EDITORIAL

Can Capsule Colonoscopy and Computed Tomographic Colonography Accurately Evaluate Patients With Positive Results From the Fecal Immunochemical Test, and Are These Ready for Prime Time?

Although the historical gold standard guaiac testing for fecal occult blood (FOBT) has shown improvement in colon cancer detection and a reduction in related mortality,1,2 the current gold standard has changed to fecal immunochemical testing (FIT) based on the performance characteristics.3 In 2008, several US professional societies endorsed the use of FITs to replace FOBTs because of the former’s improved performance characteristics and potential for higher participation rates.4-6 Countries in Europe and Asia also have adopted widespread colorectal cancer (CRC) screening programs using FITs.7,8 However, the diagnostic characteristics of these tests have been difficult to estimate, with reported sensitivities ranging from 25% to 100%.3 When performed for CRC screening, a positive guaiac FOBT or FIT requires a colonoscopic diagnostic work-up to examine the entire colon to rule out the presence of cancer or advanced neoplasia.4,5

Although conventional optical colonoscopy is the current gold standard for evaluation of the entire colon, it is useless if patients refuse to have it performed. In addition, for a variety of reasons, a colonoscopist may be hesitant or unwilling to perform this in high-risk patients with significant comorbidities or in patients who cannot interrupt their anticoagulant or antiplatelet therapies. The concept of a relatively noninvasive structural examination that can image the colon and detect significant lesions is appealing to many patients and/or the physicians directing their care. To date, the 2 most widely studied noncolonoscopic technologies for panocolonic imaging are computed tomographic colonography (CTC) and colon capsule endoscopy (CCE).8

The United States Multi-Society Task Force (MSTF) on CRC, the American College of Radiology (ACR), and the American Cancer Society (ACS) have supported the use of CTC as an option for CRC screening in average-risk individuals at 5-year intervals starting at the age of 50.9 In addition, the American College of Gastroenterology lists CTC as a screening option for patients who are unwilling or who do not have access to colonoscopy, which specifically is cited as the preferred strategy.6 The US Preventive Task Force, however, did recommend CTC as a recommended screening option in their most recent published analysis,4 and the recently released outline for their 2014 re-analysis lists this as a screening option being considered in their forthcoming review and recommendations.9

Although previously reserved primarily for small intestinal imaging, there is a growing body of evidence on the use of wireless capsule endoscopy in colonic imaging with CCE (PillCam Colon; Given Imaging, Ltd, Yoqneam, Israel). This ingestible capsule technique is performed without the need for the sedation/air insufflation used for colonoscopy or the air insufflation used with CTC. Recently, a second-generation CCE device was released that provides a higher number of images per second and a larger viewing angle.10 CCE was neither included in the previous (2008) iterations of the MSTF/ACR/ACS9 American College of Gastroenterology CRC screening guidelines;6 nor has it has been listed in the proposed outline for the CRC screening re-evaluation by the US Preventive Task Force.9 The European Society of Gastrointestinal Endoscopy, however, recently published a consensus guideline supporting CCE for screening but not for use in diagnostic evaluation.11 That analysis noted the average sensitivity of the first-generation CCE devices for significant findings (≥6 mm size, or ≥3 polyps irrespective of size) was approximately 58%,12-14 but improved to 86% with the second-generation CCE devices.15,16 These rates are higher than the 50% cut-off value for sensitivity established in the MSTF/ACR/ACS guideline to define a test acceptable for screening purposes.5

Patients with a positive FOBT (+FOBT) are at increased risk for CRC and advanced neoplasia.1-5 In this setting, a test with a very high sensitivity is desirable and colonoscopy should be performed as a follow-up test.15,16 Plumb et al17 recently reported a retrospective analysis evaluating the use of CTC in CRC screening. After a +FOBT, 2731 subjects underwent CTC, of whom 1027 were positive for lesions suspicious of CRC or polyps. Of these, 911 patients underwent confirmatory testing with 17.1% and 4.5% found to have adenomatous polyps and CRC, respectively, compared with 50.6% and 9.0% found by colonoscopy.17 There are limited published data to date on the use of CCE in the evaluation of patients with positive fecal testing. The Eliakim et al10 study was the first multicenter study for the second-generation capsule and 21% of the 104 patients (no cancers) were indicated for optical colonoscopy because of heme positivity. The Spada et al18 study was the first multicenter trial for the second-generation capsule and 6% of the 109 patients (3 cancers) had this indication. If we combine the data from these 2 studies, the total number of patients studied for heme positivity is 28 patients.

The non–industry-supported trial reported by Ronchetti et al19 in this issue of Clinical Gastroenterology and Hepatology compares the accuracy of CCE and CTC in patients with +FOBT. Subjects 50 to 69 years old were participating in an Italian national screening program, after they tested positive they first were offered

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colonoscopy after an interview with a gastroenterologist. If they accepted, they then were offered entry into the trial whereby they were scheduled first for CCE, followed approximately 15 days later by CTC early in the morning, and then colonoscopy later that day. During the colonoscopy, the endoscopist was sequentially unblinded to the CCE and CTC results for 3 colonic segments (the investigators did not specify the segments beyond identifying one segment as the right colon). These segments then were re-examined by the endoscopist to resolve any disparities suggested by the CCE or CTC. The double unblinded colonoscopy then was established as the reference standard. Polyp size was established by a 5-mm open forceps or open snare at the time of colonoscopy.

The CCE review was performed by a single evaluator using the proprietary Rapid 7 program and ruler (Boston, MA). The CTC was performed with a 64-slice multidetector CT (LightSpeed VCT, GE Healthcare, Milwaukee, WI) and analyzed using both a 2- and 3-dimensional approach. No computer-aided detection or fecal tagging were used. All studies were analyzed by a skilled radiologist who reportedly had 8 years of experience with more than 200 CTCs. Colonoscopy was performed by 4 experienced staff endoscopists who had performed more than 250 colonoscopies per year for the past 3 years and had an adenoma detection rate of 30%, albeit unrestricted beyond only screening colonoscopies.

A total of 50 patients were enrolled in this pilot study. The overall colonic cleansing was deemed "adequate" in 70% of CCEs, 90% of CTCs, and 100% of colonoscopies. A split dose colon cleansing regimen performed the day before and on the day of the procedure was used only in the CCE group. Overall, 32 patients (64%) had at least 1 polyp, with 16 (32%) and 13 (26%) patients having a polyp 6 mm or greater and 10 mm or greater, respectively. The histology of these polyps was not reported. There were no cancers identified by the reference standard colonoscopy. Notably, for CTC and CCE by intention-to-diagnose analysis, the sensitivity was the same for polyps 6 mm or greater or 10 mm or greater (88.2% and 92.8%, respectively), and acceptably high for specificity (87.85% and 91.7% vs 93.9% and 97.2%, respectively). The respective positive and negative likelihood ratios for polyps 6 mm or greater and 10 mm or greater were 3.0, 0.7, 4.5, and 0.03 for CTC and 3.75, 0.06, 13.0, and 0.02 for CCE, respectively. Between CTC and CCE, patient preference was 78% for CCE, the primary reasons being the bloating and mild pain associated with air insufflation at the time of CTC.

Comment

Where do we go with these data in our clinical practice? This study should not be construed beyond the limitations inherent within the report.

First, we were not provided with the information regarding the behavioral characteristics of patients who refused colonoscopy. Rather, we were given the data on patients who consented to 3 procedures and 2 separate days of colon cleansing, clearly this may not represent real-world patient behavior. In addition, it would be inappropriate to extrapolate these findings to patients who might refuse colonoscopy when presented with a +FIT result, presumably performed by the primary care physician who may not be able to provide specifics on the implications of sensitivity/specificity in a way to convince all patients to comply with a colonoscopy evaluation as the necessary next test. The reference standard used was colonoscopy. This standard, however, because of the study design, may have characteristics that might supersede standard practice. After evaluation of each section of the colon, the colonoscopist was unblinded to the results of the other 2 imaging modalities and was required to reinspect the section to resolve any disparate results.

Second, this was a small pilot study with no stated sample size justification to estimate numbers for non-inferiority or superiority. The entry criteria of +FIT would suggest a superseded population of patients with some colon neoplasia, although the investigators reported only the size, but not corroborative histology, to identify low- or high-risk lesions. The investigators performed a creditable evaluation with and without size (a discriminant for high-risk adenomas was size ≥1 cm) mismatch correction. Recent evidence has shown, however, that even using the open forceps technique (the reference standard in this study) as their reference standard, there was potential variance in accuracy of the endoscopic assessment of polyp size.

Third, the comparisons for patient preference may have been subject to reporting bias because we were not told when the patients were surveyed. Typically, the most recent adverse experiences are recalled, and given the time delay between CTC and CCE, this may have been a factor. In addition, although not used in this study, the use of validated instruments with standardization of discussions with the patient, including full discussion of what the patient should expect, is recognizably important in assessing patient experience, acceptability, and preference.

Fourth, the disparities in the bowel preparation adequacy likely are best explained by the differences in the colon cleansing regimens and scales for assessment that were used. Of note also was the use of intravenous metoclopramide given the day of the capsule ingestion. The colon cleansing regimen for CTC was high-dose senna, albeit in split doses, all performed on the day before the examination. The 100% adequacy of the preparation assessed at the time of colonoscopy was surprising despite the lack of a split-dose regimen, which clearly is present day standard of care.

The strengths of this pilot study were the integrated diagnostic performances, although the real-life proportion characteristics of patients refusing colonoscopy with a +FIT may not be extrapolated appropriately to a US
population, in particular if the discussions of implications are standardized and validated. Two larger studies evaluating CCE (300 and 400 patients in France and Italy, respectively) investigating patients with +FIT are scheduled to begin in 2014 and results obtained in 2015 (personal communication, Gregory DeVault, Given Imaging, February 2014).

Given the variance in expertise and interpretations for these techniques, it also is surprising the expert Colon Capsule Endoscopy version 2 (Given Imaging) reader reviewed 20 CCE videos, yet the CTC expert had 8 years of experience with more than 200 CTCs performed. The performance characteristics of these individuals compared with other reported expert benchmarks therefore is impossible.18,23

The discussion states that the "good sensitivity and specificity suggests that whichever procedure selected, may represent a reliable test for selecting high-risk patients not to be referred for optical colonoscopy." Although this may be the case, the data from this small study should not be the basis for such a decision. Approximately 30% of the CCE patients did not have a complete examination of the left colon, albeit in this study there were 2 other visualization tests for this area, this would not be performed if CCE had been selected as the primary strategy alone.

The investigators suggested that the low negative likelihood ratio less than 0.1 means that these 2 modalities may represent reliable test options for selecting high-risk patients who should not need a referral for colonoscopy. Likelihood ratios are used for assessing the value of performing a diagnostic test. A negative likelihood ratio (the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative) should be very powerful in limiting the need for testing beyond the test defined as negative. The small number of patients and surprisingly low level of neoplasia (and no cancers) and the proportionately wide 95% confidence interval would limit the extrapolation to patients with +FIT until studied further in a more comprehensive evaluation with an appropriately determined sample size.

This study is thought provoking, yet the message should remain clear: until we have well-validated and adjudicated evidence, a patient with a +FIT should undergo an optical colonoscopy. Mitigating circumstances aside, the message should remain resonant, in particular among primary care providers who perform these tests.

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Conflicts of interest
The author discloses the following: David Johnson has served on the advisory board of Given Imaging, has served as a consultant for Epigenomics, and has been a clinical investigator for Epigenomics and Exact Sciences.

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