

KEYNOTE LECTURE

CT colonography screening: ready for prime time?

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Abstract

Every year more than one million new patients are diagnosed with colon cancer worldwide. Although multiple prospective randomized trials and observational studies have demonstrated that mortality from colon cancer can be reduced with screening and removal of adenomatous polyps, compliance with screening guidelines remains low. Recent CT colonography (CTC) trials have shown that CTC is capable of demonstrating adenomatous polyps ≥ 10 mm (and in most cases ≥ 6 mm) with sensitivities comparable to those for optical colonoscopy. Based on these results, at least two expert panels have recommended CTC as an option for colorectal cancer screening. Despite these endorsements, the Centers for Medicare and Medicaid Services (CMS) in the United States recently decided to deny coverage of CTC for colorectal cancer screening. This article addresses the reservations raised by CMS and provides a perspective on whether CTC is ready for routine use as a colorectal cancer screening test.

Keywords: *Colon, neoplasms; colon, polyps; colonoscopy; computed tomography colonography; rectum, neoplasms; rectum, polyps; virtual colonoscopy.*

Introduction

Colorectal cancer is a major health problem worldwide. In the United States, it is the third most common cancer diagnosis and the second leading cause of cancer death^[1]. Fortunately, this neoplasm is highly suited to screening because of its long preclinical phase, during which it is detectable and curable^[2]. Prospective randomized trials and observational studies have demonstrated mortality reductions associated with early detection of invasive cancer and removal of adenomatous polyps^[3–6]. Based on this evidence, a number of organizations and task forces throughout the world have issued or endorsed guidelines for colorectal cancer screening beginning at age 50 years for individuals at average risk for colorectal cancer. Nevertheless, screening programs for colorectal cancer have been only partly successful, largely as a result of poor patient compliance with screening recommendations^[7,8]. Currently only approximately 50% of adults in the United States older than 50 years are receiving any of the recommended colorectal cancer screening tests^[9].

Colorectal cancer screening guidelines

The test options for colorectal cancer screening recommended in the most recently published guidelines of the US Preventive Services Task Force (USPSTF) include annual fecal occult blood test (FOBT), flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years^[10]. In 2008 the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology issued a joint guideline on screening and surveillance for the early detection of colorectal cancer and adenomatous polyps^[11]. In this joint guideline double-contrast barium enema (DCBE) every 5 years, computed tomography colonography (CTC) every 5 years, annual fecal immunochemical test (FIT), and stool DNA test (interval uncertain) were included as screening options in addition to the tests recommended by the USPSTF. Colorectal cancer screening guidelines issued by the American College of Gastroenterology in 2009 included CTC (every 5 years) as an alternative screening test option for persons unwilling to undergo colonoscopy^[12].

Computed tomography colonography

Although two early multi-institutional clinical trials comparing CT colonography with optical colonoscopy showed poor results^[13,14], other trials in the United States and Europe using state of the art equipment, fluid and fecal tagging, and well-trained readers have demonstrated per patient detection rates of $\geq 90\%$ for adenomas ≥ 10 mm^[15–18]. A recent study involving 307 subjects compared CTC, colonoscopy, flexible sigmoidoscopy, FOBT and FIT for the detection of advanced neoplasia in an average risk population^[17]. Advanced neoplasia is defined as a lesion having one or more of the following characteristics: size ≥ 1 cm, high grade dysplasia, $>25\%$ villous histology, or invasive carcinoma. The sensitivity of CTC for advanced neoplasia was 96.7%. By comparison, the sensitivities of flexible sigmoidoscopy, FIT and FOBT (tests that are uniformly recommended as options for colorectal cancer screening and are covered by Medicare and other insurers) were 83.3%, 32%, and 20%, respectively. Another recent study compared the diagnostic yield from parallel CTC and colonoscopy screening programs which included more than 3000 patients in each arm^[19]. CTC and colonoscopy had similar detection rates for advanced neoplasia, but the numbers of polypectomies and complications were considerably smaller in the CTC group.

Insurance coverage for CTC in the United States

Insurance coverage of CTC in the United States is variable. Although several insurers provide coverage for colorectal cancer screening with CTC, the vast majority of insurers provide coverage only for diagnostic CTC when colonoscopy is either unsuccessful or contraindicated. Despite the recommendation of at least two expert panels to include CTC as a colorectal cancer screening option^[11,12], the Centers for Medicare and Medicaid Services (CMS) in the United States recently decided to deny coverage of CTC for colorectal cancer screening. Reasons for the denial that were cited in the CMS decision memo were:

- (1) CTC cannot reliably detect polyps <6 mm. **Response:** Although the ability of CTC to demonstrate polyps <6 mm is limited, the clinical significance of detecting 5 mm and smaller polyps is questionable. Fifty percent of colonic polyps ≤ 5 mm are non-neoplastic and less than 2% of all polyps ≤ 5 mm have advanced histology^[20,21]. A decision analysis of the relative yield of referring patients with polyps ≤ 5 mm to colonoscopic polypectomy demonstrated that 562 such polyps would have to be removed to avoid leaving behind one advanced adenoma^[22]. Thus, colonoscopy referral for polyps ≤ 5 mm likely would do more harm than good, as it would prove to be very costly and would introduce many unnecessary complications^[23].
- (2) A substantial percentage of patients undergoing CTC may need to be referred to colonoscopy due to identification of polyps ≥ 6 mm. **Response:** Based on data from the ACRIN trial^[16], the largest CTC screening trial published to date, if a 6 mm threshold is used to refer patients for colonoscopy, the colonoscopy referral rate after CTC would be 12%. The parallel CTC/colonoscopy screening trial of Kim *et al.*^[19] demonstrated a very similar colonoscopy referral rate of 12.9% based on a threshold of ≥ 6 mm.
- (3) Because extracolonic findings are common, the potential impact of extracolonic findings on health outcomes and costs needs to be determined. **Response:** Clinically significant extracolonic findings requiring either additional evaluation or urgent care are detected in 4.5–16% of patients undergoing CTC^[16,24–28]. In the majority of cases, the additional diagnostic testing confirms benign findings, but relevant new diagnoses are made in 2–3% of cases^[24]. The mean additional cost per patient for non-surgical procedures is US\$24–34^[24–27,29] and for surgical procedures US\$65–70^[24]. Thus, extracolonic findings should be handled judiciously to balance the cost of additional evaluation against the early detection of important disease.
- (4) The radiation exposure from CTC for colorectal cancer screening is a potential concern. **Response:** Radiation dose is an important consideration in assessing the risks and benefits of CTC for colorectal cancer screening. The effective radiation dose for CTC in recent clinical trials has been 4.5–6.0 mSv^[16,17], which is one half or less that for a standard diagnostic CT of the abdomen and pelvis. Several studies have demonstrated that good quality CTC can be performed with even further reductions in radiation dose, with effective mAs as low as 10^[30–32]. Continuing improvements in CT technology should enhance our ability to provide high quality CTC with very low radiation exposure to the patient. Nevertheless, the long-term risk of radiation exposure to individuals undergoing repeated CTC examinations is a factor that must be considered, and all efforts must be made to limit radiation dose as much as possible.
- (5) No published study has evaluated survival following participation in colorectal cancer screening with CTC. **Response:** It is true that no studies have assessed the effect of CTC screening on mortality from colorectal cancer; however, at least one study has demonstrated that CTC has a higher sensitivity for detecting advanced neoplasia than flexible sigmoidoscopy and FOBT, tests which have been shown to reduce mortality from colorectal cancer^[17].

(6) The currently available data from CTC trials is not generalizable to the Medicare population (age 65 years and older). **Response:** This is a valid comment, as the mean age of individuals in most CTC clinical trials to date have been in the range of 57–58 years. Efforts are underway to extract the data on individuals 65 years and older from previously published studies.

Additional considerations

Current data indicate that CTC is considerably safer than colonoscopy. Colonoscopy perforation rates in the general population are approximately 1/1000 colonoscopies and are as high as 1/500 in those 65 years and older^[33]. The risk of perforation with screening CTC in asymptomatic persons is very low, with no perforations reported in 2 large studies^[16,34] and only one perforation reported in a screening patient in another large study^[35]. Perforations occur more commonly in symptomatic patients undergoing diagnostic CTC^[34–36]; however, even in this patient population the perforation rate of CTC is lower than that of colonoscopy. Furthermore, up to half of the adverse events that occur after colonoscopy are cardiovascular complications resulting from sedation^[37].

If polyps ≤ 5 mm are not reported, CTC is the most cost-effective and safest screening option for colorectal cancer^[38]. Because it is a much less invasive test than colonoscopy and does not require sedation, CTC also has the potential to increase overall compliance with colorectal cancer screening guidelines.

Conclusion

In summary, recent trials have demonstrated that CTC has sensitivity comparable to colonoscopy for detecting clinically significant adenomas. CTC is also safer and more cost-effective than colonoscopy when polyps ≤ 5 mm detected at CTC are not reported. Because it is less invasive than colonoscopy and does not require sedation, it has the potential to increase compliance with colorectal cancer screening guidelines, and thus prevent many colorectal cancers from developing. At least two expert panels recently have endorsed CTC as an option for colorectal cancer screening. With the foregoing in mind, it is time to answer the question “Is CTC for colorectal cancer screening ready for prime time?” I believe the answer is yes, but with qualifications. There is no doubt in my mind that CTC is capable of serving as a sensitive, safe, cost-effective and patient-friendly test for widespread colorectal cancer screening; however, it is incumbent upon radiologists to ensure that those who perform and interpret CTC examinations are properly trained to provide the highest quality of patient care. Before CTC screening can be applied in a widespread fashion, large numbers of radiologists

(and likely non-radiologist physicians and a variety of physician extenders) need to be trained and possibly certified, a process now beginning to take place in many parts of the world. Another obstacle that needs to be overcome before screening CTC can truly become widespread, is the lack of universal insurance coverage for the procedure. Until universal coverage for screening CTC is available, only individuals wealthy enough to pay for the procedure themselves will be able to avail themselves of this screening option, thereby severely limiting its considerable potential.

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