Indications and Evidence for CTC

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Background

The clinical indications of CTC have broadened gradually over the past decade. Several interactive influences of this trend include the impact of validation data of clinical trials, health policy decisions of colorectal screening guidelines, and insurance reimbursement rates determined by payors. After the early clinical trials of CTC in the late 1990s, clinical use of CTC was limited to a few specific diagnostic indications [1]. Since 2003 with the emergence of multiple successful large screening trials, there has been broader use of CTC in asymptomatic patients. From these validation data however, health policy agencies responded differently in 2008 for the 5-year updates of colorectal screening guidelines. Specifically, the American Cancer Society, with the multidisciplinary consensus of the American College of Radiology and the US Multi-Society Task Force of colorectal cancer (comprised of the American Gastroenterology Association, American Society of Gastroenterology, and the American College of Gastroenterology), recommended the use of CTC for the first time for screening of average-risk patients [2]. Contrary to this, the US Preventative Task Force (USPTF) gave CTC an *indeterminate rating of effectiveness* and did not recommend CTC for screening purposes [3].

Payors have responded differently to rates of reimbursement for CTC. Similar to the American Cancer Society guidelines, both Kaiser Permanente and Blue Cross Blue Shield gave positive endorsements in their subsequent technology assessments for screening CTC in 2008. Although 47 states had Medicare coverage for specific diagnostic indication for CTC (largely after incomplete colonoscopy (OC)), the US Centers of Medicare and Medicaid (CMS), influenced by USPTF rating, passed a national noncoverage decision for screening indications in May 2009 [4]. Concerns raised during the initial CMS deliberation included radiation exposure, diagnostic performance in Medicare population, management of small polyps, and the cost burden of extracolonic findings. Despite these challenges, CTC continues to expand as a novel, minimally invasive structural imaging evaluation of the entire colon and rectum, holding the promise of improved patient compliance for colorectal screening.

The purpose of this chapter is twofold: (1) review the current diagnostic and screening indications for CTC and (2) review important validation data of the diagnostic performance of CTC.

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Current Indications and Uses of CTC

Diagnostic CTC

Diagnostic indications for CTC are listed in Table 4.1. The most common indication is for patients who require completion of colorectal evaluation, following an incomplete OC. This has been supported since 2004 in 47 states [1]. Other diagnostic indications for CTC that are currently reimbursed variably across states include patients at risk to undergo OC (e.g., anticoagulation or anesthesia risks) and patients who require evaluation of submucosal lesions detected at OC.

Screening CTC

Based on local reimbursement issues, only a few centers have large screening programs. At the National Naval Medical Center, in Bethesda, MD, the Colon Health Initiative (CHI) was established through a congressional grant in 2004. A dedicated team of radiologists, gastroenterologists, general surgeons, nurses, technologists, and research personnel provide a multidisciplinary clinical colon health-care program with integrated clinical research for Department of Defense beneficiaries in the national capital region. President Obama underwent screening CTC at this facility in 2010. At the University of Wisconsin, several third-party payers have provided coverage for colorectal screening with CTC. Pickhardt et al. reported very positive first-year results of screening 1,100 patients in this system in 2006, with 99% insurance coverage provided [5]. In the near future, a positive national coverage decision CTC screening in Medicare patients will have a great impact on its more widespread use.

Screening indications for CTC include patients 50 years or older with average risk for colorectal cancer (Table 4.1). This includes patients with no family history or low risk based on family history. Low-risk patients include those with first-degree relatives with colon cancer after the age of 60 years or multiple second-degree relatives with colon cancer at any age. CTC is typically not the first-line test for patients with moderate or high risk based on family history; however, it can be used in appropriate settings including contraindications for optical OC or previously unsuccessful OC (Table 4.2). Moderate risk is defined as first-degree relatives with colon cancer at or before the age of 60 or multiple first-degree relatives at any age. High-risk history includes patients with family history of known genetic syndromes at increased risk for colon cancer or personal history of ulcerative colitis.

Table 4.1 Indications for CTC

Indications for diagnostic CTC[a]
1. History of incomplete OC with colorectal symptoms
2. Patients at risk to undergo OC with colorectal symptoms
3. Further evaluation of submucosal lesion(s) found at OC
Indications for screening CTC[b]
1. Average-risk[c] patients for colorectal cancer
2. Patients at moderate risk[d] for colon cancer in appropriate clinical context
3. Patients at average risk, with history of incomplete OC
4. Noncompliant patients who will not undergo OC

OC optical colonoscopy
[a]Diagnostic CTC may be done at routine radiation dose (25.0 mGy total), with and without IV contrast
[b]Screening CTC is done at low radiation dose (12.5 mGy total), without IV contrast
[c]Average-risk patients are 50 years or older with no colorectal symptoms or risk factors, with no family history or low-risk family history (first-degree family member(s) greater than 60 years of age or multiple second-degree relatives at any age with colon cancer)
[d]Moderate risk for colon cancer based on family history is first-degree family member(s) before age 60 or multiple first-degree relatives at any age with colon cancer

Diagnostic Performance in Clinical Trials

Early Clinical Validation

In early clinical trials of CTC from 1997 to 2002, studies were predominantly validated in polyp-rich cohorts using OC as the reference standard.

Table 4.2 Relative contraindications for CTC

1.	High-risk patients[a] for colon cancer, unless OC contraindicated or history of incomplete OC
2.	Routine evaluation of anal disease
3.	Recent colorectal surgery
4.	Recent deep endoscopic biopsy or polypectomy/mucosectomy
5.	Symptomatic or high-grade small bowel obstruction
6.	Known bowel perforation
7.	Colon-containing abdominal or pelvic hernia
8.	Acute symptoms of colitis, diverticulitis, or diarrhea
9.	Evaluation of pregnant woman

[a]High risk for colon cancer includes patients with inflammatory bowel disease or family history of known genetic syndromes at increased risk for colon cancer

As technical advances in CTC evolved over the years, a range of results were reported in different cohorts of patients using different techniques [6–15]. Two early landmark studies achieved the benchmark result of 90% sensitivity to detect polyps 10 mm and larger [14, 15]. The first study was performed at Boston University by Fenlon et al. [14]. In this study, 100 patients (60 men, 40 women; mean age 62 years) at high risk for colorectal neoplasia were evaluated. Selection criteria included patients 50 years or older who had a history of adenomatous polyps, positive FOBT, or strong family history of colon cancer in a first-degree relative. A total of 115 polyps and 3 cancers were found at OC, used as the reference standard. CTC had 100% (3/3) sensitivity to detect cancers, 91% (20/22) sensitivity to detect 10-mm and larger polyps, and 82% (33/40) sensitivity to detect 6–9-mm polyps. From this study, the authors concluded that CTC may have similar efficacy to OC to detect polyps 6 mm and larger in high-risk patients.

Following this study, Yee et al. reported a study with similar results in a larger cohort of 300 patients from the University of California, San Francisco Veterans Administration trial [15]. Participants in this trial were mostly male (291 male, 9 female), with 96 enrolled for screening and 204 enrolled for evaluation of colorectal symptoms. Two readers individually interpreted the CTC data using 2D primary review, with additional 3D endoscopic fly through (mean analysis times of 27–31 min), with the results given for the subsequent consensus reading. Sensitivities were 100% (8.8) to detect cancers, 90% (74/82) to detect polyps ≥10 mm, and 80% (113/141) to detect 5–9.9-mm polyps. This study helped to reinforce the feasibility of CTC as a modality to evaluate the colon in polyp-rich cohorts.

Other studies helped define the role of CTC in the setting of incomplete OC. Several early studies demonstrated the feasibility of CTC to complete the colon evaluation in same-day incomplete OC due to an obstructing cancer [16–18].

Large CTC Trials in Higher Risk Cohorts

Following the promising results of early validation trials, three larger trials demonstrated less favorable results in studies published from 2003 to 2005 [19–21] (Table 4.3). These three trials evaluated patient cohorts of 600–700 patients, who were are at increased risk for colorectal cancer based on history of prior polyps, family risk, or colorectal symptoms. Specifically, Johnson et al. published a single-center trial of 703 patients with 153 lesions (≥6 mm in size) in 2003, using primarily 2D image display techniques for lesion detection [19]. Wide variability across results of three readers was reported with per-patient sensitivities to detect 5–9-mm and ≥10-mm polyps ranging from 41% to 69% and 35% to 72%, respectively. Cotton et al. published a multicenter trial of 615 patients with 173 lesions in 2004 [20]. Per-patient sensitivities to detect 6–9-mm and

Table 4.3 Large CTC trials in higher risk cohorts[a]

Trial	Subjects	Total lesions	MDCT	Per-polyp sensitivity		Per-patient sensitivity		Per-patient specificity	
Author, journal, year	(*n*)	≥6 mm	Scanner rows	≥6 mm	≥10 mm	≥6 mm	≥10 mm	≥6 mm	≥10 mm
Johnson et al. Gastroenterology 2003	703	153	4 row	29–57% (5–9 mm)	32–73%	41–65% (5–9 mm)	38–72%	88–95% (5–9 mm)	95–98%
Cotton et al. JAMA 2004	615	173	2–4 row	32%	52%	39%	55%	91%	96%
Rocky et al. Lancet 2005	614	234	4–8 row	49%[b]	53%[b]	51%[b]	59%[b]	89%	96%
Regge et al. JAMA 2009	937	233[c]	88% 16–64 row	76%	84%	85%	91%	88%	85%

[a]Higher risk cohorts includes patients with history of prior polyps, family risk factors, or colorectal symptoms

[b]Re-analysis of Rockey et al. data of the 152 adenomas only (excluding the 82 non-adenomatous lesions), increased sensitivity per polyp for ≥6 mm and ≥10 mm to 61% and 64% respectively and sensitivity per patient for ≥6 mm and ≥10 mm to 68% and 70%, respectively

[c]Regge et al. data only evaluates advanced adenomas and carcinomas (excludes nonadenomas and low risk adenomas)

≥10-mm polyps were 30% and 55%, respectively, using 2D for primary detection; a follow-up analysis using 3D endoscopic fly through increased results to 36% and 60%, respectively. In this study, the requirement for reader experience was set at a low standard, requiring readers to have only read ten CTC cases. The most experienced center recruited close to one-third of the patients and reported significantly higher sensitivities than the other centers, raising the concern that differences in reader experience largely affected the results. Despite low performance in sensitivity, both of these trials reported consistently high specificity results, ranging from 88 to 98% at 6-mm and 10-mm thresholds, respectively.

Rockey et al. later published the third multicenter trial in 2005, evaluating the diagnostic performance of CTC, air-contrast barium enema, and OC in 614 patients [21]. CTC was predominantly interpreted with 2D image display techniques to detect, with 3D imaging to characterize. In this trial, reader experience was more standardized; however, similar negative results were obtained. CTC results of per-patient sensitivities to detect 6–9-mm and ≥10-mm polyps were 51% and 59%, respectively, outperforming results at ACBE of 35% and 48%, respectively. Common to all three of these larger trials of patients at increased risk, results were analyzed for all histological lesions detected 6 mm and larger, including non-adenomatous and adenomatous polyps. A subsequent analysis of the Rockey trial determined that if non-adenomatous cancerous lesions were excluded ($n=87$), analysis of the remaining adenomatous and cancerous lesions ($n=147$) increased, the per-patient sensitivities to detect 6–9-mm and ≥10-mm polyps to 68% and 70%, respectively [22]. This methodology of selectively evaluating adenomatous or cancerous lesions would carry forward as the accepted methodology to evaluate CTC performance.

In contrast to these three less successful trials, the Italian Multicenter Polyp Accuracy Trial (IMPACT) was performed also in higher risk cohorts in 2009, encompassing a total of 21 centers [23]. A total of 937 patients were evaluated who had positive family history, prior polypectomy of polyps, or positive FOBT. In this trial, a total of 233 lesions with advanced neoplasia were evaluated, including advanced adenomas or cancer at histology (non-adenomatous and low-risk adenoma lesions were excluded). Per-patient sensitivity to detect polyps 6–9 mm and ≥10 mm was 85% and 91%, respectively. Per-polyp sensitivity decreased to 59% and 84%, respectively. Specificity remained high, ranging from 80 to 85% at 10- and 6-mm thresholds. Requirement of the radiologist experience was review of 50 or more cases under supervision by an expert. CT scanner technology used 16–64-row MDCT in 88% of cases. Radiologists used primarily 2D (74%) rather than 3D (26%) image display techniques, according to their preference. Stool tagging was used in the minority of cases (34%). The exclusion of low-risk adenomas from the analysis could be criticized. However, the large scale of this trial including 21 centers with strong results favorably supports generalizability into more diverse practice settings.

Larger Screening Trials in Asymptomatic Patients at Average Risk

At the same time as some of the early multicenter trials in patients at increased risk, a landmark successful trial was published which exploited new technological advances in the largest screening cohort of asymptomatic patients to date in 2003 [24]. Pickhardt et al. evaluated 1,233 asymptomatic patients for colorectal screening with CT colonography in a multicenter Department of Defense trial [24]. This trial introduced the novel techniques of stool tagging with electronic subtraction and 3D fly through as the primary image display technique in all studies. It also used the "enhanced" reference standard of segmental unblinding of CTC results during OC. This technique had been used in two of the large center trials [20, 21]. Namely, the colonoscopist evaluated each colonic segment initially, followed by a second look at the colonic segment if the disclosed CTC results demonstrated a significant lesion. This trial reported per-patient sensitivities to detect 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%. Based on the segmental unblinding methodology, miss rates at the original OC (before CTC results were disclosed) could be evaluated. A subsequent analysis of these results demonstrated that OC missed 10% of adenomas larger than 10 mm [25]. This study clearly sets a new benchmark of improved diagnostic performance for detection of polyps 6 mm and larger in screening cohorts.

Five years later in 2008, the ACRIN 6664 trial (American College of Radiology Imaging Network) became the next largest screening trial of 2,531 asymptomatic patients at average risk [26]. This trial involved a total of 15 centers in academic and private practice settings. High standards for radiologist requirements were set either to have performed 500 or more CTC examinations or to take part in a 1.5-day training session of close to 50 cases and subsequently pass a qualifying examination of 90% detection rate of polyps 10 mm or greater. Methods included state-of-the-art techniques of low-dose (50 effective mAs) 16–64-row MDCT, 2D and 3D image display techniques, and stool tagging. The validation methodology of segmental unblinding at OC, however, was not used. Overall, the major goal of the study was met with per-patient sensitivity for ≥10-mm polyps of 90%. Per-polyp sensitivity in this size threshold decreased to 84%. More modest results were seen for detection of polyps at the lower size threshold of ≥6 mm, with per-patient and per-polyp results of 78% and 70%, respectively. Despite the use of stool tagging, specificity was slightly lower with results of 88% and 86% at 6-mm and 10-mm polyp thresholds, respectively. Although overall results were not as good as the Pickhardt et al. study in 2003, the diversity of 15 centers in both academic and private practice settings was valued as being more representative of potential results in general practice.

In Germany, the Munich trial by Graser et al. [27] was another successful screening trial of asymptomatic patients at average risk that was published in 2009, modeled very closely in methodology to the military trial by Pickhardt. A total of 307 subjects with 221 adenomas were evaluated with CTC, flexible sigmoidoscopy (FS), fecal immunochemical stool testing (FIT), fecal occult blood testing (FOBT), and OC. Stool tagging, 3D primary review, and segmental unblinding were used. Enhanced data acquisition at 64-row MDCT (0.75-mm slice thickness at 0.5-mm reconstruction interval), using low-dose technique (30–70 mAs, mean radiation dose of 4.5 mSv), was also performed. CTC results of per-patient sensitivities to detect polyps at ≥6-mm and ≥10-mm thresholds were 91% and 92%, respectively, less than results at OC of 98% and 100%, but far improved compared to FS of 67% and 68%, FOBT of 18% and 24%, and FIT of 40% and 33%. Interestingly, similar results between CTC and OC were obtained for per-polyp sensitivity at 6–9 mm (CTC 90% and OC 93%) and ≥10 mm (CTC 94% and OC 100%). This study represents the highest sensitivity results of small polyps in the 6–9-mm range in a screening cohort using 64-row MCDT, despite the potential increase of image noise due to the low-dose technique (Table 4.4).

Factors That May Have Influenced Differences in Results Across Studies

What then could help explain some of the differences in results among these larger trials over a decade of efforts? First, diagnostic performance does differ between early assessments of detection of multiple polyps in enriched cohorts compared to the later challenges of detecting fewer polyps in a screening cohort. Analyses of studies must be distinguished between these two types of patient cohorts. Second, clearly advancements in multirow detector CT technology over time have improved spatial resolution (Figs. 4.1 and 4.2). Additionally, awareness in knowledge of the different morphologies of polyps and the subsequent efficiency of reader training have improved, as structured courses have been developed with individual reader workstation review of CTC libraries of 50–100 case reviews both in ESGAR and the USA. There continues to some debate about the impact of 3D over 2D in reader review, as discussed

Table 4.4 Large CTC screening trials in average risk cohortsa

Trial	Subjects	Total adenomas	MDCT	Per-polyp sensitivity		Per patient sensitivity		Per patient specificity	
Author, journal, year	(*n*)	≥6 mm	Scanner rows	≥6 mm	≥10 mm	≥6 mm	≥10 mm	≥6 mm	≥10 mm
Pickhardt et al. N Engl J Med 2003	1,233	210	4–8 row	89%	94%	89%	94%	80%	96%
Johnson, et al. N Engl J Med 2008	2,531	374	16–64 row	70%	84%	78%	90%	88%	86%
Graser et al. JAMA 2009	307	221	64 row	90% (6–9 mm)	94%	91%	92%	93%	98%

[a]Average-risk cohorts are asymptomatic patients, with no personal history of polyps, family history of colorectal neoplasia, or colorectal symptoms

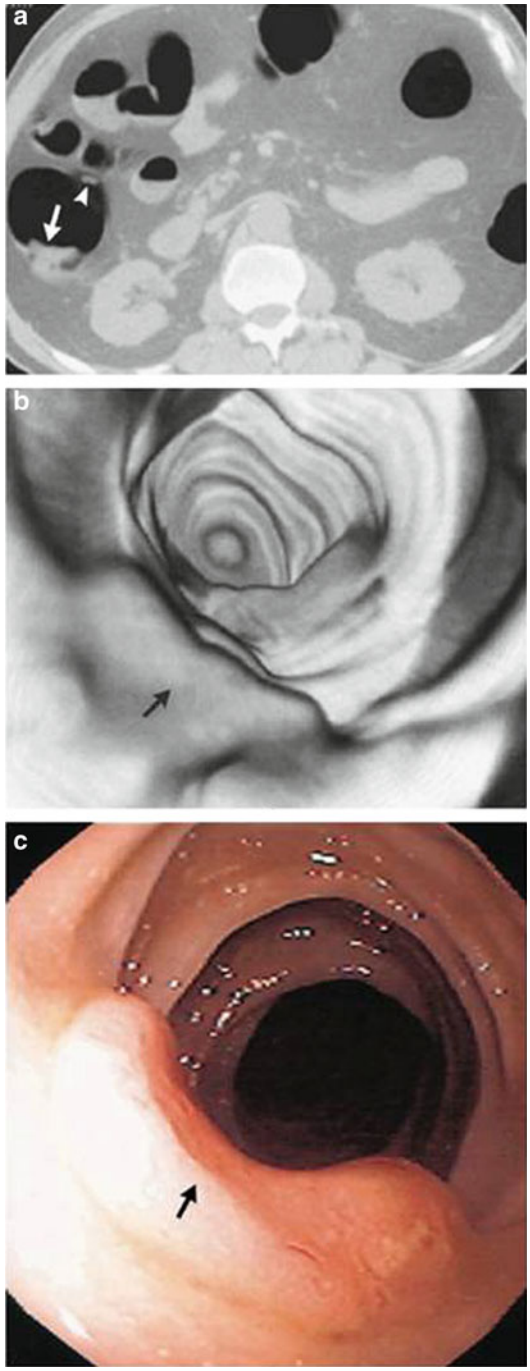

Fig. 4.1 From the Fenlon et al. trial of 1999, image quality of detection of a 2.5 cm cancer at single-row CTC at 5-mm slice thickness: (**a**) 2D axial, (**b**) 3D endoscopic view, and (**c**) optical colonoscopy image (reproduced from Fenlon HM, Nunes DP, Schroy PC, et al. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. N Engl J Med. 341, copyright © 1999 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

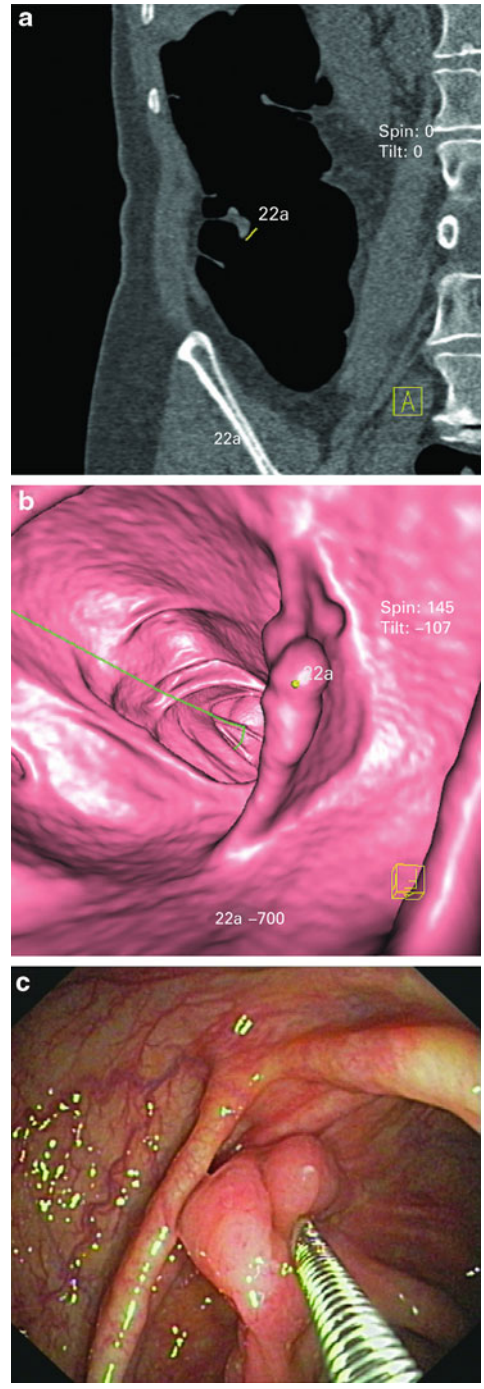

Fig. 4.2 From the Graser et al. trial of 2009, advancement of image quality of detection of a 2.2 cm sessile polyp at 64DCT at 0.75-mm slice thickness: (**a**) 2D sagittal, (**b**) 3D endoscopic, and (**c**) OC (reproduced from Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy, and fecal occult blood tests for the detection of advanced adenoma in an average-risk population. Gut. 2009;58:241–8, copyright notification year 2012, with permissions from BMJ Publishing Group Ltd.)

below. Differences may have occurred based on the analysis to evaluate all polyps in earlier studies, compared to adenomatous polyps in later studies. Finally, one less debated issue of significance is the difference in clarity of definition of polyp-size target, which Pickhardt et al. first clearly emphasized.

Among the studies of higher risk cohorts, the IMPACT trial took place 4–5 years after the first three trials of Johnson, Rockey, and Cotton. Not only were readers more familiar with the types of polyp morphologies with structured training through CTC interpretation courses, but scanner resolution with 16-DCT and 64-DCT scanners clearly improved visualization over the 2–8 row of earlier studies. Also the IMPACT trial did not include lower risk adenomas in their assessment, compared to all polyps evaluated in the first three. As discussed earlier in the reanalysis of the Rockey et al. data, sensitivity results were increased when evaluation of adenoma detection was assessed [22].

Before assessing the screening trials, there was a period of great debate during the publication of three closely spaced trials with diverging results. Namely, the screening trial of Pickhardt trial in 2003 was published at the same time as the Cotton trial and just before the Rockey trial, the latter two assessing cohorts at increased risk. The Cotton trial was largely criticized due to lack of rigorous training of radiologists at the leading edge of a new technology. However, the Rockey trial had better training and similar, if not improved, CT scanner technology, along with similar methodology of segmental unblinding of results. The enriched cohort of Rockey would have favored results over the first screening trial of Pickhardt. However, the primary technological improvements of stool tagging and 3D as a primary review were attributed to Pickhardt's success. In addition, despite having the harder task of finding fewer polyps in a screening cohort, Pickhardt also rigorously set the target size for lesion detection at 6 mm and greater, thus focusing the multi-reader task and possibly not distracting or tiring readers with the assessment of smaller polyps.

Finally, evaluation of the screening trials involves trials that are more similar in techniques. All used multirow CT scanner technology, although Pickhardt et al. had less advanced scanner technology. This likely demonstrates that good techniques in bowel preparation and insufflation clearly trump differences in 4D vs. 16–64D-scanner technique for assessment of 6-mm and larger polyps. All used stool tagging. Although ACRIN had lower specificity than Pickhardt et al. and Graser et al. despite the use of stool tagging, this might have been more influenced on the rigorous task defined by ACRIN to obtain 90% sensitivity for detection of 10-mm and larger polyps. In this context, readers did not want to miss a significant polyp, and this may have driven down specificity to some degree. All assessed adenoma detection rates. The 3D primary review in Pickhardt et al. was challenged 5 years later by equal results of 2D vs. 3D in ACRIN, with 2D being more time efficient. As readers become more familiar with image display techniques over time, 2D and 3D are both easily done, and each has advantages and disadvantages. As discussed, Pickhardt's emphasis of the target lesion size of 6 mm and larger likely focused the reader task. Finally, learning curve effects during the trials also may have been an influence. Readers who were shown the answers after cases were completed during the trial, likely benefited from awareness of case mix and improved their increased accuracy as they read additional cases [24, 27]. Lessons learned from clear definition of target lesions and feedback of results to enhance learning are key to remember as CTC clinical programs continue to expand.

Selection of Patients by CTC to Benefit from Colonoscopy

Beyond validation, Kim et al. published a study that demonstrated the efficacy of CTC to properly select patients who would benefit from therapeutic OC [28]. This was a two-pronged study comparing screening with primary CTC in 3,120 patients (with selective recommendation

for polypectomy in positive patients) to screening with primary OC in 3,163 patients. In the CTC arm, patients were recommended to have a follow-up therapeutic OC based on detection of polyps 6 mm or greater in size. The two cohorts had similar demographics, other than a slightly higher proportion of individuals with a positive family history in the OC group. A total of 7.9% of patients in the CTC arm were recommended for therapeutic OC. Both groups reported a similar detection rate of advanced adenomas (3.2% in the CTC group and 3.4% in the OC group). However, the total number of polypectomies was over four times higher in the OC group compared to the CTC group (2,434 vs. 561, respectively) [28]. This study supports that using a polyp-size threshold of 6 mm or greater, CTC can efficaciously recommend therapeutic OC for removal of advanced adenomas.

Meta-analyses of CTC Diagnostic Performance

During the first decade of effort, two meta-analyses were done to review the CTC trial results [29, 30]. The most comprehensive meta-analysis of Mulhall et al. evaluated 33 studies encompassing 6,393 patients. In this analysis on a per-patient basis, CTC sensitivity and specificity for 10-mm and larger polyps was found to be 85–93% and 97%, respectively [29]. Pooled sensitivity and specificity for small polyps (6–9 mm) was 70–86% and 86–93%, respectively. Halligan et al. reported the sensitivity of CTC to detect invasive colorectal cancer was 96% [30].

In 2011, a comprehensive meta-analysis of CTC and OC for detection of colorectal cancer reviewed 49 studies evaluating 11,151 patients, spanning the years from 1994 to 2009 [31]. The sensitivity of CTC for detection of colorectal cancer was 96.1%. No cancers were missed at CTC when both cathartic and tagging agents were used in the bowel preparation. The sensitivity of OC for colorectal cancer in a subset of 25 studies of 9,223 patients was 94.7%. Thus, the high sensitivity of CTC for detection of cancer was confirmed, similar to that of OC.

CTC Performance in Other Settings

Medicare Population

A relative paucity of studies of the Medicare population partially influenced the national non-coverage decision by the CMS in 2009. Subsequent to that decision, a retrospective review was published in 2010, which evaluated 577 older patients, ranging in age from 65 to 79 years, as part of the CTC screening program at University of Wisconsin [32]. Using the polyp-size threshold of 6 mm or greater, a total of 15.3% patients were referred for therapeutic OC. This was greater than the prior published referral rate of 7.9% in average-risk patients (mean age, 57 years). Given the higher rate of neoplasia with aging, the establishment of this increased referral rate to OC was important to establish for cost considerations. For adenomas, the per-patient positivity rates at 6-mm and 10-mm polyp-size thresholds were 10.9% and 6.8%, respectively. The prevalence of advanced neoplasia was 7.6%. In addition, the effects of extracolonic findings were also evaluated, which can also add additional costs. The reported extracolonic findings led to an additional work-up rate of 7.8%. No major complications occurred in this age group. Overall, these results were favorable, suggesting that CTC could be a safe and effective screening modality in this age group.

At New York University, a retrospective evaluation of the extracolonic findings and polyp prevalence was compared between senior and non-senior patients [33]. A total of 454 patients were evaluated, with 204 non-seniors (age < 65 years) and 250 seniors (age ≥ 65 years). Among the seniors, 82 patients (33%) underwent CTC for screening indications. No significant difference in the percentage of patients with one reported clinically significant polyp (defined as ≥6 mm in size) was present, encompassing 14.2% of the non-senior and 13.2% of senior patients. The percentage of patients with at least one extracolonic finding was less in the non-senior group (55.4%) compared with the senior group (74.0%). However, most patients (92% of non-seniors and

91.8% of seniors) had extracolonic findings of low clinical significance. Subsequently, there was no statistical difference in the frequency of recommendation for additional imaging between groups (4.4% in non-seniors and 6.0% in seniors). Thus, investigators from two different demographic regions, NYU and University of Wisconsin, concurred from their colorectal screening programs that 15% or less of Medicare-aged patients would undergo therapeutic OC, using the index size threshold of 6 mm or larger for polyps detected at CTC. It is also reassuring for cost considerations that the additional imaging recommendations based on extracolonic findings were also found to be low in this population.

A reanalysis of the ACRIN data in the Medicare population of 477 patients 65 years of age and older demonstrated that the sensitivity and specificity per patient for detection of polyps 6 mm and greater was 72% and 86%, respectively, compared to 82% and 83%, respectively, for detection of polyps 10 mm and larger [34]. Per-polyp sensitivity in this age group for polyps larger than or equal to 6 mm and larger than or equal to 10 mm was 59% and 75%, respectively. Overall, the majority of these results in Medicare-aged patients did not differ significantly from patients less than 65 years of age.

Flat Lesions

Flat colorectal lesions are challenging, both at OC and CTC. Debates of both the prevalence and pathological risk have occurred. The diagnostic performance of CTC for flat lesions has varied, with recent improvements reported as technological improvements with 3D software and CT spatial resolution have occurred. Some of this variability may be due to differences in definitions of the morphology and terminology of flat lesions.

Using the definition of "sessile" (height of lesion less than half of length), Fidler et al. reported a sensitivity to detect sessile lesions of less than 50% [35]. In a subanalysis of sessile lesions, Pickhardt et al. reported a sensitivity of 83% [36].

Other terminology for flat lesions has included a recent description by Soetikno et al. [37]. Polypoid lesions are defined as sessile or pedunculated in morphology. Non-polypoid lesions are defined as superficially elevated, flat, or depressed. In a series of OC screening of veterans, the overall prevalence of non-polypoid neoplasia was 9.4% vs. 5.8% [37]. In this report, concerns for failed detection of such lesions at CTC were raised. However, all CTC trials reported to date have not described significant trends of false negatives of flat lesions at CTC, using OC as a gold standard. In addition, this morphological type of lesion is well recognized in CTC and is a part of standardized training.

The Paris classification of flat lesions defines these lesions as being less than 3 mm in height. A subcategory is the carpet lesion or laterally spreading lesion, which spans a distance of over 3 cm. Using this terminology, Pickhardt et al. published a series evaluating 5,107 consecutive asymptomatic patients at screening CTC [38]. All lesions larger than 6 mm in size were labeled as sessile or pedunculated (combined as polypoid type) vs. flat. Lesions larger than 3 cm in length that were flat were labeled as carpet lesions. A total of 125 out of 964 polyps (13.1%) were labeled as flat in 106 adults. Flat lesions between 6 and 30 mm averaged a maximum height of 2.2 mm (≤3 mm in 86%). Further improvements in CT acquisition, computed-aided diagnosis, and 3D image display techniques should continue to improve detection of this morphological type of colorectal lesion.

Low-Dose CTC

Radiation dose imparted at CTC is a critical factor to keep efficient. Several investigators have reported successful use of low-dose CTC protocols [11, 39–41]. 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 [11]. 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. 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 [39]. 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 thirteen 10-mm and larger polyps, and 83% sensitivity for the 6–9-mm (20/24) polyps. Further decreases in radiation dose have been achieved with advances in automatic tube current exposure and dose modulation techniques [42], which differentially change 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 close to, or less than, 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 [43]. Brenner et al. recently addressed the issue of radiation dose screening with CTC and concluded that the benefit-risk ratio was high and that radiation-induced cancer risks were very low [43]. Brenner concluded that potential lifetime cancer risk for one CTC exam at age 50 was 0.14% (0.07% if 70), which could be reduced by factors of five or ten with optimized low-dose protocols. Potential limitations of these estimates of cancer risk include use of the linear non threshold model from whole body exposure of A bomb survivors of all ages, compared to the more limited abdominal-pelvic exposure of CTC in patients 50 years and older. Recently, the American College of Radiology 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 [44]. In addition, quality metrics for CTC developed by the ACR include the documentation of low-dose CT protocols for screening cohorts.

Summary

CTC continues to rapidly evolve with technological improvements in bowel preparation, low-dose CT acquisition, and novel 3D display techniques. Although diverse results were initially obtained in the first decade during rapid improvement in the technology, more consistent results of diagnostic performance have now been realized in larger screening cohorts. These validation data will continue to drive implementation and reimbursement, likely promoting further expansion of utilization of CTC in clinical practice.

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