REVIEW ARTICLE

Should computed tomographic colonography replace optical colonoscopy in screening for colorectal cancer?

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KEY WORDS

colorectal cancer (CRC), colonoscopy, computed tomographic colonography (CTC), screening, virtual colonoscopy

ABSTRACT

Clinical evidence amassed over the last several decades indicates that routine colorectal cancer (CRC) screening, compared to no screening, detects CRC at an earlier stage, reduces the incidence of CRC or the progression early CRC through polypectomy, and reduces CRC mortality. Computed tomographic colonography (CTC) is a minimally invasive, structural evaluation of the entire colorectum that has recently been advocated by multiple American professional medical societies as an effective alternative for CRC screening. The potential advantages of CTC, including rapid image acquisition and processing, non-invasiveness, and decreased procedural risks of perforation, bleeding, and sedation complications may serve to improve the low rates of colorectal cancer screening that are currently observed in our society. Several large studies of CTC as a CRC screening test have reported excellent results but have been criticized because of the expertise of CTC interpreters participating in those trials. As a response to these criticisms, the long-awaited results of the American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial were recently published. The purpose of this study was to assess the accuracy of CTC in a "community based" environment to determine if previous results obtained at expert sites could be replicated. All CTC were confirmed and compared to conventional colonoscopy, the gold-standard colorectal cancer screening test. For polyps >10 mm, the results obtained in the ACRIN trial were comparable to previous studies with a mean CTC sensitivity of 90% and a mean CTC specificity of 86%. The sensitivity of CTC fell to 78% for lesions >6 mm, a value that some studies have suggested is comparable to the detection rate of conventional colonoscopy. This study adds to the body of literature regarding the efficacy of CTC and will likely be cited by many as evidence supporting CTC as an acceptable CRC screening test, in the same league as colonoscopy. Issues remain, however, regarding the extension and reproducibility of these results in the true community setting. There are concerns regarding thresholds for referrals, appropriate intervals between studies, the optimal management of extracolonic findings, and radiation exposure with CTC that remain unanswered by these data.

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Colorectal cancer (CRC) is the 3rd most common type of cancer and 2nd leading cause of cancer death in the United States.[1] Clinical evidence amassed over the last several decades indicates that routine CRC screening, compared to no screening, detects CRC at an earlier stage, reduces the incidence of CRC or the progression of early CRC through polypectomy, and reduces CRC mortality.[2] Computed tomographic colonography (CTC) is a minimally invasive, structural evaluation of the entire colorectum that has recently been advocated by multiple American professional medical societies as an effective alternative for CRC screening.[3,4] The potential advantages of CTC, including rapid image acquisition and processing, non-invasiveness, and decreased procedural risks of perforation, bleeding, and sedation complications may serve to improve the low

rates of colorectal cancer screening that are currently observed in our society.[5,6] As with any new screening test, CTC has come under much scrutiny when considered in the broader context of recommended CRC screening tests. Specifically, issues related to test accuracy, programmatic feasibility and compliance, and the cost and management of intracolonic and extracolonic findings continue to generate debate in the medical and healthcare regulatory communities.

Over the last 10 years, the efficacy of CTC has been debated and contested due to variable results from multiple studies of this screening modality. Pickhardt et al.[7] reported a very high adenoma detection rate, claiming sensitivity and specificity of CTC of 94% and 96%, respectively, compared to colonoscopy on a per patient analysis in the New England Journal of Medicine. This study was well publicized and was among the first to lend credence to CTC as a legitimate screening tool. Within a year after that publication, the Journal of the American Medical Association published another CTC study by Cotton et al.[8] that reported sensitivity of CTC to be significantly worse (55%) for polyps >10 mm. These contradicting findings led to a meta-analysis by Mulhall et al.[9] in an attempt to pool all available data from quality studies, which detected a pooled sensitivity of 85% with CTC for polyps >10 mm diameter. However, the significant heterogeneity among studies included in this analysis raised concerns for reproducibility of CTC performance in community practice arising from technical variability and reader experience.

Recently, the New England Journal of Medicine published the results of the American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial. The paper is entitled "Accuracy of CT Colonography for Detection of Large Adenomas and Cancers" and was published in September 2008.[10] The purpose of the ACRIN trial was to create a multi-center study with up-to-date technology that could assess the accuracy of CTC and strive to reproduce the superlative results of the Pickhardt study. This study hoped to answer concerns regarding the reproducibility of the previously reported excellent CTC results. High polyp detection rates across 15 study centers would highlight the reproducibility and accuracy of CTC at non-expert centers and solidify the case for CTC as a viable CRC screening alternative to more invasive tests or those with less patient acceptance or adherence.

This multi-center study was conducted at 15 sites and compared the polyp detection rate of CTC to that of colonoscopy. Two thousand, six-hundred patients were recruited for this study, which was comprised of a screening population of asymptomatic patients 50 years of age and older. The majority of study participants (89%) had no known risk factors for CRC. Patients with a family history of CRC in a first-degree relative were allowed to enroll in the study (9%) as were patients with a previous history of polyps or cancer (<2%). The study excluded patients with gastrointestinal bleeding, inflammatory bowel disease, polyposis syndromes, anemia, positive stool Hemoccult testing, and anybody with a colonoscopy within the previous 5 years.

CTC technique and technology have advanced significantly over the last 10 years to maximize polyp detection rate and minimize radiation exposure. The techniques and technology used in this study were similar to the sophistication used in the Pickhardt study,[7] and all 15 sites used similar image acquisition methods. A criticism of prior studies with poor outcomes was the antiquity of the technology being used, which has the potential to impact efficacy, safety, and patient tolerance. All patients underwent a laxative purge as well as stool and fluid tagging. After these preparations, the colon was insufflated with carbon dioxide and 1 mg of glucagon was injected 7–15 minutes prior to examination to help limit peristalsis to improve image quality unless contraindicated or declined by the study participant. Scans were performed in both the prone and supine positions to maximize visualization and help distinguish liquid and stool artifact. A minimum of 16-row multi-detector CT scanners with image reconstruction of slice thicknesses of 1.0 to 1.25 mm, with a reconstruction interval of 0.8 mm was used. Both 2-dimensional and 3-dimensional reconstruction views were independently assigned to participating radiologist CTC interpreters. The 3-dimensional reconstruction software produces a virtual image of the colon allowing radiologist to "fly through" the colon looking for polyps similar to endoscopists searching for polyps on colonoscopy. Both methods allow for "problem" solving and lesion confirmation with the other method and the use of both forms of interpretation is considered a complementary approach that increases polyp detection versus the use of one interpretation method in isolation.

In order to take part in the trial, all participating radiologists had to submit documentation that they had interpreted at least 500 CTC or, failing that, had to participate in a 1.5 day training session on CTC. In addition, all participating radiologists had to demonstrate minimal detection accuracy (90% detection of polyps >10 mm) on a qualifying examination. Among the 20 radiologists who met the stringent entry criteria, the 15 with the highest accuracy scores on the qualifying examination were invited to participate in the study.

Radiologists were instructed to identify all polyps greater than 5 mm in greatest dimension seen on CTC. The sensitivity of CTC for the identification of polyps ≤5 mm is considered too low to confidently proceed to colonoscopy and the clinical significance of polyps of this size is unknown. While this remains an area of contention between proponents and detractors of CTC as an alternative to colonoscopy screening, it should be remembered that the detection rate of these small

lesions with colonoscopy has also not been well characterized. Additionally, recent evidence from the Clinical Outcome Research Initiative database have shown that the prevalence of cancer and colorectal polyps harboring advanced histology (high-grade dysplasia, villous histology) in polyps ≤6 mm is 0% and 1.2%, respectively.[11]

Another aspect of CTC that remains controversial is how best to quantify accuracy. The two accepted methods of analysis and subsequent reporting of CTC accuracy include "per-patient" or "per-polyp" detection rates. The per-polyp method describes the ability of CTC to find every polyp in an individual undergoing CTC. This is a measure of the technology's idealized ability to detect colorectal neoplasia. More clinically relevant is the per-patient analysis, in which the number of patients with at least 1 polyp of any size (typically >5 mm) is detected. This is more clinically relevant because even if only 1 polyp (regardless of the total number of polyps present) is identified on CTC, the patient would be referred for colonoscopy. Presumably, any additional polyps that may have been missed on CTC could be noted and removed during this colonoscopy. Thus, the determination of a minimal polyp size by which colonoscopy can be reliably recommended is central to the potential success of CTC as a screening test. In the analysis by Johnson et al. the more clinically relevant per-patient analysis was used to quantify the polyp detection rate with CTC.

The "gold standard" in this study, as in most other CTC efficacy studies, was a colonoscopy immediately following each CTC. Colonoscopy is not a perfect test and miss rates for small polyps (≤6 mm) have been reported as high as 27% in the literature.[12,13] However, colonoscopy is an acceptable and well-established "gold standard". Comparison to the established "gold standard" is an important methodologic component for studies of new diagnostic tests in terms of defining the accuracy of the diagnostic test being evaluated.[14] All gastroenterologists and surgeons who performed colonoscopies in the ACRIN trial were blinded to the results of the CTC. If the "gold standard" missed a lesion >10 mm as described on CTC, a repeat colonoscopy was performed within 90 days of the original colonoscopy to establish whether the polyp seen on CTC was a false positive finding or the polyp was missed on colonoscopy. When repeat colonoscopies were required, endoscopists were provided with the CTC reports prior to the procedure, so these repeat colonoscopies were not blinded. The primary outcomes measured in the ACRIN trial were the per-patient accuracy, sensitivity, specificity, positive predictive value and negative predictive value of CTC for the detection of colorectal polyps >5 mm. These results were averaged among all 15 radiologists (TABLE).

Tissue samples from all lesions >5 mm were identified as adenomatous or nonadenomatous lesions. Polyp size was based on the pathology report unless the polyp was removed in a piecemeal fashion, fulgurated or not removed. CTC polyp and optical colonoscopy (OC) polyp lesion matching was determined by 2 blinded radiologists. An established method for matching polyps that incorporates the location of lesion (within 1 colonic segment) and its size (50% of the reference standard measure) was used in the ACRIN trial.[7,8,15,16]

For polyps ≥10 mm, the results were comparable to the Pickhardt study with a mean CTC sensitivity of 90% and a mean CTC specificity of 86% in the per-patient analysis. The sensitivity of CTC fell to 78% for lesions ≥6 mm (TABLE). However, the positive predictive value was low at 23%, suggesting that only 1 of every 4 polyps found on CTC was actually a polyp on optical colonoscopy. The low positive predictive value in this study appears to be a by-product of the relatively low prevalence of adenomas in the study patients. One possible explanation for the high sensitivity and relatively low specificity is that the radiologists were trained to *not* miss polyps, which potentially could increase sensitivity and decrease specificity. However, it is ultimately high sensitivity for detection of the target lesion or disease that is the hallmark of an effective screening test.

Amongst the undetected adenomas on CTC, the mean size was 6 mm and there was no association with location or histology. CTC missed one rectal cancer that was found on OC. There were 27 patients who had possible adenomas found on CTC that were not confirmed on OC. Among these, 15 patients with a possible 18 lesions had repeat colonoscopy and 5/18 lesions were confirmed to be present on the 2nd colonoscopy. Two of these polyps were inflammatory polyps and 60% (3/5) were adenomas. While all of these large polyps missed by colonoscopy would be considered advanced based on their diameter ≥10 mm, 1 of them actually harbored villous histology with dysplasia on pathologic analysis. The remaining 13/18 lesions were considered false positives on CTC.

The average time required to read the CTC examinations was approximately 20 minutes using both the 2-dimensional images as a primary read with 3-dimensional image confirmation or vice versa. This study also showed there was no difference in accuracy using either the 2-dimensional approach as a primary read or the 3-dimensional approach, as long as both techniques were used.

The findings from the ACRIN study demonstrate that CTC is an effective modality for CRC screening with sensitivity for detecting polyps ≥10 mm of at least 90%. These results remained consistent over the 15 sites involved in the study. The sensitivity for smaller lesions is lower, but there is uncertainty and controversy regarding the significance of polyps measuring between 5 and 9 mm.[17] At this time, it is recommended that patients with lesions ≥6 mm identified on CTC be referred to colonoscopy for

TABLE This is a summary of Table 2 from Johnson et al. This is the estimated per-patient accuracy in detecting adenomas on computed tomographic colonography by polyp size.[10]

	≥5 mm	≥6 mm	≥7 mm	≥8 mm	≥9 mm	≥10 mm
sensitivity	0.65	0.78	0.84	0.87	0.90	0.90
specificity	0.89	0.88	0.87	0.87	0.86	0.86
PPV	0.45	0.40	0.35	0.31	0.25	0.23
NPV	0.95	0.98	0.99	0.99	0.99	0.99
ROC curve	0.80	0.84	0.87	0.88	0.89	0.89

Abbreviations: NPV – negative predictive value, PPV – positive predictive value, ROC – receiver operating characteristic

polyp confirmation and resection.[4] According to the ACRIN study, this translates into 12% of patients screened with CTC requiring follow-up colonoscopy. The acknowledgment that colonoscopy is an imperfect "gold standard" implies that the overall sensitivity for CTC may also be underestimated and that at least some of the lesions classified as false positives on CTC are prevalent lesions missed on colonoscopy.

This study adds to the body of literature regarding the efficacy of CTC and will likely be cited by many as evidence supporting CTC as an acceptable CRC screening test, in the same league as colonoscopy. However, issues remain regarding the extension and reproducibility of these results in the community setting. This study attempted to "train" radiologists to read these tests in a manner that could translate into a training program for the community radiologist. The reality, however, is that CTC is reader dependent and experience does matter. At our institution, we have radiologists who read over 2000 studies a year and in our own evaluation they are impeccably accurate with sensitivities for polyps ≥6 mm of more than 90%. At this time, CTC does appear to be an acceptable screening modality at institutions with experienced radiologists and up-to-date technology and technique as described in the ACRIN study. Another crucial aspect of CTC as a possible CRC screening test is the close collaboration between interpreting radiologists and endoscopists. While this was clearly present in the ACRIN trial, the reproducibility of such close collaboration in the community setting remains unproven.

In addition to the clinical results and reproducibility of this study, there are concerns regarding thresholds for referrals, appropriate intervals between studies, the optimal management of extracolonic findings, and radiation exposure with CTC that still need to be addressed. The US Preventive Services Task Force recently gave CTC an indeterminate grade as a CRC screening test based on the lack of clarity regarding many of these issues, specifically the long-term implications of radiation exposure and the financial and clinical implications arising from the identification of extracolonic findings.[18] Detection of extracolonic abnormalities may lead to unnecessary or invasive diagnostic testing of incidental findings, which could add substantial cost and potential burden to the patient. One study reported 12% of patients underwent additional testing to better characterize and evaluate extracolonic findings, with real clinical benefit accruing to only a few.[18] The radiation dose resulting from CT colonography ranges from 5–10 mSv per examination.[19] The long term impact of this dose, while generally felt to be inconsequential, is not known and needs to be considered when advocating for serial screening using this test.

The true promise of CTC is that it will provide a more appealing alternative to CRC screening to those individuals unwilling to undergo colonoscopy to the extent that there will be an increase the overall CRC screening rates which in turn would be expected to ultimately reduce CRC incidence and mortality. Many proponents and detractors take an all-or-nothing approach to CTC, suggesting that it should (or should not) be viewed as a replacement to colonoscopy. CTC is clearly not a replacement for colonoscopy, nor is it likely to become one, since polypectomy via colonoscopy remains the primary modality for preventing CRC development and it is likely that a sizable proportion of patients eligible for screening will opt for the "one-stop shop" approach of colonoscopy. So for the foreseeable future there will continue to be a need for colonoscopy that outstrips the supply of endoscopists skilled in colonoscopy. Projections regarding the impact of CTC on colonoscopy volume vary, but the truth is that no one really knows how CTC will affect the practice of colonoscopy.[20,21] Ideally these 2 tests will be used in a complimentary fashion, with both of them increasing worldwide screening and decreasing the overall burden of CRC. Whether or not the various stakeholders, including practitioners, professional societies, and policy-makers, will foster such collaboration between CTC interpreters and endoscopists, and whether or not CTC will turn out to be cost-effective and socially acceptable, remains to be seen.

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Czy kolonografia metodą tomografii komputerowej powinna zastąpić kolonoskopię optyczną w badaniach przesiewowych w kierunku raka jelita grubego?

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badanie przesiewowe, kolonografia metodą tomografii komputerowej (CTC), kolonoskopia, rak jelita grubego (CRC), wirtualna kolonoskopia

STRESZCZENIE

Dane kliniczne zgromadzone przez ostatnie dziesięciolecia wskazują, że rutynowe badania przesiewowe w kierunku raka jelita grubego (*colorectal cancer* – CRC), w porównaniu z ich niewykonywaniem, pozwalają na wykrycie CRC na wcześniejszych etapach, zmniejszenie częstości występowania CRC albo progresji wczesnych postaci CRC dzięki wykonaniu polipektomii oraz na zmniejszenie umieralności. Kolonografia metodą tomografii komputerowej (*computer tomographic colonography* – CTC) jest minimalnie inwazyjną metodą strukturalnej oceny całego jelita grubego, ostatnio polecaną przez wiele północnoamerykańskich towarzystw medycznych jako skuteczna alternatywa w badaniach przesiewowych w kierunku CRC. Potencjalne zalety CTC, takie jak szybka akwizycja i obróbka obrazu, nieinwazyjność oraz mniejsze ryzyko powikłań związanych z samą procedurą (perforacja i krwawienie) i z sedacją, mogłyby się przyczynić do poprawy rozpowszechnienia badań przesiewowych w kierunku CRC w społeczeństwie. W kilku dużych badaniach z użyciem CTC jako metody badań przesiewowych w kierunku CRC uzyskano doskonałe wyniki, ale były one krytykowane z powodu dużego doświadczenia lekarzy oceniających CTC uczestniczących w tych badaniach. W odpowiedzi na te zarzuty ostatnio opublikowano długo oczekiwane wyniki badania National CT Colonography Trial przeprowadzonego przez American College of Radiology Imaging Network (ACRIN). Celem tego badania była ocena dokładności diagnostycznej CTC w warunkach „terenowych", aby ustalić, czy można w nich powtórzyć wyniki uzyskane w ośrodkach specjalistycznych. Wszystkie wyniki CTC weryfikowano i porównywano z konwencjonalną kolonoskopią – „złotym standardem" badań przesiewowych w kierunku CRC. Dla polipów o wielkości ≥10 mm wyniki badania ACRIN były porównywalne z uzyskanymi uprzednio – średnia czułość CTC wyniosła 90%, a swoistość 86%. Czułość CTC zmniejszyła się do 78% w przypadku zmian ≥6 mm, co – jak sugerują wcześniejsze badania – jest porównywalne z wynikami konwencjonalnej kolonoskopii. Badanie to stanowi ważne uzupełnienie piśmiennictwa na temat skuteczności CTC i zapewne będzie przez wielu uznane za argument na rzecz uznania CTC za akceptowalne badanie przesiewowe w kierunku CRC, tej samej klasy co kolonoskopia. Pozostają jednak nierozwiązane kwestie dotyczące ekstrapolacji tych wyników na warunki realnej praktyki ogólnej i ich powtarzalności. Istnieją wątpliwości, których nie wyjaśniają uzyskane dane, dotyczące kryteriów kierowania na badania, właściwych odstępów czasowych między badaniami, optymalnego postępowania w przypadku zmian pozajelitowych oraz ekspozycji na promieniowanie podczas CTC.

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