Computed Tomography Colonography (Virtual Colonoscopy): Climax of a New Era of Validation and Transition into Community Practice

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ABSTRACT

Colorectal cancer, which kills more than 50,000 patients every year in the United States and costs more than \$6 billion in direct health costs, is a prime target for cancer prevention. Computed tomography colonography (CTC) has emerged as a minimally invasive, structural examination of the entire colon that can complement the current tools of cancer prevention and may improve patient compliance. Large trials have suggested a sensitivity of roughly 90% and specificity greater than 97% for CTC for patients with polyps ≥ 10 mm. Bowel preparation by diet restriction, catharsis, and stool and fluid tagging are typically used. A prepless CTC protocol is an active area of research with a focus on improving patient compliance. Insurance coverage of CTC is a key factor affecting current dissemination and local and national coverage decisions are ongoing. CT examination of the abdomen allows visualization of extracolonic organs, where detection of additional disease must balance any unnecessary anxiety and testing. Estimates of CTC cost-effectiveness are generally favorable, but vary due to the high sensitivity of these models to costs, polyp sensitivity, compliance rates, and other parameters, which are difficult to accurately assess. Quality initiatives are being developed that will be key for implementation into community practice.

KEYWORDS: Colorectal cancer, virtual colonoscopy, computed tomography colonography, prevention, screening

Objectives: On completion of this article, the reader should understand how computed tomography colonography (CTC) is performed, including bowel preparation, stool tagging techniques, bowel insufflation, and CT low-dose protocols. The reader should also be aware of the clinical trial validation results to date, current indications and uses, issues of extracolonic findings and cost effectiveness, and quality initiatives being defined.

Colon cancer is the second most common cause of cancer death in the United States. With more than 100,000 new cases and 50,000 deaths every year, colon

cancer exacts a huge burden on our country.¹ Affecting ~6% of individuals over their lifetime, colon cancer will take an estimated 13 years off of the lifespan of those

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diagnosed with the disease.² In addition to the suffering and lost years of life, colon cancer represents a large monetary toll on our health care system, costing nearly \$6.5 billion each year.³

This large impact is one of the reasons that colon cancer is a prime target of preventive screening. Additionally, colon cancer is a largely silent disease, tending to cause symptoms, like anemia or changing bowel habits, once the cancer is more advanced. This advancement is especially important as there is an enormous difference in survival between stages of colon cancer. Localized disease has 5-year survival near 95%, whereas distant metastatic disease has less than 5% survival over that same time period.⁴ Another factor favoring the utility of screening is that there exists a long preclinical period where lesions that may form cancer can be found. It is estimated that adenomas require 10 years to form into invasive cancer.⁵ Finally, effective interventions are available during this preclinical period to not only find early cancers, but prevent lesions from ever becoming cancer.

The proven cost-effectiveness and mortality benefit of screening in average-risk populations suggests that colorectal screening is required for all patients in the appropriate age group.⁶ The current armamentarium of tools widely available to patients and their doctors includes optical colonoscopy, flexible sigmoidoscopy, fecal occult blood testing, and double contrast barium enema.

In March 2008, the American Cancer Society (ACS) released a joint guideline with the US Multi-Society Task Force of Colorectal Cancer and the American College of Radiology (ACR), recommending computed tomography colonography (CTC) along with the other established tests for colorectal screening.⁷ CTC has gained widespread multidisciplinary attention as a minimally invasive, structural imaging evaluation of the entire colon and rectum. Over the past decade, there have been rapid technological advancements in both CT image acquisition and three-dimensional (3D) display techniques. These gains have allowed CTC to provide interactive, real-time "endoscopic" visualization of the colon, along with evaluation of the extracolonic findings in the abdomen and pelvis. Recently, a climactic new era of clinical trial results has led to a convincing level of improved validation for the detection of clinically significant colorectal lesions. These validation results and the recent ACS recommendations, along with implementation of quality assurance guidelines, will begin to pave the transition from research investigation to community implementation.

This review article will focus on (1) bowel preparation and insufflation, (2) CTC techniques and 2D–3D image display, (3) current indications and uses, (4) diagnostic performance in clinical trials, (5) extracolonic findings, (6) cost effectiveness of CTC, and (7) standardization and quality assurance initiatives.

BOWEL PREPARATION AND INSUFFLATION

The bowel preparation is a key aspect of the examination, which has the greatest impact on patient compliance. Overall, patient preference studies have demonstrated positive patient responses to CTC compared with colonoscopy^{8–11}; however, the bowel preparation is still a critical issue. In a study of 120 patients at increased risk for colorectal neoplasia, patients significantly rated more negative overall appraisals of the bowel preparation, compared with appraisals of the CTC and colonoscopy examinations.¹⁰

Current clinical efforts of CTC require a full bowel preparation. The three components of the bowel preparation for CTC are typically: (1) dietary restriction of clear liquids the day before the examination, (2) catharsis similar to colonoscopy, and recently (3) stool and fluid tagging.^{12–15} The use of stool tagging agents offers several advantages because residual stool can mimic polyps and cause false-positives (Fig. 1). First, tagging with iodine or barium products tends to densely tag residual stool and thus can decrease false-positives of retained stool. In addition, fluid tagging can help increase the sensitivity to detect submerged polyps, which appear as lower density soft tissue lesions surrounded by the more dense fluid. Importantly, the tagging of stool needs to be differentiated from the thin linear tagging, which can occur over the surface of polyps. Namely, in a subanalysis of 216 screening patients, 46% of 312 polyps demonstrated some adherent contrast coating the surface of polyps from the tagging agents.¹⁶ Thus, the recent development of tagging stool and fluid can improve diagnostic performance, but patient compliance must also be enhanced.

With the hopes of improving compliance, there is active research to develop a prepress CTC examination.^{17,18} This refers to a CTC examination without catharsis and typically less dietary restrictions (e.g., low fiber diet); however, stool tagging is still used. In 2004, Iannacone et al evaluated a cohort of 203 patients using low-dose CTC without cathartic preparation.¹⁸ Fecal tagging was performed with a total dose of 200 cc of Gastrografin[®] (Bracco Diagnostics, Inc., Princeton, NJ), divided up with meals for 2 days prior to CTC. Colonoscopy was the reference standard, performed 3 to 7 days after CTC when patients had undergone a conventional bowel preparation. Overall, per patient analyses demonstrated that CTC had a sensitivity of 89.9%, specificity of 92.2%, and positive predictive value of 88% (18). The disadvantage of prepress CTC is the residual tagged stool can slow down the reader evaluation compared with the more efficient evaluation of a clean colon of a prepped patient. Continued research will be essential to develop an efficient and well-tolerated prepress protocol, which provides high diagnostic accuracy.

Figure 1 Key aspects of stool and fluid tagging at computed tomography colonography are illustrated. (A) Areas of densely tagged stool (black arrows) help to decrease false-positives of retained stool. (B) Submerged 8 mm polyp (black arrow) is contrasted by densely tagged residual fluid. (C) 10 mm rectal polyp (white arrow) demonstrates surface tagging.

Beyond the bowel preparation, the bowel insufflation technique performed at CT is the next patient-related step that greatly impacts image quality. Without adequate bowel insufflation, the collapsed segments of colon can greatly impair visualization of the mucosal surface of the colon for polyp detection. Initial studies performed manual insufflation of room air. More recent advances have developed the use of automated carbon dioxide insufflation, with monitoring of both volume and pressure.^{19,20} Typically, a total of 2 to 4 L of carbon dioxide are instilled over less than 2 minutes. The patient is imaged in two positions (typically supine and prone) to improve surface area visualization due to shifting areas of fluid or collapse.^{21,22} Total examination time on the CT table typically is 10 minutes or less.

There have been rare reports of the risks of perforation at CTC, ranging from 0% to 0.059% across asymptomatic and symptomatic cohorts.^{23–25} In the

United States, the collective experience of the International Working Group of Virtual Colonoscopy reported no cases of perforation in 11,707 screening CTC examinations and two perforations in 10,216 (0.02%) diagnostic CTC examinations.²³ In Israel, a collective study of a mixed cohort across 11 centers reported seven perforations in 11,870 CTC examinations (0.059%); six of the perforations were in symptomatic patients at high risk for colorectal cancer and one perforation was in an asymptomatic patient.²⁴ Four of the seven patients required surgical intervention. In the United Kingdom, there were nine reported perforations in a mixed cohort of 17,067 (0.053%) patients; four patients were asymptomatic and five patients were symptomatic.²⁵ One of the nine patients required surgical intervention. These rates of perforation at CTC are similar to barium enema, with reported ranges of 0.004 to 0.04%,^{24,26} but are significantly lower than colonoscopy, with reported ranges of ~0.1 to 0.2%.^{27–29}

COMPUTED TOMOGRAPHY COLONOGRAPHY TECHNIQUES AND IMAGE DISPLAY

With advances in multidetector CT from 4-row to 16- and 64-row CT devices, image acquisition of the abdomen and pelvis can now be done within 5- to 15-second breath-hold acquisition times, using thin collimation of 1 mm or less slice thickness. Dose profiles continue to improve with the newer CT scanners. In addition, CTC techniques require significantly less radiation dose compared with routine CT examinations of the abdomen and pelvis. This reduced dose requirement is due to the intrinsic high contrast between the soft tissue polypoid structures and surrounding air.

Radiation dose imparted at CTC is a critical factor to keep efficient. Several investigators have reported successful use of low-dose CTC protocols.³⁰⁻³³ In 2002, a study of 105 patients was performed with the CT scan protocol of 1-mm slice thickness and low dose of 50 effective mAs.³⁰ The total effective dose to the patients for both supine and prone imaging of the abdomen and pelvis was 5.0 mSv for men and 7.8 mSv for women, which is comparable to dose ranges of barium enema. Excellent sensitivity of 90% for 1 cm polyps was achieved.³⁰ In 2003, further dose reduction was achieved in a cohort of 158 patients predominantly at increased risk of colorectal neoplasia, using 10 effective mAs and a slightly thicker slice thickness of 2.5 mm.³¹ This protocol resulted in total effective doses to the patients of 1.8 mSv in men and 2.4 mSv in women. In this study, there was 100% sensitivity for all 22 cancers, 100% sensitivity for the 13 $\geq$ 10 mm polyps, and 83% sensitivity for the 6 to 9 mm (20 of 24) polyps. Further decreases in radiation dose have been achieved with advances in automatic tube current exposure and dose modulation techniques,³⁴ which change differentially the delivered dose over the anatomy scanned in real time (e.g., more dose given to penetrate the bony pelvis and less dose given over the soft tissues of the abdomen). With these new dose reduction techniques, the effective dose from CTC becomes in the range of yearly background radiation. These low-dose radiation techniques have now become standard of care for screening CTC in both research and clinical practice.

Recent reports have discussed the controversy of low radiation dose exposure.^{35,36} Brenner et al recently addressed the issue of radiation dose screening with CTC and concluded that the benefit-risk ratio was high and that cancer risks were very rare.³⁵ Brenner concluded that potential lifetime cancer risk for one CTC exam at 50 was 0.14% (0.07% if 70), which could be reduced by factors of 5 or 10 with optimized low dose protocols.³⁵ However, most estimates of the potential cancer risk have assumed a linear nonthreshold model by extrapolating from A-bomb survivors, but there is controversy over whether this model applies for low-dose

exposures. Recently, the American College of Radiology (ACR) created a Blue Ribbon Panel on Radiation Dose in Medicine and published recommendations and quality initiatives for the safe use of ionizing radiation, including CT, in clinical practice.³⁶ As will be discussed later in this review, the quality metrics being defined for CTC include the documentation of low-dose CT protocols for screening cohorts.

IMAGE DISPLAY OF 2D AND 3D TECHNIQUES

After the CT examination has been completed, typically 600 to 1,000 images can be produced. Both 2D and 3D image display techniques are useful for image interpretation (Fig. 2).³⁷ The 2D multiplanar reformations (MPR) in the axial, sagittal, and coronal planes provide a time-efficient evaluation of colorectal lesions, with the additional value of demonstrating lesion location in the colon and lesion density (e.g., fat in a lipoma or pockets of air in retained stool). The 3D endoscopic display can improve surface area visualization of lesions behind folds with the performance of both retrograde and antegrade flight paths. Some lesions, such as flat or sessile lesions along a fold, can be better demonstrated in the 2D views with soft tissue settings. Thus, an integrated approach of both 2D and 3D display techniques is essential for complete evaluation of the colon.

CURRENT INDICATIONS AND USES

In clinical practice today, the level of reimbursement of CTC has largely influenced its current implementation. Currently, there is not a national coverage decision for general use of CTC. In this interim before wide coverage is available, 47 states have local coverage decisions for specific diagnostic uses of CTC.³⁸ A recent review by Knechtges et al summarizes the status of reimbursement and the local coverage decisions, which differ across states.³⁸

The current range of indications for CTC that are currently reimbursed include (1) evaluation of the remaining colon following incomplete colonoscopy, largely in patients who have colorectal symptoms (Fig. 3); (2) evaluation of submucosal lesions detected at colonoscopy; and (3) evaluation of the colon in patients at increased risk to undergo colonoscopy (e.g., anticoagulation or anesthesia risks).

Large screening programs are in clinical practice only in a few areas. At the National Naval Center, the Colon Health Initiative was established through a congressional grant in 2004. A dedicated team of radiologists, gastroenterologists, general surgeons, nurses, technologists, and research personnel are providing colon health care to the Department of Defense beneficiaries in the National Capitol region. A large study on

Figure 2 Different two-dimensional (2D) and three-dimensional (3D) image display techniques used at computed tomography colonography (CTC) illustrate a 12 mm sessile polyp (white and black arrows) along a fold. (A) Axial 2D image. (B) 3D CTC "endoscopic" view. (C) Optical colonoscopy image. (D) 3D CTC transparency view gives anatomic location of polyp.

the use of CTC screening of asymptomatic patients is being performed. At the University of Wisconsin, several third-party payers have provided coverage for colorectal screening. Pickhardt et al reported very positive first-year results of screening 1,100 patients in this system, with 99% insurance coverage provided.³⁹ In the near future, a national coverage decision of CTC for colorectal screening will have the greatest impact on its more widespread use.

DIAGNOSTIC PERFORMANCE IN CLINICAL TRIALS

To date, clinical trial results of CTC have been validated predominantly using colonoscopy as the reference stand-

ard. During the evolution of the CTC technical advances from 1995 to 2005, a range of results were reported in different cohorts of patients using different techniques.^{40–47} Early validation trials of predominantly polyp-rich patient cohorts demonstrated encouraging results of the sensitivity to detect ≥ 10 mm polyps of $\sim 90\%$.^{41,42} However, several large trials to follow demonstrated less favorable results. Specifically, in the multicenter trials of 600 patients of Cotton et al⁴⁸ and 614 patients of Rockey et al,⁴⁹ sensitivities to detect the ≥ 10 mm polyps ranged from 55 to 59%. These efforts did not evaluate asymptomatic patients and did not use the latest technological advances of stool tagging or 3D as primary imaging review. Detection of sessile or flat lesions has been variable, ranging from sensitivities of

Figure 3 Same-day incomplete colonoscopy. (A) Three-dimensional computed tomography colonography (3D CTC) transparency view demonstrates marked colonic tortuosity. (B) 3D CTC "endoscopic" view of normal cecum well visualized.

13 to 65% in early CTC studies⁵⁰ to 80% when using MDCT (multidetector CT) and combined 3D-2D polyp detection.⁵¹

During this first decade of effort, two meta-analyses were done to review the CTC trial results.^{52,53} The most comprehensive meta-analysis, undertaken by Mulhall et al, evaluated 33 studies encompassing 6,393 patients; on a per patient basis, CTC sensitivity and specificity for ≥ 10 mm polyps was found to be 85 to 93% and 97%, respectively.⁵² Pooled sensitivity and specificity for small polyps (6 to 9 mm) was 70 to 86% and 86 to 93%, respectively. Halligan et al reported the sensitivity of CTC to detect invasive colorectal cancer was 96% (Fig. 4).⁵³

One of the first large CTC trials, which evaluated an asymptomatic cohort of screening patients was the Pickhardt et al trial of 1,233 patients.⁵⁴ This trial introduced the novel techniques of stool tagging with electronic subtraction and 3D as a primary imaging

review. This trial also used the "enhanced" reference standard of segmental unblinding of CTC results during colonoscopy. Namely, each colonic segment was evaluated by the colonoscopist initially, followed by a second look at the colonic segment if the disclosed CTC results demonstrated a significant lesion. This trial reported sensitivities to detect patients with adenomas at size thresholds of ≥ 6 mm and ≥ 10 mm of 88.7% and 93.8%, respectively; specificities at these two size thresholds were reported at 79.6% and 96.0%, respectively.⁵⁴ Based on the segmental unblinding methodology, miss rates at the original colonoscopy (before CTC results were disclosed) could be evaluated. A subsequent analysis of these results demonstrated that colonoscopy missed 10% of adenomas > 10 mm.⁵⁵

Further trials' results with screening cohorts in the United States and Europe are currently being completed and reviewed for publication. In a recently finished Germany screening trial led by Graser et al⁵⁶ and an ongoing Navy trial in the United States led by Cash et al,⁵⁷ results of diagnostic performance have been similar to Pickhardt et al.⁵⁴ Regge et al reported recently the results of the completed Italian Multicenter Polyp Accuracy CTC study group (IMPACT) of 934 asymptomatic patients at increased family or personal risk for colorectal neoplasia.⁵⁸ Using low-dose techniques of < 50 mAs, sensitivities and specificities for patients with ≥ 6 mm versus ≥ 10 mm polyps were 84.2% and 90.4% versus 90.7% and 84.6%, respectively.⁵⁸

One of the largest screening trials which has attracted great attention in the United States has been the recently completed ACR Imaging Network (ACRIN) 6664 trial. This trial finished accrual of 2,531 asymptomatic patients across 15 centers in November 2006, using state of the art techniques of low dose (50 effective mAs) 16- to 64-row CT, 2D and 3D image display techniques and stool tagging. At the national ACRIN meeting in September 2007, the trial results reported sensitivities to detect patients with adenomas at similar levels of diagnostic performance as Pickhardt et al.⁵⁴ As the largest multicenter screening trial to date, the anticipated publication of the ACRIN 6664 trial results could greatly help establish reproducibility of prior excellent results and likely will have a high impact on validation for CTC as a screening modality.

A recent study demonstrated the efficacy of CTC to properly select patients who would benefit from therapeutic colonoscopy. Kim et al recently reported results of a two-pronged study comparing screening with primary CTC in 3,120 patients (with selective recommendation for colonoscopy for patients with detected polyps ≥ 6 mm in size) to screening with primary optical colonoscopy (OC) in 3,163 patients.⁵⁹ The two groups were similar, other than a slightly higher proportion of individuals with a family history in the OC group. Both groups reported a similar detection rate of

Figure 4 Advanced mural cancer (white arrows) at computed tomography colonography (CTC). (A) Axial two-dimensional image. (B) Three-dimensional (3D) CTC "endoscopic" view. (C) 3D CTC transparency view of advanced cancer (arrows) gives anatomic road map helpful for surgical planning.

advanced adenomas (3.2% in the CTC group and 3.4% in the OC group); however, the total number of polypectomies was over 4 times higher in the optical colonoscopy group compared with the CTC group (2,434 vs 561, respectively).⁵⁹ This study demonstrates that CTC, using a size threshold of ≥ 6 mm polyps to recommend therapeutic colonoscopy, can lead to efficient removal of advanced adenomas.

EXTRACOLONIC FINDINGS

CTC provides additional screening of organs within the abdomen, pelvis, and inferior thorax allowing for detection of extracolonic and in some cases, extraabdominal disease. The ability of CTC to detect abnormalities

outside of the colonic lumen proves beneficial when clinically significant, extracolonic disease is diagnosed at an early stage reducing morbidity and mortality. However, equally great limitations of this examination include the additional costs and anxiety generated from further evaluation of extracolonic findings (ECF), which are later proven clinically insignificant.⁶⁰ The ECF in most studies are categorized by high, moderate, or low clinical importance. Some of the most common extracolonic findings of high clinical importance include solid organ lesions, undiagnosed aortic aneurysms, uncalcified pulmonary masses or nodules, or lymphadenopathy. Extracolonic findings of moderate importance most commonly include cholelithiasis, nephrolithiasis, hernias, ascites, cirrhosis, and splenomegaly. Those findings

that are unlikely to require any additional medical treatment are assigned to low importance and most commonly include cysts, hiatus hernia, fat deposition within the liver, diverticulosis, and atherosclerotic calcifications.⁶¹

Several studies have demonstrated that ECF are common in patients undergoing CTC; however, the number of findings of high clinical importance is actually quite low. The overall incidence of ECF has varied from 15 to 85%, with the overall percentage of subjects with findings of high importance ranging from 4.5 to 25% in both symptomatic and asymptomatic cohorts.⁶²⁻⁷¹ The incidence of high importance findings within high risk cohorts of symptomatic patients has varied from 8 to 25%,⁶⁷⁻⁷¹ whereas screening cohorts of asymptomatic patients have reported ranges of 4.5 to 10%.^{54,60,63-65} Furthermore, ECF of high importance are lower in patients without malignancy (17%) compared with patients with known malignancy (75%). Not surprisingly, the overall number of ECF of clinical importance also increases with patient age.⁷² The use of intravenous contrast correlates with a higher incident detection of ECF; however, studies that used intravenous contrast have all been performed on symptomatic or high-risk cohorts.^{68-70,72} The majority of high importance ECF will prove to be benign upon completion of further testing.⁷² Approximately 1 to 3% of patients will eventually undergo medical or surgical treatment of ECF considered to be of high clinical importance; the majority for aortic aneurysm or extracolonic malignancy. Fortunately, less than 1% of patients will have an undiagnosed extracolonic malignancy at the time of CTC and less than 1.5% of patients will have an ECF of high importance that is missed by the radiologist.⁷²

COST EFFECTIVENESS OF COMPUTED TOMOGRAPHY COLONOGRAPHY

In the current reimbursement climate, safety and clinical efficacy alone are no longer sufficient to fully induct CTC into our available arsenal of colon cancer screening tools and bring it to widespread use. In the United States, a threshold level of \$100,000 per life-year prolonged has been widely accepted for evaluating if diagnostics and therapeutic interventions are cost effective.⁷³ However, there are important caveats to the use of cost-effectiveness analysis in colorectal screening. Cost and benefit models are often sensitive to parameters for which estimated values lack accuracy or vary considerably in practice. Particularly, the costs of colonoscopy and CTC vary widely by region, type of practice and individual practitioner. Additionally, much research has focused on direct comparisons of OC to CTC. This ignores the significant portion of patients who are either not screened by any means or by means other than

optical colonoscopy. CTC is not intended to replace the use of OC, but rather to add to available tools and reach additional patients. Further, often indirect costs, those difficult-to-quantify costs borne by patients, are ignored by these studies. Specifically, the use of sedation for OC often requires that the patient take an entire day off work and that someone other than the patient drive to and from the testing center, requiring additional expense or time off for that person. Also, trials up to this point have focused on programmatic testing, while in practice there is considerable variation in how these tests are applied. It remains to be seen if individual testing episodes are as effective as the programmatic testing used in studies.

The cost effectiveness of CTC is highly sensitive to the polyp detection rate, especially at the > 10 mm threshold. In one Canadian study, CTC was determined to be a strategy dominated by OC, costing more and leading to more deaths.⁷⁴ This is primarily due to the use of an outdated sensitivity parameter: 61% for 6 to 9 mm polyps and 71% for ≥ 10 mm polyps. An Italian study determined that CTC was cost effective, using a sensitivity of 70% for 6 to 9 mm and 85% for ≥ 10 mm polyps.⁷⁵ In a U.S. study using sensitivities of 82% and 91% for 6 to 9 mm and ≥ 10 mm polyps, respectively, compared with no screening at all, CTC is very cost effective at either 5- or 10-year intervals at \$8,000 to \$17,000 per life-year prolonged.⁷⁶ Since only about 50% of eligible persons engage in any screening for colorectal cancer, there is a large potential for CTC to screen individuals who would otherwise not be screened. When compared with other screening modalities such as flexible sigmoidoscopy every 5 years, CTC was both cheaper and more effective. In the case of flexible sigmoidoscopy with fecal occult blood testing, CTC was still the dominant screening strategy. CTC every 5 years compared with annual fecal occult blood testing (FOBT) alone was found to be more expensive, but more effective at a cost of \$22,000 per additional life-year saved.⁷⁶

These are favorable comparisons to tests already recommended by multiple established guidelines (American Cancer Society, American College of Gastroenterology and Gastrointestinal Consortium) for colorectal cancer screening.⁷⁷⁻⁷⁹ Comparisons between CTC every 10 years and OC every 10 years suggest that CTC is likely to be slightly cheaper and less effective with an additional cost of \$7,000 per life-year gained with the use of optical colonoscopy.⁷⁶ CTC every 5 years was found to be more effective, but more expensive with a cost of \$150,000 per life-year gained. Using the \$100,000 cutoff, OC is the preferred strategy in either case. For CTC performed every 5 years, increasing adherence to follow-up colonoscopy to 95% from 75% improved the cost per additional life-year prolonged to \$33,000, bringing it well within the accepted threshold for cost effectiveness.⁷⁶

This impact has led to the idea of dedicated resources with the possibility of obtaining CTC with OC follow-up the same day with the same bowel preparation. Where such centers are available they may greatly increase adherence to follow-up and therefore, the economic viability of CTC. The number of available endoscopists is insufficient to perform OC on all those eligible to be screened. This combined paradigm can on one hand improve the therapeutic results to CTC positive patients and also provide an enriched cohort of diagnostic and therapeutic rather than screening colonoscopies to endoscopists.

An additional issue with CTC screening is the use of size thresholds. Reporting of all lesions regardless of size to optical colonoscopy is still cost effective at a cost of \$7,000 per life-year prolonged, while reporting only those lesions > 5 mm reduced that cost to \$4,000.⁸⁰ The incremental cost per life-year for reporting small lesions was \$120,000. These small lesions significantly increased the number of OCs performed, but had little impact on clinical efficacy. In addition, the possibility of surveillance for 6 to 9 mm polyps is a poorly studied, but promising avenue for further reducing the overall cost of CTC screening and unnecessary invasive diagnostics.

Finally, the consequences of extracolonic findings are difficult to assess due to the lack of long-term longitudinal studies on the benefits of abdominal evaluation or unnecessary anxiety produced. The additional cost of evaluating extracolonic findings has generally been reported to be low, ranging from \$24 to \$34 based upon Medicare reimbursement.⁶³⁻⁶⁶

STANDARDIZATION AND QUALITY ASSURANCE INITIATIVES

Standardization and quality assurance guidelines of CTC will be essential for effective implementation in clinical practice. In 2005, the ACR published the first guidelines for CTC.⁸¹ These guidelines discussed the current uses, proper CT techniques, bowel preparation, training requirements, and communication of results for CTC.

Also in 2005, a consensus statement was published by the Virtual Colonoscopy Working Group regarding a standardized CTC reporting structure named C-RADS.⁸² This reporting structure was modeled after the successful development of Bi-RADS used in reporting of mammography. For CTC, this reporting structure describes how to report lesion size, morphology, and location of colorectal findings. Importantly, it also develops a per patient category scale summarizing all colorectal findings, including C0 (incomplete study), C1 (no polyps or polyps ≤ 5 mm, C2 (indeterminate lesions or less than three in number of 6 to 9 mm polyps), C3 (three or more in number of

6 to 9 mm polyps or ≥ 10 mm lesions), and finally C4 (suspected or known cancer). In addition to the colorectal scores, a similar scale of the extracolonic findings was developed, ranging from E0 (limited exam) to E4 (clinically significant finding requiring further testing). Further adoption of this reporting structure and is evolving.

Clinical management of reported lesions detected at CTC is critical to define. Although there is wide agreement on the need for removal of large polyps (≥ 10 mm), management of diminutive (≤ 5 mm) and small (6 to 9 mm) lesions detected at CTC remains controversial. The risks of advanced neoplasia in polyps ≤ 5 mm versus 6 to 9 mm ranges from 1.7%⁸³ versus 3.4 to 6.6%,^{83,84} respectively. The benefits of immediate polypectomy versus short-term surveillance of these low-risk neoplasia need to be balanced with the considerations of cost and complications of polypectomy. Namely, Levin et al reported in a retrospective review of 16,318 patients of Kaiser Permanente, 82 serious complications (5 in 1,000); 95% of these complications followed biopsy or removal of polyps and 62% of polyps removed were < 10 mm.⁸⁵ Various policies have been published on the management of lesions detected at CTC.^{81,86-88} Currently, longitudinal data on the natural history of small colorectal polyps is being collected with CTC surveillance studies. For current clinical practice, appropriate patient management of lesions detected at CTC will need to incorporate the clinical context of patient age, comorbidity, colorectal symptoms, and size and number of polyps. Further multidisciplinary consensus agreements for clinical management are now being pursued, possibly within the efforts of the Colorectal Round Table.

In 2008, the ACS jointly revised the 5-year update of the colorectal screening guidelines with the multisociety gastrointestinal task force (American Gastroenterology Association [AGA], American Society for Gastrointestinal Endoscopy [ASGE], American College of Gastroenterology [ACG]) and the ACR. In this guideline, CTC was included as one of the recommended modalities for colorectal screening for detection of cancer and advanced neoplasia.⁷ As was stressed across the recommended modalities, compliance with defined quality standards is essential to promote high-quality screening.

Like the initiative for measuring quality of colonoscopy,⁸⁹ quality metrics for CTC are also being developed. In 2006, the ACR began to outline individual- and practice-based quality metrics for CTC, including low-dose CT technique, bowel preparation, adequacy of insufflation, and outcomes measures of diagnostic performance, complications, and significant extracolonic findings. These metrics began a pilot phase in late 2007 using the National Radiology Data Registry (NRDR), which is an active ACR national data warehouse. In time,

these data may help provide a pay-for-performance model for CTC to promote quality of performing and interpreting the examination.

SUMMARY

With recent successful clinical trial results of ACRIN and other international trials, along with the recent colorectal screening recommendations by the ACS, CTC is now at the forefront of a new level of acceptance as a screening algorithm for colorectal polyps and cancers. However, multiple key factors are important to optimize for more widespread implementation. The bowel preparation, aided by stool tagging techniques, is a critical influence on patient compliance. Low-dose CTC protocols are essential for screening patients, with current protocols used imparting a radiation exposure in the range of yearly background radiation levels. Although the recommendation for immediate polypectomy of ≥ 10 mm lesions detected at CTC is well established, the management of smaller lesions continues to be debated. Currently the patient needs to be managed in the appropriate clinical context of age, risk, and colorectal symptoms, with the benefits of small polyp removal versus surveillance balanced with considerations of costs and complications. Extracolonic findings are important to report responsibly, with a low incidence of high clinically significant findings, which require further workup in screening cohorts. Cost-effective modeling studies have shown promise for CTC as a screening modality. The ACR has defined specific quality metrics for CTC, which will be important to implement as the transition from research centers to community practice begins. When these challenges are overcome, the true potential of CTC as a minimally invasive colorectal screening test could be reached in the near future.

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