Efficacy of Computer-aided Detection as a Second Reader for 6–9-mm Lesions at CT Colonography: Multicenter Prospective Trial[1]

Daniele Regge, MD
Patrizia Della Monica, PhD
Giovanni Galatola, MD
Cristiana Laudi, MD
Antonella Zambon, PhD
Loredana Correale
Roberto Asnaghi, MD
Brunella Barbaro, MD
Claudia Borghi, MD
Delia Campanella, MD
Maria Carla Cassinis, MD
Riccardo Ferrari, MD
Andrea Ferraris, MD
Rita Golfieri, MD
Cesare Hassan, MD
Franco Iafrate, MD
Gabriella Iussich, MD
Andrea Laghi, MD
Roberto Massara, MD
Emanuele Neri, MD
Lapo Sali, MD
Silvia Venturini, MD
Giovanni Gandini, MD

[1] From the Radiology Unit, Institute for Cancer Research and Treatment, Candiolo, Italy (D.R., P.D.M., D.C., G.I.); Gastroenterology Unit, Institute for Cancer Research and Treatment, Candiolo, Italy (G. Galatola, C.L.); Unit of Biostatistics-Department of Statistics, Bicocca Universiy of Milano, Milan, Italy (A.Z.); im3D, Torino, Italy (L.C.); Radiology Unit, Salvatore Maugeri IRCCS Foundation, Novara, Italy (R.A.); Department of Bioimaging and Radiological Sciences, Catholic University of Rome, A. Gemelli Hospital, Rome, Italy (B.B., R.M.); Radiology Unit, Valduce Hospital, Como, Italy (C.B.); Diagnostic Imaging Division-Department of Medical and Surgical Disciplines University of Turin, AOU S. Giovanni Battista, Turin, Italy (M.C.C., A.F., G. Gandini); Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome Polo Pontino, Rome, Italy (R.F., A.L.); Radiology Unit-Department of Digestive Disease and Internal Medicine, S. Orsola-Malpighi Hospital, Bologna, Italy (R.G.); Gastroenterology Unit, Ospedale Nuovo Regina Margherita, Via Morosini 30, 00153 Rome, Italy (C.H.); Department of Radiological Sciences, Sapienza University of Rome, Rome, Italy (F.I.); Diagnostic and Interventional Radiology-Department of Oncology Transplants and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy (E.N.); Radiodiagnostic Section-Department of Clinical Physiopathology, University of Florence, Florence, Italy (L.S.); and Radiology Unit, National Cancer Institute, Aviano, Italy (S.V.). Received March 16, 2012; revision requested April 23; revision received May 16; accepted June 11; final version accepted July 11. The study sponsor (im3D, Torino, Italy) provided hardware, software, technical assistance, and financial support for the study. Trial registration: *http://clinicaltrials.gov/ct2/show/NCT01399710?id=NCT01399710&rank=1* (trial ID number: 01399710). **Address correspondence to** P.D.M. (e-mail: *patrizia.dellamonica@ircc.it*).

Purpose: To assess the effect of computer-aided detection (CAD) as a second reader on the sensitivity and specificity of computed tomographic (CT) colonography in detecting 6–9-mm colorectal cancer (CRC) lesions.

Materials and Methods: Individuals with clinical indications for colonoscopy—either for symptoms or as part of participating in a surveillance program or CRC screening—were prospectively enrolled at one of 10 academic centers between July 2007 and May 2009. Institutional review board approval was obtained at each clinical site, and all participants provided written informed consent. All participants underwent CT colonography and colonoscopy on the same day. Experienced readers interpreted the CT colonography images unassisted and then reviewed all colorectal lesion–like structures pinpointed by the CAD algorithm. Segmental unblinding of CT colonoscopy findings at colonoscopy was utilized. The sensitivity and specificity of unassisted and CAD-assisted reading in identifying individuals with 6–9-mm lesions were calculated and compared by means of pairwise analysis.

Results: A total of 618 participants (mean age, 57.9 years; 54.5% male) were included in the final analysis. Of these participants, 464 (75.1%) had no lesions 6 mm or larger, and 52 (8.4%) had 6–9-mm lesions. The sensitivity of CT colonography with unassisted reading and that with CAD-assisted reading in identifying individuals with 6–9-mm lesions was 65.4% (95% confidence interval [CI]: 50.9%, 78.0%) and 76.9% (95% CI: 63.2%, 87.5%; P = .016), respectively. No significant change in specificity was observed: The specificity of CT colonography with unassisted and that with CAD-assisted reading was 91.8% (95% CI: 88.9%, 94.1%) and 90.9% (95% CI: 88.0%, 93.4%; P = .063), respectively. Evaluation of CAD candidates required an additional 1.6 minutes (25th–75th percentile: 1.0 minute to 3.4 minutes).

Conclusion: The addition of CAD to reading performed by experienced readers resulted in a significant benefit in the detection of 6–9-mm polyps at CT colonography in this cohort.

Supplemental material: *http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.12120376/-/DC1*

Colorectal cancer (CRC) is a major cause of morbidity and mortality in Western countries (1). CRC screening has been shown to prevent CRC incidence and mortality (2,3). This has been related to the efficacy of polypectomy in preventing CRC incidence and the increase in 5-year CRC survival because of early diagnosis of already developed CRC (2,3).

Computed tomographic (CT) colonography represents a minimally invasive imaging examination of the colon and rectum and has been endorsed by several key medical groups for CRC screening and diagnosis (4). A high sensitivity for large (≥10 mm) lesions has been consistently shown in high-quality CT colonography studies (5–8). Although the sensitivity of CT colonography for 6–9-mm polyps appeared to be higher than 85%—similar to the sensitivity of colonoscopy for such lesions—in studies performed in dedicated centers (5–8), it has been substantially lower in multicenter trials, ranging between 59% and 78% (5,6,9). Despite the fact that 6–9-mm polyps represent only a minor fraction of all the advanced neoplasia (<10%) present in screening population compared with lesions that are 10 mm or larger, they are still regarded as a suitable target for CRC screening and diagnosis, because of their nonnegligible risk of high-grade dysplasia and/or villous component (10–12). For this reason, the U.S. Preventive Services Task Force considered the variability of CT colonography sensitivity for 6–9-mm polyps as a source of uncertainty regarding the potential health impact of CT colonography (13).

Computer-aided detection (CAD) was initially implemented to assist radiologists in identifying suspicious findings on mammograms (14,15). CT colonography interpretation is time consuming (5–9), and therefore the involvement of an additional expert for double reading would not be cost effective (16). CAD could help reduce the frequency of false-negative studies at CT colonography and improve sensitivity, especially in the detection of subcentimetric lesions. However, the addition of CAD to CT colonography has been evaluated only in retrospective series and in a controlled environment (17–22). Therefore, the results reported in these studies may not reflect the additional factors that may influence reader performance when using CAD in daily clinical activity.

The purpose of this multicenter prospective trial was to prospectively assess the effect of CAD as a second reader on CT colonography sensitivity and specificity in identifying patients with 6–9-mm lesions.

Advances in Knowledge

- In a prospective multicenter study including 618 patients undergoing CT colonography and same-day colonoscopy for diagnostic or screening indications, the addition of computer-aided detection (CAD) to interpretation by experienced readers increased per-patient sensitivity for 6–9-mm polyps from 65.4% to 76.9%.
- The addition of CAD did not result in a significant decrease in specificity (91.8% vs 90.9%).
- Evaluation of CAD candidates required, on average, only an additional 1.6 minutes.

Materials and Methods

Study Design and Population

The company im3D (Torino, Italy) supported the study by partially financing it and by providing the CAD interpretation hardware and software free of charge. Authors who were not employees or consultants of im3D (P.D.M., C.H.) had full control of inclusion of any data and information that might present a conflict of interest for those authors who are employees of or consultants for im3D (D.R., L.C., G.I.). One site (contributing 285 cases) had contributed cases for development of the software and had two readers who were familiar with the software prior to the initiation of this study.

Ten academic centers participated in the study, in which each participant underwent CT colonography and colonoscopy on the same day. Local institutional board approval was obtained at each clinical site, and all study participants provided written informed consent before enrollment. Patients aged 18 years or older with a clinical indication for colonoscopy, either for symptoms or for participating in a personal surveillance program or CRC screening, were eligible. Participants were excluded if they had a clinical diagnosis of familial adenomatous polyposis or hereditary nonpolyposis CRC syndrome, inflammatory bowel disease, or celiac disease; if they had evidence of increased risk of harm from colonoscopy as judged by the endoscopist; if they had psychologic or physical conditions that contraindicated colonoscopy, including anticoagulant therapy or pregnancy at the time of study inclusion or CT colonography; if

Implication for Patient Care

- The CAD system studied may significantly improve the detection of 6–9-mm neoplastic lesions in clinical practice, improving the accuracy of the technique for advanced neoplasia in these lesions.

Published online before print
10.1148/radiol.12120376 **Content code:** GI

Radiology 2013; 266:168–176

Abbreviations:
CAD = computer-aided detection
CI = confidence interval
CRC = colorectal cancer

Author contributions:
Guarantors of integrity of entire study, P.D.M., C.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, P.D.M., G. Galatola, C.L., A.Z., L.C., C.B., D.C., C.H., F.I., R.M.; clinical studies, D.R., G. Galatola, C.L., R.A., B.B., C.B., D.C., M.C.C., R.F., A.F., R.G., C.H., F.I., G.I., E.N., L.S., S.V., G. Gandini; experimental studies, B.B., C.B., M.C.C., R.F., A.F., R.G., F.I., R.M., S.V., G. Gandini; statistical analysis, P.D.M., A.Z.; and manuscript editing, D.R., P.D.M., G. Galatola, A.Z., L.C., B.B., C.B., C.H., F.I., A.L., S.V.

Conflicts of interest are listed at the end of this article.

intravenous contrast material was used for CT colonography; and if they were not compliant with the study protocol. Enrollment started in July 2007 and finished in May 2009.

Center Selection

Participating centers were required to have all of the following: at least one 16-section CT scanner; a gastrointestinal endoscopy unit with state-of-the-art video endoscopy capability and endoscopists who had already performed at least 500 colonoscopies and 100 polypectomies; a general surgery unit; and a pathology unit with a pathologist experienced in evaluating colorectal diseases. Participating radiologists were required to have interpreted more than 100 CT colonography studies that showed colonoscopy-proved lesions prior to participation in the investigation.

CT Colonography

Bowel preparation was performed according to common practice in the participating centers. All participants followed a low-residue diet starting 3 days before the examination and a liquid diet on the day before the examination. In six of 10 centers, bowel preparation consisted of administration of a 4-L polyethylene glycol solution on the afternoon before the examination (cathartic preparation) without fecal tagging. In three centers, on the afternoon before CT colonography, a 45-mL solution of sodium biphosphate and sodium phosphate was administered together with an iodine-based solution prepared by diluting 150 mL of sodium diatrizoate and meglumine diatrizoate (Gastrografin; Bayer Schering Pharma, Berlin, Italy) in 1.5 L of water (fecal tagging preparation). In the remaining center, participants were given only an iodine-based solution prepared by diluting 150 mL of sodium diatrizoate and meglumine diatrizoate in 1.5 L of water (fecal tagging preparation) on the afternoon of the day before the examination. In both regimens, tagging solutions were usually administered in two doses 2 hours apart, typically at 4:00 and 6:00 PM.

Participants were placed on a CT table, and a small flexible rectal catheter was positioned. *n*-Butyl-scopolamine was administered intravenously if this was common practice in the participating center (eight centers). Immediately before scanning, pneumocolon was achieved by means of the patient-controlled insufflation of room air or carbon dioxide, either manually by means of a balloon pump or with an automatic device. CT colonography was performed with the participant in the supine and prone positions with the following scanning protocol: 120 kVp (140 kVp in obese patients [body mass index $\geq$ 30 kg/m^2]); 50 mA (effective) or less per second (without the use of any system for dose modulation); a rotation time of 0.5–0.7 second; a pitch between 0.9 and 1.5, depending on the scanner; and a section thickness not greater than 1.25 mm (21). The total study effective dose was less than 4 mSv. Intravenous contrast medium was not used.

CAD System

Each center was equipped with the same commercial CAD workstation (CAD-Colon 1.10; im3D, Torino, Italy), and the radiologists participated in a 2-day onsite training course before the trial began. The platform allowed two- and three-dimensional rendering and digital subtraction of tagged feces. In CAD mode, suspicious areas on the colon mucosa were highlighted on the two-dimensional and three-dimensional images and a list of suggestions (CAD candidates) was displayed on the sides of both prone and supine scans. The software detection algorithm threshold set by the manufacturer operated at a detection sensitivity of 90% (95% confidence interval [CI]: 86%, 93%) for lesions 6 mm or larger (stand-alone sensitivity), with a corresponding false-positive rate of nine lesion candidates per series, as computed in a retrospective evaluation of a previously published series (6,23). Readers were not informed of the stand-alone sensitivity of the CAD algorithm.

Image Interpretation

Each CT colonography study was interpreted by one of 17 radiologists (Table E1 [online]) within 3 hours of the end of the examination by using a sequential reading design. In the first phase, the radiologist interpreted the study without activating the CAD algorithm. A two-dimensional primary reading mode with three-dimensional viewing for problem solving was used in this phase. Lesion characteristics were recorded, and their positions were marked by means of manual drawing of a three-dimensional region of interest with a freehand tool imbedded in the software. This phase of reporting was defined as unassisted reading. Once the unassisted reading phase was completed, the results were locked by the software (ie, it was impossible for the readers to change the results of the unassisted reading phase). At this stage, the radiologist activated the CAD algorithm, which pinpointed a series of lesion candidates on both prone and supine acquisitions. The radiologist then examined all lesion candidates by using both two- and three-dimensional viewing. Each lesion candidate was classified as a CAD false-negative finding (rejected candidate) or as a new identified lesion, and its characteristics were recorded. Previously detected lesions were visible in this phase and were locked (ie, the radiologist was allowed to add only newly identified lesions). The second phase of reporting was defined as CAD-assisted reading.

Readers were informed that individuals with lesions 6 mm or larger at CT colonography would be classified as having positive findings in the analysis and were aware of the patient's clinical history, as reporting the examination was part of their daily clinical work. On the worksheets, lesions were assigned to one of the following six bowel segments: cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. Lesion size at CT colonography was reported as the largest measured diameter (when visible, the stalk of the lesion was not considered for measurement) on two-dimensional reformatted images, by using a standard window width of 2000 HU and a window level of −200 HU. The results of CAD-assisted reading were recorded on different pages—one for each of the six bowel segments—and were put

separately into sealed envelopes that were delivered to the endoscopy unit where colonoscopy was scheduled. Because of the low specificity of CT colonography for small lesions (24), lesions smaller than 6 mm were recorded in the database but were not included in the study worksheets delivered to the endoscopy unit. The number of candidates generated by the CAD algorithm in each examination and the reading time for each phase were automatically recorded by the software.

Colonoscopy Protocol

Colonoscopy was performed at least 3 hours after CT colonography. Patient sedation was performed according to the common clinical practice of each participating center. 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 CT colonography; at the end of each bowel segment evaluation, CT colonography results for that segment were disclosed (segmental unblinding). If a lesion measuring 6 mm or larger was detected at CT colonography but not at colonoscopy, the segment was reexamined to resolve the discrepancy (25). Complications occurring during or immediately after colonoscopy (eg, bleeding, perforation) were systematically recorded.

Lesion Classification and Matching

Lesion size was measured at endoscopy by using open biopsy forceps. All visible lesions were endoscopically removed whenever possible; those retrieved were sent to local pathologists for evaluation and were classified according to the World Health Organization criteria (26). Any lesion measuring 6 mm or larger with nonadenomatous, adenomatous, or cancerous histologic features was included in the analysis. According to the adopted segmental checking procedure, a lesion found at CT colonography was matched to a corresponding one found at colonoscopy when it was located in the same or an adjacent colon segment and when its size differed by no more than 50% (6). Matching was performed immediately after the conclusion of both examinations, if necessary by reviewing colonoscopy video registration and CT colonography images (6).

Review Process

At the end of the study, all CT colonography studies in which lesions remained undetected after CAD-assisted reading were collected in a centralized archive. Two radiologist reviewers (D.R. and G.I. [readers 8 and 16, respectively, in Table E1 {online}]) who were aware of the colonoscopy findings and of the original CT colonography records reexamined in consensus the reject CAD candidate. Any prospectively missed lesion was reconciled (ie, regarded as correctly detected by CAD) if it corresponded to a rejected candidate in the same or an adjacent colonic segment at colonoscopy with a size difference of no more than 50%. For reconciled candidates, the reviewers judged the most likely cause for the rejection, according to a predefined checklist. For the purpose of this additional analysis, on a lesion basis, the theoretical detection with CAD-assisted reading was defined as the fraction of lesions reconciled by reviewers in addition to those detected prospectively by readers, over all colonoscopy-detected lesions.

Statistical Analysis

Primary end point.—The primary end point of the study was the per-patient sensitivity of CT colonography, with and without the use of CAD, in patients whose largest colorectal lesion measured 6–9 mm. The reference standard was unblinded colonoscopy, along with histologic evaluation of the removed lesions. A negative result at the reference standard examination was assigned to all patients without 6 mm or larger lesions at endoscopy; otherwise, patients were assigned a positive result. When two or more lesions were removed in the same patient, the largest lesion was used for patient classification; accordingly, patients were classified as having a positive result for a lesion in that size range (ie, 6–9 mm, ≥10 mm).

A positive result was assigned to CT colonography with unassisted reading when at least a 6-mm or larger lesion was detected in the first reading phase; otherwise, it was reported as negative. In a similar way, a patient was defined as having a positive result at CT colonography with CAD-assisted reading when at least a 6-mm or larger lesion was detected in the first or in the second reading phase. Positive cases at the unassisted reading that were confirmed at the reference standard examination were defined as true-positive results in that size range; cases classified as negative at colonoscopy were defined as false-positive results. The same criterion was adopted to evaluate the results of CT colonography with CAD-assisted reading. Sensitivity and specificity, along with 95% CIs, were calculated for each reading modality according to lesion size range.

Secondary end point.—Per-lesion sensitivity was calculated as the fraction of positive CT colonography matching findings among all lesions sized in the range of interest and detected at colonoscopy, by using the previously described matching algorithm. The sensitivity of each reading modality was calculated according to the size and histologic features of the lesions. We also report per-reader before-and-after-CAD sensitivities for 6–9 mm lesions, as well as cumulative values according to whether or not tagging was used.

We tested whether CAD-assisted reading improved sensitivity as compared with unassisted reading and whether specificity was not significantly lower in CAD-assisted reading. The MacNemar test for pairwise analysis was used to assess the statistical significance of differences. All P values involved hypothesis tests against a one-sided alternative and were considered to indicate significance at $P < .05$. The analyses were performed by using statistical software (SAS, release 9.1; SAS Institute, Cary, NC).

Sample size estimate.—The sensitivity of CT colonography for the identification of patients with 6–9-mm lesions was estimated to be around 65%, with a specificity of 95% (5,6). We hypothesized that if CAD were to be effective, sensitivity for the detection of 6–9-mm

lesions would have to increase to at least 80% and specificity should not decrease by more than 5%. Assuming a type I error equal to 5% and a power of 80%, respectively, at least 48 participants with 6–9-mm polyps and 514 participants with negative findings would be required to show as significant the increase in CT colonography sensitivity due to the use of CAD, without substantially modifying specificity. As the expected prevalence of such lesions in the participants was originally estimated to be around 10% (6), we calculated a sample size of at least 600 participants.

Results

Six hundred fifty-one participants were enrolled in the study. Overall, 33 patients were excluded for the following reasons: dropping out before CT colonography (20 cases), use of intravenous contrast material (seven cases), refusal of colonoscopy (five cases), and an endoscopic diagnosis of attenuated familial adenomatous polyposis (one case). Thus, the final population was 618 (94.9%) participants (Figure, Table 1). The number of participants recruited per center varied from nine to 285. The mean age was 57.9 years (range, 45–78 years). Overall, 159 (25.7%) patients were either symptomatic or undergoing work-up for a positive fecal test. The remaining patients were asymptomatic and were undergoing either CRC screening or surveillance. Fecal tagging was utilized in 374 cases (60.5%). Before CT, *n*-butyl-scopolamine was administered intravenously in 273 cases (44.2%). Colon distention was achieved with carbon dioxide insufflation in 318 cases (51.5%) and with room air in the remaining cases. At colonoscopy, cecal intubation was achieved in 576 cases, accounting for a completion rate of 93.2%. No lesion that was 6 mm or larger was detected at CT colonography (with or without CAD) in the segments not reached by the colonoscope in the incomplete colonoscopies.

At colonoscopy, 154 (24.9%) patients were reported as having positive findings: Fifty-two (8.4%) and 102 (16.5%) patients had 6–9-mm lesions or lesions that were 10 mm or larger, respectively. At histologic examination, 95 (15.4%) and 22 (3.6%) patients were found to have an advanced adenoma and a cancer as the most severe lesion, respectively, while 19 (3.1%) patients had nonadenomatous lesions. One 10-mm polyp located in the ascending colon was initially missed at colonoscopy (being detected only after unblinding), corresponding to a 1% miss rate, while no 6–9-mm lesion appeared to have been missed at colonoscopy. CT colonography with unassisted reading and that with CAD-assisted reading were recorded as yielding positive results in 168 (27.2%) and 178 (28.8%) patients, respectively (Table 2). The use of CAD improved the sensitivity of CT colonography in identifying patients whose largest lesion was 6–9 mm from 65.4% (95% CI: 50.9%, 78.0%) to 76.9% (95% CI: 63.2%, 87.5%; P = .016). No significant change in specificity was observed when CAD was added to CT colonography interpretation: The specificity of CT colonography with CAD-assisted reading was 90.9% (95% CI: 88.0%, 93.4%).

The improvement in CT colonography reporting induced by CAD was related to lesion size. The sensitivity for the identification of patients with lesions 10 mm or larger was not increased by the use of CAD; the sensitivity of unassisted reading and that of CAD-assisted reading were both 94.1%. The accuracies of unassisted and CAD-assisted reading according to the use of tagging and for individual readers are reported in Tables E2, E3, and E4 (online).

The median reporting time of unassisted reading was 6.5 minutes (25th–75th percentile, 4.1–10.6 minutes). Evaluation of lesion candidates pinpointed by the CAD algorithm required a median of an additional 1.6 minutes (25th–75th percentile, 1.0–3.4 minutes). The median number of lesion candidates generated per scan was seven (25th–75th percentile, four to 12).

On a per-lesion basis, colonoscopy helped identify 234 lesions with a diameter of at least 6 mm in 154 participants. Of these 234 lesions, 227 were retrieved and sent for histologic evaluation, including 99 (43.6%) 6–9-mm lesions and 128 (56.4%) lesions that were 10 mm or larger (Table 3).

The per-lesion sensitivity of CT colonography according to lesion size and histologic features are shown in Table 3. CAD-assisted reading allowed the identification of 10 additional lesions, including nine adenomas in the 6–9-mm range. All cancers were correctly diagnosed in the unassisted reading phase of reporting. One additional false-positive lesion was also found at the per-lesion analysis, as compared with the per-patient analysis. Overall, 42 lesions 6 mm or larger (ie, 26 between 6 and 9 mm; 16 ≥ 10 mm) were not identified by the readers using CAD-assisted reading.

In terms of the review process, the reviewers reconciled 11 (42.3%) of 26 missed 6–9-mm lesions and six (37.5%) of the 16 lesions that were 10 mm or larger. If all CAD candidates had been properly accounted for, CAD-assisted reading could have reported 84 (84.8%) of 99 6–9-mm lesions and 118 (92.2%) of 128 lesions that were 10 mm or larger.

According to the checklist detailed in Table E5 (online), bowel preparation was the main factor that induced the reader to dismiss a candidate. Poor bowel cleansing or coating of the lesion with tagging agent was the suggested etiology in eight (47.1%) of the 17 dismissed cases. Other possible causes of error were abnormal lesion morphology, lesion visible only in one decubitus, lesion inconspicuity, and position of the lesion in relation to a fold (Table E5 [online]).

No adverse events were recorded for CT colonography. There were three cases of bleeding following colonoscopic polypectomy, all of which were managed endoscopically, and one case of hypotension at diagnostic colonoscopy. No case of perforation occurred.

Discussion

This multicenter study shows that the addition of CAD substantially improves

Table 1

Demographic and Clinical Characteristics of Study Patients Overall and according to Colonoscopy Findings

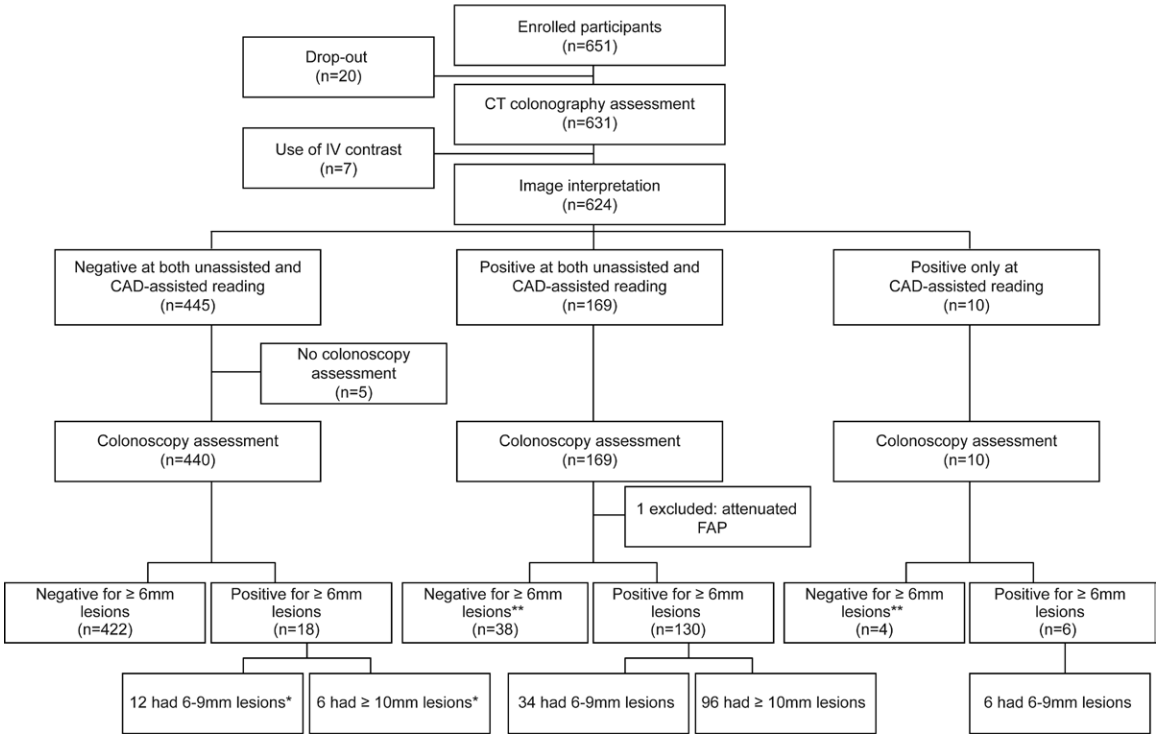
Demographic Characteristic	Colonoscopy Findings: No Lesions ≥ 6 mm (n = 464)	Lesions 6–9 mm (n = 52)*	Lesions ≥ 10 mm (n = 102)*	Total (n = 618)
Age at enrollment (y)†				
Overall	56.5 ± 10.1	59.2 ± 9.1	63.8 ± 10.3	57.9 ± 10.4
Female patients	57.0 ± 10.0	60.5 ± 8.1	64.2 ± 12.4	58.3 ± 10.5
Male patients	56.0 ± 10.2	58.3 ± 9.7	63.5 ± 8.9	57.6 ± 10.3
Sex				
Female	221 (47.6)	20 (38.5)	40 (39.2)	281 (45.5)
Male	243 (52.4)	32 (61.5)	62 (60.8)	337 (54.5)
Clinical indication				
Symptoms of CRC	68 (14.7)	10 (19.2)	25 (24.5)	103 (16.7)
Surveillance	47 (10.1)	5 (9.6)	12 (11.8)	64 (10.4)
CRC screening‡	349 (75.2)	37 (71.2)	65 (63.7)	451 (73.0)

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. Percentages may not add up to 100% owing to rounding.

* Including nonadenomatous lesions.

† Data are means ± standard deviations.

‡ Ninety-one patients underwent CT colonography as a triage technique after a positive fecal occult blood screening test. Of these patients, 49 had no colorectal lesions, 15 had 6–9 mm lesions, and 27 had lesions 10 mm or larger.



Flow diagram of study cohort. The reported polyp sizes refer to those at endoscopic assessment. *FAP* = familial adenomatous polyposis, *IV* = intravenous. ∗ = False-negative at CAD reading. ∗∗ = False-positive at CAD reading.

Table 3

Per-Lesion CT Colonography Sensitivity according to Reading Modality and Lesion Characteristics

Lesion Size (mm) and Characteristics	Unassisted Reading	CAD-assisted Reading	*P* Value
≥6	175/227 (77.1) [71.1, 82.4]	185/227 (81.5) [75.8, 86.3]	.001
6–9	64/99 (64.6) [54.4, 74.0]	73/99 (73.7) [63.9, 82.1]	.002
Nonadenomatous	16/21 (76.2) [52.8, 91.8]*	16/21 (76.2) [52.8, 91.8]	Not estimable
Not advanced adenoma	28/46 (60.9) [45.4, 74.9]	32/46 (69.6) [54.3, 82.3]	.063
Advanced adenoma	20/32 (62.5) [43.7, 78.9]	25/32 (78.1) [60.0, 90.7]	.031
≥10	111/128 (86.7) [79.6, 92.1]	112/128 (87.5) [80.5, 92.7]	.5
Nonadenomatous	9/10 (90.0) [55.5, 99.8]†	9/10 (90.0) [55.5, 99.8]	Not estimable
Advanced adenoma	80/96 (83.3) [74.4, 90.2]	81/96 (84.4) [75.5, 91.0]	.5
Cancer	22/22 (100) [87.3, 100]	22/22 (100) [87.3, 100]	Not estimable

Note.—Sensitivities for lesion detection are expressed as number of lesions/total number of lesions, with percentages in parentheses and corresponding 95% CIs in brackets.

* At histologic examination, 18 of these lesions were found to be hyperplastic; two, inflammatory; and one, lymphoid.

† At histologic examination, nine of these lesions were found to be hyperplastic; and one, inflammatory.

Table 2

Per-Patient CT Colonography Performance according to Reading Modality and Lesion Size

Parameter and Lesion Size (mm)	Unassisted Reading	CAD-assisted Reading	*P* Value
Sensitivity			
≥6	130/154 (84.4) [77.7, 89.8]	136/154 (88.3) [82.2, 92.9]	.016
6–9	34/52 (65.4) [50.9, 78.0]	40/52 (76.9) [63.2, 87.5]	.016
≥10	96/102 (94.1) [87.6, 97.8]	96/102 (94.1) [87.6, 97.8]	Not estimable
Specificity for lesions ≥ 6 mm	426/464 (91.8) [88.9, 94.1]	422/464 (90.9) [88.0, 93.4]	.063

Note.—Sensitivities and specificities for lesion detection are expressed as number of lesions/total number of lesions, with percentages in parentheses and corresponding 95% CIs in brackets. Nonadenomatous lesions were included.

the identification of patients with 6–9-mm lesions by experienced readers at CT colonography. Of note, all the additional 6–9-mm lesions detected at CAD-assisted reading were histologically verified adenomas, more than half of which were also advanced adenomas (ie, they had high-grade dysplasia or a villous component). This is relevant in proposing CT colonography for the diagnosis of clinically important lesions, considering that the prevalence of advanced histologic features in intermediate-size lesions is not marginal (10–12), being 32% according to the present series. Improving the detection of 6–9-mm lesions resulted in a higher sensitivity for lesions 6 mm or larger, the latter being regarded as the main target of CT colonography (4). Conversely, CAD did not improve sensitivity in detecting lesions that were 10 mm or larger. This was presumably explained by the very high sensitivity for such lesions with unassisted reading (ie, 94%) shown in our study, which is in agreement with findings of trials involving experienced readers (5–7).

Our results provide further support to the positive findings reported in prior retrospective studies, which examined the effect of CAD as a second reader on the performance of CT colonography (17–22). However, in those studies, the beneficial effect of CAD was demonstrated mainly for readers with limited experience in interpreting CT colonography studies, and the gain in sensitivity was paralleled by a reduction in specificity. Conversely, in our study, specificity was uniformly higher than 90%, and it was not affected by the use of CAD. The apparent lack of any effect on specificity was most likely related to the ability of experienced readers to reject CAD false-positive results.

A large number of CAD true-positive marks were mistakenly dismissed by the readers as false-positive hits. This may be due in part to the fact that readers might not have been sufficiently confident with the performance of the software, considering that prior to this study CAD was not routinely used in their clinical practice. This suggests that there is potential to further improve the CAD-assisted performance of CT colonography, as already outlined in a previous study, in which seven of 60 patients with polyps were dismissed by CT colonography–inexperienced radiologists despite having been correctly identified by the CAD program (17). Hypothetically, if the readers had properly accounted for all CAD candidates, CAD-assisted reading would have resulted in detection of 90% of the 6–9-mm lesions. This finding compares favorably with the sensitivity shown by colonoscopy for these lesions in tandem colonoscopy studies (27).

There is a strong rationale for the addition of CAD to CT colonography in clinical practice. First, it is well

known that most polyps missed at unassisted reading are actually visible on the CT scan when studies are reviewed in retrospect by experienced readers (28,29). In this trial we have shown that observer error is reduced by the addition of CAD.

We have shown that CAD adds less than 2 minutes to the unassisted CT colonography reporting time, making its routine use as a second reader cost effective in terms of working time. This reading time was similar to that shown in some previous studies (17,19).

A strength of our study is that it had a prospective design, and CAD was tested in a clinical environment and not, as in previous studies, a laboratory setting. Conversely, our results may not be generalizable as there are several commercial and academic CAD platforms available, which differ in stand-alone performance, interface design, visualization modes, and candidate coding techniques, all of which may affect the diagnostic performance and reporting time.

There were limitations to our study. Some of the bowel preparations adopted in our study are not conventionally used in other countries. In particular, the use of sodium phosphate is decreasing in the United States because of Food and Drug Administration warnings. However, it is unlikely that the type of preparation regimen may have affected the additional effect of CAD on CT colonography accuracy. Although fecal tagging was not uniformly adopted in our study, the subanalysis showed that CAD was also effective when the assessment was restricted to the procedures with tagging. The fact that we could only identify a trend toward decreased performance in the examinations in which tagging was not adopted was not unexpected, since the sample size was not calculated to determine differences in CAD efficacy due to the preparation adopted. Since our aim was to assess the effect of CAD on the accuracy of CT colonography for 6–9-mm lesions, we enrolled a disease-enriched population by including patients with CRC symptoms and with positive fecal occult blood tests. This may also explain the relatively high prevalence of lesions that were 10 mm or larger in our series, as well as the high rate of advanced neoplasia within 6–9-mm lesions. To define the CAD-related change in accuracy for 6–9-mm lesions, we based our sample size calculation on the cumulative number of cases collected by all the readers. Such a study design prevented us from performing a statistical analysis of interreader variability in the impact of CAD among the different readers, as a much larger sample size would have been needed. Finally, no specific training or posttraining examination was required, the readers being selected only on the basis of their previous CT colonography experience. Although it cannot be excluded that the eventual restriction of readers on the basis of their performance at a qualifying examination would have increased the overall accuracy computed in our study (5), it would also have introduced a selection bias, potentially undermining the generalizability of the study results.

In conclusion, in this multicenter trial, we have shown that CAD improves the sensitivity of CT colonography in patients with 6–9-mm lesions, without reducing specificity and adding less than 2 minutes to the reading time.

Acknowledgments: We thank Dr S. Carenzi, Dr M. Falchini, Dr P. Occhipinti, Dr S. Saettone, Dr M. T. Gallo, Dr D. Molinar, and Dr F. Coppola for local assistance; all the technical staff members of im3D for continuous assistance; and all the patients who participated in the study.

Disclosures of Relevant Conflicts of Interest: **D.R.** Financial activities related to the present article: institution has received a grant of 1500 Euro from im3D. Financial activities not related to the present article: serves on the advisory board of Bracco Imaging; is a consultant for im3D. Other relationships: none to disclose. **P.D.M.** No relevant conflicts of interest to disclose. **G. Galatola** No relevant conflicts of interest to disclose. **C.L.** No relevant conflicts of interest to disclose. **A.Z.** No relevant conflicts of interest to disclose. **L.C.** Financial activities related to the present article: is an employee of im3D. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **R.A.** No relevant conflicts of interest to disclose. **B.B.** No relevant conflicts of interest to disclose. **C.B.** No relevant conflicts of interest to disclose. **D.C.** No relevant conflicts of interest to disclose. **M.C.C.** No relevant conflicts of interest to disclose. **R.F.** No relevant conflicts of interest to disclose. **A.F.** No relevant conflicts of interest to disclose. **R.G.** No relevant conflicts of interest to disclose. **C.H.** No relevant conflicts of interest to disclose. **F.I.** No relevant conflicts of interest to disclose. **G.I.** No relevant conflicts of interest to disclose. **A.L.** Financial activities related to the present article: institution received free workstation from GE Healthcare for research and case reviewing. Financial activities not related to the present article: has received payment for development of educational presentations from im3D, GE Healthcare, Bracco, and Bayer Healthcare; has received money for travel/accomodations/meeting expenses from Bracco, Bayer Healthcare, and GE Healthcare. Other relationships: none to disclose. **R.M.** No relevant conflicts of interest to disclose. **E.N.** No relevant conflicts of interest to disclose. **L.S.** No relevant conflicts of interest to disclose. **S.V.** No relevant conflicts of interest to disclose. **G. Gandini** No relevant conflicts of interest to disclose.

References

1. Weir HK, Thun MJ, Hankey BF, et al. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst 2003;95(17):1276–1299.

2. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375(9726):1624–1633.

3. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol 2008;103(6):1541–1549.

4. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134(5):1570–1595.

5. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008;359(12):1207–1217.

6. Regge D, Laudi C, Galatola G, et al. Diagnostic accuracy of computed tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. JAMA 2009;301(23):2453–2461.

7. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349(23):2191–2200.

8. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy,

sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58(2):241–248.

9. Heresbach D, Djabbari M, Riou F, et al. Accuracy of computed tomographic colonography in a nationwide multicentre trial, and its relation to radiologist expertise. Gut 2011;60(5):658–665.

10. Lieberman D, Moravec M, Holub J, Michaels L, Eisen G. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology 2008;135(4):1100–1105.

11. Regula J, Rupinski M, Kraszewska E, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355(18):1863–1872.

12. Yoo TW, Park DI, Kim YH, et al. Clinical significance of small colorectal adenoma less than 10 mm: the KASID study. Hepatogastroenterology 2007;54(74):418–421.

13. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149(9):638–658.

14. Chan HP, Doi K, Galhotra S, Vyborny CJ, MacMahon H, Jokich PM. Image feature analysis and computer-aided diagnosis in digital radiography. I. Automated detection of microcalcifications in mammography. Med Phys 1987;14(4):538–548.

15. Gilbert FJ, Astley SM, Gillan MG, et al. Single reading with computer-aided detection for screening mammography. N Engl J Med 2008;359(16):1675–1684.

16. Regge D, Hassan C, Pickhardt PJ, et al. Impact of computer-aided detection on the cost-effectiveness of CT colonography. Radiology 2009;250(2):488–497.

17. Halligan S, Altman DG, Mallett S, et al. Computed tomographic colonography: assessment of radiologist performance with and without computer-aided detection. Gastroenterology 2006;131(6):1690–1699.

18. Baker ME, Bogoni L, Obuchowski NA, et al. Computer-aided detection of colorectal polyps: can it improve sensitivity of less-experienced readers? preliminary findings. Radiology 2007;245(1):140–149.

19. Mang T, Peloschek P, Plank C, et al. Effect of computer-aided detection as a second reader in multidetector-row CT colonography. Eur Radiol 2007;17(10):2598–2607.

20. Petrick N, Haider M, Summers RM, et al. CT colonography with computer-aided detection as a second reader: observer performance study. Radiology 2008;246(1):148–156.

21. Taylor SA, Charman SC, Lefere P, et al. CT colonography: investigation of the optimum reader paradigm by using computer-aided detection software. Radiology 2008;246(2):463–471.

22. Dachman AH, Obuchowski NA, Hoffmeister JW, et al. Effect of computer-aided detection for CT colonography in a multireader, multicase trial. Radiology 2010;256(3):827–835.

23. Agliozzo S, Bert A, Baggio R, et al. Validation of a CT-Colonography CAD system on the IMPACT multicenter trial data. Proc. CARS 2009, Int J Comput Assist Radiol Surg, Vol 4, Supp. 1.

24. Edwards JT, Mendelson RM, Fritschi L, et al. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. Radiology 2004;230(2):459–464.

25. Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. Ann Intern Med 2004;141(5):352–359.

26. Hamilton SR, Vogelstein B, Kudo S, et al. Pathology and genetics. In: Hamilton SR, Aaltonen LA, eds. Tumours of digestive system: WHO classification of tumours. Lyon, France: IARC, 2000.

27. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112(1):24–28.

28. Doshi T, Rusinak D, Halvorsen RA, Rockey DC, Suzuki K, Dachman AH. CT colonography: false-negative interpretations. Radiology 2007;244(1):165–173.

29. Gluecker TM, Fletcher JG, Welch TJ, et al. Characterization of lesions missed on interpretation of CT colonography using a 2D search method. AJR Am J Roentgenol 2004;182(4):881–889.