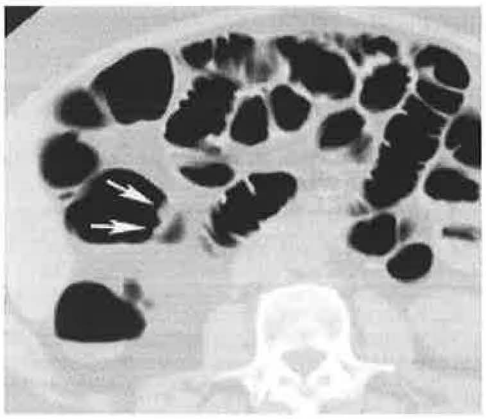
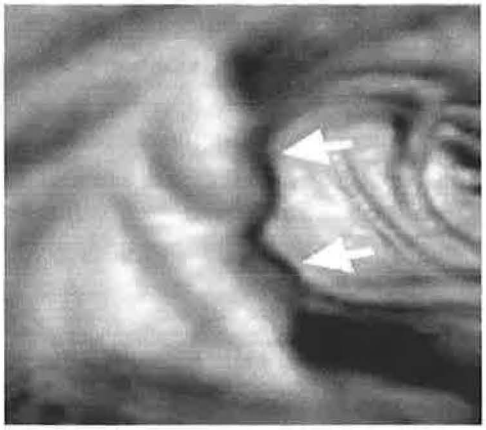
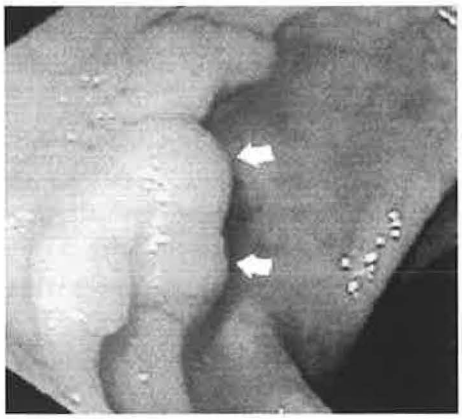
Colon Cancer Screening: Options, Options, Which One is Best?

University of Texas Southwestern Internal Medicine Grand Rounds

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This is to acknowledge that Dr. Burdick has disclosed no financial interest or commercial concerns directly or indirectly related to this program. Dr. Burdick will be discussing non-FDA approved uses in his presentation.

Additional members involved in the virtual colonoscopy studies at UTSW for Department of Defense trial included D Magee, L Bilhartz, C Dykes, C Brewington, T Forte, for NIH trial include J Sreenarasimhaiah, L Bilhartz, C Dykes, C Brewington, T Forte, A Parker, M Ulissey, S Kircher.

Case presentations

A 63-year-old professor of surgery presents with bright red blood per rectum. His exam is normal except for hemoccult positive stool. A colonoscopy is performed identifying a partial obstructing nodular exophytic lesion in the left colon. A subsequent evaluation notes a single liver metastasis. He undergoes colectomy and a partial hepatectomy. His disease reoccurs in less than a year with metastasis to the lung, liver and spine. He succumbs to metastatic colon cancer within a few years.

A 54-year-old Asian pharmacist is asymptomatic and stops to chat in the hallway regarding colon cancer screening. A clinic exam reveals hemoccult positive stool, and a colonoscopy identifies 8 polyps 1-3 cm each with 3 polyps having intramucosal cancer. He was treated with polypectomy and had surveillance endoscopies at one year and three years later and he remains tumor free.

The head of the IRB at a regional institution calls to request the status on virtual colonoscopy as a screening technique. His wife prefers this technique over colonoscopy. He asks if I would recommend a virtual colonoscopy exam for his loved one.

These cases illustrates several points:

1) Outcomes of cancer are based upon the extent of disease.
2) Asymptomatic tumors must be identified with screening to impact on disease outcomes.
3) Screening rates remain low secondary to several barriers.
4) A proliferation of new techniques will be available in the near future to potentially augment the fight against colon cancer and potential patients may prefer these techniques.

Colorectal Cancer is the third leading cause of cancer and cancer deaths in the United States with 146,500 cases of colon and rectal cancer and 57,100 deaths in 2003.[1] Texas is estimated to have 9,200 colon and rectal cancers and 3600 deaths in 2003. The lifetime risk of developing colon and rectal cancer is 1 in 17 or 18, depending on gender. The probability of developing invasive cancer increases with age.

	Birth to 39	40-59	60-79	Birth to death
Males	0.06 (1/1,616)	0.88 (1 /144)	4.00 (1/25)	5.88 (1/17)
Females	0.06 (1/1,630)	0.69 (1/145)	3.03 (1/33)	5.56 (1/18)

Survival of colon cancer is dependent on the stage of disease. When colorectal cancer is recognized at an early-localized stage the 5-year relative survival rate is 90%. However, only 37% of tumors are recognized at that stage. Sporadic colorectal cancer accounts for

80% of lesions and screening the average risk population begins at age 50 including: annual fecal occult blood test, or flexible sigmoidoscopy every 5 years, or the combination of annual fecal occult blood testing and flexible sigmoidoscopy every 5 years, or colonoscopy (if normal, repeat every 10 years), or double contrast barium enema (if normal repeat every 5 years). A digital rectal exam is recommended at the same time of sigmoidoscopy, colonoscopy or barium enema. These tests offer the opportunity to detect colorectal cancer at an early stage when successful treatment is likely and to prevent cancers by the detection and removal of polyps. These methods are comparable to costs per year of life gained with mammography for breast cancer or PAP smear for cervical cancer screening. However, screening rates are low at approximately 40% and are influenced by consumer resistance to lower endoscopy, digital rectal exam, and fecal screening. The yield for therapeutic benefit with colonoscopy is variable and dependent on the indication with lower yields in screening asymptomatic populations. New techniques including virtual colonoscopy offer a new means to detect screen for colon cancer and may be more attractive to prospective patients than other methods.

Leading Sites of New Cancer Cases and Deaths – 2004 Estimates*

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 230,110 (33%)	Breast 215,990 (32%)	Lung & bronchus 91,930 (32%)	Lung & bronchus 68,510 (25%)
Lung & bronchus 93,110 (13%)	Lung & bronchus 80,660 (12%)	Prostate 29,500 (10%)	Breast 40,110 (15%)
Colon & rectum 73,620 (11%)	Colon & rectum 73,320 (11%)	Colon & rectum 28,320 (10%)	Colon & rectum 28,410 (10%)
Urinary bladder 44,640 (6%)	Uterine corpus 40,320 (6%)	Pancreas 15,440 (5%)	Ovary 16,090 (6%)
Melanoma of the skin 29,900 (4%)	Ovary 25,580 (4%)	Leukemia 12,990 (5%)	Pancreas 15,830 (6%)
Non-Hodgkin lymphoma 28,850 (4%)	Non-Hodgkin lymphoma 25,520 (4%)	Non-Hodgkin lymphoma 10,390 (4%)	Leukemia 10,310 (4%)
Kidney 22,080 (3%)	Melanoma of the skin 25,200 (4%)	Esophagus 10,250 (4%)	Non-Hodgkin lymphoma 9,020 (3%)
Leukemia 19,020 (3%)	Thyroid 17,640 (3%)	Liver 9,450 (3%)	Uterine corpus 7,090 (3%)
Oral cavity 18,550 (3%)	Pancreas 16,120 (2%)	Urinary bladder 8,780 (3%)	Multiple myeloma 5,640 (2%)
Pancreas 15,740 (2%)	Urinary bladder 15,600 (2%)	Kidney 7,870 (3%)	Brain 5,490 (2%)
All sites 699,560 (100%)	All sites 668,470 (100%)	All sites 290,890 (100%)	All sites 272,810 (100%)

Digital Rectal Exam

A case-controlled trial examined the effect of digital rectal examination on death from colorectal cancer.[2] Patients age 45 and older who died of distal rectal cancer between 1971 and 1986 were selected and matched for controls. Records were examined for screening digital rectal examination within a year of diagnosis. Investigators found no difference between groups after controlling for confounders. Less than 10% of colorectal cancers are within the reach of a digital rectal exam.

Fecal Occult Blood Testing

Three trials support a reduction in mortality rates with fecal occult blood testing (FOBT).[3,4,5, 6,7] The oldest trial compared annual and biennial testing with no screening and rehydrated most cards 83%.[3] Compliance was high at 90% initially. Colorectal cancer rates were reduced by 33% CI 95% (17-49%) at 13 years follow-up in the annual FOBT

group than control group with no screening. Absolute death rates were 9.5/1000 deaths vs. 14.1/1000 deaths in the control group. Biennial produced a non-statistically significant reduction in colorectal mortality rates at 13 years. Follow-up was extended to 18 years at which time a 17% reduction in colorectal cancer with biennial screening was noted 0.83 odds ratio (95% CI 0.73-0.94).

49% of colorectal cancers were identified through screening in the annual screening group. 38% of participants had at least one colonoscopy in the annual screening group. Biennial screening detected 39% of colorectal cancers and 28% of patients had at least one colonoscopy.

Two trials were based in Europe and had participation rates of 60-70% of patients. FOBT was used and did not rehydrate the stools.[4,5] Screening detected 27% of patients who developed colorectal cancer and only 5% of patients had a colonoscopy.

A systematic review from 1997 found that a single unrehydrated FOBT was 40% sensitive for colon cancer with a specificity of 96-98%.[7,8] Rehydration increased the sensitivity to 50-60% but decreased the specificity.

Sigmoidoscopy

Case controlled trials note a reduction in colon cancer occurrence and mortality. Rigid sigmoidoscopy reduced mortality by 59% odds ratio 0.41 (CI 0.25-0.69).[9] There was no difference in cancer mortality above the level examined and the protection extended for 10 years from the examination. A second trial found an 80% reduction odds ratio 0.21 (CI 0.08-0.52) in mortality from rectosigmoid cancers.[10] Two prospective trials on the use of flexible sigmoidoscopy are awaited. The prostate, lung, colo-rectal, and ovarian (PLCO) cancer screening trial in the United States and an Italian multi-centered trial on once only sigmoidoscopy (SCORE) are ongoing.[11,12] The PLCO trial has enrolled nearly 150,000 patients age 55-74 in a randomized controlled study to determine whether certain screening practices will reduce the deaths from these cancers.[11] The SCORE trial uses once only sigmoidoscopy. 34,292 patients were enrolled and 17,148 were assigned to the screening group.[12] 9911 were actually examined. 15.5% of patients had a lesion requiring colonoscopy. Colorectal cancer was identified in 54 patients (5.4%). Two perforations have occurred one at sigmoidoscopy rate 1/9911 and one in 775 colonoscopies. One hemorrhage occurred in a patient treated with polypectomy.

Fecal Occult Blood Testing (FOBT) and Sigmoidoscopy

The combination of one time fecal occult blood testing with rehydration and sigmoidoscopy in the identification of advanced neoplasia was 75.8% combined.[13] Sigmoidoscopy identified 70.3% of patients and one time FOBT 23.9% of patients with advanced neoplasia. In two randomized trials subjects offered both FOBT and sigmoidoscopy had higher rates of detection than the group offered fecal occult blood testing alone.[14,15] In a third study, which was non-randomized, a group that had FOBT

and sigmoidoscopy had longer survival rates than a group evaluated with sigmoidoscopy alone.[16]

Barium Enema

No published trials have examined the effectiveness of double-contrast barium enemas in reducing the incidence or death from colon cancer.[7] The national polyp study examined the role of barium enema in detecting polyps after prior polypectomy.[17] The study may have limited application as it was not used as a screening technique. A prior polypectomy reduces the likelihood of large polyps or tumors. Thus, the inclusion criteria for this trial is different than a screening population. The sensitivity of double contrast barium enema was 53% (CI 40-66%) for polyps 0.6 to 1.0 cm and 48% (CI 24-67%) for polyps larger than 1 cm. False positive were positive in 83/470, which detected no polyps in 17.6%.

A multi-centered trial examined the role of barium enema in conjunction with virtual colonoscopy and colonoscopy with similar results to the national polyp study.[18] The sensitivity of 1 cm polyps was 45% (CI 33-57%) in 34 of 76 patients. The specificity was 90% (CI 87-92%). The patient experience was inferior to colonoscopy in regard to comfort or willingness to undergo a repeat examination and will be reviewed in the virtual colonoscopy section.

A retrospective review of 2193 consecutive cases of colon cancer identified at 20 Indiana hospitals noted the sensitivity for detection of cancers was 82.9% with barium enema.[19] There was no difference in single contrast or double contrast barium enema exams. The odds ratio of a missed lesion having a barium enema compared to colonoscopy was 3.93 (CI 95% 2.76-5.58). Lesions on the left or right colon were equal in recognition.

The risk of perforation is low with barium enema with perforation estimated at 1 in 25,000 examinations and death in 1 in 55,000 examinations.[20]

Colonoscopy

The ability of colonoscopy to prevent colorectal cancer or death has not been measured in a screening trial in the average risk population. The inference that colonoscopy reduces cancer deaths is indirect in the population from the use of colonoscopy with positive lesion at sigmoidoscopy or hemoccult testing.[3-10] The national polyp study estimates that 76 to 90% of cancers could be prevented by regular surveillance and removal of polyps.[21] The participants all had polyps detected and removed and the control group were not from the same population. The trial participants and control groups risks may not be similar and assumptions from this trial may not be applicable to the general population. A case controlled study noted a protective effect with colonoscopy for the diagnosis of colon cancer. The odds ratio was 0.51 colon cancer diagnosis (CI 0.44-0.58) and 0.55 rectum diagnosis (CI 0.47-0.64).[22]

The accuracy of colonoscopy in tandem examinations was found to have false negative in 6% for large adenoma and 13% for 6-9 mm adenomas.[23] The combined results with the NIH trial and Department of Defense trials for optical endoscopy was 127/130 (97.7%) sensitivity of large polyps.[18,24] The Pickhardt et al tandem exam with optical and virtual colonoscopy detected 87.5% (42/48) of 1 cm or greater sized polyps with optical technique.[25] It is speculative as to the inferior optical results in this trial but questions arise on whether the preparation, endoscopists, or endoscopic techniques account for the differences among those three trials. Most endoscopists view the colon primarily upon colonoscopic withdraw. The lowest miss rate of the 26 colonoscopists in one study had the longest withdraw mean time.[23] The average withdraw time in the Department of Defense trial was 22 minutes and exceeds the 6-10 minutes suggested by national guidelines.[26]

Endoscopy by non-gastroenterologists is practiced. A retrospective evaluation of colon cancers associated a colonoscopy by a non-gastroenterologists with a lower sensitivity than a gastroenterologist with an odds ratio of 5.36 CI (2.94-9.77) for a missed colon cancer.[27] This compares to a 3% miss rate by gastroenterologists. The location of missed tumors and an absence of adequate documentation of cecal landmarks suggested that several missed lesions may be related to inadequate insertion.

Colonoscopy risk in an average risk screening population had major complications in 10/3121 during or immediately after the procedure.[28] Six had bleeding, and one of each of the following occurred: myocardial infarction, stroke, Fournier gangrene, and thrombophlebitis. A second study among 1994 patients age 50 or greater resulted in one (0.05%) had a perforation that did not require surgery and three (0.15%) had bleeding that required emergency visits but not surgery.[29]

Fecal DNA

Molecular alteration in fecal DNA is a potentially non-invasive method for the detection of colorectal cancer. Randomized trials of fecal occult blood testing to trigger colonoscopy have noted a reduction in cancer and deaths from colorectal cancer. However, the ability to diagnosis cancer is less than 50% with FOBT despite annual testing. The fecal stream comes in contact with the colonic mucosa and DNA is shed into the lumen. Our understanding of the molecular changes associated with colon cancer and improved techniques for DNA isolation and amplification have made possible the detection of mutations in the stool to detect neoplasia.[30] This technique involves the collection of a whole bowel movement. This potentially avoids sampling error and maximizes yields. The sample is stored at -80° C until processing. The stool is homogenized in EDTA buffer to prevent enzymatic degradation of DNA. The crude DNA is separated from fecal matter and cellular debris and isolated by hybridization with sequence specific probes. These fragments are amplified using PCR and analyzed for mutations.

The knowledge that a single mutation is limited to 50% of tumors suggests that false negatives would occur if only one marker is used. A battery of mutational probes to

assess for colon cancer has yielded improved results. Assays include the use of K-*ras, p53,* Adenomatous polyposis coli (APC), BAT26 microsatellite instability (MSI) and long DNA a marker for disordered apotosis.[30,31,32,33]. Those results are shown in polled form. The following trials are shown in order of publication.[34,35,36,37]

Panel Components	*Sensitivity*	*Specificity Controls*
APC, k-ras, p-53, BAT26, long DNA (Exact Sciences)	99/146 (67.8%) CI (59.6-75.3)	230/240(95.8%) CI (92.5-98.0%)
P 53, k-ras, BAT-26	36/51 (71%)	NA
APC	26/46 (57%)	28/28 (100%)
BAT 26	17/46 (37%)	69/69 (100%)
P 53, k-ras, APC, 5 MSI markers, long DNA	33/53% (62%)	37/38 (97%)

If the test is positive and colonoscopy does not yield a diagnosis, then evaluation in the upper GI tract may be needed. No studies have addressed the appropriate interval for testing. The fervor for this technique has cooled as the ability to diagnose cancer has not held up to the 80% yields expected with 62% reported in the last study. The specificity appears high at greater than 95%. The cost associated with multiple genetic probes results in higher cost per year of life gained than other techniques including virtual colonoscopy. The test is not approved for use at this time.

Virtual Colonoscopy

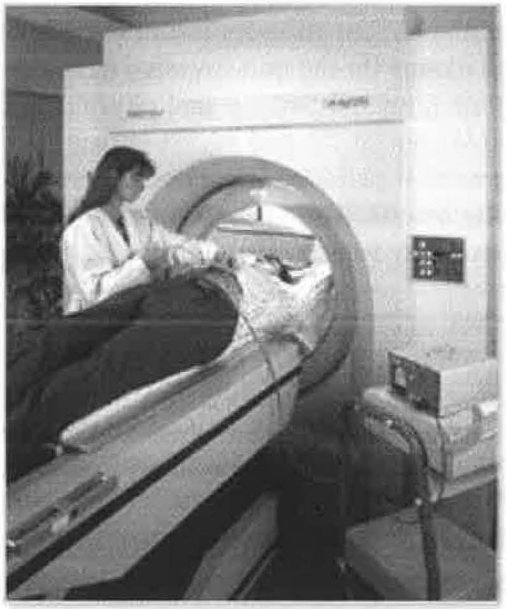
Optical or Virtual Colography is a promising technique to aid in the screening and detection of colon cancer. However, the results have been variable in multi-centered clinical trials.[18,24,25] Potential patient attitudes from both primary care physicians and patients may favor virtual exams for the non-invasive nature and the lack of sedation.[38] Considering the information potential patients and physicians favored virtual exams over colonoscopy 60.2 percent versus 25.7% and 44.9% versus 30.3% respectively. Additionally, 82.3% of potential patients would comply more with recommendations for colorectal cancer screening and 61.7% of physicians would refer more patients for screening, if virtual colonoscopy were available.[38]

Virtual Colography involves multiple thin slices of the abdomen and reconstruction of the images by computers to produce 2 and 3-dimension formats with fly-through to simulate colonoscopy. The technique was first described by Vining in 1994 and has been performed with both Magnetic Resonance Imaging (MR) and spiral Computerized Axial Tomography (CT). The examination is performed primarily with CT Technique and can be divided into 4 steps.[39]

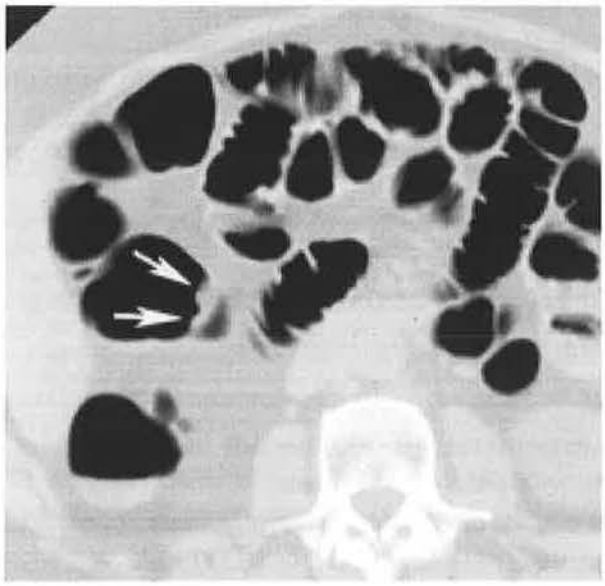
1) Bowel Preparation
2) Pneumocolon
3) Spiral CT
4) Computer Generation of Image

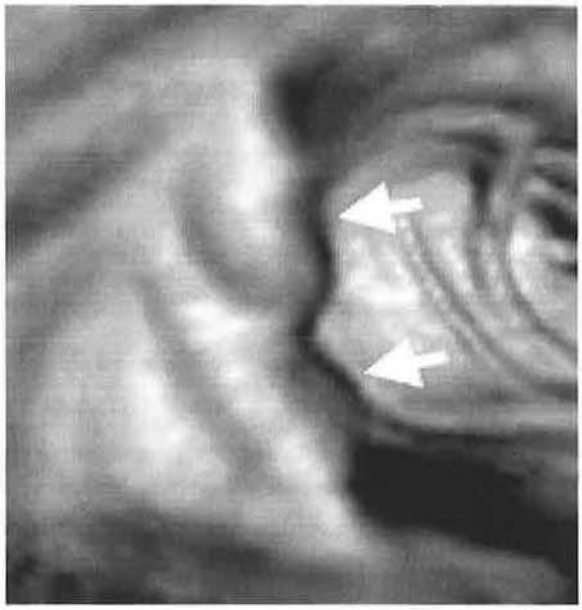
Bowel preparation is needed as the removal of stool and minimal residual fluid avoid artifact. Cleaning with osmotic agent oral phosphosoda offers low fluid residuals and has high patient acceptance.[40] Select centers have incorporated oral intake of gastrograffin and barium to tag the stool and colon wall.[25] Feasibility studies are being performed to identify polyps by oral contrast tagging without bowel cleaning.[41,42,43, 44, 45, 46] The colon is then insufflated with room air or carbon dioxide via a rectal tube. 2-D imaging is obtained to document distension prior to imaging. Non-distended segments of bowel may obscure or simulate abnormalities. Spiral CT scanning has significant advantages over standard CT. Conventional scanning obtains sequential static cross sectional images during separate breath holds. Spiral CT moves the patient continuous through a rotating beam during a single breath hold eliminating image gaps and motion artifact. Patients may be scanned in the prone and supine positions. The images are then processed by commercially available software that simultaneously displays two-dimensional axial, coronal, and sagittal images at any designated point. The software will simultaneously display a three-dimensional luminal view simulating colonoscopic images. Computerized programs may aid in detection of lesions and allow features such as multi-directional viewing, color enhancement, automatic luminal centering, reporting of the lesion location, and simulated gross anatomic views, and electronic cleanings. Automated software is being developed to interpret images.

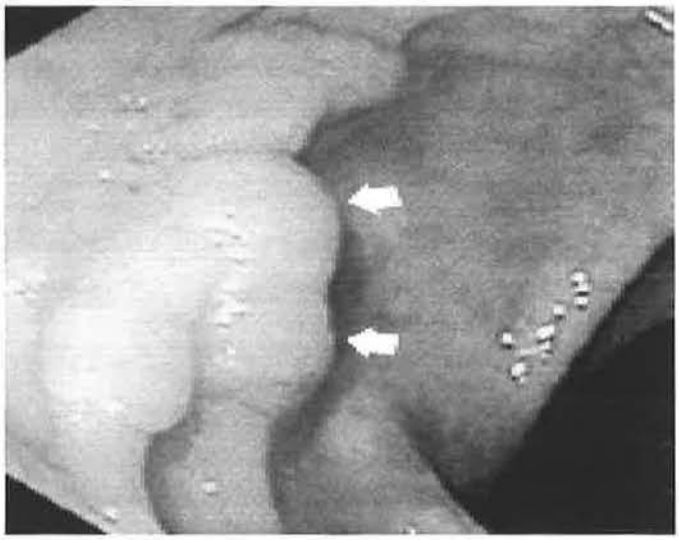
Multi-detector CT scanners have shortened the acquisition time to 15-20 seconds as compared to two minutes. Image generation can be as short as 10 minutes with interpretation times from 7-65 minutes. Sedation is not used and therapy cannot be rendered for lesions detected. A potential advantage is the detection of extracolonic lesions.



Complications include those related to colonic preparation, colon insufflation and radiation exposure with CT imaging. Perforation with Virtual colonoscopy has been reported.[47,48] The dosage of radiation is comparable to a barium enema examination. MR colography does not expose patients to radiation but has the restrictions with regard to implanted metallic devices.







Lesion is shown in three images with arrows by 2-D CT colography, 3-D CT colography, and optical colonoscopy respectively from left to right and inferior.

Indications

Virtual colonoscopy is indicated in incomplete colonoscopy due to technical factors or obstructing lesions. The American Cancer Society, US Multi-Society Task fForce on Colorectal Cancer, and the US Preventive Services Task Force have not recommended virtual colonoscopy for colorectal cancer screening.[7,39]

Efficacy

The results for polyp detection are variable and decrease in correlation with polyp size. The indication for the examination and techniques has been variable. Technical differences including software, fecal tagging, operator experience, 2-D versus 3-D primary reviews, and air insufflation have been suggested as possible reasons for discrepancies.

A meta-analysis was performed with the following entry criteria: prospective, full colorectal preparation who underwent CT colography, reference standard was colonoscopy, reviewers were blinded to the results of conventional colonoscopy, exams performed in both the supine and prone positions after insufflation with either CO2 or air using at least a single detector CT scanner with slice thickness no greater than 5mm, studies in which both 2-D and 3-D analysis were performed and performance results in absolute numbers and percentages for polyps of different sizes.[49] Of 146 articles, 14 fulfilled the inclusion criteria involving 1,324 patients and 1,411 polyps. The pooled per patient sensitivities were as follows: 10mm or greater a sensitivity of 0.88 (0.84-0.93 95% CI), 6-9mm 0.84 (0.80-0.89 95% CI), and polyps 5mm or smaller was 0.65 (0.57-0.73). The pooled per polyp data was as follows: 10mm or greater 0.81 (0.76-0.85), 6-9mm 0.62 (0.58-0.67) and polyps 5mm or smaller was 0.43 (0.39-0.47). The pooled specificity of polyps larger than 10mm was 0.95 (0.94-0.97).

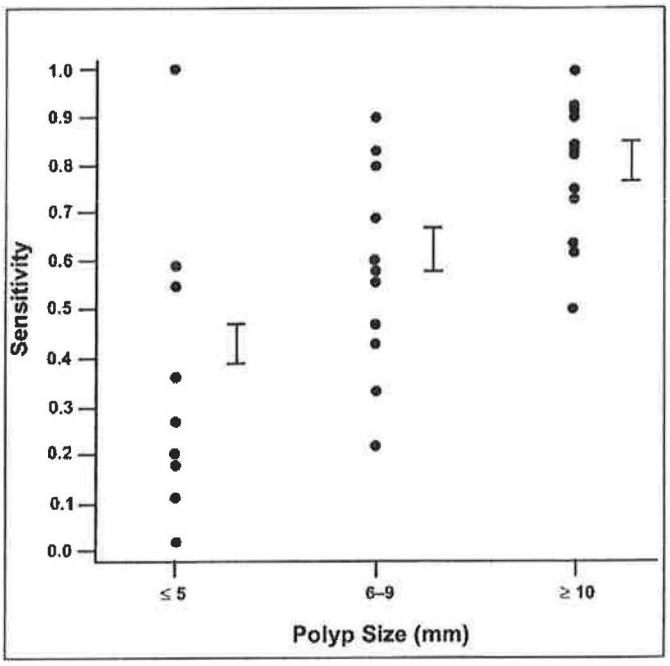


Diagram of sensitivity per polyp size of various trials from Sosna et al.

The rules of evidence based medicine weigh prospective trials at a higher degree of influence than meta-analysis. In this regard prospective trials have been completed with conflicting results using virtual colonoscopy. The use of fecal and fluid tagging and 3-dimensional imaging were suggested as potential differences.

Pickhardt et al published data noting sensitivity of 93.8 % for polyps of at least 10mm in diameter, 93.9% for polyps at least 8mm in diameter and 88.7% for polyps greater than 6 mm in diameter.[25] This multi-centered trial enrolled 1233 asymptomatic patients (mean age of 57.8 years), who underwent virtual colonoscopy and colonoscopy on the same day. This trial employed the use of solid stool tagging with barium 500cc (2.1% by weight) and 120cc of diatrizoate meglumine and diatrizoate sodium (Gastrografin, Bracco Diagnostic) for the opacification of luminal fluid. Colonic insufflation was patient controlled. Scan was performed in supine and prone positions with 4 or 8 channel CT scanners with reconstruction at 1mm interval. Image processing was performed using commercially available system (Viatronix V3D Colon, version 1.2, Viatronix). This software electronically removes from images the opacified residual fluid in a routine postprocessing step. The 3-D images were relied upon for initial detection of polyps. The scans were read by 6 board-certified radiologists who had been involved in the reading of a minimum of 25 virtual colonoscopy exams. Two of the radiologist had interpreted more than 100 studies each.

A 2nd trial comparing virtual colonoscopy and optical colonoscopy had divergent results from Pickhardt et al. This trial was prospective, evaluator blinded, non-inferiority study

design of 615 participants age 50 years or greater using multi-slice scanners and same day colonoscopy.[24] Six hundred patients underwent both exams. Although maintaining a high specificity of 90.5% for lesions 6mm or greater in size the sensitivity was low at only 55% for lesions 10mm or greater and 39% for lesions 6-9mm. The negative predictive value for lesions on 10mm or greater was 96.5%. Among the 9 centers there was significant variation from 0 to 100% detection of lesions 6mm or greater. The largest enrolling center had 83% in 188 exams. The accuracy of virtual colonoscopy did not improve as the study progressed. The initial interpretation was with 2-D imaging; however, the same radiologist examined a 3-D rendering with fly-thorough later without referring back to their initial read. The sensitivity did not improve with 36.4% detection of lesion 6mm or greater and 55.6% for lesion of 10mm or greater. Fecal tagging and luminal evaluation were not performed. Preference questionnaires were completed and returned from 518 patients. 46% preferred virtual colonoscopy while 41% preferred conventional express. There was no statistically significant difference in satisfaction with either examination.

A third trial comparing barium enema, virtual colonoscopy and colonoscopy had similar inferior results, consistent with the JAMA paper.[18] The study was designed for equivalence of virtual colonoscopy, and colonoscopy in the evaluation of high-risk patients. An enriched population was sought with study entry including hematochezia, fecal occult blood positive, iron deficiency, or family history of colon cancer. The trial was prospective, blinded, and additionally included the evaluation of barium enema 1-2 weeks prior. Standard colon preparation was with oral phosphates. A minimum of 4-slice spiral CT was used with primary 2-D read and 3-D troubleshooting. A subsequent read with 3-D by an independent committee is being performed. Three software programs were used: Viatronix, Vitrea, and Advantage Windows. No fecal tagging or colon enhancements were used. Seven of the 15 readers had previously performed more than 50 exams. The study was halted at less than 1/3 intended study enrollment by the National Cancer Institute (NCI) safety monitoring board as a statistically significant result had been achieved. 775 patients were enrolled and 614 patients completed all three exams. The mean age was 57 years.

Size of lesions	Number of patients	Number of lesions	Adenoma/Cancer
10 mm or greater	63	76	46/9
6-9mm	116	154	97/0

Sensitivity of Lesions 1 cm or greater

Test	Sensitivity	Number P/I	CI 95%	P value
Barium Enema	45%	34/76	33-57	
VC	53%	40/76	41-64	0.20
Colonoscopy	99%	75/76	93-100%	<0.001

Specificity of Lesions 1 cm or greater

Test	Specificity	Number P/I	CI 95%	P value
Barium Enema	90%	496/551	87-92%	
VC	96%	530/551	94-98%	< 0.0007
Colonoscopy	100%	549/551	99-100%	<0.0001

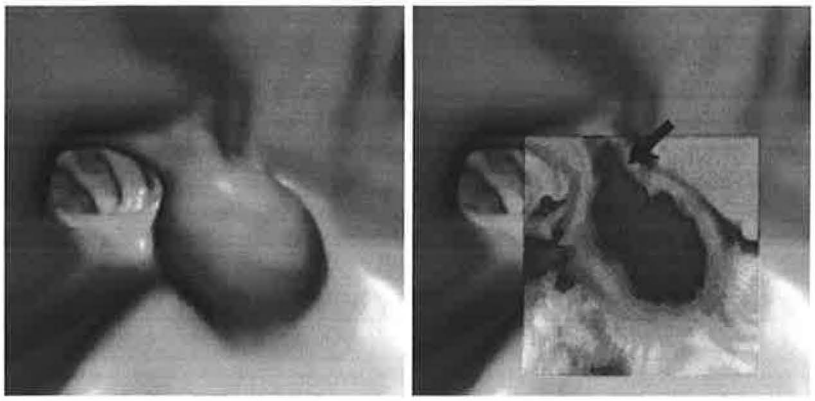
The patients were queried after the exams for difficulty with preparation, respect, comfort, and willingness to undergo a repeat exam. Colonoscopy reached a significant score over the other tests with regard to comfort score and willingness to undergo a repeat exam.

Reader experience did not influence the sensitivity of virtual colonoscopy. A high quality preparation verus a moderate quality of colon preparation also did not influence reader sensitivity of virtual colonoscopy.

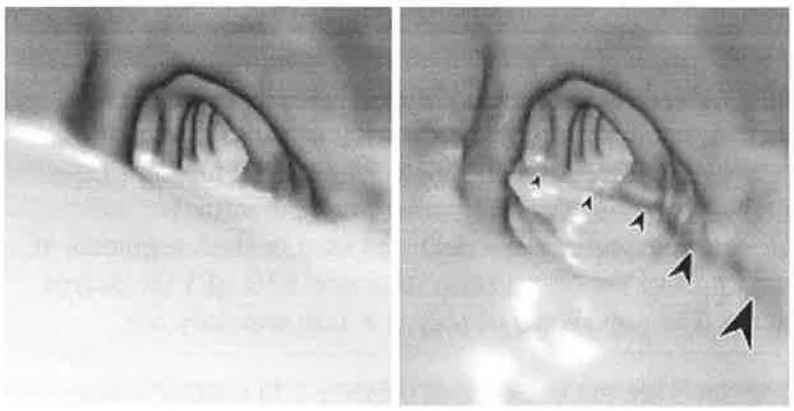
The conclusions from this study were that barium enema and virtual colonoscopy were accurate for the diagnosis of cancer, but colonoscopy is a more accurate test for polyp detection. Patients were most willing to undergo repeat colonoscopy.

A fourth prospective trial from the Mayo clinic noted high interobserver variability with the kappa scores ranging from –.67 to 0.89 for 10mm polyps.[50] This involved 703 asymptomatic persons. A high-risk population was sought with the indication of iron deficiency anemia, family history of colorectal cancer, or prior personal history of colorectal neoplasia. Two of the three reviewers had greater than 150 virtual colonography exams with colonoscopic verification. 3-D was used in short segments of the colon to problem solve and improve the observers confidence. 63% of 1 cm polyps were detected with virtual exams. The prevalence of polyps > 1cm was only 5%.

Before we conclude that 3-D reviews are the answer and primary 2-D reading was a flawed concept the available data at the time of study design for above trials was that neither initial technique was favored. A study testing different display techniques in a data set of 30 colonic segments comparing 2-D multiplanar view, 3-D endoluminal views, and 3-D thickness of slab reformations did not find a statistical difference in polyp detection.[51] Newer techniques of 3-D rendering may allow electronic cleanings and translucent polyp evaluation.[52,53]

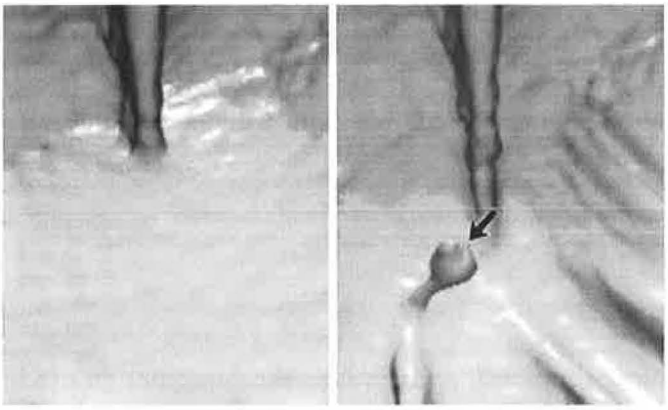


Images of virtual colonoscopy with a 15 mm pedunculated polyp on the left image and translucent imaging on the right. Translucency rendering can often elucidate pedunculated morphology. The surrounding white area represents tagged fluid on this unsubtracted image. Translucency rendering applied to 3-D image shows color pattern characteristic of soft-tissue polyps. Note continuity of red polyp core with its connecting stalk (*arrow*).



A) B)

Electronic cleansing of contrast-opacified luminal fluid on three-dimensional CT colonography in asymptomatic 65-year-old man undergoing screening for colorectal polyps. Uncleansed (**A**) and cleansed (**B**) images from same endoluminal perspective show increase in visualized mucosal surface after digital subtraction of residual fluid. Characteristic linear artifact where air-fluid level interfaces with colon wall (*arrowheads,* **B**) has been likened to residue that remains in tub after bath.



CT colonography of submerged polyp in average-risk 58-year-old man undergoing screening for colorectal polyps. Three-dimensional endoluminal image obtained with electronic cleansing uncovers pedunculated polyp (*arrow*) that was submerged under fluid. Lesion was less conspicuous on imaging obtained with patient in prone position (not shown). Note subtle linear artifact occurring at air-fluid-wall interface. Eight-millimeter adenomatous polyp was confirmed at optical colonoscopy and pathologic evaluation.

Extracolonic Findings

The importance of extracolonic lesions is variable. In one prospective study 75 patients with either colorectal cancer or previous history of adenomas had surveillance exams with virtual colonoscopy.[53] Sixty-five percent (95% CI 55-73) had extracolonic abnormalities and 12% of patients had additional workup for these lesions. One lung cancer diagnosis was made, but the patient died one year after surgery. An ovarian cyst, fibromatous uterus, endometrioma, incidental adrenal lesions 2, renal cyst and fatty sparing of the liver simulating a mass were the other findings. Surgery was also required on the endometrioma, which became infected after FNA was performed.

Pickardt et all had high clinical importance of extracolonic findings in 4.5%, 56 patients out of 1,233.[25] However, only five were subsequently later proven to have extracolonic tumors, which were as follows: one with lymphoma, two with bronchogenic carcinoma, one with ovarian carcinoma, and one with renal-cell carcinoma. Nephrolithiasis and gallstones were frequently noted at 7.9% and 5.6% respectively.

Billing

Medicare has established new CPT codes for the procedure effective July 1, 2004. The codes are 0066T for a screening virtual colonoscopy and 0067T for a diagnostic virtual CT colonoscopy. A global fee of 893 dollars is available for Dallas.

	Medicare Fee	RVU
74150 CT abdomen w/o dye	$299.24	6.06
The professional component (26)	$62.62	0.39
The technical component (TC)	$236.62	5.67

Previous standard codes for Virtual colonoscopy billing including the combination of CT of the abdomen, pelvis, and 3-D reconstruction. These codes were Abdominal CT 74150-26, pelvic CT 72192-26, and 3-D reconstruction 76375-26. The American College of Radiology has no opinion on MR colonography.

Models for Potential Impact

Virtual colonoscopy is rapidly evolving and likely will have a place in screening patients in the future. Questions remain over the significance of lesion size. Do we ignore lesions less than 5mm? What interval of time do we follow up lesions, and if so, with which technique? Flat lesions or depressed lesions are difficult to image and are more likely to represent high-grade dysplasia despite their size.[54] The head to head trials have compared the ability of the two procedures to detect raised lesions. Flat adenomas were found in 22.7% of patients undergoing colonoscopy by an endoscopist skilled in the detection of flat lesions.[55] Are we comparing apples to oranges when the real difference is a reduction in colon cancer and death?[56] In order to assess the impact of virtual colonoscopy on the practice of colonoscopy, models have been formulated. Models are often based upon assumptions, which may later be proven to be incorrect. The potential impacts of these colon screening strategies have been calculated based upon variables. The most important variable for virtual colonoscopy is the sensitivity of lesion detection in prospective trials. Calculations based upon the sensitivity for polyp detection have been varied to assess potential cost effectiveness and the impact on the demand for colonoscopy.[57,58,59] Calculations have been performed for comparisons to the natural history of disease and other screening tests with predictions on infrastructure and colonoscopy needs.

Summary of Health Care costs in Billions for Colon Cancer Care

Exam	Testing (Millions)	Colon Ca care Billions	Total costs Billions
Natural history	0.2	5.3	5.5
Hemoccult (FOB)	3.6	3.4	7.0
Flexible Sig (FS)	4.8	3.1	7.9
FOB and FS	6.2	2.7	8.9
Colon	6.5	2.5	9.0
Fecal DNA	7.5	3.9	11.4

Virtual Colon	7.0	3.0	10.0

Colonoscopy is more effective than other screening methods to reduce colon cancer deaths. However, other strategies cost less per year of life saved. The incremental cost in dollars per year of life gained are 18,800 for colonoscopy, 26,600 for virtual colonoscopy using Pickhardt et al data, and 33,800 for virtual colonoscopy using Cotton et al JAMA data.[58]

Exam	Life years gained per 100K	Cost per year of life gained
Fecal occult blood test	4200	8,100
Flexible sigmoidoscopy	3600	17,300
FOB/ FS	4700	18,700
Colonoscopy	4600	18,800
Fecal DNA	3400	49,200
VC Baseline	4200	28,700

Infrastructure requirements to screen 75% of population

Exam	Total colonoscopies	Total CTC
Colonoscopy	6,914,000	
CTC base	2,650,000	5,450,000
CTC Pickhardt	3,150,000	5,370,000

This data suggests that CT colography may reduce endoscopic services in exchange for new infrastructure requirements in radiologic services. CT colography would be equally effective in this model if it were 2/3 the cost of colonoscopy and 80% sensitivity for the detection of adenomas.

Another 2nd model for comparing virtual colonoscopy to colonoscopy had similar results.[59] CT colography was less cost effective than endoscopic colonoscopy per year of life saved. For CT colography to become as cost effective as colonoscopy, the initial compliance rates needed to be 15-20 % higher or procedure costs 54% lower than endoscopic colonoscopy. False positives and extracolonic lesions may lead to additional investigation and costs.

A third model predicts the demand for colonoscopy will fall 19% if virtual colonoscopy is implemented.[60] This assumes compliance with screening remains at 41%. If compliance increases to 80%, lesions prevalence is 36%, and sensitivity is 56% then demand for colonoscopy will be neutral to current needs.

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