Computer-Aided Detection for Computed Tomographic Colonography Screening

A Prospective Comparison of a Double-Reading Paradigm With First-Reader Computer-Aided Detection Against Second-Reader Computer-Aided Detection

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Objectives: The objective of this study was to prospectively compare diagnostic performance and time efficiency of a double-reading paradigm in which a first-reader computer-aided detection (CAD) is followed by a fast 2-dimensional review (DR FR-CAD) with those of a double reading with second-reader CAD (SR CAD).

Materials and Methods: The local ethical committee approved this study. Consecutive immunological patients who have positive results for fecal immunological test who were scheduled for colonoscopy were enrolled for a 10-month period. Computed tomographic colonography studies were read with CAD (CAD COLON-1.20; im3D, Turin, Italy) by using both SR CAD (applied after unassisted interpretation primary 2-dimensional) and DR FR-CAD (CAD-prompts evaluation followed by a fast 2-dimensional review) in randomized order with the radiologist for each reading paradigm masked to the other reader's results.

Per-patient sensitivity and specificity of unassisted and CAD-assisted readings for detecting 6-mm adenomas or larger were calculated by using unblinding colonoscopy as reference standard. Reporting times were also calculated. Pairwise comparisons were performed.

Results: A total of 182 participants (median age, 65 years; range, 58–76) were included in the final analysis. Of these, 93 (51%) had at least 1 cancer or a 6-mm adenoma or larger. At the 6-mm threshold, sensitivity of unassisted reading (79.6%; 95% confidence interval [CI], 69.9–87.2) increased significantly with the use of both SR CAD (86.0%; 95% CI, 77.3%–92.3%) and DR FR-CAD (89.2%; 95% CI, 81.1%–94.7%), without differences between CAD readings ($P = 0.500$). No significant differences in specificity among the 3 paradigms were observed. Double reading with first-reader CAD required less reading time than that for SR CAD (378 vs 496; Δ118 seconds; $P < 0.001$) and was 59 seconds longer than the unassisted reading ($P = 0.058$).

Conclusions: When compared with unassisted reading, a double-reading paradigm in which first-reader CAD is followed by a fast 2-dimensional review improves the adenoma detection rate to the same level achieved by a second-reader CAD while decreasing reporting times.

Key Words: CT colonography, computer-aided detection, screening, colon-rectal cancer, adenomas

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Computed tomographic colonography (CTC) has been considered among the available strategies for colorectal cancer (CRC) screening.[1] However, several issues still need to be addressed before the adoption of CTC as the primary test for mass screening programs. The interpretation of CTC screening is challenging. The necessity of viewing a large number of images to detect a small number of clinically significant lesions, the subtle nature of many radiological characteristics of colonic lesions, and radiologist fatigue or distraction may contribute to false-negative CTC interpretations.[2–5] Double reading of medical images has been shown to improve sensitivity in some settings, such as in the interpretation of mammograms.[6] However, CTC interpretation is time-consuming[7–9]; therefore, the involvement of an additional expert for double reading would not be cost-effective.[10] This is especially true when considering that CTC cost already needs to be reduced to become a cost-effective alternative to other screening tests.[11] Computer-aided detection (CAD) has the potential to improve the cost-effectiveness of CTC for population screening by increasing detection and/or reducing reporting times.[12] As a second-reader CAD (SR CAD), applied after a complete and unaided assessment, CAD has been shown to increase reader's sensitivity, albeit at the cost of increasing reading times.[13–18] This is generally undesirable if a large number of cases must be read sequentially as in a screening setting. A potentially more time-efficient paradigm is the first-reader CAD, in which reader's interpretation is restricted to CAD-prompts alone.[19] However, with this mode, colonic areas unprompted by CAD will be inevitably ignored and the benefit of first-reader CAD remains controversial. Furthermore, detection of colonic findings typically not targeted by CAD systems, such as masses or atypical lesions, poses challenges.[20–22]

A potential approach to overcome these limitations is to add, after CAD-prompts evaluation, a short 2-dimensional review of the unprompted areas of the colon.[23,24] A prior study on an artificially and retrospectively selected population[24] suggests that this CAD approach maintains sensitivity and specificity of unassisted reading while reducing reporting times. However, the retrospective nature of this evaluation imposes important limitations. Prospective studies are, therefore, needed to assess its diagnostic performance in a working

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Authors Correale and Bert are employees of im3D, and author Iussich is a research consultant for im3D. Authors Laudi, Campanella, Hassan, Senore, Segnan, Regge, and Galatola, who are not employees of or consultants for im3D, had control of any data and information that might present a conflict of interest for those authors who are employees of or consultants for im3D. The authors of the study did not submit preventively the manuscript of this article to the sponsors for approval. There are no other conflicts of interest to be stated.

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clinical setting. Furthermore, the issue whether this CAD reading paradigm could have advantages over the widely tested SR CAD remained unanswered. Thus, a prospective investigation on the use of different formats for CTC-CAD–assisted interpretation was warranted. This study was designed to prospectively compare diagnostic performance and time efficiency of a double-reading paradigm in which a first-reader CAD is followed by a fast 2-dimensional review (DR FR-CAD) with those of a double reading with SR CAD.

MATERIALS AND METHODS

The company im3D (Torino, Italy) supported the study by partially financing it and by providing the CAD interpretation hardware and viewing software. Two authors (L.C. and A.B.) are employees of im3D, and 1 author (G.I.) is a research consultant for im3D. All authors (including those who are employees of or consultants for the sponsoring company) gave substantial contribution to the design of the study, clinical investigation, data collection, data analysis, and/or manuscript drafting. Those authors who are not employees of or consultants for the sponsoring industry had access to and control of the data that might have represented a conflict of interest for those authors who are employees or consultants for the sponsoring company.

Design and Patient Population

This was a single-center cross-sectional study, in which each participant underwent CTC and colonoscopy on the same day. Local institutional board approval was obtained, and all participants provided written informed consent before enrollment. Patients aged 59 to 69 years with a clinical indication for colonoscopy due to a positive fecal immunological test (FIT) result from a population-based screening program[25] were eligible. Participants were excluded if they had a clinical diagnosis of familial adenomatous polyposis or hereditary nonpolyposis CRC syndrome and inflammatory bowel disease or if they had psychological or physical conditions that contraindicated colonoscopy. Enrollment started in October 2009 and finished in August 2010.

Computed Tomographic Colonography Protocol

All patients followed a low-residue diet starting 3 days before the examination and a liquid diet on the day of the examination. Bowel preparation consisted of administration of 1 sachet of Macrogol 3350-based mild laxative (Movicol; Norgine Italia, Milan, Italy) at each of the 3 main meals, starting 3 days before examination in patients who had no constipation. A 45-mL solution of phospho-soda vials (Fosfo-Soda Fleet; Bergamon, Rome, Italy) at 8 AM and 6 PM of the day before examination was used in patients with constipation (ie, frequency of defecation less than 3 times per week and stool consistency ≤3 on the Bristol stool form scale). On the day of examination, all patients ingested a 70-mL dose of sodium diatrizoate and meglumine diatrizoate solution (Gastrografin; Bayer Schering Pharma, Milan, Italy) diluted in 500 mL of water 2 hours before CTC. The patients were also asked to drink an additional 500 mL of water. The patients were placed on a computed tomographic (CT) table, and a small flexible rectal catheter was positioned. Immediately before scanning, pneumocolon was achieved by means of the inflation of carbon dioxide using automatic device (Protocol Colon Insufflator; Bracco, Milan, Italy). *n*-Butylscopolamine was not administered. Computed tomographic colonography was performed with the participant in the supine and prone positions with the following scanning protocol: 120 kilovolt (peak) (kV[p]) (140 kV[p] in patients with obesity [body mass index, >30 kg/m^2]); 50 mA s (effective) or less (without the use of any system for dose modulation); a rotation time of 0.5 to 0.7 seconds; a section thickness not greater than 1.25 mm; and a reconstruction interval of 1.25 mm. The total effective dose of the study was less than 4 mSv. The median total dose-length product for all patients was 246 mGy·cm (mean [SD], 252 [60]; interquartile range, 234–257).

Intravenous contrast medium was not used.

Computer-Aided Detection System

A commercially available visualization platform was used with an integrated CAD system (CAD COLON-1.20; im3D, Torino, Italy). The CAD algorithm and its performance have been described in detail elsewhere.[13,26–28] In brief, after electronic cleansing, the software extracts the colon from input CT images by applying a 3-dimensional region–growing algorithm. Colon surface voxels with suspicious curvature properties are then selected, and those whose shape and curvature indexes are within a predefined range are clustered according to spatial density rules to yield initial marks and candidates are extracted. A classifier using shape, density, and texture information then attributes a score to each candidate. Candidate lesions with a score higher than a certain threshold (operating point) are then shown to the user. The corresponding CAD prompts are displayed on both 2- and 3-dimensional images with rectangular bounding boxes. The CAD operative point was set by the manufacturer to reach a sensitivity of 90% (95% confidence interval [CI], 86%–93%) for lesions of 6 mm or larger, with a corresponding false-positive rate of 10 false-positives per series, as computed in a retrospective evaluation of a previously published series.[28] The selected operative point of our CAD remained constant throughout the study.

Image Interpretation

Three experienced radiologists (range, 600–1200 examinations; 5–10 years of experience, at least 200 CTC examinations verified by colonoscopy) participated in the study. All readers have been using the CAD system used for this study for at least 2 years.

Immediately before colonoscopy, the CTC study was randomly assigned to be prospectively read by using either SR CAD or DR FR-CAD paradigm by 1 of the 3 study readers. This first reading was used for segmental unblinding colonoscopy (see below). One to 2 weeks later, the study was reviewed by a second radiologist, blinded to the first CTC reading and colonoscopy results, with the opposing CAD paradigm. This reading represented the second CTC reading. Thus, each case was independently double read by 2 of the 3 study radiologists by using the 2 different CAD reading implementations (SR CAD and DR FR-CAD). For both readings, the radiologists were aware of disease prevalence and were told to ignore polyps 5 mm or less. Also, the readers were free to use the full functionality of the workstation (ie, 2-dimensional transverse images, multiplanar reconstruction, 3-dimensional view, and full endoluminal fly-through), as normally done in clinical practice.

Second-Reader CAD

We used a sequential reading design to minimize the number of reading sessions required in our study. In the first phase, the radiologists interpreted the study without activating the CAD algorithm. A 2-dimensional primary reading mode with the use of 3-dimensional viewing for problem solving was used in this phase. This interpretation served as benchmark for unassisted CTC performance. The radiologists documented polyp morphology as well as its maximal transverse diameter and assigned each finding to the colonic segment. The position on CT images of each detected lesion was marked by drawing a 3-dimensional region of interest with freehand tool imbedded in the software. The radiologists also provided the overall confidence that the case was abnormal (scored from 0 [least confident] to 100 [most confident]), and they assessed the images according to C-RADS guidelines.[29] *Interpretation time* (defined as the time taken to read the data once loaded on the workstation) was automatically recorded. Once the unassisted reading was complete,

the results were locked by the software (ie, it was impossible for the readers to change the results of unassisted interpretation). At this stage, the radiologist activated the CAD system, which pinpointed a series of lesion candidates on both prone and supine acquisitions. The radiologists then examined all lesion candidates by using both 2-and 3-dimensional viewing. Each lesion candidate was systematically rejected as a CAD false-positive finding or accepted as an additional lesion. Any additional lesion was documented by the readers exactly as done in the previous phase. The time taken for additional CAD-assisted review, the overall reader confidence, and the C-RADS score were recorded, as described before. For each lesion reported at this phase, the 3-dimesional box on CT images automatically estimated by the CAD was also stored.

Double Reading With First-Reader CAD

A sequential reading mode was used. In the first phase, the radiologist activated the CAD system and then examined all lesion candidates, on both prone and supine series, by using both 2- and 3-dimensional viewing. Each lesion candidate was systematically rejected as a CAD false-positive finding or accepted as a suspicious abnormality. This phase of reporting was defined as *FR-CAD*. Documentation of perceived abnormalities, the overall diagnostic confidence, C-RADS score, and the reading time were noted as described previously. Also, positions of all accepted CAD findings were recorded by saving the 3-dimensional boxes on CT images automatically estimated by the CAD. After evaluating the CAD detections, an additional quick 2-dimensional evaluation of the data set was performed in both supine and prone positions to address areas unprompted by CAD. Any additional detection was documented exactly as before and was manually marked by the reader by tracing a 3-dimensional box on CT images containing the lesion. The overall diagnostic confidence, C-RADS score, and the reading time used in this phase were automatically recorded for each patient.

Colonoscopy Protocol

Bowel Preparation

Colon hydrotherapy (HCT)[30,31] was used as bowel preparation for the subsequent colonoscopy. The procedure was performed by appropriately trained nurses at least 1 hour after CTC examination. In the left lateral position, a rectal speculum was positioned and connected to the HCT apparatus (Hydroterapy CD mod. 004 RA; Bionex S.R.L., Milan, Italy). The patient was then rotated in the supine position, and purified, ultraviolet light-irradiated water, preheated to a temperature comprised between 36°C and 39°C, was infused through the rectal tube at low pressure (filling phase). The flow was stopped at the onset of an urgency to evacuate, and the outflow valve was opened, allowing spontaneous emptying of bowel contents (emptying phase). During the emptying phase, the operator performed a gentle circular massage of the abdominal wall to help loosening the stool residues from the colon wall and to encourage peristalsis. A series of filling and emptying phases were carried out until the discharging effluent was clear of fecal matter. The speculum was then removed. Time taken to complete the HCT sessions varied between 25 and 85 minutes with a mean of 55 minutes (range, 15–85 minutes).

Colonoscopy Procedure

Colonoscopy was performed at least 3 hours after CTC. Patient sedation was not used according to the common clinical practice of our institute. The endoscope was advanced to the cecum, and the entire length of the bowel was examined during endoscope withdrawal. The endoscopist was initially blinded to the result of CTC; at the end of each bowel segment evaluation, CTC results for that segment were disclosed (segmental unblinding). If a lesion measuring 6 mm or larger was seen at CTC but missed at colonoscopy, the segment was carefully re-examined to resolve discrepancy, as previously reported.[32] All detected lesions were photographed and measured by using the open biopsy forceps. Visible lesions were endoscopically removed; those retrieved were sent for local pathologist evaluation and classified according to the World Health Organization criteria.[33] Complications occurring during or immediately after colonoscopy (eg, bleeding, perforation) were systematically recorded.

Matching of CTC Detections With CC Polyps

A lesion found at the first CTC reading (by using either SR CAD or DR FR-CAD) was matched to a corresponding one found at colonoscopy when it was in the same or an adjacent colonic segment and its size differed by no more than 50%.[9] Matching was performed during the colonoscopy procedure. To match a lesion found at the second CTC reading (by using either SR CAD or DR FR-CAD) to a corresponding one found at colonoscopy, a lesion matching process was electronically performed as follows. A CTC finding was matched to a colonoscopy polyp if (1) there were location matches between CTC and colonoscopy within 1 colonic segment and size matches within a 50% error margin or (2) if there was an overlap between the bounding box of this lesion and that of a lesion reported at the first CTC reading with a matching polyp on colonoscopy. This criterion was overruled by the first criterion for polyps found at colonoscopy that were not found at the first CTC interpretation. An experienced radiologist (G.I.) adjudicated discrepancies in the results of the lesion-matching analysis.

The Reference Standard

The reference standard was unblinded colonoscopy, along with a histologic evaluation of the removed lesions. *Advanced adenomas* were defined as lesions showing high-grade dysplasia, more than 20% villous component, or a size of 10 mm or larger. *Advanced neoplasia* was defined as cancer or advanced adenoma. We grouped serrated sessile adenomas and other adenomas together unless they had specific features of advanced adenomas. The primary study metric was performance for adenoma detection. Therefore, a negative result at reference standard was assigned to all patients with no 6-mm adenomas or larger at endoscopy; otherwise, the patients were assigned a positive result. When 2 or more adenomas were removed in the same patient, the one with the worst histology was classified as the index lesion; for multiple lesions with the same histology, the largest one was considered.

Statistical Analysis

Statistical analyses were performed by using software R (The R Foundation for Statistical Computing).[34] All statistical tests were 2-sided and were considered statistically significant at $P < 0.05$. All CIs were reported at the 95% level.

Primary End Points

The primary end point of the study was the per-patient sensitivity and specificity of CTC with unassisted reading, SR CAD, and DR FR-CAD for detecting patients with at least one 6-mm adenoma or larger. We defined, as a positive CTC result with each reading paradigm, the identification of at least one 6-mm lesion or larger. This determination was then deemed as either a true positive or false positive depending on whether the reference standard confirmed the presence of a 6-mm adenoma or larger. Negative results of CTC with each reading paradigm were similarly deemed as true negatives or false negatives depending on the results of the reference standard. Sensitivity, specificity, positive predictive value, and negative

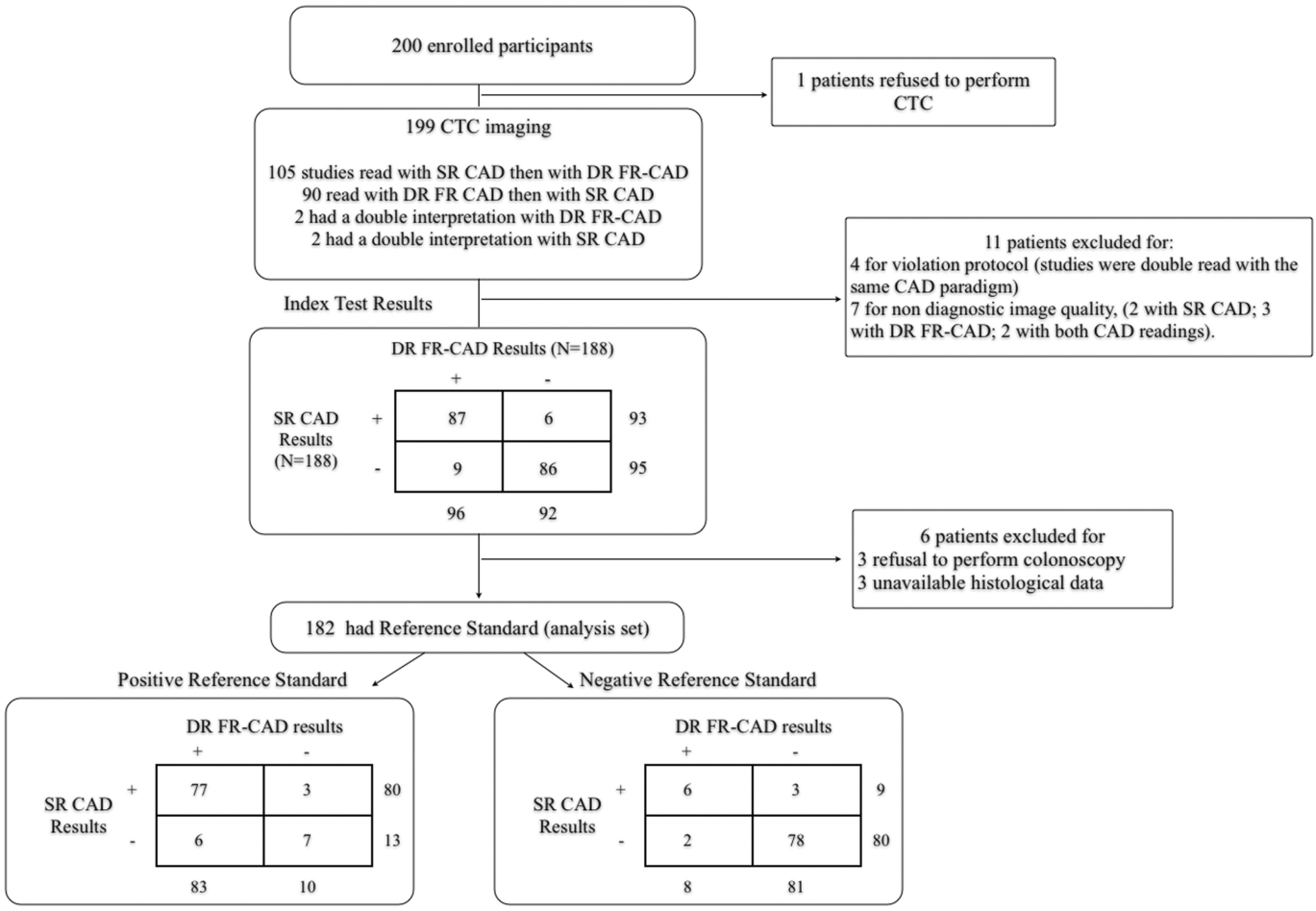

FIGURE 1. Flow diagram of the study.

predictive value, along with 95% CIs, were calculated for each reading modality according to lesion size range. The McNemar test for correlated proportions was used to assess significance for differences in sensitivity and specificity. Accuracy of all reading modalities was also assessed with the use of receiver operating characteristic (ROC) curves. The ROC curves were estimated from the continuous confidence scale with the use of data pooled among the radiologists because of the small number of positive cases read by each radiologist. Smooth ROC curves were generated under binomial assumptions by using software implemented for the R statistical system.[35] Interpretation times were compared by using paired *t* test. The relationships between the reporting time and the number of CAD prompts per series and the reporting time and reading methods were analyzed by mixed-effects regression model[36,37] to account for the data correlation (ie, the same cases read with all reading modalities).

Secondary End Points

Additional secondary analyses focused on the evaluation of per-polyp performance. Per-polyp sensitivity of CTC with each reading modality was calculated as the percentage of matching findings among all lesions sized in the range of interest that were found at colonoscopy, using the matching algorithm described previously. Per-polyp analysis was not limited to adenomas.

Multivariate logistic regression analysis was undertaken to identify factors associated with the risk for missing polyps at CAD-assisted reading. We fitted a model in which polyps were considered as random, but CAD reading modality and polyp features were considered as fixed.[36,37] Tests of interaction assess whether there is any important effect modification, for example, whether the effect of 1 factor (such as reader paradigm) changes for different levels of other factors (such as polyp histology or morphology). To assess the validity of the mixed-effects analyses, we performed likelihood ratio tests comparing the models with fixed effects to the null models with only the random effects. We rejected results in which the model including fixed effects did not differ significantly from the null model. Data were presented as odds ratios (ORs) and 95% CIs.

Sample Size Estimate The sensitivity of SR CAD in detecting patients with 6-mm adenomas or larger was estimated to be approximately 85% with a specificity of 90%.[13] A power calculation (at 5% significance and 80% power) performed on the basis of these estimates suggested that at least 84 patients containing at least one 6-mm adenoma or larger were required to detect a 10% difference in adenoma detection between SR CAD and DR FR-CAD (85% vs 75%). Because the expected prevalence of target cases was originally estimated to be approximately 45%, it was calculated that at least 190 participants would have to be enrolled for the study.

RESULTS

Two hundred participants were enrolled in the study. Of these, 18 patients were excluded from the analysis because of the following

reasons: 1 patient for CTC refusal, 4 for protocol violation (CTC studies read by 2 radiologists with the same CAD paradigm), 7 for nondiagnostic image quality (2 studies were judged as nondiagnostic examinations with SR CAD; 3, with DR FR-CAD; and 2, with both CAD readings), and 6 for missing data on reference standard (3, colonoscopy refusal; 3, histological data unavailable). Thus, the final population was 182 (91.4%) participants (Fig. 1). Patient demographics and clinical characteristics are listed in Table 1. The median age was 65 years (range, 58–76 years), and there was no age difference between men (median, 65 years; range, 59–77 years) and women (median, 65 years; range, 58–76 years) ($P = 0.900$). At colonoscopy, cecal intubation was achieved in 178 cases, accounting for a completion rate of 98%. No lesion of 6 mm or larger was detected at CTC in the segments not reached in the incomplete colonoscopies. At reference standard, 93 (51%) patients were reported as having positive findings (ie, containing at least one cancer or 6-mm adenoma or greater). Thirteen (7%) and 63 (34%) patients were found to have a cancer and an advanced adenoma as the most severe lesion, respectively. Using a CTC cutoff size of 6 mm, unassisted, SR CAD, and DR FR-CAD reading yielded positive results in 80 (44%), 89 (49%), and 91 (50%) patients, respectively.

Per-Patient Analysis

Table 2 shows per-patient performance of each reading modality. At 6-mm threshold, CTC sensitivity in detecting adenomas with unassisted reading was 79.6% (95% CIs, 69.9–87.2). Sensitivity increased significantly with the use of SR CAD (86.0%; 95% CIs,77.3–92.3; $P = 0.020$) and DR FR-CAD (89.2%; 95% CIs, 81.1%–94.7%, $P = 0.030$), with no significant differences between CAD paradigms ($P = 0.500$). Also, sensitivity of FR CAD alone (84.5%; 95% CIs, 76.0%–91.5%) was not significantly lower than that of either SR CAD ($P = 1.000$) or DR FR-CAD reading ($P = 0.130$). At 10-mm threshold, sensitivity of unassisted reading (93.3%) for detecting adenomas larger than 9 mm at colonoscopy was not significantly inferior to that of SR CAD (97.6%, $P = 0.400$) and that of DR FR-CAD (98.6%, $P = 0.500$). All patients with cancers were detected with all 3 reading strategies for a sensitivity of 100%. Of the 80 patients with positive findings detected with SR CAD, 6 patients (4 advanced adenomas, 2 adenomas) initially missed on the unassisted reading were identified during the CAD component of the second-reader paradigm. Of the 83 patients with positive findings detected with DR FR-CAD, 4 patients (one 33-mm cancer, 2 advanced adenomas, 1 adenoma) originally missed by CAD were identified during the 2-dimensional review component of DR FR-CAD. During the unassisted reading, there were 6 patients who are false positive for a specificity of 93.3% (83/89); the application of SR CAD resulted in a total of 3 additional false-positive cases, for a specificity of 89.9% (80/89; $P = 0.300$). At the FR-CAD reading, 6 patients with negative findings were incorrectly classified as individuals with 6-mm lesions or larger, for a specificity of 93.3% (83/89); application of the 2-dimensional review resulted in a total of 2 additional false-positive cases for a specificity of 91.0% (81/89; $P = 0.480$). Diagnostic performances of CTC reading paradigm assuming a 10 mm polyp size threshold for colonscopy referral are shown in Supplemental Digital Content 1 (http://links.lww.com/RLI/A140).

The number of CAD prompts per series did not adversely influence the readers' specificity for both CAD paradigms; at the multivariate analysis, the ORs of having a false positive per 1-unit increase in the number of CAD prompts were 1.1 (95% CI, 0.96–1.2; $P = 0.200$) for SR CAD and 0.99 (95% CI, 0.88–1.1; $P = 0.800$) for DR FR-CAD. The reader individual performances are listed in Supplemental Digital Content 2 (http://links.lww.com/RLI/A113). The individual sensitivity ranged from 74% to 85% ($P = 0.700$) for the unassisted reading, from 84% to 89% ($P = 0.800$) for SR CAD, and from 80% to 96% ($P = 0.400$) for DR FR-CAD. The individual specificity ranged between 91% and 95% ($P = 0.401$) for the unassisted reading, between 88% and 91% ($P = 0.917$) for SR CAD, and between 80% and 95% ($P = 0.200$) for DR FR-CAD.

TABLE 1. Characteristics of the Study Participants and Clinical Results

Characteristics	No. Patients (N = 182)
Age at enrollment, y	
Median (range)	65 (58–76)
Sex, n (%)	
Female	78 (43)
Male	104 (57)
CAD reading-paradigm order, n (%)	
First CTC interpretation* using CAD as second reader	97 (53)
First CTC interpretation* using double reading with first-reader CAD	85 (47)
Colorectal lesions, n (%)	
Negative for cancer or adenoma measuring 6 mm or larger on CC	89 (49)
No lesions	58 (32)
Advanced adenoma <6 mm	6 (3.3)
Nonadvanced adenoma <6 mm	17 (9.3)
Nonadenomatous polyps†	8 (4.4)
Positive for cancer or adenoma measuring 6 mm or larger on CC	93 (51)
Advanced adenoma 6–9 mm	15 (8.2)
Advanced adenoma ≥10 mm	48 (26.4)
Nonadvanced adenoma 6–9 mm	17 (9.3)
Carcinoma‡	13 (7.1)

*First CTC interpretation: the first CTC evaluation immediately before CC examination.

†In 8 cases, the index lesion was nonadenomatous: in 3, 3, and 2 cases, this was a hyperplastic polyp measuring 5 mm or less, a hyperplastic polyps of 6 mm in size, and a normal mucosa 5 mm or less, respectively.

‡ One cancer measured 7 mm on CC.

CAD indicates computer-aided detection; CC, colonoscopy; CTC, computed tomographic colonography.

Receiver Operating Characteristic Analysis

The mean area under curve (AUC) was 86.5% (95% CIs, 81.3%–91.8%) for the unassisted reading; 90.1% (95% CIs, 85.4%–94.7%) for SR CAD, and 92.0% (95% CIs, 87.9%–96.1%) for DR FR-CAD. The use of CAD resulted in a statistically significant increase in the mean AUC: the improvement was 4% (95% CIs, 0.6%–6%) with SR CAD ($P = 0.019$) and 5% (95% CIs, 0.6%–10%) with DR FR-CAD ($P = 0.027$). No statistically significant differences in AUC were seen between the SR CAD and DR FR-CAD paradigm ($P = 0.330$).

Reporting Times

The mean reporting time of the unassisted reading was 318 seconds (95% CI, 264–371). The SR CAD added a mean of 177 seconds (95% CIs, 137–217) to the unassisted reading (56% increase). When DR FR-CAD was used, the mean reporting time for the reader evaluating CAD prompts was 261 seconds (95% CIs, 218–305); an additional 113 seconds (95% CIs, 97–135) was required for the 2-dimensional review (43% increase). The DR FR-CAD required less reading time than that for SR CAD (378 vs 496;

TABLE 2. Per-Patient Diagnostic Performance of Each Reading Modality Per Lesion Size Category

	Unassisted Read	SR CAD	FR-CAD	DR FR-CAD	*P*
Sensitivity, %					
≥6 mm	79.6 (74/93)* (69.9, 87.2)	86.0 (80/93)* (77.3, 92.3)	84.9 (79/93)‡ (76.0, 91.5)	89.2 (83/93)*‡ (81.1, 94.7)	0.500
≥10 mm	93.3 (56/60) (84.3, 98.1)	96.7 (58/60) (84.5, 99.6)	95.0 (57/60)† (86.1, 99.0)	98.3 (59/60)† (91.1, 99.9)	1.000
Specificity, %					
≥6 mm	93.3 (83/89) (85.9, 97.5)	89.9 (80/89) (81.6, 97.1)	93.3 (83/89) (85.9, 97.5)	91.0 (81/89) (83.1, 96.0)	1.000
≥10 mm	92.6 (113/122) (86.5, 96.5)	92.6 (113/122) (86.5, 96.6)	93.4 (114/122) (87.4, 97.1)	93.4 (114/122) (87.4, 97.1)	1.000
PPV, %					
≥6 mm	92.5 (74/80) (84.4, 97.2)	89.9 (80/89) (81.6, 95.3)	92.9 (79/85) (85.3, 97.4)	91.2 (83/91) (83.4, 95.1)	0.884
≥10 mm	70.0 (56/80) (58.7, 79.7)	65.2 (58/89) (54.3, 74.9)	67.1 (57/85) (56.0, 76.8)	64.9 (59/91) (54.1, 74.6)	0.879
NPV, %					
≥6 mm	81.4 (83/102) (72.4, 88.4)	86.0 (80/93) (77.3,92.3)	87.4 (83/95) (79.0, 93.3)	89.0 (81/91) (80.7, 94.6)	1.000
≥10 mm	96.0 (98/102) (90.2, 98.9)	97.8 (91/93) (92.4, 99.7)	96.9 (94/97) (91.2, 99.4)	98.9 (90/91) (94.0, 99.9)	0.659

Diagnostic performances for adenoma detection are expressed as percentage (number/total number). The 95% confidence intervals are within parentheses.

Positive predictive value indicates the proportion of patients with positive findings at CTC (with a size cutoff of 6 mm) who had lesions on colonoscopy (of specified size).

Negative predictive value indicates the proportion of patients with negative findings at CTC (with a size cutoff of 6 mm) who had also no lesions colonoscopy (of specified size).

* At 6-mm threshold, unassisted reading was significantly less sensitive to detect adenomas compared with both CAD reading paradigms ($P = 0.020$ for SR CAD and $P = 0.039$ for DR FR-CAD). Also, sensitivity of FR-CAD was not statistically different than that of the unassisted reading ($P = 0.332$), SR CAD ($P = 1.000$), and DR FR-CAD ($P = 0.130$).

†At the 10-mm threshold, sensitivity of the unassisted reading was not less than that of SR CAD ($P = 0.400$) and DR FR-CAD ($P = 0.500$). Also, differences in sensitivity between FR-CAD and DR FR-CAD reading were not statistically significant ($P = 0.250$).

DR FR-CAD indicates double-reading with FR-CAD; FR-CAD, computer-aided detection as a first reader; NPV, negative predictive value; PPV, positive predictive value; *P*, comparison between SR CAD versus DR FR-CAD; SR CAD, computer-aided detection as a second reader.

Δ118 seconds; 95% CI, 52–185; $P < 0.001$) and was 59 seconds (95% CI,1–116) longer than that for the unassisted reading ($P = 0.058$). The regression coefficient relating the number of CAD prompts to CAD reporting time was 13.3 seconds (95% CIs, 5–22; $P = 0.036$) for DR FR-CAD and 8.5 seconds (95% CI, 0.07–17.3; $P = 0.046$) for SR CAD. Difference in regression coefficients was not statistically significant ($P = 0.33$). Finally, interpretation of every additional CAD prompts increased unassisted reporting time by 11.7 seconds (95% CIs, 1.6–22.3; $P = 0.026$) with DR FR-CAD and by 6.9 seconds (95% CIs, −3.5 to 17.1; $P = 0.19$) with SR CAD.

Per-Polyp Analysis

Colonoscopy identified 163 lesions of 6 mm or larger of any histological type in 96 patients. Blinded colonoscopy missed 2 polyps: one 6-mm pedunculated adenoma in the transverse colon and one 6-mm sessile adenoma in the rectum. The distribution, histological type, and size of the lesions observed at colonoscopy are listed in Supplemental Digital Content 3 (http://links.lww.com/RLI/A114). There were one hundred sixty-three 6-mm lesions or larger, regardless of the histological type, in the 96 patients. Of these, 93 (57%) lesions fell into the small (6–9 mm) size category. Within this subgroup of small polyps, 1 (1%) was a cancer, 30 (32%) were advanced adenomas, 54 (58%) were adenomas, and 8 (9%) were nonadenomatous polyps. Of the seventy 10-mm lesions or larger, 12 (17%) were cancers and 58 (83%) were advanced adenomas.

Stand-Alone CAD Performance

At a prompts rate of 11.6 (SD, 6.5; range, 1–40; median, 10) per series, the CAD sensitivity for lesions of any histology was 85% (139/163; 95% CI, 79%–90%) and 91% (64/70; 95% CI, 82%–97%) at 6- and 10-mm threshold sizes, respectively. The CAD sensitivity for cancer was 85% (11/13; 95% CI, 56–98). Of the 24 lesions unprompted by CAD, 7 (29%) polyps were invisible on CTC retrospective evaluation. As shown in Table 3, CAD sensitivity was higher for advanced adenomas compared with that of polyps of other histology (ORs, 2.9; 95% CI,1–8.6; $P = 0.030$). There was no significant correlation between CAD sensitivity and lesion shape ($P = 0.700$). Similarly, there were no significant differences in sensitivity for left-sided polyps compared with right-sided polyps (89% vs 83%; $P = 0.300$).

Per-Polyps Sensitivity of the Readers

Table 3 shows polyp detection of each reading mode according to various polyp characteristics.

All 13 cancers were correctly diagnosed in the unassisted reading phase of SR CAD. Two cancers unprompted by CAD were

TABLE 3. The CTC Sensitivity For Lesions Detected at Colonoscopy According to Morphologic and Histologic Features

Category	Stand-alone CAD	Unassisted Reading	SR-CAD	FR-CAD	DR FR-RAD	*P**
All polyps						
≥6 mm	85 (139/163) (79 90)	65 (106/163)† (57, 72)	75 (123/163) (69, 82)	67 (110/163 (60, 75)	73 (119/163) (66, 80)	0.584
≥10 mm	91 (64/70) (83–97)	91 (64/70)† (83, 97)	96 (67/70) (89, 99)	86 (60/70) (75, 93)	91 (64/70) (82.3, 96.8)	0.449
Cancers						
≥6 mm	85 (11/13) (55, 98)	100 (13/13) (75, 100)	100 (13/13) (75, 100)	85 (11/13) (55, 98)	100 (13/13) (75, 100)	1.000
≥10 mm	83 (10/12) (52, 98)	100 (12/12) (74, 100)	100 (12/12) (74, 100)	83 (10/12) (52, 98)	100 (12/12) (74, 100)	1.000
Advanced adenoma						
≥6 mm	91 (80/88) (83, 96)	82 (72/88) (72, 89)	89 (78/88) (80, 94)	83 (73/88) (73, 90)	85 (75/88) (76, 92)	0.579
≥10 mm	93 (54/58) (83, 98)	90 (52/58) (79, 96)	95 (55/58) (86, 99)	86 (50/58) (75, 94)	90 (52/58) (79, 96)	0.450
Nonadvanced Adenomas						
≥6 mm	78 (42/54) (64, 88)	33 (18/54) (21, 47)	46 (25/54) (34, 62)	43 (23/54) (29.3, 56.8)	50 (27/54) (36, 63)	0.610
Nonadenomatous polyps						
≥6 mm	75 (6/8) (35, 97)	38 (3/8) (9, 76)	88 (7/8) (47, 99)	62.5 (5/8) (24.5, 91.5)	50 (4/8) (16, 84)	0.300
Sessile	82 (55/67) (71, 90)	48 (32/67) (35, 60)	61 (41/67) (49, 74)	59.0 (39/67) (46, 71)	68 (43/67) (55, 79)	1.000
Pedunculated	86 (64/74) (77, 93)	77 (57/74) (66, 86)	85 (63/74) (75, 92)	75.7 (56/74) (64, 85)	78 (58/74) (67,87)	0.3
Flat (a lesion having a height <one half the width)	89 (8/9) (52, 100)	44 (4/9) (14,79)	67 (6/9) (30, 93)	56 (5/9) (21, 86)	56 (5/9) (21, 86)	1.000
Stenosing lesions	88 (6/7) (42–100)	100 (7/7) (59–100)	100 (7/7) (59–100)	100 (7/7) (59–100)	100 (7/7) (59–100)	1.000
Vegetating lesions (endoluminal growing lesion with a maximum diameter of >3 cm)	100 (7/7) (54–100)	100 (6/6) (54–100)	100 (6/6) (54–100)	100 (6/6) (54–100)	100 (6/6) (54–100)	1.000
Left lesions	83 (85/102) (75–90)	72 (73/102) (62–80)	81 (83/102) (72–88)	72 (73/102) (62–80)	80 (82/102) (71–87)	1.000
Right lesions	88 (54/6) (78–95)	54 (33/61) (41–67)	66 (40/61) (52–77)	56 (34/61) (42–69)	61 (37/61) (47–73)	0.645

Sensitivities for detection of lesions are expressed as percentage (number/total number). The 95% confidence intervals are within parentheses.

**P* value for the comparison between SR CAD and DR FR CAD.

†Compared with the unassisted reading, polyp detection significantly increased by using both SR CAD ($P < 0.001$) and DR FR-CAD ($P = 0.040$). Differences in polyp detection were not statistically significant for lesions larger than or equal to 10 mm ($P = 0.248$ and $P = 1.000$ for SR CAD and DR FR-CAD, respectively).

CAD indicates computer-aided detection; CTC, computed tomographic colonography; DR FR-CAD, double-reading with FR-CAD; FR-CAD, computer-aided detection as a first reader; SR CAD, computer-aided detection as a second reader.

marked by the radiologists alone during the 2-dimensional review component of DR FR-CAD. Per-polyp sensitivities of both SR CAD and DR FR-CAD readings were significantly higher than that of the unassisted reading. According to the multivariate analysis (Table 4), the effect of CAD-reading mode on missed detections was not significant (ORs, 0.9; 95% CIs, 0.5–1.8; $P = 0.868$). Of polyps at least 6 mm in diameter, low-risk adenomas (ORs, 6.7; 95% CIs, 3.6–12.7; $P < 0.001$) and polyps unprompted by CAD (ORs, 5.0; 95% CIs, 2.0–12.0; $P = 0.004$) had a greater risk to be missed. No interactions between reading mode and CAD-prompted polyps ($P = 0.397$) and between reading mode and polyp histology ($P = 0.398$) were found. However, there was evidence for a 2-way interaction between histology and polyp size: for a low-risk adenoma, the risk for missed detections decreased with increasing polyp size (ORs, 0.37; 95% CIs, 0.18–0.78; $P = 0.03$), whereas, for an advanced adenoma, the risk did not seem to have any obvious relation with polyp size (ORs, 0.9; 95% CIs, 0.8–1.03; $P = 0.130$). Polyps having pedunculated (ORs, 0.14; 95% CIs, 0.03–0.57; $P = 0.006$) or sessile (ORs, 0.27; 95% CI, 0.06–1.04; $P = 0.074$) shape were less likely to be missed than flat lesions. An example of a polyp detected using CAD is provided in Figure 2.

Assessment of False-Positive Detections

During the unassisted analysis, there were 19 false-positive detections of 6-mm adenoma or larger in 16 patients (size range, 6–27 mm,

TABLE 4. Results of Multiple Logistic Regression Modeling

Variable	Odds Ratio	*P*
Histological type	<0.001	
Advanced Adenoma (ref)	1.0	
Low-risk adenoma	6.7 (3.6, 12.7)	
CAD-reading mode		
DR FR-CAD (ref)	1.0	0.868
SR CAD	0.9 (0.5, 1.8)	
CAD detections		
Prompted polyps (ref)	1.0	0.004
Unprompted polyps	5.0 (2.0, 12.0)	
Morphology		
Flat polyp (ref)	1.0	
Pedunculated polyp	0.14 (0.05, 0.5)	0.006
Sessile polyp	0.27 (0.06, 0.9)	0.073
Polyp diameter × histology		
Polyp diameter × advanced adenoma	0.9 (0.8, 1.03)	0.130
Polyp diameter × low-risk adenoma	0.37 (0.18, 0.77)	0.003

Data are the odds of a polyp being incorrectly missed with CAD either for the 1-unit increase in the explanatory variable (for variables on a continuous scale) or for each category relative to the odds of baseline category (for categorical explanatory variables). Data in parentheses are 95% confidence intervals.

Last row highlights the interaction between polyp size and histology.

In the model polyp, diameter is entered as a continuous determinant, being fit using 2 different indicator variables to advanced adenoma and low-risk adenoma.

Table reports the estimated effect of polyp diameter on the odds of false negatives in each histological group.

CAD indicates computer-aided detection; DR FR-CAD, double-reading with FR-CAD; SR CAD, computer-aided detection as a second reader; reference category.

see Supplemental Digital Content 4, http://links.lww.com/RLI/A115). Application of SR CAD resulted in a total of 8 additional false positives in 8 patients. With the DR FR-CAD reading, there were 16 false positives in 12 patients; 2 of these were false positives (13 mm, bulbous fold; 30 mm, normal anatomy) and were incorrectly reported during the 2-dimensional review component of DR FR-CAD. Of the 14 CAD detections incorrectly accepted as polyps during the FR-CAD reading, 12 matched false positives of the unassisted reading. Regardless of paradigm, the most frequent source of false positives was fecal or fluid residues.

DISCUSSION

According to our prospective study, DR FR-CAD appeared to be equally effective and more time-efficient in detecting patients with 6-mm or larger adenomas than SR CAD did in a selected setting represented by the workup of patients with positive FIT results in the context of a population-based screening program. Of note, we restricted our primary analysis to the detection of neoplastic rather than morphological equivalents, underlining the clinical importance of our results. The results of our study are relevant for several reasons.

First, this is the first time that a more automatized human-CAD integration paradigm has been shown to be equally effective and more efficient than the conventional second-reader mode. In other words, the addition of the human component to the first-reader CAD as a quick correction of eventual electronic (CAD) errors appeared to be superior in terms of time efficiency to the addition of an electronic control to a more prolonged unassisted human reading. Shortening interpretation time (while maintaining an equally high sensitivity) may be important if a large number of cases must be read sequentially, which could be the case, in the future, if CTC will be implemented as a primary screening strategy in low-prevalence populations. Second, our study has shown that the addition of a post-CAD human check in the DR FR-CAD scenario allowed the detection of 2 invasive cancers that would have been missed by the implausible use of CAD as the only reader in a clinical setting. Indeed, a simple FR-CAD paradigm without full 2-dimensional review would have missed 2 cancers. Thus, limiting the human reading to accept or reject CAD prompts, as previously done in studies on CAD as first reader,[19] would seem at least questionable. Third, our prospective study showed the superiority of CAD-assisted paradigms to a solely human-unassisted reading, indicating the usefulness of the implementation of such CAD-assisted paradigms at least in a screening setting. Of note, this is the first time that DR FR-CAD appeared to be statistically significantly more accurate than unassisted reading, whereas DR FR-CAD was only shown to be noninferior to the unassisted reading in our previous study.[24] Moreover, our study confirmed that the CAD-related increase in sensitivity is not associated with a relevant reduction in specificity,[13,15,38] further supporting the efficiency and cost-effectiveness of CAD-assisted paradigms in this setting.

Fourth, our prospective study confirmed the preliminary evidence that the actual CAD contribution to CTC sensitivity is limited to 6 to 9 mm adenomas,[13] the sensitivity for 10-mm lesions or larger being unaffected by the CAD implementation in our analysis. Even if the relatively high prevalence of advanced neoplasia within 6 to 9 mm lesions might be related to the selection in our study of participants with positive FIT findings, who are probably more likely to harbor advanced lesions, the increased sensitivity for adenomas of CAD reading would still be clinically relevant in a screening population. Using CTC as a primary screening strategy, the examination would likely be offered only at long intervals (5–10 years); therefore, the issue of missed lesions might be relevant even among people with a lower prevalence of advanced lesions.

Fifth, our multivariate analysis showed that the CAD-detected polyps were more likely to be diagnosed, irrespective of the selected reading paradigm, indicating that CAD features are intrinsic characteristics of CTC-detectable lesions, further validating the addition of CAD to human reading in CTC setting.[39] Indeed, the fact that a small percentage (<15%) of polyps would be unmarked by CAD does not seem to influence reader sensitivity with CAD because most of these would be dismissed anyway at the unassisted reading. Independent from the reading mode, advanced adenomas had greater chance to be correctly detected than did low-risk adenomas; however, for the low-risk adenomas, the chance increased with increasing polyp size.

Validation of a new technology is essential before its implementation into clinical practice. Thus, we used a rigorous and sequential approach to verify the clinical utility of DR FR-CAD that moved from its initial validation[24] to the present clinical verification by using an independent clinical data set. The 2 studies we performed are substantially different because of hypotheses, study populations, readers, comparators, and methods. Our earlier research was a retrospective study, whereas this one was prospective. Data from retrospective studies could not reflect the additional factors that may influence reader performance when using CAD in a daily clinical activity. The risk of this effect may have been particularly high with our earlier study given the small sample size and the artificially enriched cohort. Also, our early research investigated the diagnostic performance of DR FR-CAD in comparison with that of the unassisted reading. Thus, there was no evidence of the benefits of this CAD reading mode in comparison with those of second-reader CAD. Therefore, a larger study in a specific population that simulated the real-work practice conditions was necessary to fully evaluate the clinical potential of DR FR-CAD reading paradigm.

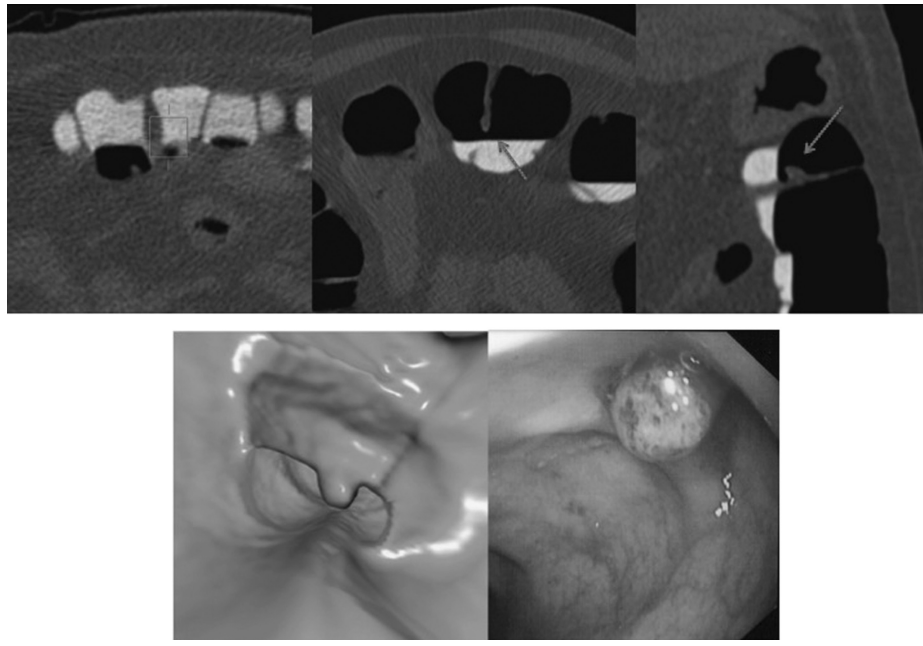

FIGURE 2. A 7-mm pedunculated advanced adenoma in the transverse colon in a 66-year-old man with positive FIT findings in the screening program. The polyp was detected during the first-reader CAD component of the DR FR-CAD paradigm. A, Prone axial image of the polyp marked by CAD (yellow bounding box). B, Supine axial image of the polyp not marked by CAD (pointed out by the red arrow). C, Supine sagittal view of the polyp (pointed out by the red arrow). D, Three-dimensional endoluminal view. E, Endoscopic view.

The strength of this study is that it has a prospective design; thus, this is the first time that different CAD readings strategies were compared in a clinical environment and not, as previous studies, in a laboratory setting.[40] Also, different from our previous study,[24] no artificial selection of patients was performed. The study population was homogeneous, and patients with positive FIT findings from a population-based screening were consecutive and prospectively enrolled. Therefore, the observed prevalence of diseases ensures that the findings reported here can be generalized to the study sample to the entire population. Of note, the patients with positive FIT findings in previous CAD studies were not recruited from a screening population.[13] Such population represents an ideal setting to assess test accuracy among asymptomatic patients, as already reported.[8] The use of unblinding colonoscopy had a positive effect on the performance characteristics found in our study. However, there were limitations. Colonoscopy was performed immediately after the first CTC interpretation and random allocation of the cases to either SR CAD or DR FR-CAD was used to reduce potential biases in the comparison of the 2 CAD readings. In our study, the readers' performance immediately before activating SR CAD served as the unassisted performance accuracy. This sequential design is less time-consuming and much less expensive to complete with respect to a full crossover study where all images were separately read without and with CAD. Sequential design may bias reader performance because observers may perform differently when they know they will soon be shown the CAD marks. However, in our study, adenoma detection of the unassisted reading for adenoma detection was 80%, which is well within the range of data in many prior CTC studies.[7] Thus, this may be indirect evidence that the readers were vigilant during the unassisted interpretation and that they did not activate CAD prematurely. The study readers had considerable experience in CTC; thus, our results may not be able to be generalized to less-experienced radiologists. Such a study design prevented us from performing a statistical analysis of interreader variability in the impact of CAD among the different readers because a much larger sample size would have been needed. Similar to other studies,[7] we deliberately powered the study only with 6-mm adenomas or larger, which the radiology community has considered clinically important.[41] Although hyperplastic polyps may seem indistinguishable from adenomas on CTC images, they have no malignant potential and consequently, it is less important to detect them. However, we also performed a per-polyp analysis for detection of all lesions, without histological restriction. Finally, our results reflect one particular CAD system; therefore, they may not be generalized to other systems. Further studies on larger populations, using different CAD schemes, will be needed to understand how system design and performance may affect results.

In conclusion, when compared with unassisted reading, a double-reading paradigm in which first-reader CAD is followed by a fast 2-dimensional review improves the adenoma detection rate to the same level achieved by a second-reader CAD while decreasing reporting times. Therefore, it may be an attractive reading in a screening setting, where cost-effectiveness is an issue.

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