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Computed tomography colonography: emerging evidence to further support clinical effectiveness

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Abstract

Purpose of review—Computed tomography colonography (CTC) continues to mature and evolve as a noninvasive imaging test of the large intestine. The aim of this review is to provide an update on the recent and emerging data that further supports the clinical effectiveness of CTC.

Recent findings—The diagnostic performance of CTC for detecting colorectal polyps and masses is well established, but its precise clinical role is yet to be determined. Recent data on test performance, patient acceptance, and study technique may help to clarify the role of CTC and accelerate its clinical implementation.

Summary—Recent advances and refinements in CTC should help to clarify and expand its clinical role, both as a screening and diagnostic test. High patient acceptance for CTC could lead to increased adherence rates. Ultimately, the complementary nature of CTC and optical colonoscopy should result in improved patient care.

Keywords

colorectal cancer; colorectal polyps; Computed tomography colonography; screening; virtual colonoscopy

INTRODUCTION

The clinical utility of computed tomography colonography (CTC) as a screening tool for colorectal polyps and cancer was established a decade ago [1]. However, although CTC has been validated as a well tolerated and effective diagnostic and screening examination, it remains underutilized due to a number of logistical, political and fiscal obstacles. This delay in implementation of CTC is particularly true within the United States, where early progress has since stagnated compared with the steady gains seen in a number of other countries. The

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Conflicts of interest

P.J.P. has served as a consultant for Viatronix, Bracco, iCAD, and Check-Cap; and is co-founder of Virtuo CTC. Grant support: NIH 1R01CA144835, 1R01CA155347.

aim of this review is to provide an update on the recent and emerging data addressing the clinical utility of CTC.

The clinical indications for performing CTC can be broadly divided into 'screening' and 'diagnostic' categories. Since the time of my last CTC update for this journal [2], a host of studies and publications have provided further validation for both clinical scenarios. The preponderance of important new data surrounds the use of CTC for diagnostic indications, reflecting the most common patterns of CTC utilization throughout the world, where screening of asymptomatic adults by either optical colonoscopy or CTC is seldom performed save for a few select practices. Among the specific diagnostic indications evaluated that are worthy of discussion include symptomatic patients in whom the primary clinical concern is colorectal cancer and postoperative surveillance following colorectal cancer resection. New data regarding the performance of CTC among medicare-aged patients will also be discussed, as will the use of CTC in the general screening population, other performance indicators, patient acceptance, and some additional technical advances.

DIAGNOSTIC COMPUTED TOMOGRAPHY COLONOGRAPHY

Perhaps the most significant CTC trial to be completed in recent years is the so-called SIGGAR trial, which was a UK multicenter randomized comparison of CTC versus standard investigation with colonoscopy or barium enema in the diagnostic setting [3]. Effectively, the study was composed of two separate randomized controlled trials: CTC ($n=1280$) versus double-contrast barium enema ($n=2541$) and CTC (533) versus colonoscopy ($n=1057$). The primary inclusion criterion was symptoms or signs considered suggestive of colorectal cancer by the referring physician (e.g., change in bowel habit, rectal bleeding, abdominal pain, or anemia). The primary diagnostic end points were colorectal cancer and polyps measuring 1 cm or larger. The final, peer-reviewed, trial results have not yet been published but the main findings have been presented in abstract form at scientific meetings. In summary, CTC detected significantly more cancers and large polyps than barium enema, whereas there was no significant difference in detection between CTC and colonoscopy (although there was less 'clinical uncertainty' following CTC, according to the study authors). Given the trial design and preliminary reports, these findings are expected to provide high-level evidence that CTC may be comparable to colonoscopy for initial evaluation of patients with suspected colorectal cancer.

CTC is an attractive test for surveillance after colorectal cancer resection, given its ability to non-invasively combine colonic and extracolonic evaluation. Although smaller patients series had suggested that CTC might be useful in this clinical setting, Kim *et al.* [4] published a more definitive retrospective study of 742 consecutive patients who underwent CTC with IV contrast following curative-intent colorectal cancer surgery, including 548 with colonoscopic correlation. In this series, all six metachronous cancers were identified at CTC, as well as over 80% of all advanced neoplasms. The negative predictive value for nondiminutive adenomas was 100%. In addition, extracolonic evaluation uncovered metastatic recurrence in an additional 11 patients beyond what was detectable by colonoscopy. The study conclusion was that contrast-enhanced CTC is an accurate and practical surveillance tool following colorectal cancer surgery, allowing for simultaneous

evaluation of both the colon and extracolonic organs. To validate these retrospective results and to assess the economic benefit, we are currently involved in an ongoing prospective NCI-sponsored multicenter trial (in collaboration with the Mayo Clinic and Fox Chase Cancer Center) evaluating the use of combined contrast-enhanced computed tomography (CT)/CTC against the standard combination of CT and colonoscopy.

Dating back to its earliest incarnations in the 1990s, CTC has consistently demonstrated high sensitivity for detecting colorectal cancer, which was confirmed in a recent meta-analysis and systematic review [5[■]]. A total of 45 published CTC studies dating back to 1994 entailing over 11 000 patients yielded a cumulative sensitivity of 96.1% (398 of 414 cancers). Interestingly, no cancers were missed by CTC when the bowel preparation included both cathartic and tagging agents. These results compared favorably with optical colonoscopy, in which a sensitivity for cancer of 94.7% was found within the studies wherein unblinding of CTC results was performed. The consistently high sensitivity of CTC for colorectal cancer, even in its formative stages, is primarily due to the fact that these lesions are generally readily detectable on two-dimensional evaluation, and do not require high-end three-dimensional evaluation. The importance of bowel preparation and colonic distention must be emphasized, however, as a separate study showed that colorectal cancer detection falls off considerably on routine CT without preparation or distention [6].

COMPUTED TOMOGRAPHY COLONOGRAPHY PERFORMANCE IN A MEDICARE-AGED COHORT

When the Center for Medicare & Medicaid Services (CMS) issued its national coverage determination in 2009 that left CTC screening noncovered for medicare beneficiaries, one of the major evidence gaps cited was the specific performance characteristics in a cohort aged 65 years and older. To address this perceived shortcoming, a number of publications followed that specifically focused on this concern [7,8[■],9[■],10[■]]. Kim *et al.* [7] reported on results in 577 seniors undergoing initial CTC screening and concluded that CTC was a well tolerated and effective screening modality for the older adult population. Abdominal aortic aneurysms accounted for the majority of important extracolonic findings. Macari *et al.* [8[■]] compared colorectal and extracolonic results in 250 seniors undergoing CTC against non-senior adults and showed similar results for both polyp detection and for recommendations for additional imaging. Johnson *et al.* [9[■]] reported on CTC screening results from 477 adults age 65 years and older from the ACRIN trial and concluded that the difference between senior-aged participants and those younger than 65 years was not statistically significant for most measures of diagnostic performance. Finally, Cash *et al.* [10[■]] published their results in over 1400 senior adults undergoing CTC and concluded that the low rates of referral to colonoscopy, the relatively low prevalence of advanced neoplasia, and the low prevalence of important extracolonic findings make CTC a viable option for medicare-aged patients. These cumulative results should satisfy CMS' concerns regarding the perceived lack of CTC data in the medicare cohort. Interestingly, President Obama himself underwent colorectal cancer screening with CTC in 2010, despite the fact that this test is not covered for medicare beneficiaries under his current watch.

SCREENING COMPUTED TOMOGRAPHY COLONOGRAPHY

Although Medicare does not yet cover CTC for screening purposes as described above, it should be noted that a number of national third-party payors will now cover CTC screening. However, widespread implementation of CTC for population screening will require even broader coverage to achieve the critical mass necessary to sustain a robust screening program. Compared with diagnostic CTC, fewer studies have been published recently that focus on screening as the study indication, although most of the Medicare-aged cohort studies described above dealt with asymptomatic screening. Another important study by Stoop *et al.* is discussed below under the section on patient adherence to screening. A recent study by Kim *et al.* [11] assessed the incidence of colorectal cancer 5 years out from a negative CTC screening examination. The very low rate of incident cancer compared favorably with similar outcome measures following negative colonoscopy screening. These data are important because it supports the CTC practice of nonreporting of diminutive lesions (5 mm and smaller) [12]. Another article found very low rates of cancer and high-grade dysplasia among small (6–9 mm) and even large (1–2 cm) polyps identified at CTC screening [13].

OTHER COMPUTED TOMOGRAPHY COLONOGRAPHY PERFORMANCE DATA

Within the artificial setting of a clinical validation trial evaluating CTC, all patients generally undergo subsequent optical colonoscopy to serve as a reference standard, regardless of CTC findings [1]. This framework allows for determination of sensitivity and specificity, which cannot be derived in actual clinical practice in which patients are not referred to colonoscopy unless a significant finding is identified at CTC. Going forward in this clinical setting, positive predictive value (PPV) becomes an important quality measure. Several articles have specifically evaluated the PPV of CTC in clinical practice [14–16]. All of these publications demonstrate a PPV for polyps at least 6 mm that is well above 90% for both by-polyp and by-patient considerations. In general, PPV increases with lesion size and was also higher for sessile and pedunculated lesions compared with a flat morphology. It should be noted that these PPV results are substantially higher than what had been previously reported in the clinical trial setting. A high PPV improves the efficiency and cost-effectiveness of CTC as fewer unnecessary (i.e., nontherapeutic) colonoscopy procedures are performed.

Flat lesions, especially those in the right colon have received considerable attention in recent years, as the serrated polyp pathway to cancer has been elucidated. As with optical colonoscopy, superficially elevated lesions are less conspicuous at CTC compared with classic sessile and pedunculated polyps, but are nonetheless detectable with appropriate technique [12]. For a given linear size, however, flat lesions are significantly less aggressive histologically than nonflat lesions [17], which is somewhat reassuring. At CTC (and colonoscopy), small hyperplastic polyps tend to be flatter than adenomatous polyps [18], which seems to be accentuated by increased luminal distention. One useful feature at CTC that likely improves detection of flat lesions is the tendency for oral contrast to adhere to their surface. As noted above, the PPV for flat lesions detected at CTC is considerably lower

[14,15], which likely reflects a combination of over-calling (i.e., CTC false positives) and lesions missed at optical colonoscopy (i.e., colonoscopic false negatives). Carpet lesions, also referred to as 'laterally spreading tumors', are large (> 3 cm) flat lesions that are most often found in the cecum and rectum. With reasonable technique, these are readily detectable at CTC. At histology, they often have a villous component, with or without high-grade dysplasia, but are less often malignant compared with nonflat colorectal masses.

PATIENT ACCEPTANCE AND ADHERENCE

The ultimate success of any new colorectal screening test will depend in large part on the willingness of individuals to submit to it. Put another way, even the most accurate tool will fail if patient acceptance and adherence are poor. Although some limited data on patient acceptance with CTC exists from the earlier clinical trials, experience in the actual clinical setting was generally lacking until recently. In addition, little was known about the potential or actual impact CTC might have on overall screening adherence. A number of key publications have recently addressed these important areas.

A survey of 250 consecutive individuals undergoing CTC screening published by Moawad *et al.* [19] found that over one-third would have foregone colorectal cancer screening if CTC had not been an available option. Furthermore, of the 57 patients in this cohort who had experienced both CTC and colonoscopy, an overwhelming 95% preferred CTC. A subsequent larger multicenter study by Pooler *et al.* [20[■]] which surveyed over 1400 adults who underwent CTC screening also found a very high satisfaction rate. Over 90% rated their screening experience with CTC as 'excellent' or 'good', and over 90% indicated that they would choose CTC again for their next screening. Among individuals who had experienced both CTC and colonoscopy, CTC was favored by a nearly 6 : 1 ratio. Importantly, 30% indicated they might not have undergone screening if CTC were not an option, suggesting a positive impact on overall adherence rates for colorectal cancer screening.

As mentioned, increasing adherence rates to colorectal cancer screening is a critical goal for success. Two additional recent studies have shed new light on the potential impact CTC can have on screening participation. A Dutch randomized controlled trial by Stoop *et al.* [21[■]] evaluated participation in screening and found an impressive 55% increase with CTC over colonoscopy. If these results are reflective of a general screening population, the clinical and economic benefits of CTC screening would be substantial. Furthermore, if both CTC and colonoscopy were offered as screening options, the additive value would increase adherence even more. Cash *et al.* [22[■]] recently reported on the impact of CTC screening on participation rates within US military treatment facilities. At the National Naval Medical Center, which has a dedicated CTC screening program, compliance rates for colorectal cancer screening increased by more than 15% in 2009 and 2010 because of CTC alone. At our own medical center, the overall volume of optical colonoscopy has significantly increased since the introduction of a parallel CTC screening program, allaying any fears of a 'turf battle'.

TECHNICAL ADVANCES

Recent noteworthy advances in CTC technique include new data on noncathartic bowel preparations [15,21[■],23[■]] and computer-aided detection (CAD) [24,25]. Potential benefits of noncathartic or laxative-free CTC include improved patient acceptance and adherence, but these must be weighed against the potential disadvantages, which include the inability for same-day polypectomy and reduced accuracy. The aforementioned randomized controlled trial by Stoops *et al.* [21[■]] employed a noncathartic preparation, which may explain the somewhat lower per-patient yield for advanced neoplasia. A recent noncathartic CTC trial by Zalis *et al.* [23[■]] in 605 adults showed a reasonable per-patient sensitivity for large adenomas (91%) but a reduced specificity (85%). Sensitivity for small adenomas (6–9 mm) dropped off considerably but patient experience with CTC was improved over colonoscopy. At present, noncathartic CTC appears to represent a reasonable screening alternative for individuals unwilling to undergo a cathartic preparation (for either CTC or colonoscopy). The studies by Mang *et al.* [24] and Lawrence *et al.* [25] evaluated the stand-alone performance of CAD for polyp detection at CTC. Both studies demonstrated good CAD performance, with sensitivities of 90% or more, associated with an acceptable false-positive rate, indicating the maturation of CAD as a supplementary diagnostic tool.

CONCLUSION

Recent advances and more extensive clinical experience with CTC provide further support for its utility in practice. CTC has now matured as a diagnostic tool and is poised to make a positive impact on patient care as both a useful diagnostic and screening test. CTC should not be viewed as a potential replacement for colonoscopy, but rather as an additional effective option that could significantly increase overall screening rates, as well as provide for colorectal evaluation in cases unfit for colonoscopy.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- ■ of outstanding interest

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KEY POINTS

- Randomized controlled trial data demonstrate the diagnostic equivalence of computed tomography colonography (CTC) and optical colonoscopy for colorectal cancer and large polyps.
- Recently published studies on CTC performance in older participants address the perceived data gaps for the medicare-age population.
- New data on patient preference and screening participation suggest that widespread availability of CTC would greatly improve adherence to colorectal cancer screening.