Published in final edited form as:
Acad Radiol. 2006 December ; 13(12): 1517–1531.

Current Status of CT Colonography

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Keywords

CT; colon; Colorectal cancer; CT; colonography; MR; colonography; colonoscopy

In 2006, over 55,000 Americans are expected to die of colorectal cancer (CRC) (1). It is estimated that there is over a 5% chance that an American will develop CRC in their lifetime and over a 2% chance that an American will die from CRC (2). Fortunately, in most cases, controlling CRC is possible with the proper screening methods and the subsequent removal of suspicious polyps, adenomas, and carcinomas. If CRC is detected at an early stage, the 5-year survival rate is 90%. Unfortunately, less than 40% of colorectal cancers are detected at an early stage. Once the cancer has developed distant metastases, the 5-year survival rate is less than 10% (2).

From 1998 to 2002, the incidence rate of CRC decreased by 1.8% per year, which is believed to have occurred due to increased awareness of the importance of CRC screening and consequent polyp removal (2). However, CRC is still predicted to cause about 10% of all cancer-related deaths in the United States in 2006. Relatively accurate screening methods are available to patients, but patient participation in CRC screening continues to be low. Computed tomography colonography (CTC) is a relatively new screening technology that aims to achieve a high patient acceptance, diagnostic accuracy, and screening effectiveness thereby decreasing mortality rates due to CRC.

BACKGROUND OF CTC

The use of CT imaging for the detection and staging of CRC was proposed as early as 1980 (3,4). In 1983, the authors of a small study concluded that CT had potential as a mass screening method for colorectal polyps (5). Over a decade later, in 1994, the term “virtual colonoscopy” was formally introduced (6). Since then, great advances in software and hardware have occurred. Clinical studies began to include more patients, better technologies were developed, and improved techniques were used. In 1996, a small study was conducted to determine the optimal CTC scanning parameters based on an artificial colon model and to determine the feasibility of using CTC in a clinical setting by using optical colonoscopy as the reference standard (7). Since 1996, studies have been conducted using multiple scanning parameters, different risk populations, multiple stool and fluid tagging techniques, multiple colon preparation techniques, different image processing techniques, and differing radiologist

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Potential financial interest.
Author Summers has pending and/or awarded patents for the subject matter described in the manuscript and receives royalties from iCAD.

Grant Support: This work was supported by the Intramural Research Program of the N.I.H. Clinical Center.

experience with CTC to determine the best technique for screening. Recent advancements in CTC include new reconstruction techniques and advanced image processing.

POLYPS & CANCER

Studies have indicated that less than 5% of adenomatous polyps progress into carcinomas (8, 9). However, clinical studies suggest that over 95% of colorectal carcinomas arise from these slow-growing, adenomatous polyps (9). Consequently, polypectomy of colorectal adenomas was shown to reduce the incidence of CRC by nearly 80% (10). Progression of an adenoma into cancer can be predicted by size, villous histology, degree of dysplasia, and inherited or environmental factors (9).

Size

The risk of a polyp being cancerous increases as the size of the polyp increases. A study found that there is only a 1.3% risk that a polyp that is less than 10-mm is a carcinoma (11). In comparison, a polyp 10-mm to 20-mm in size has a 9.5% chance of malignancy and a polyp greater than 20-mm has a 46% chance of malignancy. Polypectomy of polyps that are at least 5-mm (12), 6-mm to 8-mm (13–15), or 10-mm (16) have been suggested by various experts. The progression of an adenoma into a carcinoma is predicted to take about 10 years (9,17).

Type

The chance of malignancy in a polyp has been found to be related to polyp type in addition to size. Large flat or depressed polyps have an especially high chance of malignancy. In a study conducted by Rembacken *et al.*, 1000 patients in the United Kingdom underwent optical colonoscopy (18). The study found that only 10% of the 321 adenomas contained severe dysplasia, but over 50% of those were flat or depressed. Similarly, of the six carcinomas found, two were flat and two were depressed. The likelihood of cancer or severe dysplasia depended on the size and appearance of the polyp: 4% in flat lesions less than 10-mm, 29% in flat lesions greater than or equal to 10-mm, and 75% in depressed lesions. Knowledge about the risk of malignancy in a polyp based on physical characteristics can help to ensure that the polyps that are more prone to cancer are detected and resected before CRC develops.

SCREENING

The American Cancer Society estimates that 90% of CRC cases and deaths are preventable with regular CRC screening (19–21). It has been recommended that an average-risk person begin screening at age 50. Persons with an increased risk may be advised to be screened more often or begin screening sooner than persons of average risk (22). Indications for CRC screening apply to patients of all ages. They include, but are not limited to, altered bowel habits, rectal bleeding, and long-term abdominal pain (18). The American Cancer Society recommends a variety of screening methods for CRC that include fecal occult blood testing, flexible sigmoidoscopy, double-contrast barium enema, and optical colonoscopy (23).

An example of a screening recommendation for an average-risk person may be an optical colonoscopy every 10 years. Optical colonoscopy is currently the standard, most accurate procedure available for the detection of CRC. Limitations and drawbacks of optical colonoscopy include the need for a trained endoscopist, need for patient sedation, risk of perforation, need for bowel preparation, and failed completion of the procedure in about 10% of patients (13,21,24). CTC is not currently an endorsed screening method (25); however, CTC seems to be a promising screening method that may reduce or eliminate many of the problems associated with optical colonoscopy.

PATIENT PREPARATION FOR CTC

A standard preparation for a CTC may begin several days before the procedure. One to two days before the procedure, the patient's diet is restricted to clear liquids or low-fiber foods. The day before and the day of the procedure, the patient must drink some form of laxative. The laxative may be a phospho-soda or polyethylene glycol (PEG) electrolyte solution (26).

Immediately before the CT scan, the colon must be insufflated. Insufflating the colon with air or carbon dioxide (CO_2) allows for polyps to be seen on a CT scan because of the large contrast difference between air and soft tissue. The use of CO_2 to insufflate the colon has been shown to decrease immediate and delayed pain compared to those who receive air (27,28). CO_2 is more easily absorbed through the wall of the colon and therefore causes less cramping and discomfort. However, because CO_2 is absorbed into the body, additional insufflations or an automated pressure-sensing machine may be necessary to maintain the proper colonic distension (27).

SCANNING TECHNIQUE

From 1996 to 2004, the use of multi-detector scanners increased significantly (29). Higher sensitivity values have been achieved by radiologists when reading CT scans done by a multi-detector scanner versus a single-detector scanner (30). Multi-detector scanners are less dose-efficient than single-detector scanners due to the penumbra effect; however, because of the decrease in tube current and collimation that has occurred due to efforts to optimize the method of screening, the effective dose of radiation has remained relatively constant over the last decade (29).

Two-Scan Protocol

Currently, patients are scanned in two positions: supine and prone. Altering the patient's position helps air to shift and insufflate collapsed regions of the colon and allows for fluid to move and expose hidden polyps. Having a prone scan in addition to a supine scan has been shown to increase the sensitivity of detecting polyps by 13%–15% (31), but have little effect on or decrease specificity (31,32).

Slice-thickness

Polyps that are smaller than or equal to the CT slice thickness may be affected by partial volume averaging and may not be detected by the radiologist (33). Large slice thicknesses result in broadening of polyp edges, which cause the image to appear blurred (34). A review of over 30 CTC studies revealed that for every 1-mm increase in slice thickness, the sensitivity decreases by 5% (30). It has also been shown that the specificity decreases as slice thickness increases (35).

Optimal Settings

The optimal settings for CTC aim to decrease scanning time, decrease radiation exposure, and increase image quality. A high pitch value decreases the scanning time, a lower tube current reduces the radiation exposure, and a smaller slice thickness improves image quality. A study found that polyps 5-mm or larger in size could be detected with 1.25-mm collimation, pitch of 6, and 60 mA tube current (36). The same study found that the optimal settings for detecting polyps less than 5-mm in size were 1.25-mm collimation, pitch of 3, and 150mA tube current (36). Studies are also being conducted to reduce radiation exposure while still maintaining high sensitivity and specificity values (37). The results of these studies will be discussed later in this review.

CTC PERFORMANCE

Several studies have been conducted to determine the efficacy of CTC as a screening method for colon cancer. Unfortunately, the results of various studies have a wide range in sensitivity values for CTC. Several studies on 100 patients or more found that CTC has a per-polyp sensitivity value that was above 90% for polyps at least 10-mm in size (13,14,32,38–44). Other studies on 100 patients or more found that CTC has a per-polyp sensitivity value that ranged from 46.3% to 77.8% for polyps at least 10-mm in size (38,45–50). There are several factors that may contribute to the inconsistent results between CTC studies: different stool tagging and fluid opacification protocols were used or none were used at all, different display methods were used for interpretation, image processing techniques like electronic fluid cleansing were used in some studies and not in others, double readings were performed in some studies and not in others, multiple risk populations were used, and depending on the study, radiologists had varied experience and training with CTC.

Poor Results

In a study conducted by Rockey *et al.*, ground truth was established by segmental unblinding of the CTC results during optical colonoscopy (46). Segmental unblinding was conducted by revealing the results of the CTC after the gastroenterologist finished evaluating one section of the colon and then allowing reinspection of that section to locate potential optical colonoscopy false negatives. In this study, no stool tagging or fluid opacification was conducted. CTC readers had experience reading more than 50 CTC cases or were required to complete a CTC training module. Interpretation was done with 2-D viewing along with 3-D viewing available for areas of concern. Patients with a high likelihood of colon abnormalities were recruited for the study. A multi-detector CT scanner was used with a 2.5-mm collimation and 1-mm reconstruction interval. There were 614 patients that participated in all three screening methods. The per-polyp sensitivity values for polyps 10-mm or larger in size were 45% for air-contrast barium enema, 53% for CTC, and 98.7% for optical colonoscopy. Specificity was found to be high for all of the screening methods; in particular, CTC had a specificity of 96%. However, because the CTC procedure had sub-par sensitivity values, optical colonoscopy was determined to be the only reliable screening method in this study of high-risk participants.

Johnson *et al.* conducted a study on 703 asymptomatic patients with a greater-than-average risk for CRC (47). The optical colonoscopy was videotaped and viewed in retrospect to establish the reference standard. The results of this study found that having two radiologists interpret each case improved the average detection rate for colorectal polyps. In this study, no stool tagging or fluid opacification was performed. The CT scans were interpreted in 2-D with 3-D viewing available in areas of concern. A single-slice helical CT scanner was used with a 5-mm collimation and 3-mm reconstruction interval. All three radiologists had experience with at least 150 cases. When each radiologist interpreted the case alone, the average detection rate was 46% (32%, 34%, and 73% for each individual radiologist) for polyps at least 10-mm in size. However, when interpretations by two randomly-assigned radiologists were combined, a detection rate of 64% was achieved. Specificity values ranged from 95%-98% for polyps at least 10-mm in size. The authors of this study concluded that in a low prevalence cohort, polyp detection rates were much lower than those of optical colonoscopy. Johnson *et al.* speculated that reader fatigue may have occurred because of the low-prevalence of polyps in the screened population. The authors also indicated that further investigation is justified due to the high interobserver variability.

Promising Results

Alternatively, a study conducted by Pickhardt *et al.* found that CTC was an effective screening method that compared favorably to optical colonoscopy on average-risk, asymptomatic adults

(13). There were two main factors that differentiated this study from the studies conducted by Rockey *et al.* and Johnson *et al.*: the radiologists utilized 3-D endoluminal displays to detect polyps during the CTC procedure and stool tagging and fluid opacification were conducted along with electronic fluid cleansing. Segmental unblinding of the CTC results to the endoscopists during optical colonoscopy established the reference standard. Multi-detector CT scanners were used with a 1.25 to 2.5-mm collimation and a 1-mm reconstruction interval. For adenomatous polyps of at least 8-mm in size, the per-patient sensitivity of CTC and optical colonoscopy was 93.9% and 91.5%, respectively. The per-patient specificity of CTC was 92.2% for the adenomas greater than 8-mm in size. Only two cancers were found in the pool of 1233 subjects. Optical colonoscopy detected one of these malignant polyps, but missed the second because it was located behind a haustral fold, which is an inherent blind spot for optical colonoscopy. CTC found both of these cancers and led to the detection of the second cancer that would have otherwise been overlooked. The interpretation was done at 3 centers by a total of six radiologists who had received training on a minimum of 25 CTC studies. The performance across centers had a low variability; each center ranged from 92.9%-94.9% in sensitivity and 91%-93.8% in specificity. The authors of this study concluded that CTC along with 3-D endoluminal displays is an acceptable screening method for CRC in asymptomatic average-risk adults. The Pickhardt trial, although multicenter, maintained a uniformity of training and reading technique that allowed for excellent results.

CTC Detection of Flat Lesions

The prevalence and clinical significance of flat lesions in western populations is a subject that has been highly debated by gastroenterologists (51). Scientists in Japan have developed advanced methods (e.g. chromoscopy with magnification) to detect small, flat lesions during optical colonoscopy, but many believe that widespread use of these techniques are not necessary in the western world.

Pickhardt *et al.* conducted a study to determine the clinical significance of flat polyps and investigate the performance of CTC on flat polyps in a western population (51). Stool tagging and electronic fluid subtraction techniques were used along with a 3-D endoluminal fly-through as the primary method of polyp detection. The study found 344 polyps that were 6-mm or greater in 1,233 asymptomatic adults. Of those polyps, 17% were classified as flat. Of the flat polyps, 49.2% were adenomatous. CTC detected 82.8% of flat adenomas and 80% of all flat polyps 6-mm or greater in size. In comparison, this study found the CTC detection sensitivities for sessile or pedunculated polyps at least 6-mm in size were 86.2% and 81%, respectively. Thus, the authors of the study concluded that CTC performance on flat lesions was comparable to CTC performance on polypoid lesions. While the CTC results were promising when compared to the traditional western optical colonoscopy procedures, advanced techniques to detect small flat polyps were not used; therefore, clinically significant small flat adenomas may have been missed by both optical colonoscopy and CTC.

The detection of flat lesions over 10-mm in size is especially important because they are nearly twice as likely to be cancerous than a polypoid lesion of similar size (18). A study conducted by Fidler *et al.* found CTC sensitivity was 68% for flat polyps 4-mm or greater and 100% for flat adenomas 5-mm or greater when the scans were viewed by two radiologists (52). A study done by Park *et al.* found that a CTC with oral contrast only detected flat polyps that were at least 2-mm in height and 7-mm in diameter (53).

Radiologist Experience & Training

A study conducted by Cotton *et al.* showed that accuracy varied considerably between screening centers (45). The radiologists at each of the nine centers were required to have

minimal experience; only ten CTC interpretations were necessary. In addition, only one of the nine centers had substantial prior experience with CTC and had a sensitivity of 82%, while all of the other centers had a sensitivity of only 24%. These results indicate that experience with CTC increases the sensitivity of radiologist interpretations.

Alternatively, in the study conducted by Rockey *et al.*, half of the radiologists had read over 50 CTC cases while the other half were required to complete a CTC training module (46). The results of the study showed that the less experienced radiologists detected 23% more polyps that were greater than 10-mm in size than the more experienced radiologists. These results suggest that experience with CTC does not indicate that proper training has been completed; perhaps the training that the radiologists initially received was not sufficient or refresher training is needed to maintain a high level of accuracy.

3-D vs. 2-D Interpretation

Three-dimensional imaging often results in higher sensitivities and specificities than 2-D imaging alone; however, 3-D imaging without 2-D imaging does not allow for the extra-colonic organs to be seen (54), and may result in false positives due to residual stool, diverticuli, the ileocecal valve, and extra-colonic organs pressing up against the colon.

A study conducted by Cotton *et al.* found that the sensitivity of CTC increased when a 3-D fly-through was provided instead of 2-D CT scans (45). There was a 12% and 17% increase in sensitivities for polyps greater than 6-mm and 10-mm, respectively, when a 3-D view was provided. In this study, no stool tagging or fluid opacification were used. The study conducted by Cotton *et al.* suggests that the sensitivity of the CTC procedure is highly linked to the center's use of the 3-D fly-through imaging.

Shi *et al.* conducted a study to determine if ability of radiologists to classify polyp candidates which were identified by a CAD (computer-aided detection) system as false positives or true positives was affected by the reading mode. Shi *et al.* also investigated which features affected the acceptance of a true positive and the rejection of a false positive. The study found that polyp height was associated with a higher reader confidence level with 2-D viewing than with combined 2-D and 3-D viewing; however, combined 2-D and 3-D viewing significantly helped readers to correctly classify short lesions. Supplementing 3-D viewing in addition to the 2-D viewing helped to classify thickened haustral folds as false positive polyps. Thus, combined 2-D and 3-D viewing modes may be beneficial for reader confidence as well as increased accuracy in properly classifying polyp candidates.

Despite these studies, the differences in accuracy of image interpretation among 2-D viewing alone, 3-D viewing alone, and 2-D and 3-D viewing combined has not been clearly delineated in the literature. Nevertheless, there is a consensus that combined 2-D and 3-D viewing is the most accurate way of measuring and detecting polyps. Whether 2-D or 3-D viewing is the primary interpretation method, with the other as a backup for problem solving, depends to a great extent on the capabilities of existing image interpretation software. For example, software that maintains accuracy and promotes radiologist efficiency by reducing interpretation time is likely to be desirable in clinical practice. These software factors will strongly influence a radiologist's choice of primary 2-D versus primary 3-D image interpretation.

A special feature in some 3-D imaging software is a translucency rendering technique that has been shown to increase specificity and decrease interpretation time (55). Translucency rendering decreases the time that the radiologist must spend referencing the 2-D images because the attenuation beneath the surface can be viewed. Thus, when stool is tagged it can be distinguished from that of a polyp. With this tool, interpretation time can be less than 15

minutes (55). The 3-D fly-through technology has been shown to have a high sensitivity, but has not been used in many studies (30).

Double Reading

Studies have shown that having two radiologists interpret the CT scans improves the sensitivity for detecting polyps (47). Double-reading may help the overall sensitivity of a reading; however, having radiologists perform double-readings is not an efficient or cost-effective solution to increase sensitivity in the clinic. Therefore, it has been suggested that trained non-radiologists perform a second reading to improve the sensitivity for each case. Bodily *et al.* found that non-radiologist performance was comparable to that of a radiologist and may play a part in quality control of the CT scan interpretation (56).

Cancer Staging

CTC allows for cancer staging, but has a few limitations. CTC has a limited ability to distinguish between T stages because it cannot distinguish the multiple layers of the colon wall (57). CTC also has difficulty in detecting microscopic tumor involvement (57). Studies have been conducted to determine the effectiveness of CTC as a cancer staging technique (43,58). A study conducted by Laghi *et al.* found that CTC allowed for correct staging of 96.9% of all tumors (43). In addition, Filippone *et al.* found that the overall accuracy of T staging was 73% with transverse CT images and 83% when transverse CT images and multiplanar reformations were evaluated (58). The overall accuracy of N staging was 59% with transverse images and 80% when multiplanar reformations were also evaluated. The study concluded that CTC is an accurate technique for staging colorectal carcinomas. More data is needed to confirm these promising results.

Pre-operative Technique

CTC can also be used as a pre-operative procedure to detect synchronous carcinomas in patients where CRC is known. It has been found that 1.5%-9.0% of patients with a colorectal carcinoma have a second carcinoma (59). In addition, 27%-55% of patients with a carcinoma have additional adenomatous polyps. Surgeries to remove large carcinomas can be dangerous; open transabdominal colotomy and polypectomy have a 5% mortality rate, with a 14%-20% complication rate (60–62). Thus, the pre-operative screening process is important to ensure that each of the carcinomas and potentially dangerous adenomas are detected before surgery.

Future Studies

Despite the large number of clinical evaluations of CTC, most have been relatively small single-center studies. Some of the large multi-center trials have been done with out-of-date technology or significant methodologic weaknesses. These problems have been recognized and consequently a number of high-impact clinical trials are underway. These studies are likely to be more reliable and report more consistent data.

The American College of Radiology Imaging Network (ACRIN) is conducting a national trial to validate CTC as a screening method for CRC in a screening population (63). The clinical trial is taking place at 15 hospitals around America. Data accrual will end when the participant count reaches 2,607 or on December 31, 2006. The study will compare CTC performance to colonoscopy, optimize the CTC procedure, optimize the detection of lesions by studying morphology, and observe and evaluate patient preference and cost.

The British Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) 1 is conducting a multi-center CTC trial (64). The goal of the trials is to assess the sensitivity

and specificity of CTC in detecting advanced adenomas and carcinomas against the performance of optical colonoscopy and barium enema. The study is aiming to screen 4,500 patients who are 55 years or older at 15 centers. The results are expected in 2007.

A multicenter CTC trial, called IMPACT, is also being conducted in Italy that is associated with the Istituto per la Cura e la Ricerca sul Cancro (IRCC) in Candiolo and the University of Turin (64). The goal of the study is to assess the sensitivity and specificity of CTC for advanced adenomas and carcinomas in subjects with an increased risk for CRC. Data will be collected concerning the optical colonoscopy miss rate, costs, interobserver variability, 2-D versus 3-D interpretation, patient acceptance, and the prevalence and impact of extracolonic findings. As of late 2005, 200 subjects had been recruited to participate in the study.

COMPUTER-AIDED DETECTION

CTC seems to be a promising diagnostic tool for detecting colorectal polyps and preventing colon cancer; however, CTC requires a trained radiologist to do a lengthy interpretation of the CT images, which is both costly and prone to human error (65). Challenges associated with CTC include a lack of consistency in results between radiologists and difficulty detecting smaller polyps (6-mm to 9-mm). Proposed solutions to these obstacles include double readings or a computer-aided detection (CAD) system. CAD has the potential to decrease the time needed to complete an interpretation and increase the accuracy of the diagnosis.

CAD Objective

The objective of the CAD system is to identify and mark suspicious lesions on the CT scan. Radiologists can use the results from the CAD system along with 3-D or 2-D CT images to make a final diagnosis. Radiologists have been found to detect carcinomas with a high sensitivity during CTC because carcinomas tend to be large in size (usually greater than 10-mm). Focus has been placed on detecting precancerous polyps 6-mm and larger with CAD because these polyps are more difficult for the radiologist to detect due to their small size.

CAD Systems

There are several computer-aided polyp detection systems under development (65). Each uses different algorithms to identify polyps (66–70). One classifies a surface based on its local shape using a geometric curvature parameter (69). Principal (minimum and maximum) curvatures of the colonic surface are assessed to distinguish colorectal polyps from the haustral folds and other normal colonic structures. Textural features and attenuation are examples of other useful features that can be incorporated into a CAD system.

CAD Study Results

Since CAD is still under intensive development, most studies of CAD to-date have reported its performance in the laboratory setting rather than in the radiology reading room. The largest such study to-date was in 1186 patients for which the performance of CAD alone was compared to optical colonoscopy (71). The patient data was randomly divided into a training set of 394 patients and test set of 792 patients for CAD to analyze. For polyps 10-mm or greater in size, the sensitivity of CAD on the test set was 89.3%, while the sensitivity of optical colonoscopy was only 85.7%. Similarly, there were two carcinomas found in the study; the detection rate of carcinomas was 100% for CAD and 50% for optical colonoscopy. Optical colonoscopy performed significantly better than CAD for polyps 6-mm or greater in size (87.2% compared to 66.1%) but comparably for adenomas 8-mm or greater in size (89.6% compared to 85.4%). CAD also had a false-positive rate of 7.9, 6.7, and 2.1 polyps for polyps that were at least 6-mm, 8-mm, and 10-mm, respectively. There was a false positive rate of 0.7 carcinomas per

patient. The authors of this study concluded that CTC with computer-aided detection had similar results compared to optical colonoscopy for polyps that are 8-mm or larger in size.

Future Improvements in CAD

Improvements in sensitivity and specificity are anticipated as new methods to identify polyps are being implemented. Optimization must be achieved between the two conflicting measurements: identifying all true positives and eliminating all false positives. Future developments in the CAD system include improved filtering and smoothing techniques to allow the detection of small polyps, improved display techniques that allow for the reader to have an accurate idea of spatial location in the colon, and improved image processing techniques that diminish the negative effects that artifacts and stool can have on image quality.

Electronic Subtraction—Electronic stool and fluid subtraction allows for stool and fluid that has been treated with oral contrast (e.g. barium or iodine-based solutions or pills) to be removed from the processed CT images (65). With these image processing techniques, the computer-aided detection system can detect hidden polyps and eliminate false positives, which may lead to a more accurate CAD that does not require laxatives or a liquid diet.

Oral contrast may also play a role in helping CAD to identify pre-cancerous polyps. Barium oral contrast has been found to adhere to the surface of a large percentage of polyps (72). A large percentage, 46%, of polyps, that were not submerged in contrast, had contrast adhered to their surface in at least one view (prone/supine). It was also found that a larger percentage, 77%, of polyps with a villous component had contrast adhered to the surface (72). Polyps with a villous component have a greater chance of progressing into a carcinoma; therefore, if CAD is able to detect the polyps with adherent contrast, then the sensitivity for detecting pre-cancerous polyps may be improved.

Positioning Techniques—Some polyps are visible in only the supine or prone view. Radiologists can become fatigued and frustrated when searching through the supine and prone images to identify a single polyp on both scans. When trying to find the same polyp on the alternate view, a polyp can be incorrectly matched with a different polyp, which can lead to a false negative. Developing a positioning technique to identify longitudinal and circumferential positions in the colon may aid in matching polyps between supine and prone scans or between a current scan and a scan done years before.

Detection of anatomic landmarks in the colon can allow for registration of the supine and prone data sets (73). In one study, six anatomic landmarks were used; complete or partial correspondence occurred in 71% of 121 CTC cases. The false positive rate was reduced from 3.0 to 2.4 false positives per patient (19% reduction) when this method of registration was used in conjunction with a CAD system. No true positives were lost in the process.

A possible positioning technique that is being developed uses the three smooth muscle bands that run longitudinally along the colon wall, the teniae coli (74). Identification of the teniae coli can allow for a centerline to be computed and a circumferential position of the polyp in the colon to be identified. The centerline allows for the radiologist to know relatively how far along the colon the polyp is located, with some error due to possible stretching. A circumferential coordinate system can be established in reference to one of the teniae bands.

Future Studies

Many CAD systems have only been tested on small or biased data sets. The data sets may be based on a high-risk population, a ground truth that was poorly established by optical

colonoscopy, or different properties, like the use of oral contrast, that may decrease or increase the likelihood of polyp detection. A CTC CAD competition is planned for 2007 with a 200-patient dataset from the American College of Radiology Imaging Network (ACRIN). About a dozen research groups are expected to participate. Unifying the dataset that each CAD system is tested against will help identify which CAD algorithms are superior and should allow for progress in the field (75).

COMPLICATIONS

Complications associated with optical colonoscopy and CTC include negative reactions to laxatives and possible surgical complications associated with the insertion of the colonoscope, polypectomy, and insufflation of the colon.

Bowel Preparation Complications

While laxative-free CTC may be possible in the future, today bowel cleansing is still required for optimum CTC. Complications related to bowel preparations are rare. The two general classes of laxative solutions are polyethylene glycol (PEG) solutions and non-PEG solutions (magnesium citrate or sodium phosphate). These solutions can cause reactions in elderly patients or patients who have renal impairment, congestive heart failure, or severe electrolyte or fluid volume abnormalities (61). Sodium phosphate solutions are generally contra-indicated in patients with renal failure.

Perforation & Bleeding

In a study conducted on over 11,000 patients, the risk of perforation from a CTC procedure was 0.059% (76). In another study conducted on over 17,000 symptomatic patients, the risk of adverse events occurring related to the CTC procedure was 0.08%, where 0.053% was due to perforations (77). To compare, the rates of perforation and bleeding from optical colonoscopy with and without polypectomy are estimated to be 2.38% and 0.35%, respectively (78). Out of over 83,000 procedures, a death rate of 0.006% was reported for optical colonoscopy and sigmoidoscopy (61,79).

BENEFITS OF CTC THAT OVERCOME LIMITATIONS OF OPTICAL COLONOSCOPY

Limitations associated with optical colonoscopy include an inability to complete the procedure on all patients, a fraction of missed adenomas, and a risk of perforation and bleeding. Other inconveniences associated with optical colonoscopy include the necessity of harsh colonic cleansing and a high cost associated with the need for a trained endoscopist and sedation.

Missed Adenomas

Optical colonoscopy does not allow for bidirectional viewing, which can lead to missed adenomas during the procedure. Pickhardt *et al.* conducted a study where the results suggested that the majority, 14 out of 15, of 6-mm or greater non-rectal adenomas that are missed during optical colonoscopy are located on a fold. Furthermore, 71% of the missed polyps located on a fold were on the back of the fold, an inherent blind spot with the limited viewing capabilities of the colonoscope. Optical colonoscopy miss rates for adenomas at least 6-mm and 10-mm in size have been found to be 10%–19% and 6%–12%, respectively (80,81).

Unlike optical colonoscopy, CTC has the capability of viewing the entire surface of the colorectal wall. A CTC interpretation with a unidirectional retrograde 3-D fly-through often excludes at least 20% of the colorectal surface (82). A study was conducted to determine the

effect of bidirectional (retrograde and antegrade) interpretation on CTC results (83). When the unidirectional retrograde 3-D fly-through was viewed, the sensitivity was 78.1%. Alternatively, when the bidirectional 3-D fly-through was viewed, the sensitivity was 88.4%. A drawback to this increase in sensitivity is that the CTC interpretation time had a statistically significant increase; a unidirectional interpretation took 25 minutes and a bidirectional interpretation took 39 minutes (83).

Incompletion Rates

A study done by Dafnis *et al.* reported an inability to complete optical colonoscopy on 19% of 5,145 patients (84). Completion rates were found to be influenced by sex, age, indication, surgical history, and presence of diverticulosis (84). Other studies have reported lower incompletion rates (3%–10%) (42,85).

When an optical colonoscopy cannot be completed, CTC has been shown to allow examination of the area in 90% of the patients (86). A study on 34 patients with clinical suspicion of CRC and 20 patients without suspicion of CRC found that the incomplete optical colonoscopy had a sensitivity and specificity of 56% and 92%, respectively. After the incomplete colonoscopy, CTC was performed and resulted in 100% sensitivity and specificity for polyps 10-mm or greater and a sensitivity and specificity of 100% and 80%, respectively, for polyps 5 to 10-mm in size (87).

Extra-colonic Findings

One benefit of having a CTC rather than an optical colonoscopy is that a CTC also allows for imaging of other organs around the colon. Several studies have been conducted to determine the prevalence and clinical significance of extracolonic findings (13,88–90). In a study of 681 asymptomatic patients, extra-colonic findings during a CTC were classified as having a high, medium, or low clinical importance (89). Ten percent of patients had an extra-colonic finding of high importance (i.e. required surgery, medical intervention, or further investigation during the patient's visit), 27% of medium importance (i.e. required treatment at a later time), and 50% had findings of low importance (i.e. unlikely to require medical treatment such as diverticulosis and small hernias). Similar results have been found in another study where important extra-colonic findings were made in 11% of greater-than-average risk patients (90). In asymptomatic patients, one study showed potentially clinically significant extra-colonic findings in 4.5% of the patients (13).

PATIENT PREFERENCE

Several patient preference studies have shown that CTC is the preferred CRC screening method when compared to other screening methods (91–94). Preference levels for CTC over optical colonoscopy range from 41%–72%. From those same studies, only 11%-24% of patients preferred optical colonoscopy, while the remaining patients had no opinion.

The three most common deterrents that patients expressed about receiving optical colonoscopy was bowel preparation, embarrassment, and fear of discomfort (95). Patients have expressed negative reviews with regard to bowel preparation that is currently necessary for both optical colonoscopy and CTC (21,96). After one colonoscopy and CTC, 43% of patients were less willing to have either test again because of the bowel preparation (96).

Patient acceptance of CTC is thought to be greatly increased if laxatives were to be eliminated from the bowel preparation. Callstrom *et al.* conducted a small study to determine if oral contrast alone was a sufficient bowel preparation for the detection of polyps during a CTC (97). It was determined that the average stool labeling score increased as the oral contrast

dosage increased; specifically, with seven doses of dilute barium over a 48 hour time period, the average stool labeling score was 88%. The sensitivities were found to be similar to that of the prepared colon. With optimization of the dosage, timing, and contrast agent there is promise in developing a reliable preparation that does not involve laxatives or fasting. Larger studies must also be conducted.

REGULATORY ISSUES

Regulatory concerns associated with CTC include a lack of consistency in study results and the radiation dosage that the patients will receive. In addition, effective regulations may be needed on communication and quality control of data to analyze properly and draw correct conclusions from various CTC studies.

Consistency

Inconsistent results during clinical studies may be hindering the endorsement of CTC as a CRC screening method. Factors such as radiologist experience and training, scanning parameters, and visualization methods have varied widely depending on the study. If factors are optimized and consistent results are obtained over large population samples then endorsement in the United States may soon follow. In England, Wales, and Scotland, The National Institute for Clinical Excellence (NICE) has issued full guidance for CTC as a screening method for CRC (98).

If radiologists continue to have inconsistent results regardless of training, CAD may be a possible solution that will allow for the endorsement of CTC as a reliable screening method in the United States. Currently, a few CAD-like systems for detecting CRC and colonic polyps have been granted marketing clearance or approval by the United States FDA. However, these systems are not yet widely utilized.

The idea of a computer as a first-reader in detecting CRC is an exciting possibility, but would be a major departure from current practice and would lead to significant additional regulatory review. A study conducted on the performance of computer-diagnosis indicated that computer-diagnosis had a similar sensitivity when compared to a radiologist interpreting the CTC scans without CAD (99); however, the sensitivity of the CTC reading made by radiologists was only 63% for polyps greater than 10-mm in size. Thus, computer diagnosis is currently a concurrent or secondary reader that aims to improve, not replace, the trained eye of the radiologist.

Radiation Exposure

Another regulatory concern with CTC is the radiation exposure that the patients receive. For CTC, optimization between radiation dosage and image quality is important for the patients' long-term cancer-risk (100). Screening of the colon can be done with a relatively low dose of radiation and can limit the radiation exposure to the abdomen. If the CT scans are performed with a low dosage, patients risks are small (101). The cost-benefit ratio of finding a carcinoma while receiving a small dose of radiation may be favorable for patients with an average or above-average risk for CRC.

In 2004, the effective radiation dosage ranged from 1.2–11.7 mSv with a median of 5.1 mSv per position (10.2 mSv per CTC exam) (29). The International Commission on Radiological Protection (ICRP) estimates the risk of developing serious cancer due to ionizing radiation exposure at the age of 50 years to be 2.5% per Sv (102). If the risk is linearly proportional to dose (an uncertain assumption), then the risk of a 50 year old developing cancer from a single CT screening at 10.2 mSv is 0.026%. As age increases, the risk of developing cancer decreases;

it is estimated that a 70 year old has half the chance of a 50 year old of developing cancer due to the same dose of radiation.

Studies have found that radiation dosage can be considerably decreased if polyps only larger than 5-mm are detected (103,104). A recent study in 2005 reported success in the detection of polyps at least 6-mm in size at 1.61 mSv (105). Similarly, other studies have found values of 1.7 mSv to 3.6 mSv to be a sufficient radiation dosage for the detection of colorectal polyps (41,102). As a result, the risk of developing cancer from screening may decrease.

However, using a relatively high radiation dosage is necessary to find clinically important abnormalities outside of the colon during a CTC. For example, since the contrast between a lesion and adjacent normal tissue in extra-colonic organs is poor when the ionizing radiation dose is low, a high radiation dosage may be favorable (89). In addition, a low dose of radiation may not allow for the use of stool tagging. For laxative-free CTC, barium and iodine containing oral contrast agents tend to increase noise and streak artifacts, which may inhibit the use of low-dose CT scans when oral contrast is used (102). Thus, laxatives may be a requirement if a low-dose of radiation is used.

Magnetic resonance colonography (MRC) is a promising screening method for colon cancer because, unlike CTC, MRI does not emit ionizing radiation. MRC has had similar accuracy results to CTC, but the studies have been fewer in number and smaller in sample size. In a study conducted by Luboldt et al., MRC was evaluated against optical colonoscopy. Of 132 symptomatic patients, the MRC sensitivity and specificity values for polyps at least 6-mm in size were 93% and 99%, respectively (106). Similarly, a study was conducted by Hartmann et al. on 92 women; forty-nine of those women had a combined total of 107 polyps (82 adenomas, 25 hyperplastic polyps) and 7 carcinomas (107). The MRC per-patient sensitivity and specificity for lesions from 6-mm to 9-mm in size were 84% and 99%, respectively. Similarly, the per-patient sensitivity and specificity for lesions at least 10-mm were 100%. All seven carcinomas were at least 10-mm in diameter and were detected with MRC. The authors of the study concluded that MRC is a promising method to detect polyps at least 5-mm in size.

Communication

The FDA began enforcing a regulatory act, called the Mammography Quality Standards Act (MQSA) in 1995, to ensure that women are receiving quality exams to screen for breast cancer (108). Similar regulatory issues may be needed for CTC. In 2005, Zalis *et al.* proposed the use of a CT Colonography Reporting and Data System (C-RADS) to facilitate communication of CTC results (109). The C-RADS consists of three distinct parts: the first suggests methods, terms, and ranges that are useful for reporting size, morphology, and location of the lesions; the second provides a classification scheme and also suggests follow-up procedures; and the third describes a method of reporting extra-colonic findings. Using a set system to communicate results between doctors may help to unify data collected in studies and therefore increase understanding and maximize the potential of CTC.

ECONOMIC ISSUES

The cost to the patient of CRC screening by CTC versus optical colonoscopy directly affects patient compliance and ultimately may determine the success of CTC.

CTC vs. OC

A cost-effectiveness study was conducted on a hypothetical 100,000 subject pool of 50-year-old patients. The baseline cost of the procedures were estimated: CTC costs $478, MRC costs $579, optical colonoscopy costs $728, and optical colonoscopy plus polypectomy costs $1139

(110). If polyps of concern are found during the CTC then an optical colonoscopy and polypectomy must be performed. Based on the Markov process, CTC was found to cost $24,586 per life-year saved and optical colonoscopy was found to cost $20,930 per life-year saved. It was determined that for CTC to be cost effective, one of two conditions must be met: patient compliance rates for CTC must be 15%-20% higher than patient compliance rates for optical colonoscopy or procedural costs of CTC must be less than half (46%) of colonoscopy costs (110).

While it is unclear whether the cost of CTC may be markedly reduced, patient preference sways heavily toward CTC over optical colonoscopy, even without the elimination of the bowel preparation. In four studies, preference levels for CTC ranged from 41–71% while preference levels for optical colonoscopy ranged from 11%–24% (91–94). If these differences in patient preference can be leveraged to improve patient compliance, then it may be possible to achieve a 15%–20% increase in patient compliance to CTC over optical colonoscopy. In addition, promising results have been found in studies that have eliminated the bowel preparation requirement for CTC (97,111). If the bowel preparation were to be eliminated from the CTC procedure, then an increase of at least 15–20% in CTC patient preference over optical colonoscopy patient preference is very likely.

Screening with CTC

There are differing opinions about the use of CTC as a screening method on the population as a whole. Using CTC to screen a population may be cost-effective if the ratio of high-risk to average-risk patients decreases. In this instance, CTC may have an acceptable cost-efficacy ratio to be approved as a screening method for the overall population. Alternatively, using CTC on high-risk patients may not be cost-effective. It may be wise to advise high-risk patients to bypass CTC and receive an optical colonoscopy as their first screening method. More studies are needed to determine the most effective screening method for different risk populations (112).

An advantage of CTC as a screening method for the whole population is the benefit of identification of potentially serious extra-colonic abnormalities. Studies have found that the average cost of radiologic follow-up on extra-colonic findings adds $28–$34 to the cost of a CTC study (89,113). Considering the potential benefit to a significant percentage (4.5%–37%) of the patient population (13,89,90), this added cost of evaluating extra-colonic findings has been determined to be relatively low.

Some gastroenterologists have expressed financial concerns about CTC becoming popular and thereby reducing the number of optical colonoscopy procedures. If CTC becomes the primary CRC screening method, it is predicted that there will be an 8.8% or 22.2% reduction in optical colonoscopies if the size threshold for a polypectomy is at least 6-mm or 10-mm, respectively (114). These estimates are based on a patient compliance rate for CTC of 55%, a 15% increase from the current compliance rate with optical colonoscopy. If bowel preparation were to be eliminated from CTC, the patient compliance rate is estimated to increase significantly (114).

Reimbursement

The acceptance of CTC as a CRC screening method by insurance agencies is essential for acceptance of CTC by the population as a whole. Currently, Medicare does not cover CTC as a CRC screening method (115). Diagnostic CTC depends on the local coverage decision made by each state. Diagnostic CTC reimbursement can be rejected or may provide limited or total coverage for those patients who had an incomplete optical colonoscopy. Private insurance

companies have varying policies ranging from no coverage to full coverage of CTC as a screening method.

Oddly, double contrast barium enema (DCBE), a CRC screening method, is covered by Medicare, but many studies have shown DCBE to have lower sensitivity values than CTC (46,116). However, DCBE is much less expensive than optical colonoscopy (117) and CTC. The added expense and the lack of acceptance of CTC by organizations such as the American Cancer Society contribute to insurance companies' acceptance of DCBE and rejection of CTC as a CRC screening method.

FUTURE OF CTC

Currently, CTC is expensive to the patient and not practiced regularly in most American imaging centers. Patients prefer CTC over optical colonoscopy, but for Americans to embrace CTC as their preferred CRC screening method, insurance companies must begin reimbursing for CTC. If the cathartic part of the bowel preparation can be eliminated, it is likely that patient compliance rates to CTC will increase leading to reduced cost per life year saved and greater economic benefit to society. CTC is a low-risk CRC screening method; the radiation dosage and risk of perforation are minimal when compared to the potential benefits that CTC provides.

Some studies have shown that CTC has the potential to perform well when compared to other screening methods. Still, more studies must be conducted for CTC to be an endorsed CRC screening method in the United States. The results of several large clinical trials currently underway are eagerly anticipated. Previous studies have shown that combined 2-D and 3-D displays and adequately trained readers are essential to the success of CTC as a reliable screening method. Further studies must be conducted on varying risk populations to establish the proper screening recommendations for the population as a whole. In addition, maintaining uniformity in technology and reading technique within future trials and ultimately in the community radiology setting may allow for more accurate and consistent results.

With sensitivities approaching 90%, CAD shows promise in improving the sensitivity of polyp detection beyond the capability of a radiologist alone. CAD may enable CTC to overcome large barriers that CTC alone would potentially face in the clinical setting. A good CAD system may reduce the dependency that CTC has on an experienced, well-trained radiologist. In addition, CAD may greatly reduce the amount of time a radiologist needs to spend on each CTC case, thereby making CTC more cost-effective, as well as reduce the number of significant polyps missed during a CTC. The results of future CTC and CAD studies may provide the necessary foundation for the acceptance of CTC as a consistent and reliable screening method for CRC.

Acknowledgements

We thank Andrew Dwyer, M.D. for critical review of the manuscript. This work was supported by the Intramural Research Program of the N.I.H. Clinical Center.

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