

ORIGINAL ARTICLE

CT Colonography versus Colonoscopy for the Detection of Advanced Neoplasia

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ABSTRACT

BACKGROUND

Advanced neoplasia represents the primary target for colorectal-cancer screening and prevention. We compared the diagnostic yield from parallel computed tomographic colonography (CTC) and optical colonoscopy (OC) screening programs.

METHODS

We compared primary CTC screening in 3120 consecutive adults (mean [\pm SD] age, 57.0 \pm 7.2 years) with primary OC screening in 3163 consecutive adults (mean age, 58.1 \pm 7.8 years). The main outcome measures included the detection of advanced neoplasia (advanced adenomas and carcinomas) and the total number of harvested polyps. Referral for polypectomy during OC was offered for all CTC-detected polyps of at least 6 mm in size. Patients with one or two small polyps (6 to 9 mm) also were offered the option of CTC surveillance. During primary OC, nearly all detected polyps were removed, regardless of size, according to established practice guidelines.

RESULTS

During CTC and OC screening, 123 and 121 advanced neoplasms were found, including 14 and 4 invasive cancers, respectively. The referral rate for OC in the primary CTC screening group was 7.9% (246 of 3120 patients). Advanced neoplasia was confirmed in 100 of the 3120 patients in the CTC group (3.2%) and in 107 of the 3163 patients in the OC group (3.4%), not including 158 patients with 193 unresected CTC-detected polyps of 6 to 9 mm who were undergoing surveillance. The total numbers of polyps removed in the CTC and OC groups were 561 and 2434, respectively. There were seven colonic perforations in the OC group and none in the CTC group.

CONCLUSIONS

Primary CTC and OC screening strategies resulted in similar detection rates for advanced neoplasia, although the numbers of polypectomies and complications were considerably smaller in the CTC group. These findings support the use of CTC as a primary screening test before therapeutic OC.

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ADVANCED NEOPLASIA OF THE LARGE INTESTINE consists of both adenocarcinomas and a subgroup of benign neoplasms referred to as advanced adenomas. The advanced adenoma represents the optimal target lesion for strategies to prevent colorectal cancer. This benign lesion is considered to be associated with a relatively high risk of progression to cancer.¹ The advanced adenoma is specifically defined as an adenoma that meets one or more of the following criteria: a size of at least 10 mm, the presence of a substantial villous component, and the presence of high-grade dysplasia.^{1,2} Removal of detected advanced adenomas effectively disrupts the potential pathway to the development of cancer that is believed to be responsible for the majority of colorectal carcinomas.²⁻⁴

Most subcentimeter polyps are not adenomatous, and only a small fraction of all adenomas are advanced, suggesting a need for more selective alternatives to the practice of universal polypectomy.^{3,5,6} The purpose of this study was to compare computed tomographic colonography (CTC) and optical colonoscopy (OC) when applied to the same general screening population. Important outcome measures included detection rates for advanced adenomas and adenocarcinomas for various categories of polyp size and overall polypectomy rates. These observations provided an assessment of CTC as a selective filter for therapeutic OC in the detection of advanced neoplasia.

METHODS

STUDY GROUP

Our study, which complied with the guidelines of the Health Insurance Portability and Accountability Act, was approved by the institutional review board at the University of Wisconsin Medical School. The requirement for informed consent was waived. The clinical databases from parallel CTC and OC colorectal screening programs at a single institution were analyzed to evaluate the diagnostic yield of each approach. We compared results from 3120 consecutive patients enrolled in the CTC screening program during a 25-month period with those from 3163 consecutive patients seen at OC screening during a 17-month period (with partially overlapping time periods). The two programs drew patients from the same general screening population and geographic region.

The patients in each program were referred by the same groups of primary care providers for the indication of colorectal-cancer screening. Exclusion criteria included polyp surveillance or a history of a bowel disorder, such as inflammatory bowel disease, polyposis syndromes, and the hereditary nonpolyposis colorectal cancer syndrome. The characteristics of the two groups are shown in Table 1. The majority of patients were asymptomatic and at average risk for colorectal cancer.

STUDY DESIGN

We identified all pathologically proven neoplasms that were detected by each screening method from the pool of resected polyps. From this group, the advanced neoplasms were extracted. Large polyps were defined as measuring at least 10 mm in size, small polyps as measuring 6 to 9 mm, and diminutive lesions as measuring 5 mm or less. Prospective assignment of polyp characteristics at both CTC and OC screening included size, morphologic characteristics, and anatomical location. The morphologic characteristics of the polyps were classified as sessile, pedunculated, or flat; frankly invasive masses were considered as a separate category. The location of the polyp was originally assigned according to anatomical segment but, for the purpose of this study, was condensed into proximal and distal locations, relative to the splenic flexure. Adenomas were classified histologically as tubular, tubulovillous (25 to 75% villous component), villous, or serrated subtypes. Invasive carcinoma was defined as malignant spread beyond the muscularis mucosa.

We compared the prevalence of high-grade dysplasia, invasive adenocarcinoma, and overall advanced neoplasia in each study group. The rates of positive results for both screening tests were calculated at various thresholds of polyp size. A test was considered to be positive at a given size threshold when one or more polyps of that size or greater were detected.

CTC PROTOCOL

Referral by a physician was required for primary CTC screening. Bowel preparation for CTC involved both a cathartic agent and oral contrast tagging agents.⁷ A single 45-ml dose of sodium phosphate was used for catharsis in most patients⁸; magnesium citrate or, rarely, polyethylene glycol was substituted in a minority of patients with renal or car-

diac conditions. Single doses of 2% barium (250 ml) and diatrizoate (60 ml) were given to tag residual stool and fluid, respectively. No sedating or spasmolytic agents were given. Colonic distention was achieved with automated low-pressure delivery of carbon dioxide (PROTOCO₂L, E-Z-EM). A multidetector 8-channel or 16-channel computed tomographic (CT) scanner was used (LightSpeed Series, General Electric Medical Systems). The CT technique involved the use of 1.25-mm collimation and scanner settings of 120 kV_p and 25 to 75 mAs with the patient in both supine and prone positions. The imaging data were reviewed on a dedicated three-dimensional CTC workstation (V3D Colon, Viatronix).

The CTC examinations were immediately interpreted by one of five gastrointestinal radiologists who were experienced in CTC. Polyp size was determined on the optimal CTC view with the use of electronic calipers.⁹ Colonic and extracolonic findings on CT were classified according to designations of CTC Reporting and Data System (C-RADS).¹⁰ For all polyps of at least 6 mm, the patient was offered same-day therapeutic OC, unless the procedure was contraindicated. Patients with only one or two polyps of 6 to 9 mm were given the option of CTC surveillance.¹⁰ Potential diminutive lesions (≤ 5 mm) were not reported.^{5,11} After CTC, patients resumed their regular activities but remained in a fasting state to allow for same-day OC, if necessary. Final CTC results were relayed to patients within 2 hours after the procedure.

OC PROTOCOL

Primary OC screening operates as an open-access system. Bowel preparation was usually accomplished with polyethylene glycol (4 liters), although some patients instead received two 45-ml doses of sodium phosphate. Moderate sedation was accomplished with intravenous midazolam and fentanyl. The OC examinations were performed with the use of standard colonoscopes (EC-3872LK and EC-3470LK, Pentax) by 1 of 10 experienced gastroenterologists. OC after a positive CTC study was performed in a fashion similar to that of primary OC, with the exception that the physician had knowledge of CTC polyp findings before performing the OC study.

The colonoscope was advanced to the cecum; examination for polyps was performed on both

Table 1. Demographic Characteristics of the Patients.*

Variable	Primary CTC (N=3120)	Primary OC (N=3163)	P Value
Mean age — yr	57.0 \pm 7.2	58.1 \pm 7.8	<0.001
Male:female ratio	1372:1748	1404:1759	0.74
Symptoms — no. (%) [†]	70 (2.2)	65 (2.0)	0.61
Family history of colorectal cancer — no. (%)	159 (5.1)	265 (8.4)	<0.001

* Plus-minus values are means \pm SD. CTC denotes computed tomographic colonography, and OC optical colonoscopy.

[†] Symptoms included changes in bowel habits, blood in stool, anemia, and pain (if indication for examination).

insertion and withdrawal of the scope. Polyps that were identified during OC were removed with standard techniques. Polyp size was based on in vivo OC estimation before polypectomy. Detected polyps, including diminutive lesions, were generally removed at OC evaluation, regardless of whether the study was performed as a primary screening test or after CTC.

STATISTICAL ANALYSIS

Primary comparisons were made between the patients enrolled in the CTC screening program and those in the OC screening program. The two groups were compared with the use of the Student's t-test for independent samples for continuous outcomes and Pearson's chi-square test for categorical outcomes. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

The diagnostic yields from primary CTC and primary OC screening are summarized in Table 2. The total number of advanced neoplasms and the prevalence in patients were similar for the two screening approaches. No statistical difference between the groups was seen in the number of large or small advanced adenomas that were removed. However, the number of polypectomies performed to achieve these similar outcomes differed significantly between the two groups, with more than four times as many polyps removed in the OC group as in the CTC group.

Overall, 246 of 3120 patients in the CTC group (7.9%) were referred for therapeutic OC (Fig. 1). Of note, the numbers of polyps in the primary

Table 2. Diagnostic Yield of Primary CTC and Primary OC Screening.

Variable	Primary CTC (N=3120)	Primary OC (N=3163)	P Value
Use of OC — no. of patients (%)	246 (7.9)	3163 (100)	<0.001
Total no. of polyps removed	561*	2434	<0.001
No. of advanced adenomas			
≥10 mm	103	103	0.92
6–9 mm	5*	11	0.14
≤5 mm	1†	3	0.32
Invasive carcinoma			
No. of carcinomas	14	4	0.02
No. of patients (%)	12 (0.4)	4 (0.1)	0.04
Total advanced neoplasia‡			
No. of neoplasms	123*	121	0.81
No. of patients (%)	100 (3.2)*	107 (3.4)	0.69

* The numbers of polyps in this group do not include the 193 unresected polyps of 6 to 9 mm in the subgroup of 158 patients undergoing continuing CTC surveillance.

† This polyp was not reported during CTC but was removed when it was detected during therapeutic OC.

‡ Advanced neoplasia includes all advanced adenomas and carcinomas. Advanced adenomas include all adenomas of at least 10 mm and subcentimeter adenomas with a prominent villous component or high-grade dysplasia.

CTC group do not reflect the 193 unresected polyps of 6 to 9 mm in 158 patients undergoing continuing surveillance. On the basis of previous experience with CTC screening, approximately 60% of polyps of 6 to 9 mm detected by CTC would be expected to be adenomatous,¹² and approximately 3% of CTC-detected adenomas of 6 to 9 mm contain advanced histologic findings.⁶ Therefore, we estimated that CTC surveillance would yield three to four advanced adenomas ($193 \times 0.6 \times 0.03$), resulting in a yield of advanced neoplasias among small lesions that was very similar to the yield associated with OC.

Limited follow-up data regarding these polyps are available. The majority of these patients are awaiting interval CTC examination. Of the patients with 1 or 2 polyps of 6 to 9 mm who are undergoing continuing surveillance, 54 have returned for follow-up CTC with findings of 70 small polyps. In this group, 67 polyps (96%) have remained stable or decreased in size at follow-up. Three polyps grew at least 1 mm but did not cross the 10-mm threshold; these polyps were all removed. Histologic examination revealed tubular adenomas without high-grade dysplasia for all three polyps.

The rates of positive test results for the two

screening strategies are shown in Table 3. The rates for CTC and OC were similar at the 10-mm and 6-mm thresholds, but there was a disparity in overall positivity rates, reflecting the different handling of diminutive lesions.

Characteristics of advanced neoplasia, including size, histologic and morphologic characteristics, and anatomical location, are summarized in Table 4. The great majority of lesions could be classified as advanced on the basis of size alone, including 117 of 123 (95.1%) in the primary CTC group and 107 of 121 (88.4%) in the primary OC group. A total of 15 of the 6283 patients in the combined groups (0.2%) had subcentimeter advanced neoplasias. As noted above, several additional small advanced adenomas may be among the unresected polyps in the CTC surveillance group. Of the 20 subcentimeter advanced adenomas in these 15 patients, 16 of 20 (80%) had tubulovillous histologic characteristics without high-grade dysplasia; four lesions in three patients contained high-grade dysplasia. All proven adenocarcinomas were large, with a mean (\pm SD) size of 34.9 ± 14.6 mm. Of 18 invasive cancers, 15 were more than 2 cm in size, and 3 were 1 to 2 cm.

Tubular and tubulovillous histologic characteristics were common among the advanced adenomas from both groups, whereas villous and serrated histologic characteristics were relatively rare (Table 4). High-grade dysplasia without carcinoma was also quite rare and was seen in only 14 of 6283 patients (0.2%). In the CTC group, 12 of 3120 patients (0.4%) had invasive adenocarcinoma, as compared with 4 of 3163 (0.1%) in the OC group. Most advanced adenomas in both groups were characterized as either sessile or pedunculated (Fig. 2), with few flat lesions. Advanced adenomas were distributed throughout the large intestine.

Extracolonic findings detected on CTC and classified according to C-RADS criteria¹⁰ are shown in Table 5. Such classification allows for uniform reporting and indicates which imaging findings may require further evaluation. Overall, eight extracolonic cancers were seen in the CTC cohort, accounting for a prevalence of 0.3%.

Serious adverse events during primary OC screening included colonic perforation in seven patients (0.2%); in four of the patients, surgical repair was required. During primary CTC screening, there were no perforations or other serious complications related to either the CTC examination or subsequent therapeutic OC.

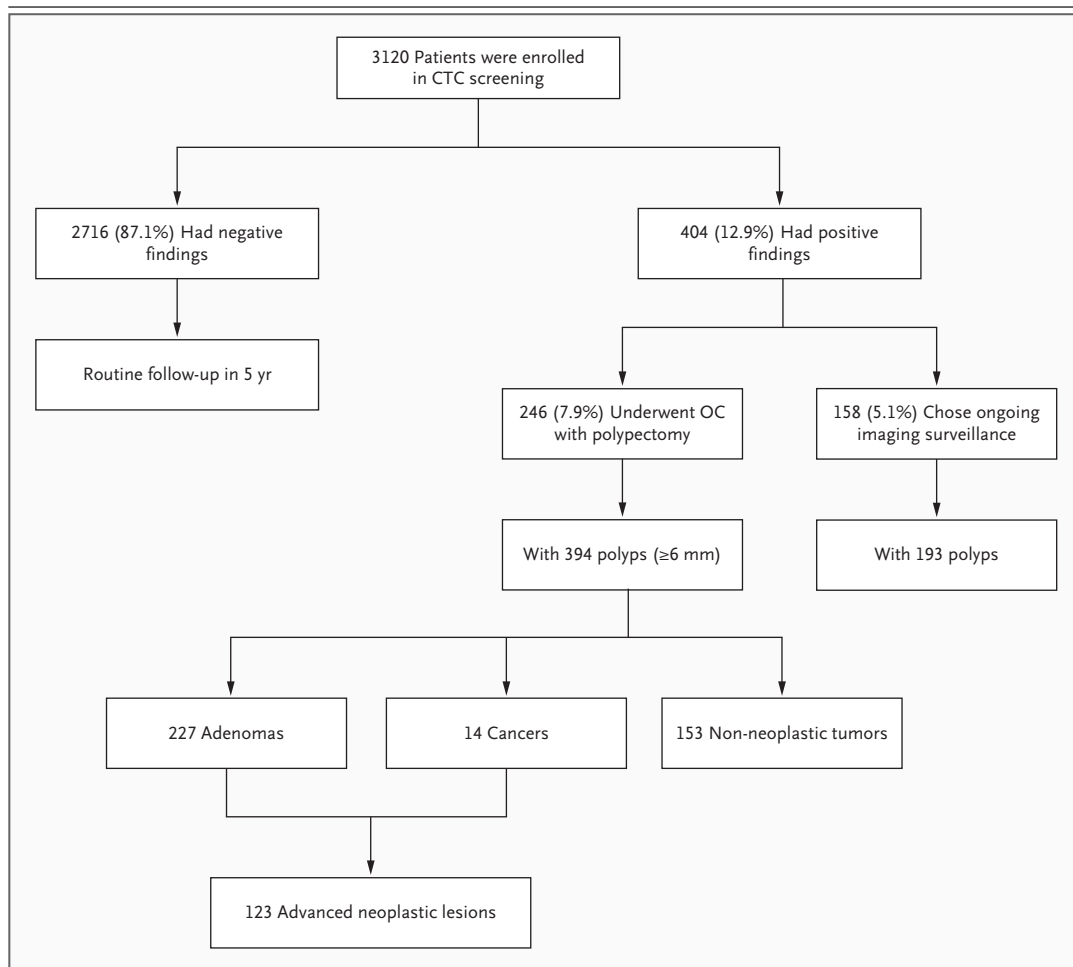


Figure 1. Enrollment and Outcomes of Patients Undergoing CTC.

The detection of polyps of 6 mm or more was considered to be a positive finding. The detection of diminutive polyps was classified as a negative finding.

DISCUSSION

Colorectal cancer is a major cause of cancer-related mortality in the United States, accounting for approximately 55,000 deaths per year.¹³ However, because this cancer has an identifiable precursor lesion, there is a genuine opportunity for prevention rather than cancer detection alone.^{3,4} In particular, targeted detection and removal of advanced adenomas may be the most effective approach to cancer prevention.¹ OC is an effective screening tool for the detection and removal of advanced colorectal neoplasia and is widely regarded as part of the preferred screening strategy.^{4,14,15} Our results suggest that primary CTC with selective OC also deserves consideration as a preferred screening strategy because it appears to achieve the same

goals of detection and prevention but with the use of substantially fewer resources in terms of OC procedures and polypectomies. Thus, CTC may provide a more targeted screening approach for detection of advanced neoplasia.

In our study, the coexistence of parallel CTC and OC screening programs at a single institution allowed for substantive comparison of diagnostic yields and the use of resources. We observed similar detection rates for advanced adenomas during both CTC and OC screenings. The diagnostic yield for advanced neoplasia was similar in the two groups, despite the fact that small lesions (≤ 5 mm) were not reported during CTC. In addition, a subgroup of patients with unresected polyps of 6 to 9 mm were undergoing CTC surveillance, and the frequency of a family history of colorectal cancer

Table 3. Rates of Positive Screening Results, According to Threshold of Polyp Size.

Size Threshold	Primary CTC (N=3120) no. (%)	Primary OC (N=3163) no. (%)	P Value
≥10 mm	164 (5.3)	134 (4.2)	0.06
≥6 mm	404 (12.9)	424 (13.4)	0.59
Overall	404 (12.9)*	1189 (37.6)	<0.001

* Diminutive lesions (≤5 mm) were not reported during CTC, so their detection was not considered to be a positive result.

Table 4. Characteristics of Advanced Neoplasms.*

Characteristic	Primary CTC (N=123)†	Primary OC (N=121)	P Value
Size (mm)	18.4±12.6	16.4±11.7	0.20
Histologic characteristic (no. of lesions)			
Tubular	59	70	0.12
Tubulovillous	42	43	0.82
Villous	4	2	0.42
Serrated	4	2	0.42
High-grade dysplasia‡	8	7	0.82
Adenocarcinoma	14	4	0.02
Morphologic characteristic (no. of lesions)§			
Sessile	56	52	0.69
Pedunculated	41	51	0.16
Flat	12	2	0.007
Other¶	14	16	0.66
Proximal:distal ratio (no. of lesions)	49:74	53:68	0.53

* Plus-minus values are means ±SD.

† This category does not reflect the subgroup of 158 patients undergoing CTC surveillance who had 193 unresected polyps of 6 to 9 mm.

‡ This category does not include frankly malignant lesions.

§ The morphologic characteristics of seven lesions were not recorded in the OC group.

¶ This category includes characteristics that were not recorded or that were described in terms such as "carpet," "saddle," "annular," and "invasive."

|| Location is described relative to the splenic flexure.

was higher in the OC screening cohort. The different handling of diminutive lesions largely accounts for the discrepancies in the overall rates of positive test results (12.9% in the CTC group vs. 37.6% in the OC group) and in the numbers of polypectomies (561 vs. 2434).

Overall, 2006 polypectomies were performed to remove diminutive polyps, which yielded four advanced lesions (0.2%). Such observations rein-

force the scarcity of diminutive and small advanced neoplastic lesions and the potential benefits of filtering strategies during CTC. In fact, Markov modeling of large cohorts has shown that the strategy of not reporting diminutive polyps detected during CTC screening is a cost-effective approach that can substantially reduce the rate of polypectomy and complications without any sacrifice with respect to cancer prevention.¹⁶

Beyond these differences, however, there were also some striking similarities between the two screening strategies. For example, the rates of positive test results at the thresholds of 6 mm and 10 mm were similar, and the characteristics of the advanced adenomas were also quite similar.

Polyps of at least 10 mm appear to represent a very useful surrogate for advanced adenomas, accounting for the great majority of all advanced lesions in our study. Large polyp size has already been singled out by some observers as the most important criterion for advanced neoplasia.¹ Only 20 subcentimeter polyps in our study were histologically advanced, which corresponded to an overall prevalence of 0.2% (15 of 6283 patients). Only four advanced adenomas were identified in the diminutive category. Furthermore, only 3 patients had four subcentimeter polyps with high-grade dysplasia (0.05%), and there were no subcentimeter cancers in more than 6000 patients. These observations suggest that a 10-mm threshold for polypectomy at asymptomatic screening would probably capture the vast majority of clinically relevant lesions.

The overall prevalence of advanced neoplasia in this healthy screening cohort of 6283 adults was 3.3%, which is somewhat lower than the prevalence of 4 to 6% reported in several other studies^{5,15,17-19} and substantially lower than the prevalence of 10.5% in a population of male veterans.¹⁴ These differences are probably multifactorial, but variations in age, sex, ethnic background, family history, and frequency of symptoms may all play a role. A recent colonoscopy study showed that the prevalence of advanced neoplasia was less than 3% in certain low-risk cohorts.²⁰ In our study, the frequency of advanced histologic findings among subcentimeter lesions, particularly high-grade dysplasia and invasive carcinoma, was also generally lower than previously reported.^{2,21-23} However, the inclusion of 10-mm lesions in the category of small polyps in some previous studies substantially increased the reported prevalence.^{22,23} Furthermore, a recent colonoscopy series evaluating a

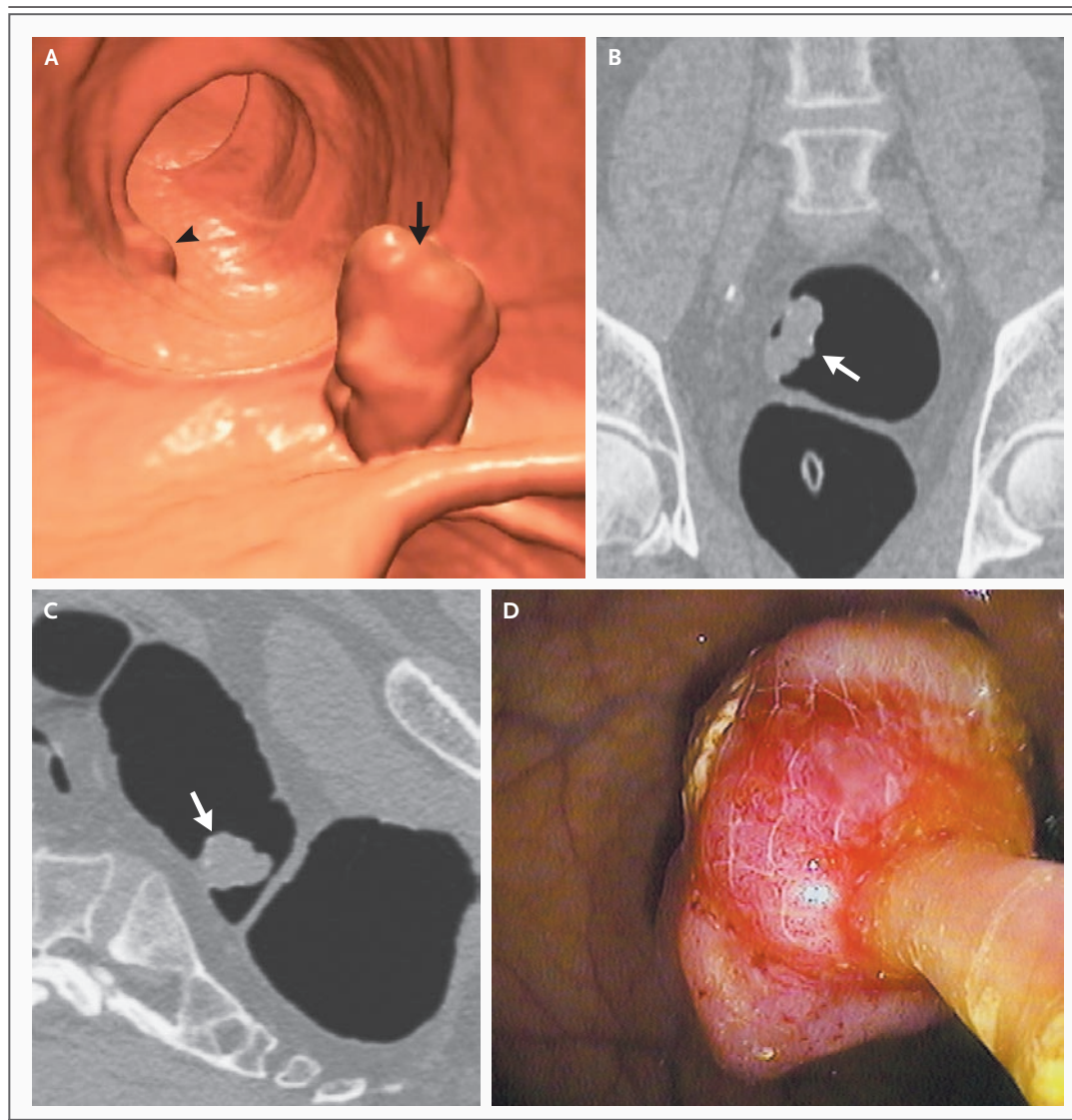


Figure 2. CTC in a Man at Average Risk for Colorectal Cancer.

In Panel A, an endoluminal three-dimensional CTC image shows a 33-mm lobulated rectal polyp (arrow), as well as a 13-mm polyp (arrowhead) near the rectosigmoid junction. Two-dimensional coronal (Panel B) and sagittal (Panel C) CTC images confirm the presence and soft-tissue composition of the larger polyp (arrows). In Panel D, a digital photograph from same-day optical colonoscopy shows the endoscopic capture of the polyp immediately before resection. Pathological evaluation revealed a large tubulovillous adenoma with high-grade dysplasia. The second lesion also had benign tubulovillous histologic characteristics but without high-grade dysplasia.

large screening population reported low cancer rates among resected adenomas measuring 6 to 9 mm (0.07%) and 1 to 2 cm (2.4%).²⁴ In our study, the exclusion of a subgroup of patients who had small, unresected polyps and were undergoing CTC surveillance probably had only a small effect on the prevalence of advanced adenomas.

The clinical management of small polyps of 6 to 9 mm that are detected during CTC is controversial. One approach is to offer OC for polypec-

tomy to all patients with CTC-detected polyps of at least 6 mm.²⁵ However, an option of short-term CTC surveillance for patients with one or two small CTC-detected polyps has also been suggested.¹⁰ Short-term CTC surveillance for small polyps allows for more efficient detection and removal of the uncommon advanced neoplasms because only the enlarging lesions are removed. As discussed previously, potential benefits include the decreased use of resources, procedural risks, and

Table 5. Extracolonic Findings in the CTC Group.

C-RADS Classification*	Representative Clinical Conditions†	Primary CTC (N=3120)	
		Extracolonic Finding	Additional Test or Procedure Recommended no. (%)
E1 (normal or anatomical variant)	Normal, retroaortic left renal vein	1295 (41.5)	0‡
E2 (clinically unimportant finding)§	Hepatic or renal cyst, incidental cholelithiasis, or nephrolithiasis	1490 (47.8)	0‡
E3 (probably unimportant, incompletely characterized)	Indeterminate renal or adnexal lesions	265 (8.5)	241 (7.7)¶
E4 (potentially important finding)	Complex solid-organ lesions, adenopathy, vascular aneurysm, pulmonary nodules ≥10 mm	70 (2.2)	

* C-RADS denotes Computed Tomographic Colonography (CTC) Reporting and Data System.

† Typical clinical conditions that are listed for each category are not exhaustive.

‡ By definition, no additional evaluations were needed.

§ This category refers to a lack of need for further workup.

¶ This number includes patients for whom any further imaging tests or surgical interventions were recommended in both the E3 and E4 categories. Such tests or procedures yielded eight extracolonic cancers, including three renal-cell carcinomas, two bronchogenic carcinomas, one non-Hodgkin's lymphoma, one endometrial carcinoma, and one gastrointestinal stromal tumor.

cost. Potential drawbacks mainly involve the possibility of following a polyp that harbors a focus of cancer or transforms to cancer during the surveillance period, resulting in a lost opportunity for cancer prevention. The presumed low risk for this subgroup of polyps is echoed by the low prevalence of subcentimeter lesions harboring high-grade dysplasia or invasive carcinoma in the population we studied. In addition, the limited natural-history data from several older longitudinal studies that monitored lesions with the use of barium enema and endoscopic examination support the practice of short-term CTC follow-up.²⁶⁻²⁹ Ultimately, more investigation will be needed to determine which strategy is more beneficial during CTC. Such a surveillance strategy for small polyps that are detected during primary OC would clearly be less appealing because the scope is already in place and the only incremental costs and risks that are incurred are related to the polypectomy itself.

Adverse events were uncommon during OC screening, and no serious complications were reported in the CTC group. The perforation rate of 0.2% (7 of 3163 patients) in the OC group was within the expected range reported in previous colonoscopy series.^{30,31} The absence of perforations in the CTC screening group was largely due

to both the minimally invasive nature of CTC³² and the decreased numbers of OC studies and polypectomies, as compared with the primary OC group. Concern has been raised regarding the potential risks associated with radiation exposure from CTC. Some observers contend that the risk is too small to quantify.³³ Proponents of the linear, no-threshold model argue that a small risk exists, but even members of this group agree that the benefits of screening for colorectal cancer appear to outweigh these small theoretical risks.³⁴

A major limitation of our study was the lack of randomization. Thus, a potential exists for selection bias affecting the composition of the study population for each program, leading to different prevalences of advanced adenomas. Although most patients in both cohorts were being screened for the first time, it is possible that some of them had undergone previous colorectal screening elsewhere. However, the groups were similar in several important respects, including a relatively young age and a predominance of women. Age and sex have been shown to be strong predictive factors for the prevalence of adenomas and high-grade dysplasias.^{1,35} The percentage of patients with a positive family history was higher in the OC group, which should have resulted in more advanced adenomas in that group. The fact that

similar numbers of advanced adenomas were seen in the two groups further reinforces the potential of CTC for screening.

In conclusion, CTC and OC screening methods resulted in similar detection rates for advanced neoplasias within the same general population. This finding is important because advanced neoplasms represent the primary target of colorectal screening and cancer prevention. The marked decrease in the use of OC and total rates of polypectomies in the CTC group suggests that this technique is a safe, clinically effective, and cost-effective filter for therapeutic OC. Furthermore, by

combining primary CTC and primary OC screening efforts, with the choice between tests driven by patient preference, the overall screening compliance for total colonic examination could substantially increase.

Dr. Kim reports serving on the medical advisory board for C.B. Fleet and receiving lecture fees from Viatronix; Dr. Pickhardt, receiving consulting fees from C.B. Fleet, Viatronix, Medicsight, and Philips Medical Systems; and Dr. Gopal, receiving lecture fees from AstraZeneca. No other potential conflict of interest relevant to this article was reported.

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