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Clinical and Radiological Considerations for Incorporating Computed Tomographic Colonography into Colorectal Cancer Screening Programs

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Abstract

Colorectal cancer is the third most common type of cancer and the second leading cause of cancer death in the United States. Clinical evidence amassed over the last several decades indicates that routine screening, compared to no screening, detects the disease at an earlier stage, and reduces the incidence of colorectal cancer by interrupting the adenoma-to-carcinoma sequence in colon polyps through colonoscopy-guided polypectomy and thus reduces mortality. Guidelines for screening include fecal occult blood testing, sigmoidoscopy, colonoscopy and – most recently – computed tomographic colonography. This review discusses each modality and the current recommendations and state of the art for colorectal cancer screening. Properly implemented in a multi-modality disease prevention and screening setting, computed tomographic colonography provides an appealing alternative to traditional optical colonoscopy for screening in populations unwilling or unable to undergo colonoscopy, thus potentially increasing screening rates and reducing colorectal cancer incidence and mortality.

Keywords: Colorectal Cancer (CRC); Computed Tomographic Colonography (CTC); Optical Colonoscopy (OC)

Introduction

Colorectal Cancer (CRC) is the third most common type of cancer and the second leading cause of cancer death in the United States [1]. In 2011, an estimated 141,000 cases of colon and rectal cancer and 49,000 deaths are expected, accounting for 9% of all cancer deaths in the U.S. Over the last two decades there has been a decline in CRC cancer rates of approximately 2.8% per year (in males) and 2.7% per year (in females) which reflects improvement in early detection and treatment. Clinical evidence amassed over the last several decades indicates that routine CRC screening, compared to no screening, detects CRC at an earlier stage, and reduces the incidence of CRC by interrupting the adenoma-to-carcinoma sequence in colon polyps through colonoscopy-guided polypectomy and thus reduces CRC mortality. When CRC is detected in an early, localized stage, the five year survival rate is 90%. However, only 39% of all CRC is diagnosed at this stage, in part due to the underuse of screening [1]. After CRC has spread regionally to involve adjacent organs or lymph nodes, the five year survival rate decreases to 70%; when the disease has spread to distant organs, the five year survival rate is only 12%. Interestingly, in contrast to the overall CRC incidence decline, among adults younger than 50 years, for whom screening is not recommended for those at average risk, CRC incidence rates have been increasing by 1.6% per year since 1998 [1].

The U.S. Preventive Services Task Force (USPTF) recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years [2]. Recently, Computed Tomographic Colonography (CTC) has been evaluated for its potential in CRC screening.

Screening for CRC

Prior to the late 1960's, barium enema was the primary means of evaluating the entire colonic luminal surface. Rigid sigmoidoscopy was used for removal of distal polyps and surgery for more proximal larger lesions, usually those greater than 2 cm diameter. The first colonoscopic polypectomy was performed in 1969; thereafter, the rapid development of flexible colonoscopes from 1970-90 made it possible to directly examine the entire colonic mucosal surface and to safely remove polyps without opening the abdomen [3]. With the realization that most colon cancers develop from adenomatous colon polyps [4], effective preventive strategies require both accurate detection and a means for safe, efficient polyp removal. Although Double Contrast Barium Enema (DCBE) and sigmoidoscopy are established methods for polyp detection, DCBE provides no means for polyp removal and misses over half of polyps, one cm or greater [5]. Because sigmoidoscopy views only the left side of the colon, it is estimated to miss half of all advanced neoplastic disease [6]. Thus, while CRC screening guidelines include fecal occult blood testing, fecal immunochemical testing, flexible sigmoidoscopy, colonoscopy, barium enema and CTC, there has been an understandable shift towards Optical Colonoscopy (OC) as the most commonly recommended screening test for CRC and the standard for surveillance of patients at high risk for CRC [7-11]. A recent report from the 2006-2007 National Survey of Primary Care Physicians Recommendations and Practices for Cancer Screening shows that in the year 2000, fecal occult blood and flexible sigmoidoscopy were the most commonly recommended CRC screening tests, but by 2007 these were supplanted by OC [12].

Standard Optical Colonoscopy (OC)

Most colon cancers are thought to arise from adenomatous polyps which over a period of years evolve into true malignancies [4]. Thus, detecting and removing such polyps prior to their progression to frank malignancy should reduce cancer occurrence. Though there are no randomized controlled studies showing that colonoscopy reduces the

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incidence of colon cancer, strong evidence for the effectiveness of OC in preventing cancer was reported in the National Polyp Study [13]. In this study, 1418 patients were followed for an average of 5.9 years after the removal of one or more adenomas by colonoscopy. Comparing the incidence of CRC in the study patients with rates of CRC in three index groups, there was a 76% to 90% reduction in CRC [13]. Another large case-control study showed similar reduction of CRC (66%) in patients who had colonoscopy in the preceding ten years [14]. Thus, with acceptable procedure times, complication rates, and the ability to find and remove polyps, it appears that OC offers an effective means for interrupting the adenoma-to-carcinoma evolution of polyps and decreases the incidence of CRC.

Flexible fiberoptic colonoscopy or Optical Colonoscopy (OC) has evolved to a routine 20-30 minute procedure. The test requires a pre-procedure preparation consisting of low residue foods and colon cleansing usually with oral, large-volume polyethylene glycol lavage the day prior to the examination [15]. Intravenous sedation, vital sign monitoring, and a 2-3 hour post-procedure recovery are also required. Though OC is considered by most to be the gold standard for viewing the colonic surface, it has limitations. In the largest studies of patients referred for a wide range of suspected colonic problems, failure to view the entire colon occurs in 3-9% and 3% of screening examinations [16-21].

OC complications consist mainly of perforation, bleeding, and cardiovascular events (Table 1). Rates vary depending on the population studied. Studies of screening OC in asymptomatic patients report major complications in 0.2- 0.3% [22,23]. A large retrospective study of non-screening colonoscopies found an overall incidence of complications of 0.5% with 0.08% in patients without biopsy or polypectomy and 0.7% in patients with biopsy or polypectomy [24]. In a prospective study of surveillance and screening colonoscopies, the pooled incidence of angina, myocardial infarction stroke or transient ischemic attack was 0.14% [25]. The rates of perforation in a large study of screening colonoscopies was 0.01% [26] and a study of colonoscopies done in ambulatory endoscopy centers in a mixed population a showed perforation rate of 0.03% [27]. While some studies have found no difference in perforations rates with or without polypectomy [27], when studied in some detail, most authors feel that perforation rates increase with polypectomy as reported in the study by Levin et al. [24] who found an overall perforation rate of 0.09% with 0.06% in patients without and 0.11% in patients with biopsy or polypectomy. As for bleeding, a large study of Medicare patients identified significant bleeding in 0.21% of patients having screening OC procedures and 0.87% of patients with polypectomy [28], while Levin found bleeding occurred in 0.48%, all of which had biopsy or polyp removal [24], but no bleeding in patients without biopsy or polypectomy. Death rates for all causes within 30 days have been noted as 0.07% but 0.007% when reported as specifically related to OC [23].

Advances in optical colonoscopy techniques

Factors such colon tortuosity, diverticular disease, observer inexperience and haste, may limit visualization of the entire colon mucosal surface by OC resulting in adenoma miss rates as high as 15-32% [29]. Of particular concern are small or flat lesions which in some studies show prevalence of up to 9% and are suspected of having higher predilection for harboring malignancy [30,31]. For this reason, endoscope makers have developed high-definition optics to improve the operator's ability to detect subtle mucosal contour changes. To date, such scopes have not consistently proven to be superior to standard equipment, though there is some evidence that they help in detecting small (1-5 mm) adenomas [29,32].

Chromoendoscopy is a technique of colonoscopically inspecting the colonic mucosa after staining it with dyes such as indigo carmine or methylene blue. Studies using this technique to look for subtle contour changes demonstrate improved rates of adenoma detection [33]. Chromoendoscopy has been combined with improvements in optics such as imaging magnification to observe staining patterns for predicting tissue malignant potential. A randomized, prospective trial of 660 patients comparing this high-definition chromoendoscopy and standard OC showed that chromoendoscopy improved sensitivity for colorectal lesions (both neoplastic and non-neoplastic) of 6-10 mm from 90% to 97% and specificity from 61% to 100% [34]. Though chromoendoscopy has not come into general use because the procedure is technically cumbersome, with continued improvement in colonoscopic optics and wider dissemination of tissue staining techniques, chromoendoscopy may eventually play a role in detecting colonic mucosal neoplastic changes.

Computed Tomographic Colonography (CTC)

Over the last ten years, Computed Tomographic Colonography (CT colonography or CTC) has become a new minimally invasive and safe approach to CRC screening, providing structural evaluation of the entire colorectal mucosal surface without colonoscopic intubation. Initially described by Vining [35] and applied clinically by Hara et al. [36], CTC has gained momentum as a best alternative test to traditional optical colonoscopy as has been suggested by a large landmark clinical trial by Pickhardt et al. [37] and a multi-center study trial conducted by the American College of Radiology Imaging Network (ACRIN) [38] demonstrating its effectiveness. This is further supported by two recent reports from European studies of CTC [39,40].

Recently, CTC has been advocated by several American professional medical societies as an effective alternative to conventional colonoscopy for CRC screening and is now included on the American Cancer Society's list of approved colorectal screening options [8]. However, despite these achievements, challenges to the widespread clinical dissemination of CT colonography for detection of colorectal cancer remain, including the need for approval and coverage by CMS.

The reported advantages of CTC are reduced procedure time, fewer complications, and avoiding the need for conscious sedation. With these advantages, a high quality CTC program can be used as a compliment to conventional optical colonoscopy for improving the

	Screening population	Mixed population	Mixed population without polypectomy	Mixed population with polypectomy
All complications	.2-.3 [22,23]	0.5 [24]	0.08 [24]	0.7 [24]
Cardiovascular	0.14 [25]			
Perforation	0.01 [26]	0.03 [27]-0.09 [24]	0.06 [24]	0.11 [24]
Bleeding	0.21[28]			0.48 [24]-0.87 [28]

Table 1: Reported Complication Rates for Optical Colonoscopy.

low rates of CRC screening currently observed. However, the goal of achieving consistently accurate lesion detection requires close attention to quality control with critically important technical, procedural, professional and interpretational requirements.

Elements of a quality CTC program

Early CTC studies showed wide variability in sensitivity and specificity for polyp detection [41,42] emphasizing the need for including the following critical elements for a credible, high-quality CTC program: 1) fastidious attention to the preparation of the patient, including adequate colon cleansing, stool tagging and optimal colon insufflation; 2) high-quality, non-contrast, CT imaging with acquisition of single breath hold, thin section slices on multislice CT scanners in the prone and supine positions; 3) dedicated 2D and 3D image reconstruction and display software; 4) adequate time for reading studies (average of 20 min in the ACRIN study); 5) ready availability of same-day colonoscopy back up for patients requiring polypectomy; and, 6) high quality, intensive reader training and tracking of reader performance. Our standard is a three day bowel preparation as outlined in the Appendix; we do not use I.V. contrast during CTC.

Similar to optical colonoscopy, CT colonography interpretation is reader dependent and highly reliant on the operator's training and experience. Generally, recommended reader training consists of at least 50-75 colonoscopically verified polyp-rich cases using dedicated workstations, high quality 2D and 3D reconstruction and display capability with immediately available expert feedback [43,44]. However, a recent study of reader training, suggests that to achieve adequate accuracy for patients in a CTC screening program, a test set population more nearly matching the smaller, less frequent numbers of polyps may require more than 160 cases for adequate reader training [44]. In addition, it is currently recommended that reader competence be reviewed every two years with at least 50 unknown cases [43]. Of note, recently, some studies have suggested that Computer-Aided Detection (CAD) as a second reader, may help, particularly novice readers, increase sensitivity with relative small sacrifices in specificity and time to read [45,46].

Complications of CTC

Though CTC appears to have fewer complications than OC, it is not complication-free, the greatest risk being that of colonic perforation. In a survey of over 21,000 patients from 16 US medical centers with wide experience in CTC, the reported incidence of perforation was 0.009% with each of the two complicated cases being done with manual insufflations of room air. However, a study from the UK reported 9 perforations in 17,067 CTC's, five of which were symptomatic and one of which required laparotomy. The other four were asymptomatic noted only at CTC. Thus, the symptomatic perforation rate (the rate that is the most meaningful for comparison to that of OC) was 0.03%.

Of the nine complications, causes were found in four including inadvertent intubation of a rectal stump, forceful catheterization, coexistent ulcerative colitis, and an obstructing sigmoid cancer. It should be noted that the patients in the UK study vs. the US study tended to be older which may at least in part explain the differences between the reported perforation rates. Other factors that appear to increase the risk of perforation, include, symptomatic colonic disease, previous deep colonic biopsy, and manual insufflation of room air. Factors decreasing risk are young, screening patients and pressure-controlled insufflation with CO_2 [47].

Controversies regarding screening for colorectal cancer by CTC

Accuracy of polyp detection by CTC: Comparison with OC: One debated aspect of CTC is how best to quantify its accuracy. Two accepted methods of analysis are the "per patient" and the "per polyp" detection rates. The "per polyp" method describes the accuracy of CTC to find all polyps in an individual undergoing the screening study. The "per patient" analysis evaluates the number of patients with at least one polyp of significant size (typically greater than 5 mm) detected. This metric is more clinically relevant because, regardless of the total number of polyps present, if only a single significant polyp is detected on CTC, the patient will undergo a subsequent colonoscopy where all polyps, including those not detected on CTC, would be removed. Thus, the determination of a minimal polyp size on CTC for which colonoscopy can be recommended is central to the potential success of CTC as a screening examination.

Another difficulty in evaluating the efficacy of CTC is that the "gold standard" in most comparative studies is optical colonoscopy. Yet it is known that colonoscopy is not a perfect test (Table 2). Van Rijn reviewed six studies totaling 465 patients who had "tandem" OC procedures, where patients had a baseline OC followed by a second OC on the same day and found miss rates of 21% for all polyps, and 2.1% of adenomas 10 mm or greater [31]. Heresbach [48] recently reported on 286 patients in a multi-center prospective trial of such tandem OC's and found a per polyp miss rate of 28% of all polyps, 20% of all adenomas, 11% of advanced adenomas, and 9% of adenomas 5 mm or greater [49]. Because these comparative studies had no independent gold standard, there is a small chance that a true polyp determined to be present on a CT colonography may be missed on OC simply due to the limitations of the latter study. Thus, with colonoscopy being an imperfect "gold standard" some lesions classified as false positives on CTC might be prevalent lesions missed by colonoscopy which underestimate the sensitivity of CTC.

	All polyps (%)	All Adenomas (%)	Adenomas 5mm or less (%)	All polyps 5mm or greater (%)	Adenomas 5mm or greater (%)	Adenomas 1-5 mm (%)	Adenomas 5-10 mm (%)	Adenomas 10 mm or greater
Van Rijn [31] 1650 polyps in 465 patients Review of six studies	21					26	13	2.1
Heresbach et al. [49] 556 polyps in 286 patients. Multi-center trial	28	20 (*)	27	12	9			

Table 2: Percent Polyps Missed in Tandem Colonoscopy Studies.

Using methods including state-of-the-art patient preparation, scanning and image analysis as well as a method of "segmental unblinding", Pickhardt et al. established a separate gold standard by which sensitivities of both CTC and OC could be determined [37]. By this means, each patient underwent CTC followed by OC on the same day. The gold standard was established by performing sequential withdrawal of the colonoscope in colon segments. The scope was first passed to the cecal tip. After examining by withdrawal from the cecum, a second observer revealed the results of the CTC exam for that segment. If there was disagreement between the CTC and the initial OC exam, the colonoscope was passed back into the cecum to establish a true gold standard finding. Next, the scope was withdrawn into the ascending colon and so on. In this manner, sensitivities were determined for both OC and CTC. Examining 1233 patients with this protocol, the per patient sensitivity of OC was 87.5, 91.5, and 92.3% for polyps 10, 8 and 6 mm largest diameter respectively; the per patient sensitivity for CTC was 93.8, 93.9, and 88.7%. Thus, the established sensitivities of both OC and CTC were comparable for polyps 10 mm in size and OC missed about 10% of adenomatous polyps 6 mm and greater in size, about the same number as the tandem colonoscopy studies had shown [31,48,50].

While Pickhardt's study showed excellent sensitivities and specificities using uniform methods for performing CTC in a small group of readers, a larger multi-center trial with 15 participating centers was recently reported by the American College of Radiology Imaging Network (ACRIN) [37]. In this study, 2531 asymptomatic patients scheduled to have screening OC patients also had CTC examinations with OC as the gold standard. CTC readers had to demonstrate they had read at least 500 CTC examinations or had to pass a test demonstrating 90% sensitivity in finding 10 mm polyps in a training examination. Segmental unblinding was not used. The results demonstrated CT colonography had per patient and per polyp sensitivities to polyps 10 mm or greater of 90% and 84% respectively. Thus, CTC identified 90% of subjects with polyps 10 mm or more in diameter (Table 3). Recently, an Italian multi-centered trial in 1103 patients considered high risk for CRC showed CTC to have an 85.3% sensitivity for detecting advanced neoplasia of 6 mm or larger with 87.5% specificity [51].

Meta-analysis studies [52-55] have reported per patient CTC sensitivities of 82-88% for polyps 10 mm or greater and specificities of 95-97%, but with more varied sensitivities for polyps in the 6-9 mm, and 5 mm or smaller range (63-84% and 48-65%, respectively). Limitations of these analyses include wide variations in numbers of patients, scanners, scanning technique, reader training, and patient preparation (Table 4).

In summary, the reported data from the largest trials evaluating CTC suggest: (1) CTC can detect polyps 10 mm or greater with sensitivities comparable to that of optical colonoscopy; (2) CTC specificity has consistently averaged 90% or above; (3) CTC is not sensitive to polyps 5 mm and smaller; AND, (4) CTC sensitivity to polyps 6-9 mm have a wider range of variation between studies, but in the best studies where there has been detailed attention to the highest quality in reader training, patient preparation, scanning, image display, and adequate time for reader interpretation, CTC approaches the sensitivity of OC.

The "Less-Than-Ten-Millimeter" Polyp Conundrum – How Should Small Polyps be Managed?

Standard practice for optical colonoscopy in a CRC screening program is to remove all polyps. If CTC is the screening modality used, robust algorithms for polypectomy referral become critical in preventing development of CRC. The specifics of such algorithms depend on determining the likelihood of malignant potential in any given polyp detected by CTC. To date, judging malignant potential relies almost exclusively on polyp size. While there is general agreement that large polyps (10 mm or greater) should be referred for removal, there is controversy about the management of polyps less than 10 mm. As noted above, studies have shown comparable sensitivities for OC and CTC (>90% in the best studies) for detecting polyps greater than 10 mm diameter (Tables 3 and 4) [31,37,38,48]. However, with the several studies reporting a wider range of CTC sensitivity for medium sized

Study	Size	≥ 5 mm	≥ 6 mm	≥ 7 mm	≥ 8 mm	≥ 9 mm	≥ 10 mm
OC [37]	Sensitivity (%) adenoma (per patient/per polyp)		92.3/90	90.9/90.2	91.5/89.5	89.5/90.2	87.5/88.2
	Specificity (%) adenoma (per patient/per polyp)						
CTC [37](3)(4)	Sensitivity (%) adenoma (per patient/per polyp)		88.7/85.7	90.9/89.5	93.9/92.6	93/91.8	93.8/92.2
	Specificity (%) adenoma (per patient)		79.6	87.4	92.2	94.9	96.0
CTC [38]	Sensitivity (%) adenoma (per patient/per polyp)	65/59	78/70	84/75	87/80	90/82	90/84
	Specificity (%) adenoma (per patient)	89	88	87	87	86	86

(1) per-polyp analysis = based on finding all polyps in an individual undergoing screening for CRC.

(2) per-patient analysis = based on finding at least one significant polyp in an individual undergoing screening for CRC.

(3) Adenoma specificity for OC not stated.

(4) Matches with non-adenomatous polyps were considered to represent false positives. If all matched polyps were considered to be true positives, regardless of histology, the per patient specificity would be 97.4% for 10 mm or larger, 95% for 8 mm or larger, 84.5% for 6 mm or larger.

Table 3: Comparison of Optical Colonoscopy with Computed Tomographic Colonography: Per Polyp (1) and Per Patient (2) Sensitivity for Detecting Adenoma Based on Polyp Size.

		5 mm or smaller	6-9 mm	10 mm or greater
Sosna et al. [52] 14 studies 1324 patients	sensitivity (%) (per pt/per polyp)	65/43	84/62	88/81
	specificity (%) (per patient)			95
		6 mm or smaller		**>9 mm**
Mulhall et al. [53] 33 prospective studies 6393 patients	sensitivity (%) (per patient)	48	70	85
	specificity (%) (per patient)	92	93	97
		5 mm or smaller	**6-10 mm**	**>10 mm**
Rosman and Korsten [54] 30 studies	sensitivity (%) (per patient)	56	63	82
	specificity (%) (per patient)			96
		5 mm or smaller	**6-10mm**	**>10 mm**
Halligan et al. [55] 24 studies 2610 patients	sensitivity (%) (per patient)		86	93
	specificity (%) (per patient)		86	97
	sensitivity (%) (per polyp)		70	77

(1) "per-polyp" analysis = based on finding all polyps in an individual undergoing screening for CRC

(2) "per-patient" analysis = based on finding at least one polyp in an individual undergoing screening for CRC

Table 4: CTC polyp sensitivities reported in meta-analyses.

CTC Finding	Recommendation
Normal colon or benign lesion	Routine screening every 5-10 years
Polyp(s) 5 mm or less	No need to report
Polyp 6-9 mm, <3 in number Indeterminate finding, cannot exclude polyp 6 mm or greater in technically adequate exam	Surveillance CTC in 3 years or colonoscopy now
10 mm or greater polyp(s) 3 or more polyps each 6-9 mm	Prompt colonoscopy to remove polyp(s)
Cancer likely	Prompt referral to colonoscopy or surgery

Table 5: ACR CTC Reporting Guidelines [60].

(6-9 mm) polyps and low sensitivity for small (5 mm and less) polyps, there is controversy regarding CTC's role in managing polyps less than ten millimeters in diameter.

Studies of polyp histology in patients referred for OC and CTC suggest that small polyps represent a low malignant potential with two recent studies [56,57] showing the percentage of such polyps having advanced histology ranging from 0.87-1.7% and the incidence of cancer 0.03-0.05%. While the natural history of such polyps is not yet clear, some studies suggest that very few of these lesions progress to malignancy and some have been documented to regress. Hofstad performed serial colonoscopies to follow polyps less than one cm for three years and found that 25% of adenomas were unchanged in size, 40% grew, and 35% regressed [58]. Other studies have suggested that the transformation to malignancy is relatively slow with the National Polyp Study estimating that it takes an average of 5.5 years for a 10 mm polyp to transform into cancer [13,59].

A decision analysis study by Pickhardt [60] estimated a 10 year risk of developing CRC in small (5 mm or less) polyps of 0.08%, medium sized (6-9 mm) of 0.7% and large (10 mm or more) of 15.5%. The study suggested that small polyps could be ignored, large polyps should be referred for prompt colonoscopic removal and patients with 6-9 mm polyps followed with surveillance CTC. With these points in mind, the current CTC reporting guidelines, listed in table 5, state that reporting polyps 5 mm and smaller is not necessary [43,60,61].

However, with imperfect knowledge of the natural history of medium and small polyps, there remains controversy regarding the management of polyps <10 mm, especially 6-9 mm. While early studies of 6-9 mm polyps showed 3.4% advanced histology with no cancers, two more recent, large studies of polyp histology have shown that 59-67.5% is adenomas with 5.3-6.6% showing advanced histology and up to 0.2% invasive cancer [56-58]. Lieberman reviewed the histology of polyps from 13,992 screening colonoscopies (Table 6) and projected

	Histology	5 mm or less	6-9 mm	10 mm or more
Kim et al. [56] Histology of 3536 polyps detected on screening CTC	% advanced histology		3.4	
	Number of cancers		0	7
Lieberman et al. [57] Histology found in 13,992 asymptomatic screening optical colonoscopies	**Histology**	**1-5 mm**	**6-9 mm**	**>10 mm**
	% "neoplastic"	50.2	67.7	82
	% advanced histology	1.7	6.6	30.6
	% cancer	.03	0.2	2.6
Rex et al. [62] Histology found in 10,034 routine referrals to optical colonoscopy	**Histology**	**5 mm or less**	**6-9mm**	
	% adenoma	48.6	59	
	% of polyps with advanced histology	0.87	5.3	
	% cancer	0.05	No cancers	

Table 6: Histology by polyp size detected by OC or CTC in 3 large trials.

that if these patients had initially been evaluated by CTC instead of OC, using the ACR referral algorithm (Table 5) for management, one in 15 screening patients with a single largest polyp of 6-9 mm would have advanced histology, but by CTC guidelines would have CTC surveillance in three years rather than prompt colonoscopic resection [57]. Similarly, Rex reviewed the histology of polyps from 10,034 colonoscopies and projected that if current CTC criteria had been used, about 30% of patients with high-risk adenoma findings would have had studies interpreted as normal and another 18-23% would be offered CTC surveillance at three years rather than prompt polypectomy [62].

Current CTC guidelines suggest colonoscopic polypectomy for polyps 10 mm or greater and three or more 6-9 mm polyps. For fewer than three 6-9 mm polyps, patients are offered prompt colonoscopic removal or 3-year CTC surveillance, and there is evidence that most patients and physicians choose colonoscopic removal [63]. At present, with the low probability that polyps 5 mm and less will proceed to malignancy, most guidelines agree these can be ignored. However with the uncertainty of knowing the natural history of small polyps, some authors modify their reporting to include polyps 5 mm or less and if greater than three in number to consider a follow-up CTC in three years [64].

CTC Radiation Dose Considerations

In 2008, the United States Preventive Services Task Force rated CTC "indeterminate" as a CRC cancer screening test because of uncertainty regarding long-term implications of radiation exposure and the potential financial and clinical implications arising from the identification of extracolonic findings [2]. The long-term impact of CTC examination doses of 5-10 mSv per study is generally felt to be inconsequential [43] but, when a radiographic examination is used for population-based screening, this issue must be strongly considered when advocating for serial use of this test to screen healthy populations. When extracolonic abnormalities (such as aortic abdominal aneurysm, hepatic masses, or renal masses) are identified on CTC, additional diagnostic testing, perhaps invasive, could add substantial cost and burden to individuals and to society. Those advocating and performing CTC must ensure that the examination does not result in the workup of excessive numbers of incidental or benign findings.

The "Extracolonic Findings" Conundrum

Incidental Extracolonic Findings (ECFs) may be defined as findings on CTC that have potential serious health effects and are asymptomatic, unsuspected, and unrelated to the colon. Because CTC is generally done without intravenous contrast material and using low radiation dose, the ability to definitively characterize incidental findings is limited and some ECFs categorized as potentially important are likely to eventually be diagnosed as having no significant effect on the patient's health. Studies performed primarily to test the effectiveness of CTC have also evaluated the frequency of ECFs [65-68]. Heterogeneous populations, varying definitions of incidental findings, and the nature of ECF assessment limit comparison of individual data. However, one systemic review by Xiong et al. [66] of prior publications reported that 2.7% of 3280 patients in the combined series had extracolonic cancers including 6 renal cell carcinomas, 5 ovarian carcinomas, 4 pancreatic carcinomas and 1 liver cancer. Only 1% of these were considered to be early stage. Approximately 1% of patients had abdominal aortic aneurysms. Older and symptomatic populations were more likely to have "important" ECFs. Approximately 1 in 100 patients undergo invasive procedures for ECFs following CTC and costs are higher for populations with higher risk subjects [66,68].

In studies assessing the cost effectiveness of CTC screening for CRC, the costs and benefits of evaluating ECFs have been reported. A study conducted by Hassan et al. [69] reported the greatest relative benefit from detecting ECFs on CTC was a decrease in deaths from abdominal aortic aneurysms, rather than from incidentally discovered extracolonic cancers. Overall, large populations undergoing CTC screening for CRC may be expected to diagnose 2% of these patients with early extracolonic malignancies and 1.9% with significant aneurysms. While the range of reported incidental findings, including important and unimportant findings may be up to 50% of patients undergoing CTC, "important" findings range from 7-12%. Estimates of the cost of examining and treating patients because of incidental findings also vary. However, studies that assessed both initial diagnostics costs and downstream diagnostic and treatment costs of ECFs indicated average added expenditures ranging from $28 to $297 [67-69], representing large costs in a small percentage of the population averaged over the entire population. Longitudinal studies are needed to determine the long-term clinical outcomes and the potential benefits and harms associated with the spectrum of extracolonic diseases and conditions that become evident with CTC.

Cost Effectiveness Considerations for CRC Screening

With ongoing discussions about modifying the health-care system in the United States, much emphasis is placed on comparative effectiveness research to inform reimbursement levels. Cost-effectiveness studies show that all screening strategies are better than no screening, but there is no agreement on which strategy is the best [70]. Small differences in baseline assumptions such as sensitivities for the detection of polyps, rates of adherence to any particular strategy, variations in procedure costs, practice patterns and resource capacity can greatly influence conclusions. While both OC and CTC have repeatedly been shown to be effective in detecting CRC, OC appears to be only marginally cost-effective and CTC is not yet clearly cost effective [71]. However, recent cost effectiveness comparisons of OC and CTC in a hypothetical Medicare population showed CTC to be more cost effective than OC when the power of CTC to screen for abdominal aortic aneurysm was included in the analysis [72]. In another cost-effectiveness study, Knudsen [73] showed that if the availability of CTC enticed 25% of otherwise unscreened individuals in the Medicare population to be screened, CTC would be cost effective at a cost estimate of $488 (2010 dollars).

Summary

If properly implemented in multi-modality disease prevention and screening setting, CTC provides an appealing alternative to traditional optical colonoscopy for CRC screening in populations unwilling or unable to undergo colonoscopy, thus potentially increasing CRC screening rates and reducing CRC incidence and mortality. For operator-dependent tests – flexible sigmoidoscopy, CT colonography and optical colonoscopy – advanced operator training and experience improve practitioner performance. Certification, quality standards, and minimal volume requirements also optimize outcomes and, therefore, sensitivity. Assuring high-quality optical endoscopy and CT colonography should be part of all screening programs. Because several screening approaches have similar efficacy, efforts to reduce colon cancer deaths should focus on implementing multidisciplinary strategies that maximize the number of individuals who undergo screening of some type. The different options available to screen for CRC are variably acceptable to patients and eliciting preferences will improve adherence through shared decision making that incorporates information on local test availability and quality as well as patient preference.

CTC is clearly not a replacement for colonoscopy; polypectomy via colonoscopy remains the primary modality for preventing CRC development; many individuals eligible for screening may prefer the "one-stop shop" approach of colonoscopy. Ideally, these two tests will be used in a complimentary fashion in high quality comprehensive colorectal screening programs where attention to excellence in quality of examination performance and interpretation and multidisciplinary approaches and collaborations are employed.

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