

Screening for Colorectal Neoplasia with Virtual Colonoscopy: Results of a Prospective Multicenter Trial in 1233 Asymptomatic Adults

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Abstract

PURPOSE: The performance characteristics of CT virtual colonoscopy (VC) for detection of colorectal neoplasia have not been established in an average-risk screening population. We conducted a prospective multicenter VC screening trial using optical colonoscopy (OC) as the reference standard.

METHODS: 1233 asymptomatic adults (mean age, 57.8 years; 728 men, 505 women) underwent VC examination followed by same-day OC. 1201 patients were classified as average risk. Prospective VC interpretation immediately preceded OC, with segmental unblinding of VC results at OC. Radiologists relied primarily on the three-dimensional (3D) endoluminal display for polyp detection.

RESULTS: VC sensitivity by patient for adenomatous polyps was 93.8% (45/48), 93.9% (77/82), and 88.7% (149/168) for size thresholds of 10, 8, and 6 mm, respectively. At the same size thresholds, OC sensitivity by patient for adenomatous polyps (prior to unblinding) was 87.5%, 91.5%, and 92.3%, respectively. VC specificity by patient for adenomatous polyps was 96.0% (1138/1185), 92.2% (1061/1151), and 79.6% (848/1065), respectively, and for all polyps (regardless of histology) was 97.4% (1131/1161), 95.0% (1050/1105), and 84.5% (826/978), respectively.

VC sensitivity by polyp for adenomas was 92.2% (47/51), 92.6% (88/95), and 85.7% (180/210) at 10, 8, and 6 mm thresholds, respectively. Two polyps were malignant; both were detected on VC and one was missed on OC before VC unblinding.

CONCLUSIONS: CT virtual colonoscopy with a 3D emphasis is an accurate screening method for detection of colorectal neoplasia in asymptomatic average-risk adults, despite the low prevalence of disease. This minimally invasive total colonic examination compares favorably with OC for detection of clinically relevant lesions.

Introduction

Colorectal cancer is currently the second leading cause of cancer-related mortality in the United States, accounting for nearly 60,000 deaths each year [1]. The vast majority of colorectal cancers are believed to arise within benign adenomatous polyps that develop slowly over many years [2]. Evidence-based guidelines recommend screening of adults at average risk [3], since detection and removal of adenomas has been shown to reduce both cancer incidence and mortality [4-6]. Unfortunately, about half of the intended U.S. population has not been screened by any means for this largely preventable disease [7].

Virtual colonoscopy (VC), also referred to as "CT colonography", could provide an attractive alternative for widespread screening since it requires no IV sedation, analgesia, or recovery time [8,9]. Although the performance characteristics of VC have been encouraging in polyp-rich populations [10-11], there is insufficient data among average-risk adults, for whom the prevalence of significant adenomas is much lower [9,12,13]. We conducted a study to evaluate the performance characteristics of VC in an asymptomatic screening population, using optical colonoscopy (OC) as the reference standard.

Methods

Study Group

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|---------------------|--|
| Inclusion criteria: | Average risk adults between 50 and 79 years of age
(40-79 years in those with a family history of colorectal cancer) |
| Exclusion criteria: | Positive stool guaiac test within 6 months of referral
Iron deficiency anemia within past 6 months
Rectal bleeding or hematochezia within past 12 months
Unintentional weight loss greater than 10 pounds within past 12 months
Optical colonoscopy within past 10 years
Barium enema within past 5 years |

History of adenomatous polyps, colorectal cancer, or inflammatory bowel disease
History of familial adenomatous polyposis or hereditary non-polyposis cancer syndromes
Rejected for optical colonoscopy for any reason
Medical condition that precludes phospho-soda preparation

A total of 1233 consecutive patients underwent same-day VC and OC between May, 2002 and June, 2003.

Study Design

Bowel preparation: 24-hour colonic prep
90 ml (two 45 ml doses) of phospho-soda and 10 mg bisacodyl
500 ml (two 250 ml doses) of 2.1% w/w barium contrast material [14]
120 ml (two 60 ml doses) of diatrizoate meglumine and diatrizoate sodium [14]

Colonic distention: Patient-controlled insufflation of room air via small, flexible rectal catheter

MDCT technique: Four- and eight-channel detectors
Single-breath-hold supine and prone acquisitions
2.5 mm collimation (1.25 for 8-channel)
15 mm/sec table speed
1-mm reconstruction interval,
100 mAs (effective) and 120 kVp

VC interpretation: Prospective reading immediately prior to OC examination.
System: Viatronix v3D Colon (version 1.2.4, Viatronix, Inc, Stony Brook, NY)
Primary 3D approach for polyp detection with 2D for correlation and problem solving
Polyps measured with electronic calipers on 3D view and recorded by segment

OC examination: Performed after VC interpretation by an experienced gastroenterologist
Segmental unblinding of VC results – allows for assessment of OC false negatives
Polyps measured with calibrated linear probe (more accurate than open-biopsy forceps [15])
All retrieved polyps were sent for histologic evaluation

Statistical Analysis

The final results from unblinded OC were regarded as the reference standard against which VC and blinded OC results were compared. Of primary interest were adenomatous polyps measuring ≥ 6 mm. Advanced neoplasia was defined as any adenoma measuring ≥ 10 mm or demonstrating high-grade dysplasia, a prominent villous component, or focus of malignancy [16]. Nonadenomatous lesions (such as hyperplastic polyps) and/or diminutive polyps (≤ 5 mm) were only of secondary interest.

A polyp-matching algorithm was employed to address inherent uncertainty in localization and size comparison. To be considered a true positive match, a polyp must be within the same or adjacent segment on VC and OC and the smaller diameter must be greater than 50% of the larger diameter.

To be considered a true positive result “by patient” at a given polyp size threshold, at least one polyp measuring that size or greater must be present on both VC and OC. By-patient performance characteristics will be emphasized given their relevance to screening.

Results

Twelve hundred thirty-three asymptomatic adults (mean age, 57.8 years; 728 men, 505 women) underwent complete VC and OC examinations. Eight patients were excluded because of incomplete OC (99.4% completion rate). Twelve patients were excluded because of inadequate preparation (n=6) or CT/VC system failure (n=6). Thirty-two patients had either a first-degree relative with colorectal cancer diagnosed before age 60 or two first-degree relatives at any age, conferring a higher than average risk for neoplasia [3,17]. The remaining 1201 patients were average risk. There were no significant complications following VC; one patient was hospitalized for delayed postpolypectomy bleeding from OC.

Of the 1,310 total polyps identified at OC in the 1233 patients, 344 (26.2%) were ≥ 6 mm and, of these, 210 (61.0%) were adenomatous. The prevalence of adenomatous polyps ≥ 10 , ≥ 8 , and ≥ 6 mm was 3.9%, 6.7%, and 13.6%, respectively. Only two of 554 total adenomas (0.4%) harbored malignancy and only one of 966 diminutive polyps (0.1%) was classified as advanced (a 4 mm tubular adenoma with villous features).

Table 1 shows the diagnostic performance of VC and blinded OC by size threshold for both by-patient and by-polyp analyses. Of the 36 additional polyps ≥ 6 mm detected at OC after unblinding of VC results, 21 (58.3%) were adenomatous. VC and OC sensitivity by polyp for all advanced neoplasms was 91.5% (54/59) and 88.1% (52/59), respectively. Both adenocarcinomas were detected on VC, whereas one cancer was missed at OC before unblinding. By-patient and by-polyp sensitivities above a 7-mm size threshold were slightly higher for VC than for blinded OC, but the differences were not statistically significant (p=0.31-0.56). At an 8-mm threshold and above, the overall by-patient accuracy for VC exceeded 92%, rising to nearly 96% at a 10-mm threshold. VC negative predictive value was 99% above a 6-mm threshold.

VC by-patient specificity as shown in Table 1 inevitably suffers somewhat due to false positives from nonadenomatous matches. This penalty was greater at lower size thresholds, where hyperplastic polyps predominate. If all matched polyps are considered true positives, regardless of histology, the corresponding by-patient VC specificity was 97.4% (1131/1161), 95.0% (1050/1105), and 84.5% (826/978) at polyp thresholds of 10, 8, and 6 mm, respectively.

Summation of the VC true- and false-positives rates yields a test-positive rate analogous to the recall rate in screening mammography [18]. Not surprisingly, this indicator is highly dependent on polyp size threshold (Table 1). For example, at a 10-mm threshold, one out of every 13.4 patients (7.5%), on average, would have been referred on for therapeutic OC.

Mean patient time in the CT suite was 14.1 minutes, compared with 31.5 minutes in the endoscopy suite (p<.0001). Including post-sedation recovery, mean patient time for OC was 95.9 minutes. Mean VC interpretation time (including extracolonic evaluation) by study center was 15.9, 17.1, and 24.0 minutes, respectively. Combined mean interpretation time was 19.6 minutes (median, 18 minutes), but dropped to 16.9 minutes (median, 15 minutes) for the second half of the study.

TABLE 1: By-Patient and By-Polyp Performance Characteristics of VC and OC for Detection of Adenomas by Polyp-Size Threshold

Size Threshold:	= 6 mm	= 8 mm	= 10 mm
By-Patient Analysis			
VC Sensitivity	88.7 (149/168)	93.9 (77/82)	93.8 (45/48)
95% CI	[82.9-93.1]	[86.3-98.0]	[82.8-98.7]
VC Specificity	79.6 (848/1065)	92.2 (1061/1151)	96.0 (1138/1185)
95% CI	[77.0-82.0]	[90.5-93.7]	[94.8-97.1]
VC Accuracy	80.9 (997/1233)	92.3 (1138/1233)	95.9 (1183/1233)
95% CI	[78.6-83.0]	[90.7-93.7]	[94.7-97.0]
VC Test Positive^a	29.7 (366/1233)	13.5 (167/1233)	7.5 (92/1233)
95% CI	[27.1-32.3]	[11.7-15.6]	[6.1-9.1]
OC Sensitivity^b	92.3 (155/168)	91.5 (75/82)	87.5 (42/48)
95% CI	[87.1-95.8]	[83.2-96.5]	[74.8-95.3]
By-Polyp Analysis			
VC Sensitivity	85.7 (180/210)	92.6 (88/95)	92.2 (47/51)
95% CI	[80.2-90.1]	[85.4-97.0]	[81.1-97.8]
OC Sensitivity^b	90.0 (189/210)	89.5 (85/95)	88.2 (45/51)
95% CI	[85.1-93.7]	[81.5-94.8]	[76.1-95.6]

95% CI – Ninety-five percent confidence interval

a – VC test-positive rate, indicating the % of VC studies called positive at each size threshold

b – OC sensitivity prior to unblinding

Summary

Our results show that VC is an accurate diagnostic tool for detecting colorectal neoplasia in asymptomatic average-risk adults, despite the low prevalence of disease. In fact, VC performance compared favorably with that of OC, the accepted “gold” standard. As a result, we plan to offer VC screening to asymptomatic average-risk adults, with the opportunity for same-day therapeutic OC if a significant lesion is detected. Our findings suggest that 8 mm should be an optimal polyp size threshold for triggering OC, given the high sensitivity and specificity at this level [19]. In patients where the largest detected polyp on VC is 6-7 mm, short-term surveillance could be offered (perhaps in the range of 2-3 years). In patients where only diminutive polyps (= 5 mm) or no polyps are seen at VC, routine surveillance would be indicated (perhaps in the range of 5-10 years) [20,21].

With regard to broad implementation of VC for screening, several there are protocol-related caveats need to be addressed. First, we relied heavily on the 3D endoluminal fly through for primary polyp detection, whereas most other investigators have used 2D for primary detection [11,22-24]. Although both 2D and 3D views are necessary regardless of approach, we found that ease of detection was much greater with the latter, owing to increased polyp conspicuity and better fold depiction on 3D. Most available VC systems, however, are simply not designed for primary 3D interpretation [25]. Second, we employed stool tagging and electronic fluid cleansing, which are not yet in standard use [14]. Tagging of solid stool with barium dramatically reduced the number of false positives that we would have otherwise encountered from adherent fecal matter. Fluid opacification and electronic subtraction allowed for assessment of a much greater proportion of the colonic surface on each dataset. Third, our study utilized

multidetector CT scanners, which allow for faster imaging with thinner sections; most of the previous studies to date have used single-detector scanners [10,11]. Although the combined effect of these approaches is difficult to quantify, we believe that they were instrumental in our success.

References

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003; 53:5-26
2. Bond JH. Clinical evidence for the adenoma-carcinoma sequence, and the management of patients with colorectal adenomas. *Semin Gastrointest Dis* 2000; 11:176-184
3. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2003. *CA Cancer J Clin* 2003;53:27-43
4. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; 328:1365-1371
5. Mandel JS, Church TR, Bond JH. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000; 343:1603-1607
6. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; 329:1977-1981
7. Colorectal cancer test use among persons aged > or = 50 years--United States, 2001. *MMWR Morb Mortal Wkly Rep* 2003; 52:193-196
8. Ferrucci JT. Colon cancer screening with virtual colonoscopy: promise, polyps, politics. *AJR* 2001; 177:975-988
9. Johnson CD, Dachman AH. CT colonography: the next colon screening examination? *Radiology* 2000; 216:331-341
10. Fenlon HM, Nunes DP, Schroy PC III, Barish MA, Clarke PD, Ferrucci JT. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N Engl J Med* 1999; 341:1540-1542
11. Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology* 2001; 219:685-692
12. Bond JH. Virtual colonoscopy--promising, but not ready for widespread use. *N Engl J Med* 1999; 341:1540-1542
13. Dachman AH, Yoshida H. Virtual colonoscopy: past, present, and future. *Radiol Clin North Am* 2003; 41:377-393
14. Pickhardt PJ, Choi JR. Electronic cleansing and stool-tagging in CT colonography: advantages and pitfalls with primary three-dimensional evaluation. *AJR* 2003; 181:(Sept)
15. Gopalswamy N, Shenoy VN, Choudhry U, et al. Is in vivo measurement of size of polyps during colonoscopy accurate? *Gastrointest Endosc* 1997; 46:497-502
16. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; 343:162-168
17. Rex DK, Lehman GA, Ulbright TM, et al. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. *Am J Gastroenterol* 1993; 88:825-831
18. Sickles EA, Wolverton DE, Dee KE. Performance parameters for screening and diagnostic mammography: specialist and general radiologists. *Radiology* 2002; 224:861-869
19. Pickhardt PJ. By-patient performance characteristics of CT colonography: importance of polyp size threshold data. *Radiology* 2003; 229:(Oct)
20. Bond JH. Clinical relevance of the small colorectal polyp. *Endoscopy* 2001; 33:454-457
21. Kulling D, Christ AD, Karaaslan N, Fried M, Bauerfeind P. Is histological investigation of polyps always necessary? *Endoscopy* 2001; 33:428-432
22. McFarland EG. Reader strategies for CT colonography. *Abdom Imaging* 2002; 27:275-283
23. Dachman AH, Kuniyoshi JK, Boyle CM, et al. CT colonography with three-dimensional problem solving for detection of colon polyps. *AJR* 1998; 171:989-995
24. Macari M, Milano A, Lavelle M, Berman P, Megibow AJ. Comparison of time-efficient CT colonography with two- and three-dimensional colonic evaluation for detecting colorectal polyps. *AJR* 2000; 174:1543-1549
25. Pickhardt PJ. Three-dimensional endoluminal CT colonography (virtual colonoscopy): comparison of three commercially-available systems. *AJR* (accepted for publication)

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