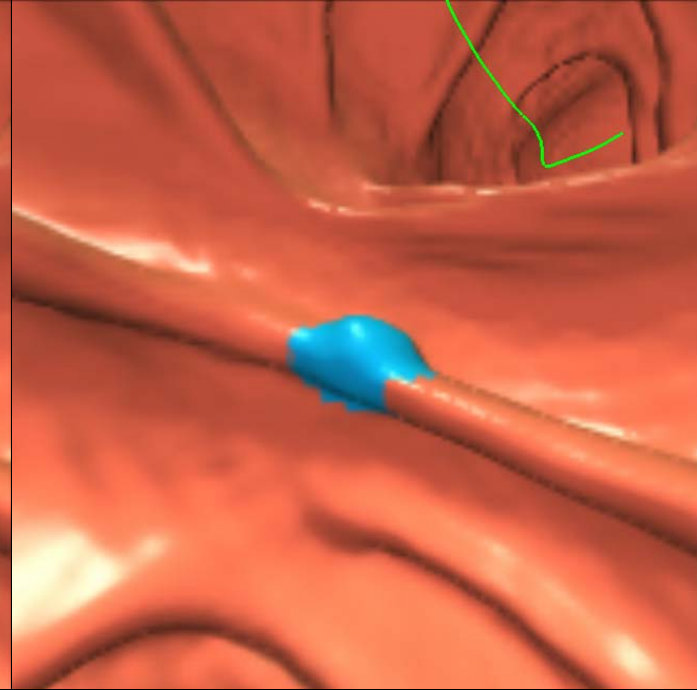
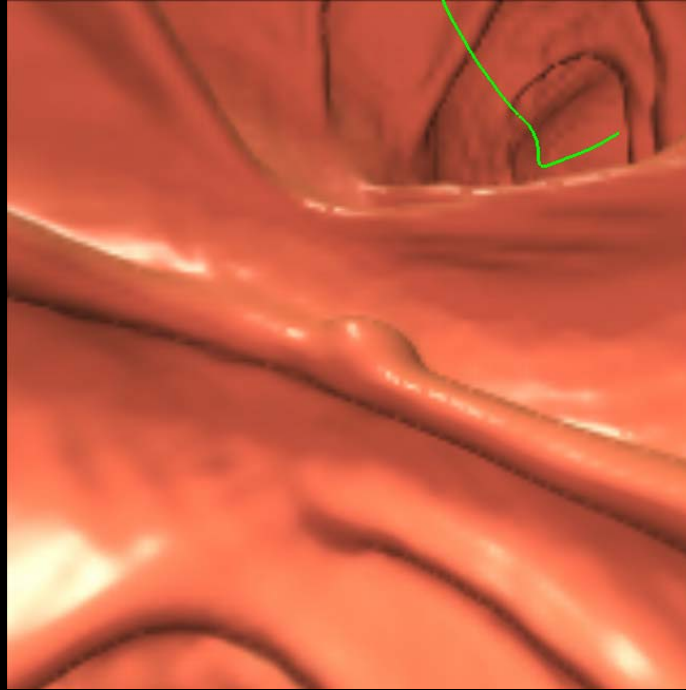


Multi-Institutional CAD Trial

- 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

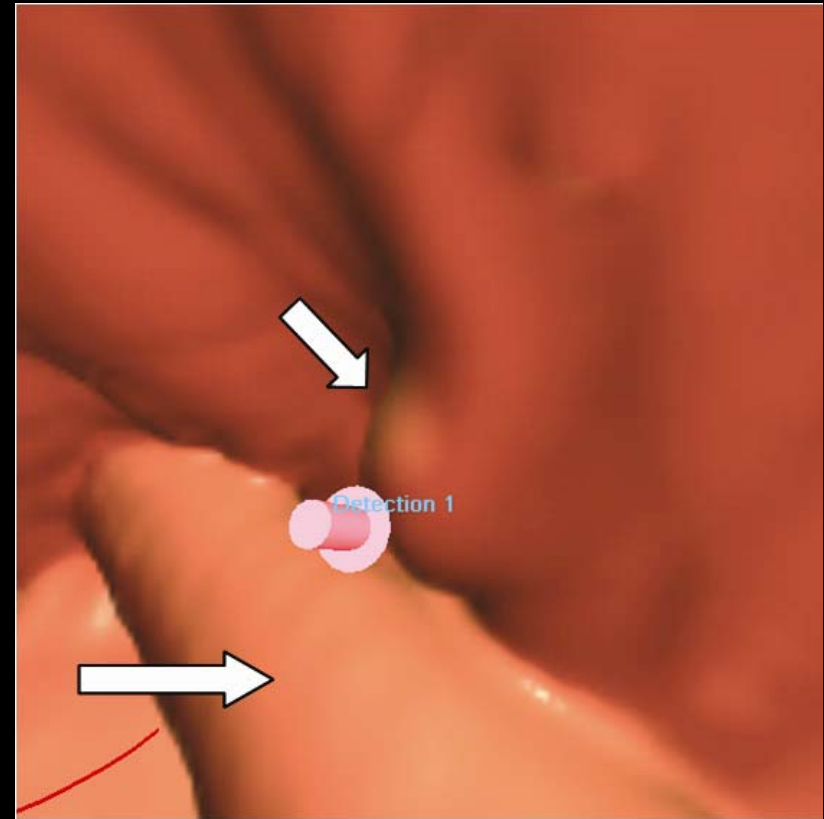
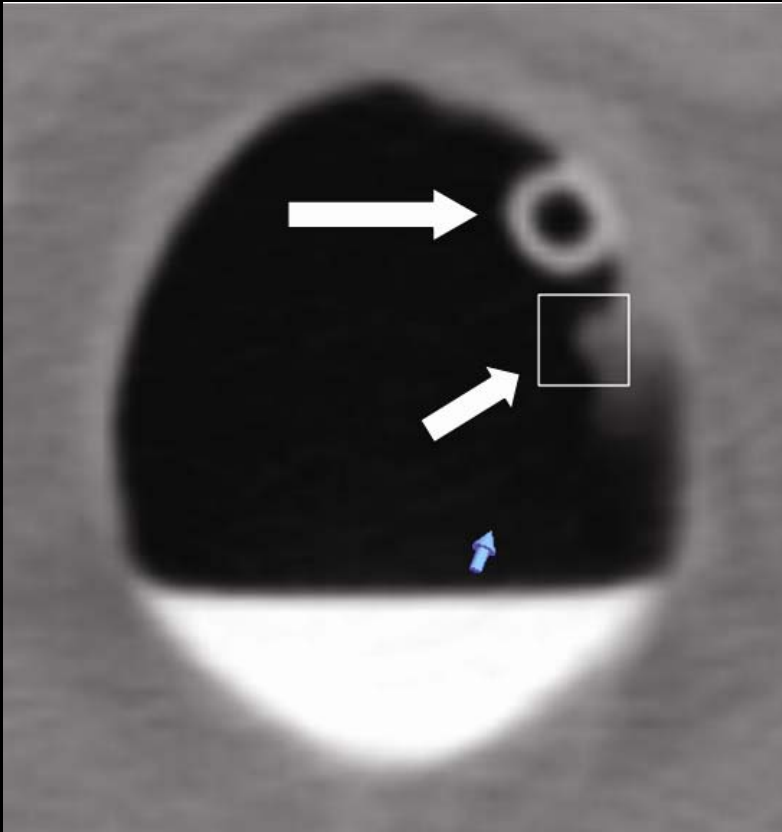
Sensitivity Per Patient and FP Rate

Size threshold	≥ 8 mm	≥ 10 mm
CAD	85.4% (41/48)	89.3% (25/28)
OC	89.6% (43/48)	85.7% (24/28)
CAD FP rate	6.7	2.1



0.6 cm polyp in transverse colon found by CAD

CAD as 2nd Reader



7 mm TA in rectum found by 3 readers with CAD

Petrack 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