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Accuracy of CT Colonography for Detection of Polypoid and Nonpolypoid Neoplasia by Gastroenterologists and Radiologists: A Nationwide Multicenter Study in Japan

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OBJECTIVES: **The objective of this study was to assess prospectively the diagnostic accuracy of computer-assisted computed tomographic colonography (CTC) in the detection of polypoid (pedunculated or sessile) and nonpolypoid neoplasms and compare the accuracy between gastroenterologists and radiologists.**

METHODS: **This nationwide multicenter prospective controlled trial recruited 1,257 participants with average or high risk of colorectal cancer at 14 Japanese institutions. Participants had CTC and colonoscopy on the same day. CTC images were interpreted independently by trained gastroenterologists and radiologists. The main outcome was the accuracy of CTC in the detection of neoplasms ≥6 mm in diameter, with colonoscopy results as the reference standard. Detection sensitivities of polypoid vs. nonpolypoid lesions were also evaluated.**

RESULTS: **Of the 1,257 participants, 1,177 were included in the final analysis: 42 (3.6%) were at average risk of colorectal cancer, 456 (38.7%) were at elevated risk, and 679 (57.7%) had recent positive immunochemical fecal occult blood tests. The overall per-participant sensitivity, specificity, and positive and negative predictive values for neoplasms ≥6 mm in diameter were 0.90, 0.93, 0.83, and 0.96, respectively, among gastroenterologists and 0.86, 0.90, 0.76, and 0.95 among radiologists ($P<0.05$ for gastroenterologists vs. radiologists). The sensitivity and specificity for neoplasms ≥10 mm in diameter were 0.93 and 0.99 among gastroenterologists and 0.91 and 0.98 among radiologists (not significant for gastroenterologists vs. radiologists). The CTC interpretation time by radiologists was shorter than that by gastroenterologists (9.97 vs. 15.8 min, $P<0.05$). Sensitivities**

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for pedunculated and sessile lesions exceeded those for flat elevated lesions ≥10 mm in diameter in both groups (gastroenterologists 0.95, 0.92, and 0.68; radiologists: 0.94, 0.87, and 0.61; $P<0.05$ for polypoid vs. nonpolypoid), although not significant ($P>0.05$) for gastroenterologists vs. radiologists.

CONCLUSIONS: **CTC interpretation by gastroenterologists and radiologists was accurate for detection of polypoid neoplasms, but less so for nonpolypoid neoplasms. Gastroenterologists had a higher accuracy in the detection of neoplasms ≥6 mm than did radiologists, although their interpretation time was longer than that of radiologists.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Computed tomographic colonography (CTC) is an established and widely used imaging technique for preoperative evaluation of colorectal cancer (CRC) (1), and it has been identified as an effective CRC examination for average- and high-risk individuals (2–9). Although there is a steep learning curve for attaining competence in CTC interpretation (10), a previous pilot study indicated that CTC-trained gastroenterologists can detect polyps on CTC with an accuracy similar to that of radiologists (11). However, the diagnostic accuracy in CTC interpreted by gastroenterologists and radiologists has not previously been compared prospectively in a multicenter clinical trial.

Soetikno *et al.* (12) have reported an increased malignant potential of nonpolypoid colon lesions compared with polypoid lesions. Nonpolypoid lesions are generally more difficult to detect by CTC because the subtle morphologic changes are not easily distinguished from normal mucosa (13). The results of studies evaluating the accuracy of CTC for nonpolypoid lesions have been variable (6,13–15), and thus CTC has not yet been proven as an accurate method for detecting nonpolypoid colorectal lesions.

Prospective, multicenter comparisons are essential for evaluation of the diagnostic potential of CTC for clinical use. We aimed to assess the sensitivity of computer-assisted CTC for detecting polypoid (either pedunculated or sessile) and nonpolypoid colorectal adenomas and cancers ≥6 mm in diameter in a prospective multicenter trial including individuals who were at various risk levels of CRC, by using colonoscopy as the reference standard. The primary end point was the sensitivity of CTC for detecting colorectal adenomas and cancers ≥6 mm in diameter, and the secondary end points were the specificity and predictive value. We also compared the diagnostic performance of CTC interpretation by gastroenterologists and radiologists, and the sensitivity of CTC for detection of polypoid vs. nonpolypoid neoplasms.

METHODS

Participants

A total of 14 hospitals in Japan participated in this prospective trial, and approval was obtained from the institutional review board at each site. The trial was registered with ClinicalTrials.gov (number NCT00997802) and the UMIN Clinical Trials Registry (number UMIN000002097). Individuals ≥20 years of age were recruited between September 2009 and August 2011 from the participating sites to undergo routine colonoscopy for first-line examination for CRC because of medical check-up, abdominal symptoms, or recent positive immunochemical fecal occult blood tests, for surveillance because of a family history of CRC or polyps, or for follow-up surveillance because of a personal history of polyps. Exclusion criteria were serious medical conditions associated with an increased risk of complications from bowel preparation and colonoscopy or CTC; having had colonoscopy, sigmoidoscopy, or barium enema during the preceding 3 years; known colorectal polyps or cancers at any site at the time of enrollment; a history of inflammatory bowel disease, hereditary nonpolyposis CRC syndrome, familial polyposis, or colorectal surgery; hyperthyroidism; or iodine contrast medium allergy. After providing written informed consent for prospective enrollment in the study, participants were registered and scheduled for same-day, same-site CTC and colonoscopy.

Reader qualifications and training

Five gastroenterologists (mean experience of 17.8 years; range 7–27 years) who were board-certified members of the Japanese Society of Gastroenterology or the Japan Gastroenterological Endoscopy Society, and three radiologists (mean experience of 13.3 years; range of 9–18 years) who were board-certified members of the Japan Radiological Society interpreted the CTC images and served as readers in this study. Two of the gastroenterologists and one of the radiologists had prior experience in interpreting >500 CTC cases. All of the readers, both gastroenterologists and radiologists, were required to complete a 2-day training course, conducted by the Japanese CTC Society, for CTC interpretation before the study. The training course consisted of lectures and hands-on training by use of CTC workstations and computer-aided detection (CAD) software. After completion of the training course, all readers underwent further training with 100 polyp-enriched CTC cases with colonoscopic correlation, and all readers achieved above 90% accuracy for polyps ≥10 mm in diameter.

Bowel preparation for CTC and colonoscopy

A single, full-cathartic bowel preparation, with polyethylene glycol-electrolyte lavage solution (PEG-ELS) and contrast-medium

bowel preparation solution (PEG-C) (16,17), was used for CTC and colonoscopy to allow participants to undergo both examinations on the same day. In the morning of the examination, each participant was given 1,620 ml of PEG-ELS (Niflec; Ajinomoto Pharmaceuticals, Tokyo, Japan) over the course of 2 h, followed by 400 ml of PEG-C consisting of 380 ml of PEG-ELS plus 20 ml of sodium diatrizoate (Gastrografin; Bayer Yakuhin, Osaka, Japan) for tagging of residual fluid. Participants were required to defecate at least six times before CT scanning. The quality of the bowel preparation of a participant was confirmed based on a four-point-scale defecation quality check sheet with sample illustration of defecated feces (1: low quality with solid stool, 4: high quality with clear fluid) by both the participant and medical staff. If the bowel preparation was found to be inadequate, additional PEG-ELS and PEG-C solution was administered until the defecated feces became clear.

Computed tomographic colonography

Participants were placed in the left decubitus position for insertion of a thin flexible rectal tube before colorectal insufflation. Intravenous spasmolytic agents were administered to 8 participants (0.6%) enrolled at the site where its use was the routine protocol; otherwise, no spasmolytics were used. Insufflation was performed mechanically with an automated CO_2 insufflator (HP-2, Horii Pharmaceutical, Osaka, Japan). All CTC examinations were performed on either 64- or 16- channel multi-detector row CT scanners with use of single-breath-hold supine and prone positioning and without intravenous contrast medium or sedation. The scanning protocol was: 120 kVp tube voltage, automatic tube current modulation or tube current of 50 mAs, and section thickness of ≤1.0 mm. The CT data sets were securely archived and randomly sent to each reader by a secure internet-based image transfer system (Cancer Scan, Tokyo, Japan). CTC interpretation was performed on a dedicated workstation (AZE Virtual Place, Aze, Tokyo, Japan) at each site, and all workstations were equipped with proprietary CAD software, the details of which have been described elsewhere (8,18,19).

The CTC images for both supine and prone positions were interpreted either by primary 3D reading (endoluminal fly-through navigation for detection of lesions, followed by review of 2D multiplanar reformatted (transverse, coronal, and sagittal) images for problem solving) or by primary 2D reading, according to reader preference. The CAD software was used in the second-reader mode in the interpretation of the CTC images. In this mode, a reader first interpreted the entire colonic surface on the CTC images without CAD output, and recorded his/her findings regarding the presence or absence of colonic lesions ≥6 mm. Then, the CAD was turned on and the reader was invited to change his/her findings or leave them the same.

Each reader was assigned a portion of the cases randomly under the constraint that no reader should read cases from his/her institution. To allow for the performance comparison between the gastroenterologist and radiologist readers, the case assignment was done so that the sum of the cases assigned to the gastroenterologist readers consisted of all the cases, and those assigned to the radiologist readers consisted of all the cases as well. Each reader interpreted the CTC images independently from other readers by use of CAD as a second reader. The locations of lesions were specified according to the six colonic segments (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). The lesion size was measured as the largest diameter seen on 2D images. All lesions were classified morphologically according to the Paris classification (20).

CTC data for statistical analysis included lesion location, distance from the anus, 3D coordinates, morphology, largest diameter, interpretation time, and a 100-point reader confidence score about the presence of lesions (0: a lesion definitely not present; 100: a lesion definitely present). The presence of extracolonic abnormalities was reported only by radiologists, and interpretation times for extracolonic findings were not recorded. The gastroenterologists were not trained to read or requested to report extracolonic findings. C-RADS (CT colonography Reporting And Data System) (21) was used for reporting of both colonic lesions (C0-4) and extracolonic lesions (E0-4).

Colonoscopy

Colonoscopy was performed after CTC on the same day. Participants received antispasmodics or sedatives based on provider and/or participant preference. All colonoscopists were board-certified members of the Japan Gastroenterological Endoscopy Society who were blinded to the results of the CTC. Photographs of all lesions ≥6 mm and photographs to document a complete colon examination (either the appendiceal orifice or the ileocecal valve) were reported. All lesions were measured in comparison with open forceps or by the endoscopic ruler and were classified morphologically according to the Paris classification (20). The height of nonpolypoid lesions was measured by use of the closed cusp of forceps that measured 2.5 mm (20). If possible, lesions ≥6 mm were removed during the colonoscopy and, if not, biopsies were performed. If a polyp of ≥10 mm was detected on CTC and not detected at colonoscopy, colonoscopists were unblinded to the CTC results, and a repeat colonoscopy was scheduled within 90 days.

Lesion matching

The results of colonoscopy (including a second colonoscopy, if performed) and tissue pathology served as a reference standard for lesion size, location, and histologic type. Matching of lesions found on CTC and colonoscopy was performed based on an established algorithm that uses the location of the lesion (within one colonic segment) and its size (within 50% of its reference standard measure) (2).

Statistical analysis

The sample size was estimated in accordance with a prior study (3). We considered that CTC could be applied to a CRC examination when the sensitivity and specificity were ≥84%. Thus, under a conservative assumption that, in the present study, the CTC sensitivity and specificity for lesions ≥6 mm were both 90%, we planned the noninferiority study with 80% power to test whether the CTC sensitivity and specificity were ≥84% at a level of significance of 0.05 (one-sided exact test). Accordingly, we determined that no fewer than 1,048 participants would be necessary for suf-

ficient statistical power. Here, we assumed that 20% of all participants had colorectal lesions ≥6 mm in diameter as identified by colonoscopy, and that the dropout or withdrawal rate was 5%. The power calculation was performed by PASS 2008 (NCSS, Kaysville, UT).

We calculated per-participant sensitivity, specificity, positive predictive value (PPV), and negative predictive value by regarding those participants whose CTC images had at least one true lesion as positive, and otherwise as negative. The per-lesion sensitivity and PPV were calculated by regarding a CTC finding as positive if it matched a colonoscopy finding based on the matching algorithm, and otherwise negative. Receiver-operating characteristic curves were calculated on a per-participant basis. We compared the CTC accuracy among gastroenterologists and radiologists by using McNemar tests. All other quantitative variables were expressed as means and s.d. values or medians, and qualitative variables as numbers and percentages. The χ^2 test was used for assessing the statistical significance of differences among proportions. All *P* values involved a hypothesis test against a two-sided alternative, and $P<0.05$ was considered to indicate statistical significance. These analyses were performed using JMP 9.03 and SAS 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Characteristics of participants and lesions

A total of 1,257 consecutive participants were recruited. Recruitment varied between 8 and 280 participants per site. Both CTC and colonoscopy were performed for 1,181 participants; 4 participants (0.3%) were excluded because of incomplete colonoscopy. Complete CTC and total colonoscopy results were available for 1,177 (94%) participants (**Figure 1**). Of these 1,177 participants, 42 (3.6%) were at average risk of CRC, 456 (38.7%) were at elevated risk, and 679 (57.7%) had had recent positive immunochemical fecal occult blood tests; the prevalence of cancer or adenoma ≥6 mm was 21.4%, 23.0%, and 29.3%, respectively, in these subgroups. The characteristics of the study participants are shown in **Table 1**. There were no clinically severe complications (e.g., colon perforation, major bleeding) after CTC or colonoscopy, although one participant experienced a vasovagal reaction during CTC (0.08%). **Supplementary Table S1** online shows the distribution of confirmed target lesions according to their location and size. Based on the reference standard, 650 lesions ≥6 mm in diameter were detected, including 93 (14.3%) carcinomas, 465 (71.5%) adenomas, and 92 (14.2%) nonadenomatous lesions. In colonoscopy, the presence of nine lesions ≥10 mm that were detected by CTC, but not detected by initial colonoscopy, was confirmed on the second colonoscopy. Of these nine lesions, two lesions were carcinomas, six were adenomas, and one was a nonadenomatous lesion. Of the two carcinomas missed at colonoscopy, one was a sessile carcinoma 10 mm in size located near the anal verge, and the other was a flat elevated-type carcinoma 40 mm in size located behind the hepatic flexure. These carcinomas were missed at colonoscopy because of technical error.

Examination and reading times

The mean time spent by participants in the CT suites was 19.6 min (s.d., 5.4 min). The mean colonoscopic procedure time (not including recovery time) was 26.5 min (s.d., 13.7 min). The mean time for CTC interpretation by gastroenterologists and by radi-

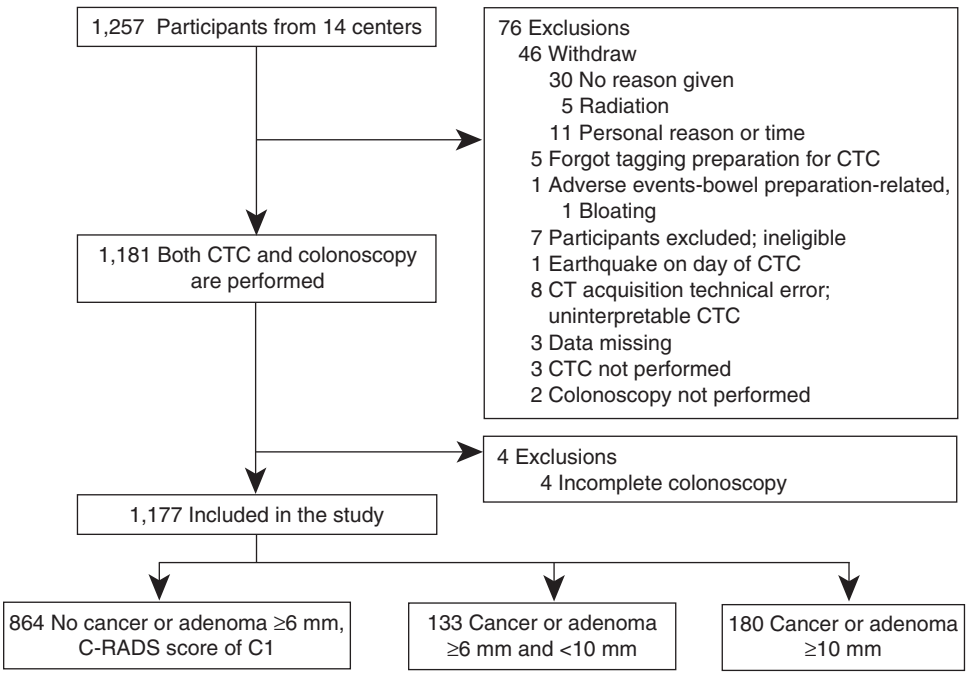

Figure 1. Study flow diagram. C-RADS, CT colonography Reporting And Data System; CTC, computed tomographic colonography.

Table 1. Characteristics of the study participants

Characteristics	No cancer or adenoma <6 mm (*n*=864)	Cancer or adenoma ≥6 mm and <10 mm (*n*=133)	Cancer or adenoma ≥10 mm (*n*=180)	Total (*n*=1,177)
Age at enrollment, years				
Mean	59.2	65.2	64.2	60.6
Interquartile range	49–70	58–73	57–73	52–71
Sex, no. (%)				
Men	464 (54)	90 (68)	114 (63)	668 (57)
Women	400 (46)	43 (32)	66 (37)	509 (43)
Medical history of polyps or CRC, no. (%)				
Average risk (first-line endoscopic screening)	33 (4)	4 (3)	5 (3)	42 (4)
Elevated risk				
Abdominal symptoms	304 (35)	29 (22)	38 (21)	371 (32)
Family history of CRC or polyps	31 (4)	12 (9)	21 (12)	64 (5)
Personal history of polyps	14 (2)	2 (2)	3 (2)	19 (2)
Both family history of CRC or polyps and personal history of polyps	2 (<1)	0 (0)	0 (0)	2 (<1)
With recent positive fecal immunochemical test	480 (56)	86 (65)	113 (63)	679 (58)

CRC, colorectal cancer.

ologists was 15.8 min (s.d., 8.0 min) and 9.97 min (s.d., 6.3 min), respectively (P<0.0001).

Performance characteristics per participant

Table 2 shows the per-participant accuracy of CTC. Gastroenterologists identified adenomas and cancers ≥10 mm in diameter with a sensitivity of 0.93 and radiologists with a sensitivity of 0.91 (P=0.45 for gastroenterologists vs. radiologists), and specificities of 0.99 and 0.98, respectively (P=0.077). The corresponding values for the PPV were 0.94 and 0.90 (P=0.086); negative predictive value 0.99 and 0.98 (P=0.45); and the area under the receiver-operating characteristic curve 0.96 and 0.95 (P=0.50). The sensitivity for detection of neoplasms ≥6 mm in diameter was 0.90 among gastroenterologists and 0.86 among radiologists (P=0.024 for gastroenterologists vs. radiologists).

Performance characteristics per lesion

Table 3 summarizes the per-lesion results of CTC. Gastroenterologists and radiologists identified neoplasms ≥10 mm in diameter with sensitivities of 0.89 and 0.86, respectively (P=0.10 for gastroenterologists vs. radiologists). The PPV was 0.94 and 0.90, respectively (P=0.025). For neoplasms ≥6 mm in diameter, the sensitivity and PPV among gastroenterologists were superior to those of the radiologists (P<0.05).

Performance for polypoid and nonpolypoid neoplasms

The sensitivity based on morphology (per-lesion) is shown in **Figure 2** and **Supplementary Table S2**. A total of 558 adenomas or cancers ≥6 mm in diameter were identified by colonoscopy, of which 441 (79.0%) were categorized as polypoid (pedunculate or sessile) or mass-like, and 117 (21.0%) were nonpolypoid (flat elevated or flat depressed), according to the Paris Endoscopic Classification (20). The sensitivities for detection of pedunculated, sessile, and flat elevated neoplasms ≥10 mm in diameter were 0.95, 0.92, and 0.68, respectively, among gastroenterologists, and 0.94, 0.87, and 0.61, respectively, among radiologists. Sensitivities for nonpolypoid neoplasms 6–9 mm, ≥6 mm, and ≥10 mm in diameter were significantly lower than those for polypoid neoplasms among all readers (P<0.0001, gastroenterologists; P<0.0001, radiologists). However, the performance difference between gastroenterologists and radiologists in the detection of nonpolypoid neoplasms was not statistically significant (P>0.05).

Extracolonic findings

There were a total of 174 extracolonic indeterminate or potentially clinically important (C-RADS scores of E3 or E4) findings detected in 157 CTC cases (13.3%); 9.3% (110/1181) of CTC cases had indeterminate findings (E3), and 4.0% (47/1181) had potentially clinically important findings (E4). These findings were identified anatomically, with 13% (23/174) occurring in the chest, 48% (84/174) in the gastrointestinal tract, 29% (50/174) in the genitourinary tract, 8% (14/174) in the vasculature, and 2% (3/174) in the musculoskeletal system.

DISCUSSION

In the present study, the participants had full bowel preparation with PEG-ELS, and images were obtained with 64- or 16- channel multi-detector row CT scanners with a section thickness

Table 2. Per-participant accuracy of gastroenterologists and radiologists in detecting cancers or adenomas on CTC[a]

Performance by participant	Cancer or adenoma ≥6 mm		Cancer or adenoma ≥10 mm	
	GI	RAD	GI	RAD
True-positive results, no.	278	265	162	160
False-negative results, no.	31	44	13	15
True-negative results, no.	798	773	978	971
False-positive results, no.	57	82	11	18
C0 (CTC image not available)	13	13	13	13
Sensitivity (95% CI)	0.90 (0.86–0.93)	0.86 (0.81–0.89)	0.93 (0.88–0.96)	0.91 (0.86–0.95)
P value	0.024		0.453	
Participants with lesions, no.	309	309	175	175
Specificity (95% CI)	0.93 (0.91–0.95)	0.90 (0.88–0.92)	0.99 (0.98–0.99)	0.98 (0.97–0.99)
P value	0.002		0.077	
Participants without lesions, no.	855	855	989	989
Positive predictive value (95% CI)	0.83 (0.79–0.87)	0.76 (0.72–0.81)	0.94 (0.89–0.97)	0.90 (0.84–0.94)
P value	0.003		0.086	
Positive test results, no.	335	347	173	178
Negative predictive value (95% CI)	0.96 (0.95–0.97)	0.95 (0.93–0.96)	0.99 (0.98–0.99)	0.98 (0.98–0.99)
P value	0.024		0.45	
Negative test results, no.	829	817	991	986
Positive likelihood ratio (95% CI)	13.50 (10.47–17.39)	8.94 (7.24–11.04)	83.23 (46.18–150.02)	50.24 (31.72–79.58)
Negative likelihood ratio (95% CI)	0.11 (0.08–0.15)	0.16 (0.12–0.21)	0.08 (0.05–0.13)	0.09 (0.05–0.14)
Area under the ROC curve (95% CI)	0.93 (0.91–0.95)	0.91 (0.88–0.93)	0.96 (0.93–0.97)	0.95 (0.92–0.97)
P value	0.029		0.499	

CI, confidence interval; CTC, computed tomographic colonography; GI, gastroenterologist; RAD, radiologist; ROC, receiver-operating characteristic.
[a]Values of RAD for detection of lesions on CTC were averaged among radiologists, and values of GI for detection of lesions were averaged among gastroenterologists. Sensitivity indicates the proportion of participants who had lesions (of the specified size) detected on colonoscopy that were also detected on CTC. Specificity indicates the proportion of participants who had no lesions detected on colonoscopy or on CTC. Positive predictive value indicates the proportion of participants with CTC findings (of the specified size) that were also detected on colonoscopy. Negative predictive value indicates the proportion of participants with no lesions of the specified size detected on CTC who also had no lesions detected on colonoscopy. The ROC curve plots sensitivity vs. the false-positive rate, and the area under the ROC curve indicates the accuracy of CTC.

Table 3. Per-lesion accuracy of radiologists and gastroenterologists in detecting cancers or adenomas on CTC[a]

Performance by lesion	Cancer or adenoma ≥6 mm		Cancer or adenoma ≥10 mm	
	GI	RAD	GI	RAD
True-positive results, no.	441	394	213	205
False-negative results, no.	97	144	25	33
False-positive results, no.	95	122	14	24
C0 (CTC image not available)	20	20	10	10
Sensitivity (95% CI)	0.82 (0.78–0.85)	0.73 (0.69–0.77)	0.89 (0.85–0.93)	0.86 (0.81–0.90)
P value	0.000002		0.10	
Positive predictive value (95% CI)	0.82 (0.79–0.85)	0.76 (0.72–0.80)	0.94 (0.90–0.97)	0.90 (0.85–0.93)
P value	0.001		0.025	

CI, confidence interval; CTC, computed tomographic colonography; GI, gastroenterologist; RAD, radiologist.
[a]Values of RAD for detection of lesions on CTC were averaged among radiologists, and values of GI were averaged among gastroenterologists.

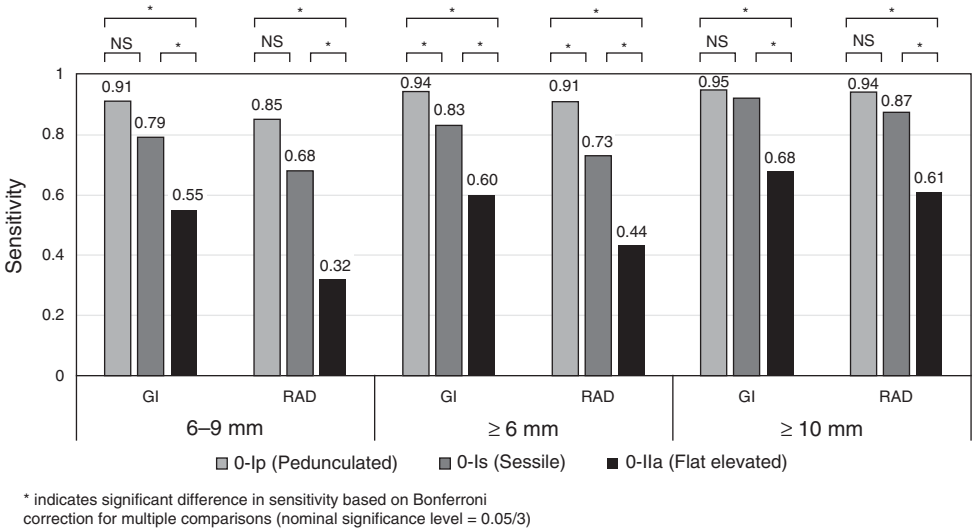

Figure 2. Per-lesion sensitivity of CTC for polypoid vs. nonpolypoid neoplasms. CTC, computed tomographic colonography; GI, gastroenterologist; NS, nonsignificant; RAD, radiologist.

of ≤1.0 mm. Only board-certified gastroenterologists and radiologists were eligible to be readers, and all readers were required to pass 100-case CTC reading test with high accuracy after completion of a 2-day training course. Moreover, CTC interpretation was assisted by CAD. All of these factors might have contributed to the high accuracy of CTC for detecting colorectal neoplasms. In particular, the specificity and negative predictive value in this study exceeded those of several previous studies (3,5). This may be attributed to the uniform bowel preparation, because PEG-ELS for bowel cleansing minimizes residual fecal materials and, mixed with a water-soluble contrast medium, allows high-quality tagging to reduce untagged feces. Use of water-soluble contrast medium without barium sulfate also made it possible to perform colonoscopy immediately after CTC, and it confirmed that same-day colonoscopy in cases of positive findings on CTC is feasible and can avoid repeated bowel preparation.

All CTC images were interpreted independently by the trained gastroenterologists and radiologists, and the accuracy of the analyses showed that both gastroenterologists and radiologists were able to interpret CTC after appropriate training. The accuracy of CTC interpretation by the trained gastroenterologists was comparable to that reported by trained radiologists in the seven prior large trials (2–6,8,9), and in the present study, the accuracy for neoplasms ≥6 mm in diameter was superior among the gastroenterologists, although the difference for neoplasms ≥10 mm between gastroenterologists and radiologists was not statistically significant (P>0.05). The gastroenterologists may have benefited from their experience with video-assisted colonic imaging, such as colonoscopy and/or capsule endoscopy. Other studies have indicated that trained nonradiologists could accurately interpret CTC for polyp detection (11,22–24), although in the present study, the mean time required for CTC interpretation by radiologists was significantly shorter than that for gastroenterologists, possibly because radiologists use the reading workstations more routinely.

Our study was motivated by the fact that the number of radiologists in Japan is the lowest among all Organization for Economic Cooperation and Development (OECD) member countries (25); thus, only 40% of CT or magnetic resonance imaging examinations are interpreted by radiologists, and it is not uncommon for gastroenterologists to interpret examinations such as barium contrast enemas or abdominal CT or magnetic resonance imaging (25). Moreover, because Japan has by far the highest number of CT scanners per capita (followed by Australia) (26), the availability of the less invasive CTC could improve adherence to CRC examinations, although widespread use of CTC will require many more trained readers than are currently available, whether they are radiologists, gastroenterologists, or others; this would also likely be true in other countries such as the United Kingdom and Ireland that have relatively low numbers of radiologists (25).

Our analyses on nonpolypoid neoplasms agreed with previous studies indicating that CTC has a lower sensitivity for nonpolypoid than that of polypoid lesions (27,28). We based our assessment on the accuracy of CTC for lesions ≤2.5 mm in height at colonoscopy according to the Paris classification (20). The proportion of nonpolypoid neoplasms among adenomas of any morphology was 21.0%, and this was within the range of prior studies in the United States and Europe (7,12,29). In this study, the sensitivity of CTC for nonpolypoid neoplasms 6–9 mm in diameter was 0.55 among gastroenterologists and 0.32 among radiologists, and 0.68 and 0.61, respectively, for nonpolypoid neoplasms ≥10 mm, and this was significantly lower than the sensitivities for polypoid neoplasms. Whereas it is difficult to compare our results with others because of the absence of uni-

formity in reporting of the height of nonpolypoid neoplasms, the European Society of Gastrointestinal and Abdominal Radiology CT Colonography Group Investigators have also reported that most large lesions missed by expert radiologists were nonpolypoid neoplasms, emphasizing the difficulty in discerning these lesions radiographically (15). Note that nonpolypoid adenomas are more likely be missed even by colonoscopy, and they are often detected only by indigo-carmine chromoscopy (12). Heresbach *et al.* (30) reported that the miss rates of colonoscopy for nonpolypoid adenomas, sessile adenomas, and pedunculated adenomas were 42%, 19%, and 4%, respectively, similar to our CTC results (**Figure 2**). Our study showed that CTC yielded a high per-participant detection performance that is considered to be clinically more significant than the per-lesion detection performance because patients are considered as positive and referred to colonoscopy for polypectomy if at least one lesion ≥6 mm is present in their CTC images. Therefore, although nonpolypoid adenomas are clinically important lesions, the low per-lesion detection performance and the associated risk of missed nonpolypoid adenomas in CTC may not present a major limitation to CTC in clinical practice.

This study has several limitations. First, we had only five gastroenterologists and three radiologists as readers, thus limiting the assessment of variations in reader performance. The American National CTC Trial showed that there was no correlation between the number of cases read and reader performance (3). Second, there were substantial differences in prior experience in interpreting CTC among the readers. It should be noted that all readers underwent a dedicated CTC training session that included not only a 2-day hands-on training course, but also a training with 100 polyp-enriched CTC cases with colonoscopic correlation, so that all readers achieved an equivalent level of CTC interpretation skills and experiences before they participated in the clinical trial. The effect of the differences in their prior experiences on the study results require further comparative analysis of the diagnostic performances of individual readers during the clinical trial. Third, we did not evaluate the effect of CAD on the reader performance because this is the first report on the primary outcome of the trial. Several studies have shown that CAD helps to reduce false-negative findings, especially for less experienced readers (8,27,31). Further analysis is expected to show the effect of CAD on the difference in performance between gastroenterologists and radiologists. Fourth, the participants in our study included various risk levels for CRC that might have affected the accuracy of CTC resulting from this study. The prevalence of cancer or adenoma ≥10 mm in our study was 14.9%. This was higher than that of the colonoscopic screening of asymptomatic participants, in which the prevalence of advanced lesions was 10.5% (32). Previous study showed a greater sensitivity and PPV for participants who had a recent positive fecal occult blood test than for those with average or elevated risk (6). In addition, various indications for colonoscopy might have affected the lesion characteristics, such as the distribution of lesion locations or morphology. Thus, our results should not be interpreted as demonstrating the accuracy of CTC in a screening population.

In conclusion, the results of this Japanese National CTC Trial demonstrated that 91% and 93% of neoplasms ≥10 mm in diameter were identified on CTC by gastroenterologists and radiologists, respectively, with a lower detection accuracy for nonpolypoid neoplasms. These findings suggest that both gastroenterologists and radiologists can accurately interpret the intracolonic findings of CTC after an appropriate training.

CONFLICT OF INTEREST

Guarantors of the article: Hiroyuki Yoshida, PhD, and Koichi Nagata, MD, PhD.

Specific author contributions: Acquisition of data: Honda, Yasuda, Hirayama, Takahashi, Kato, Horita, Furuya, Kasai, Matsumoto, Kimura, Kato, Kondo, Abe, Yamano, Takeuchi, Saida, and Fukuda; analysis and interpretation of data: Nagata, Honda, Hirayama, Kato, Furuya, Matsumoto, Utano, Ryu, and Kasai; drafting of the manuscript: Nagata and Yoshida; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: Yamamichi and Shimamoto; obtaining funding: Nagata and Yoshida; administrative, technical, or material support: Yoshida, Nagata, Endo, Näppi, Sugimoto, Yamada, Matsui, Doi, Yamano, Hanai, and Saida; study supervision: Yoshida and Nagata. All authors had access to the study data and reviewed and approved the final manuscript.

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Potential competing interests: Koichi Nagata reported that he is an inventor of PEG-C bowel preparation and holds a licensing agreement with Ajinomoto Pharmaceutical, without associated royalty, had a 1-year consulting agreement with Aze, during 2010–2011 with associated compensation, and was partially supported by the National Institutes of Health. Janne Näppi reported that he is a co-inventor of CAD software patents assigned to his home institution, without associated royalties, and was partially supported by the National Institutes of Health. Hiroyuki Yoshida reported that he is a co-inventor of CAD software patents assigned to his home institution, without associated royalties, had a 1-year consulting agreement with Aze, during 2010–2011 with associated compensation, and was partially supported by the National Institutes of Health. The remaining authors declare no conflict of interest.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Computed tomographic colonography (CTC) is an established and widely used imaging technique for preoperative evaluation of colorectal cancer.
- ✓ CTC-trained gastroenterologists can detect polyps on CTC with an accuracy equivalent to that of radiologists.
- ✓ The diagnostic accuracy in CTC interpreted by gastroenterologists and radiologists has not previously been compared prospectively in a multicenter clinical trial setting.
- ✓ CTC has not yet been proven as an accurate method for detecting nonpolypoid colorectal lesions.

WHAT IS NEW HERE

- ✓ CTC interpretation by gastroenterologists and radiologists was highly accurate in the detection of pedunculated or sessile polypoid neoplasms ≥6 and ≥10 mm in diameter.
- ✓ Gastroenterologists yielded higher accuracy in the detection of neoplasms ≥6 mm than did radiologists, although their interpretation time was longer than that of radiologists.
- ✓ Both gastroenterologists and radiologists demonstrated low sensitivity in the detection of nonpolypoid neoplasms.

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