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Virtual colonoscopy for colorectal cancer screening: current status

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Abstract

Computed tomography colonography (CTC) (also known as 'virtual colonoscopy') is a noninvasive method of imaging the colon using helical CT. Although CTC has been shown to be useful for certain clinical indications, it has not yet been endorsed as a colorectal cancer screening test. The purpose of this article is to review the current status of CTC for colorectal cancer screening. CTC is an accurate method to detect colonic polyps and to select patients who would benefit from colonoscopy. The major advantages of CTC over conventional colonography include its relatively low risk and greater tolerance by patients. In this article, the CTC procedure and results of clinical trials are reviewed, as well as potential pitfalls related to CTC performance and interpretation. Finally, radiation dose, the discovery of incidental extracolonic findings with CTC, bowel preparation methods, and computer-aided diagnosis are addressed.

Keywords: *Computed tomography colonography (CTC); virtual colonoscopy; noninvasive; colorectal cancer.*

Introduction

Colorectal cancer is the fourth leading cause of cancer death worldwide[1] but is largely preventable. Most colorectal cancers arise from benign adenomatous polyps, which grow slowly. Thus colorectal cancer is highly suited to screening because of its long preclinical phase during which it is detectable and curable[2]. Multiple organizations including the World Health Organization (WHO), the American Cancer Society (ACS), the Agency for Health Care Policy and Research (AHCPR), the US Preventive Service Task Force (USPSTF), and the American Gastroenterology Association (AGA) have issued or endorsed guidelines for colorectal cancer screening. The screening tests endorsed by these organizations include fecal occult blood testing, flexible sigmoidoscopy, air-contrast barium enema, and colonoscopy. Unfortunately, screening programs for colorectal cancer have been only partly successful, owing largely to poor patient compliance with screening recommendations[3,4]. Recent studies indicate compliance rates of only approximately 25%–40%[5–8]. Major obstacles to patient acceptance of colorectal cancer screening with colonoscopy are the requirement for a rigorous bowel preparation, the invasiveness of the procedure and the need for sedation.

Computed tomography colonography (CTC) (also known as 'virtual colonoscopy') was introduced in 1994 as a noninvasive method of imaging the colon using helical CT[9]. Although CTC has been shown to be useful for certain clinical indications, it has not yet been endorsed as a colorectal cancer screening test and is not covered by most third-party payers when used for screening purposes. This article reviews the current status of CTC for colorectal cancer screening.

Advantages and limitations of CTC

CTC has a number of potential advantages compared with conventional fiberoptic colonoscopy. It is a noninvasive technique, requires no sedation, and can be completed in a much shorter time. CTC also appears to be safer than colonoscopy. Colon perforation occurs in 1 : 1000 patients who undergo conventional colonoscopy, and the mortality rate is 1 : 5000[10–15]. Although experience with CTC is much more limited, the morbidity and mortality

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associated with CTC likely will be similar to those for the air-contrast barium enema (perforation rate of 1 : 10 000 and mortality rate of 1 : 50 000)[16–18]. The only study of morbidity related to CTC reported to date has demonstrated a perforation rate of 3 in 7180 studies (0.04%)[19]. No deaths related to CTC have been reported. In addition, CTC has the potential to eliminate some of the blind spots that can be problematic with conventional colonoscopy. For example, CT colonography is able to demonstrate lesions behind haustral folds and beyond bends in the colon because of its ability to provide an endoluminal view of the colon in both forward and reverse directions and its ability to demonstrate the colon in both two-dimensional and three-dimensional perspectives. For the same reasons, localization of colonic lesions is more accurate with CTC than with fiberoptic colonoscopy. Finally, CTC is capable of demonstrating clinically important extracolonic abnormalities[20–24].

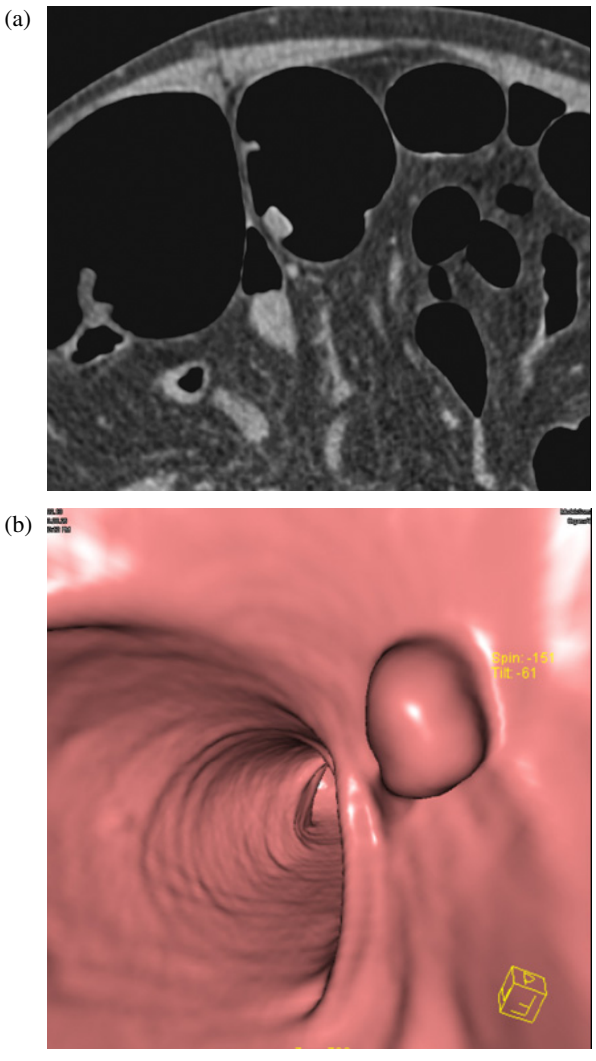

Figure 1 **Sigmoid polyp. 2D transaxial (a) and 3D endoluminal (b) images demonstrate a 1 cm sessile sigmoid polyp.**

On the other hand, CTC also has some limitations. Pitfalls that can result in false negative diagnoses include retained fluid, which can obscure lesions, incomplete distension of some colonic segments, and difficulty demonstrating flat lesions. Pitfalls that can result in false positive diagnoses include retained stool and nodular folds, which can be mistaken for polyps. An important disadvantage of CTC compared with colonoscopy is that CTC does not allow biopsy or removal of polyps that are identified. In addition, the sensitivity of CTC for detecting clinically significant polyps has varied considerably in the screening trials performed to date[25–29].

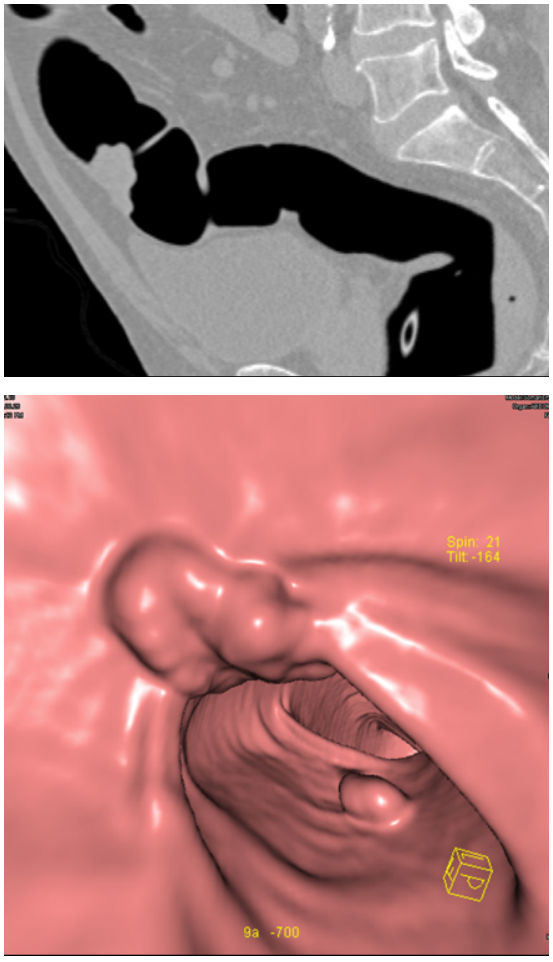

Figure 2 **Sigmoid mass and polyp. (a) A sagittal 2D image demonstrates a lobulated mass in the sigmoid colon. (b) The corresponding 3D endoluminal image shows a nearby 9 mm sessile polyp in addition to the mass.**

The standard CTC examination

Currently all patients undergo a standard bowel preparation as for colonoscopy. A recent modification in bowel preparation is the addition of oral contrast agents (see 'Bowel preparation' below). After the patient is placed on the CT scanner table, a small catheter is placed in the rectum, and the colon is insufflated with either room air or carbon dioxide. The main advantage of carbon dioxide

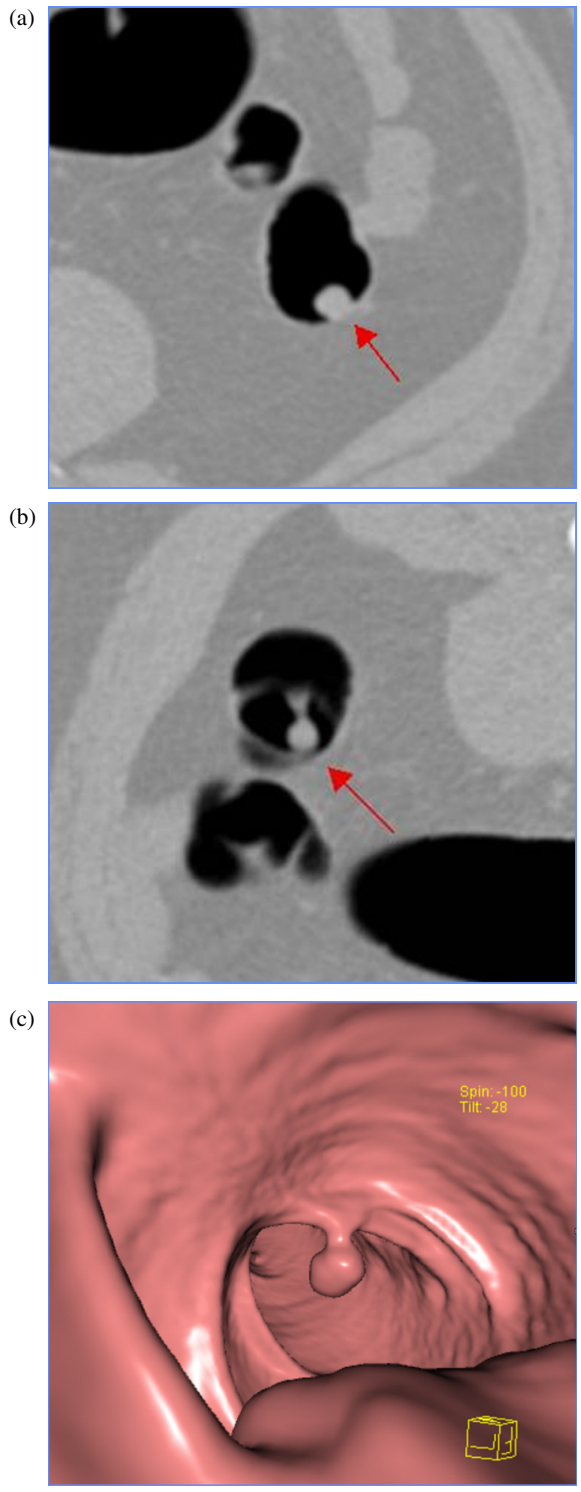

Figure 3 **Pedunculated descending colon polyp. (a) A transaxial 2D image acquired with the patient in the supine position shows a 9 mm polyp (arrow) that appears sessile. (b) A transaxial 2D image acquired with the patient in the prone position demonstrates that the polyp (arrow) arises from a haustral fold and is pedunculated. (c) The corresponding 3D endoluminal view with the patient in the prone position also demonstrates the pedunculated nature of the polyp.**

is that the gas is reabsorbed very quickly, such that within several minutes the patient no longer feels uncomfortable. When room air is used, patients may remain distended for hours after the procedure. Some radiologists routinely administer a spasmolytic medication to help relax the colon and maximize distension, whereas others do not[30]. Prior to the diagnostic CT examination the standard initial scout view (topogram) of the abdomen is used to confirm that the colon is adequately distended. The patient is then scanned in both the supine and prone positions. No oral or intravenous contrast material is administered. The entire examination generally takes approximately 10 min.

Technological evolution of CTC

During the 11 years since its inception, CTC has evolved considerably due to rapid advances in CT hardware and software and the experience gained from numerous clinical trials. When CTC was introduced in 1994, only single- and two-detector row CT scanners were available. Using 3–5 mm X-ray beam collimation, it took 30–50 s to scan the patient's abdomen and pelvis, which led to breathing artifacts in many patients. In addition, the spatial resolution of multiplanar and three-dimensional reconstructions was limited by the relatively large X-ray beam collimation. Currently, with 64 detector-row scanners the scan time is reduced to 4–10 s, and the routine detector collimation of 0.6 mm enables extremely high quality multiplanar and three-dimensional reconstructions (Figs 1–3).

Clinical results

Except for one study that was hampered by suboptimal technique and a steep learning curve[31], early CTC trials performed with single detector-row CT scanners demonstrated sensitivities of 68%–92% and specificities of 82%–98% for polyps 10 mm and larger[32–38]. A meta-analysis of these early trials confirmed reasonably high pooled sensitivities by patient and by lesion of 88% and 81%, respectively, with a pooled specificity of 95% for polyps 10 mm and larger[39]. More recent studies performed with four-detector row scanners have demonstrated sensitivities and specificities of 82%–100% and 90%–98%, respectively, for polyps 10 mm and larger[40–43]. It is important to recognize, however, that these trials were not performed on screening populations but on individuals who were at increased risk for colorectal neoplasia. A large single institution screening trial using single detector-row CT demonstrated individual reader sensitivities of 59%–73% and specificities of 95%–98% for polyps $\geq$10 mm[25]. A smaller single institution screening trial using multidetector-row CT demonstrated a sensitivity of 100% for polyps 10 mm and larger, but in that study only three patients had polyps of that size[26].

Three large multicenter trials comparing multidetector-row CTC and fiberoptic colonoscopy for detecting polyps in patients undergoing colorectal cancer screening have been published[27–29]. In the first study (Pickhardt *et al.*), the sensitivities of CTC and colonoscopy for adenomatous polyps at least 10 mm in diameter were 94% and 88%, respectively. In the second study (Cotton *et al.*), the sensitivities of CTC and colonoscopy for detecting patients with polyps at least 10 mm in diameter were 55% and 100%, respectively, and in the third study (Rockey *et al.*) 59% and 98%, respectively. Thus in one study, CTC had a very high sensitivity and outperformed colonoscopy[27], whereas in the other two studies CTC had a low sensitivity, and colonoscopy outperformed CTC by a significant margin[28,29]. These discrepant results may be related to differences in study design and reader experience. In the study by Pickhardt *et al.*, the readers used a primary three-dimensional endoluminal evaluation of the colon, whereas all other studies have used a primary two-dimensional evaluation. In addition, that study employed stool and liquid tagging (discussed later in this article) as part of the bowel preparation of all patients, whereas the other two studies did not employ stool and liquid tagging. Furthermore, the study by Cotton *et al.* suffered from inadequate reader training. Only one of the nine centers involved in that trial had substantial prior experience with CTC, and the only requirement to be a reader was performance of at least 10 CTC procedures (without any test of accuracy). For the institution in that study with prior CTC experience, the sensitivity for polyps $\geq$10 mm was 82%, compared with 24% for the other eight institutions. Also, the study by Cotton *et al.* used two and four detector-row CT scanners, whereas the other two studies used four and eight detector-row scanners.

Current technical issues, controversies and developments

Visualization methods

CTC data are viewed interactively at an image review workstation and can be viewed in two-dimensional (2-D) or three-dimensional (3-D) formats. For 2-D imaging, the reviewer generally scrolls through the image dataset in transaxial, coronal and sagittal planes. For 3-D imaging, the reviewer views the colon from an endoluminal perspective and navigates the entire length of the colon in both directions to avoid missing polyps on the back side of haustral folds. Until the study by Pickhardt *et al.*[27], all published CTC studies had employed a primary 2-D evaluation of the data, with 3-D endoluminal evaluation limited to problem solving and lesion confirmation. However, recent advances in workstation software have transformed 3-D endoluminal navigation of the colon from a cumbersome, time-consuming technique to one that can be performed relatively efficiently. Consequently, many radiologists now use a primary 3-D endoluminal approach as part of their routine CTC image review. Investigational studies currently in progress are evaluating the relative value of 2-D and 3-D image review.

Bowel preparation

In most CTC trials, the investigators have used the bowel preparation prescribed by the gastroenterologists involved in the study. The most common bowel preparations prescribed are a polyethylene glycol solution or sodium phosphate plus bisacodyl. With both preparations residual fluid may be left in the colon at the time of the CTC examination. The polyethylene glycol solution, in particular, tends to produce a large amount of residual colonic fluid, which can obscure a large portion of the colon wall and hide polyps[44]. This problem can be reduced by adding to the bowel preparation oral iodinated and barium contrast agents, which are incorporated into any residual fluid or stool. Residual stool can thus be distinguished from a polyp based on its high density, and polyps can be identified within a pool of residual fluid and fecal matter because of the higher density of the fluid and stool[45]. In an additional step, the high density residual fluid and stool can be removed from the images electronically[46], but this technique can result in subtraction artifacts and is not yet widely available.

Potentially, the use of stool and fluid tagging with or without the additional step of electronic subtraction could enable CTC to be performed with either a reduced cathartic bowel preparation or no cathartic preparation at all[47,48]. A study of CTC without cathartic preparation in over 200 patients demonstrated a sensitivity of 95.5% for polyps 8 mm and larger[48]. The feasibility of such a technique, if confirmed in subsequent studies, could have a major impact on colorectal cancer screening. It is likely that many more individuals would be willing to undergo screening if the requirement for a cathartic bowel preparation were eliminated.

Radiation dose

For clinically indicated diagnostic CT examinations, the benefit to the patient generally outweighs the potential risk from the use of ionizing radiation. However, if CTC is to be used as a screening procedure for patients at average risk of colorectal cancer, the radiation dose must be minimized to maintain the appropriate benefit-risk ratio. Fortunately, CTC can be performed with a relatively low radiation dose because of the inherently high contrast between the colon wall and the gas within the bowel lumen. Studies have demonstrated the feasibility of performing CTC with an effective mA-s (milliampere-seconds) of only 10–50, enabling a complete supine and prone examination to be done with

a total radiation dose of approximately 1.0–6.0 milli-Sieverts (mSv)[41,49,50]. Two studies have demonstrated the potential feasibility of even further dose reductions down to 0.2–1.0 mSv[51,52]. A recent study reported that even with the use of a relatively high dose CTC protocol, the estimated absolute lifetime cancer risk associated with the radiation exposure from a CTC examination would be approximately 0.14% for a 50 year old and approximately, 0.07% for a 70 year old, a large benefit-risk ratio[53]. These estimated risks can be reduced substantially with lower dose protocols like those described above.

Extracolonic findings

The imaging volume for a CTC examination includes the entire abdomen and pelvis as well as the lung bases. Thus one potential advantage of CTC is the ability to demonstrate extracolonic abnormalities that are of potential clinical importance. Studies have demonstrated that 5%–23% of individuals undergoing CTC have potentially important extracolonic findings, 3%–16% undergo further imaging to evaluate the extracolonic findings, and 1%–3% undergo surgery because of the findings[20–24,27]. Thus, on the one hand, this capability of CTC can have an important impact on an individual patient's health. On the other hand, however, the ability to detect extracolonic findings adds to the overall cost and morbidity of the colorectal cancer screening process, because many patients undergo additional medical procedures for what are proven to be benign or falsely positive findings.

Computer aided diagnosis

Computer aided diagnosis (CAD) for CTC is an automated process that detects configurations of the colon wall that might represent polyps. It is a method that has the potential to increase the diagnostic performance of radiologists in detecting polyps and cancers at CTC and to decrease the variability of diagnostic accuracy among readers without significantly increasing the reading time[54,55]. Preliminary studies have demonstrated that CAD programs are capable of identifying some polyps missed by CTC readers, but at the expense of false-positive findings[56]. Such studies indicate that CAD has the potential to reduce perceptual errors with a relatively low false-positive rate, but further improvements in the technology are required. Some of the current challenges faced by CAD researchers are optimizing the tradeoff between sensitivity and specificity, developing programs that detect polyps in patients who have undergone stool and fluid tagging, and insuring that the programs are robust even when ultra-low radiation dose CTC techniques are used.

Obstacles to widespread use of CTC for colorectal cancer screening

Several obstacles to the widespread use of CTC for colorectal cancer screening are evident. The most important obstacle is that the cost of CTC as a screening procedure is not covered by the vast majority of third party payers. Currently in the United States, individuals who undergo CTC for screening purposes pay for the study themselves. Thus, a large percentage of individuals needing colorectal cancer screening cannot afford CTC. Other important issues related to the widespread use of CTC for colorectal cancer screening are the need for reader training and the limited opportunities currently available to acquire it. Experience with CTC trials has taught us that interpretation of these examinations is associated with a learning curve. A retrospective multicenter study demonstrated a trend of better diagnostic performance with more reader experience[57]. How many CTC studies one needs to read before being considered competent and what type of CTC training should be required are issues that have not yet been resolved.

Other challenges

Several additional questions regarding the clinical implementation of CTC as a primary colorectal cancer screening examination need to be resolved[58]. What is the appropriate patient population for CTC screening? What size polyps should be reported? What size polyp threshold should trigger a conventional colonoscopy? What is the appropriate CTC follow-up interval? How should extracolonic findings be reported? These questions and others will require further study and consensus[59].

Conclusion

CTC is an exciting and rapidly evolving technology that shows great promise in the detection of colonic polyps and cancers. Although sensitivities for polyp detection with CTC have varied, one large multi-institutional screening trial has demonstrated excellent diagnostic accuracy for CTC, comparable to that of fiberoptic colonoscopy. Less impressive results for CTC in two other multi-institutional screening trials may be attributable to inadequate reader training and other study design differences. Future screening trials will help clarify the relative roles of 2-D and 3-D image evaluation and likely will establish fluid and stool tagging as important components of the CTC examination. It is likely also that computer aided diagnosis (CAD) will become an integral part of the CTC image review process, further improving the sensitivity of CTC in polyp detection and reducing interobserver variability. Numerous studies already have demonstrated the feasibility of performing CTC with a very low radiation dose.

Further research is needed to determine the feasibility of performing CTC without a cathartic bowel preparation. If feasible, the lack of a cathartic bowel preparation coupled with the relative ease and noninvasiveness of the CTC examination might encourage many more individuals to undergo colorectal cancer screening, which in turn would result in many saved lives. An important remaining obstacle to the widespread use of CTC for colorectal cancer screening, however, is the lack of coverage of screening CTC by most third party payers, making it an examination that most individuals cannot afford. The results of further clinical trials will play an important role in determining whether professional medical organizations and third party payers will endorse CTC as a legitimate screening test for colorectal cancer.

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