Accuracy of colon capsule endoscopy for advanced neoplasia

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Background and Aims: Second-generation colon capsule endoscopy (CCE-2) has shown promising accuracy for the diagnosis of overall neoplasia. Advanced neoplasia (AN) represents the main target of colorectal cancer screening programs. Our aim was to assess the diagnostic accuracy of CCE-2 for the detection of AN in patients with a positive result for the fecal immunochemical test (FIT) who are undergoing screening.

Methods: Patients aged 50 to 69 years with a positive result for the FIT in 4 population screening programs in Italy and Spain were enrolled. Screenees were asked to undergo CCE-2, followed by traditional colonoscopy (TC). TC was performed the same day or the following morning. Bowel preparation included a split-dose polyethylene glycol–based regimen, with sodium phosphate (NaP) with gastrografin as boosters. The CCE-2 video was read by an endoscopist blinded to the results of TC. The main outcomes were CCE-2 accuracy in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for AN when using 2 different size thresholds for TC referral (ie, polyps $\geq$6 mm and $\geq$10 mm).

Results: Two hundred twenty-two patients were enrolled, and 178 patients completed both CCE-2 and TC (87.7%). Overall, 59 cases of AN were detected at TC. CCE-2 sensitivity was 90%, specificity was 66.1%, PPV was 57.4%, and NPV was 92.9% for AN when using a 6-mm cut-off (TC referral rate, 52.8%) and 76.7%, 90.7%, 80.7%, and 88.4% when using a 10-mm cut-off (TC referral rate, 32%), respectively. CCE-2 detected that 8 of 9 already developed colorectal cancers. Among the 41 false positives at the 6-mm cut-off, 34 (82.9%) presented with a nonadvanced adenoma at TC. Mean transit time was 4 hours and 4 minutes, and $\geq$70% of patients excreted the capsule within 5 hours.

Conclusions: In an enriched disease setting, we showed the high sensitivity of CCE-2 for the diagnosis of AN at a 6-mm cut-off. The apparently low CCE-2 specificity is related to the choice of AN as the main outcome. (Clinical trial registration number: ISRCTN 62158762.) (Gastrointest Endosc 2020;91:406-14.)

INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality.[1,2] CRC screening with a biannual fecal immunochemical test (FIT) has been shown to reduce CRC mortality and incidence.[3,4] The FIT has also shown higher uptake rates compared with endoscopy tests, such as colonoscopy or sigmoidoscopy, and higher

detection rates for advanced neoplasia (AN),[5] compared with guaiac-based tests,[6] as well as reduced incidence of interval CRC.[7] Traditional colonoscopy (TC) represents the most-accurate imaging test for the detection of colorectal neoplasia, and it is strongly recommended for patients with a positive FIT result who are at markedly increased risk of AN compared with average-risk individuals.[8] However, its invasiveness, operator-dependent performance as shown by the variability in adenoma detection rate,[9,10] the need for sedation, and the risk of adverse events still remain a major barrier for the participation of patients in colon cancer screening programs.[11] Thus, compliance of patients with a positive FIT result with post-FIT colonoscopy remains suboptimal and varies substantially from less than 50% to 90% within 1 year of a positive test result.[12,13]

Colon capsule endoscopy (CCE) (Given Imaging, Yoqneam, Israel) is a new, minimally invasive, painless endoscopic technique that can explore the colon without requiring sedation, gas insufflation, or radiation exposure. Most studies regarding its accuracy for polyp detection refer to first-generation CCE, showing an overall sensitivity of 68% and a specificity of 85% for significant lesions (polyps $\geq$6 mm or $\geq$3 mm).[14,15] A new PillCam-Colon has now been developed to overcome some technical limitations that affect its accuracy. In particular, the capsule frame rate has been increased from 4 to 35 images per second; the angle of view has also been increased from 156° to 172° for each lens to cover nearly 360° of the colon surface and the data recorder (DR3) has also been improved by simplifying the procedure.

The second-generation CCE (CCE-2) has shown sensitivity for polyps $\geq$6 mm and $\geq$10 mm of 86% and 87%, with a specificity of 88.1% and 95.3%, respectively.[15] Despite such evidence, data on the accuracy of CCE-2 for AN are limited due to the low prevalence of AN in unselected colonoscopy populations.

This multicenter prospective head-to-head study aimed to assess the diagnostic accuracy of CCE-2 for AN among individuals with a positive FIT result within an organized population-based screening program. All recruited individuals were referred for TC, which was considered the reference standard, both in terms of findings and estimation of polyp size. Secondary aims were the evaluation of quality bowel preparation, transit time, reading time, and safety of the procedure.

METHODS

We designed a prospective multicenter trial named CCANDY (Colon Capsule Advance Neoplasia Diagnostic Yield) conducted in 4 European centers (Como, Torino, Rome, and Tenerife) all participating in an organized population CRC screening program. The trial was registered on ISRCTN (registration number ISRCTN 62158762).

Study population

The target population included consecutive patients aged 50 to 69 years who were able to understand and sign a written informed consent form and were undergoing their first colonoscopy after a positive FIT result, performed in the context of a regional population screening program. Exclusion criteria were those normally applied by population screening programs (personal history of cancer, familial adenomatous polyposis, serious illness with reduced life expectancy). Additional exclusion criteria are given in Appendix 1 (available online at www.giejournal. org).

Description of the device

The Given Diagnostic System is composed of 3 main subsystems: an ingestible capsule endoscope (ie, CCE-2), a data recorder, and a RAPID workstation. CCE-2 is 11.6 $\times$ 31.5 mm in size with a 172° angle of view for each lens and an adaptive frame rate ranging between 4 and 35 images per second. The battery life of the CCE-2 is at least 10 hours. The portable recorder consists of an antenna array, which is attached to the body, a receiver, and memory for accumulation of the data during the examination. Upon completion of the examination, the physician downloads the accumulated data from the recorder to the workstation (RAPID) for processing and interpretation.

Examination procedure

Bowel preparation regimen. Briefly, a 4-L split-dose polyethylene glycol preparation was combined with gastrografin and sodium phosphate (NaP) as a booster to enhance the propulsion of the capsule through the colon, potentially reducing colonic transit time and increasing the excretion rate. Details of the protocol are given in Table 1.

Capsule examination

In all centers, CCE-2 was performed as an outpatient procedure in the endoscopy unit, where patients were monitored after swallowing the capsule. Participants had the option to go home for some hours or to remain in the clinic after ingestion of the second booster until capsule expulsion. In each center, 2 endoscopists (C.H., C.S., M.P., T.S., E.R., E.Q., or D.G.Z.) were selected to perform colonoscopies and colon capsule reading sessions based on their documented previous experience with colon capsules or at least with small-bowel capsule examinations. Moreover, they completed a specific training course for this study and their performance levels were validated. Two independent readings were made: the complete movie and the compressed movie (20% shrinking) in QUICK-view mode, available with the new RAPID software. The accuracy of the QUICK-view mode readings are under evaluation, and they will be reported in a different article.

All patients with lesions $\geq$10 mm visualized at the capsule examination, but not detected at the time of TC,

TABLE 1. Scheme for bowel preparation

	Schedule	Intake
2 days before the procedure	All day	At least 10 glasses of water
	Bedtime	4 senna tablets (12 mg each)
1 day before the procedure	All day	Clear liquid diet
	Evening (7:00-9:00 pm)	2 L of polyethylene glycol
Examination day	Morning (05:00-7:00 am)	2 L of polyethylene glycol (at least 1.45 hours before capsule ingestion)
	~8-9 am	Capsule ingestion
	1st boost: upon small-bowel detection	40 mL of NaP* and 1 L of water and 50 mL of gastrografin
	2nd boost: 3 hours after the 1st boost	20 mL of NaP* and 0.5 L of water and 30 mL of gastrografin
	Suppository: 2 hours after 2nd boost	10 mg of bisacodyl

*PhosphoLax, Sofar Farmaceutici, Trezzano Rosa, Italy.

were recalled for a second colonoscopy aimed at detecting and eventually removing the lesion identified by the capsule. The reference standard for the comparison was then the combined results of the 2 TCs. This approach guaranteed greater protection for the patient and allowed a more-accurate estimate of the accuracy of CCE.

Colonoscopy

The colonoscopy was performed the same day, according to the standards adopted in the individual centers, but at the latest 9 hours after capsule ingestion, even when it was not already excreted (considering available data, approximately 85% of capsules are expelled within 8 hours of ingestion)[16] or if CCE-2 was excreted naturally before 4 pm. In exceptional cases or if the CCE was excreted after 4 pm, for organizational reasons, the colonoscopy was performed the following morning. If the colonoscopy was incomplete, the patient was excluded from the analysis. Excised polyps were classified according to the World Health Organization criteria.[17] All of the histology samples were reviewed by a panel of expert reference pathologists. AN was defined as adenoma >10 mm and/or with villous component >20%, and/or high-grade dysplasia, and/or invasive cancer.[5]

Sample size and statistical analysis

We assumed that a sensitivity of at least 90% could be achieved with CCE-2 for advanced neoplasms in this population. Assuming a 33% (8% CRC and 25% advanced adenomas) positive predictive value (PPV) of FIT for AN and assuming the colonoscopy results as the criterion standard,[13] a sample size of 400 people could achieve a precision of the estimated CCE-2 sensitivity equal to +8% for advanced adenomas and +5% for AN; the estimate for CRC sensitivity could have confidence intervals (CIs) ranging between 74% and 97% for a point estimate of 90%.

The main analysis focused on assessment of the sensitivity, specificity, PPV, and negative predictive value (NPV) for advanced adenomas (including sessile serrated adenomas ≥10 mm) and CRC based on a positive CCE-2 examination, defined as an examination where at least 1 polyp ≥6 mm has been identified. Only patients who had a complete CCE-2 examination (CCE-2 spontaneously excreted) and underwent TC were included in the main analysis.

In the per-patient analysis, CCE-2 cases detected with AN at colonoscopy were considered true-positive CCE-2 examinations. In the per-polyp analysis, polyps were matched based on the following matching rules: (1) size of the polyps (using the Pickhardt ±50% algorithm[18]), (2) location (3 segments: right colon, including cecum and ascending colon; transverse, including the flexures; left colon, including descending colon, sigmoid, and rectum), and (3) morphology (pedunculated versus nonpolypoid). Matching was considered positive if at least 2 of 3 of these criteria were met.

The exact method was used to calculate the 95% CIs of proportions. All statistical tests were 2-sided and statistical significance was set at $P > .05$.

The recruitment activity was implemented in the context of established population-based screening programs, and it was maintained from June 2014 to March 2017 in Turin and Rome, from September 2014 to December 2016 in Como, and from June 2016 to April 2017 in Tenerife. Because the progression of recruitment was much slower than expected as a result of organizational constraints in the endoscopy units and low compliance among individuals targeted for enrollment, the study steering committee decided to plan an interim analysis after completing recruitment of 220 patients (half of the planned sample size) to assess whether the results were consistent with the assumptions. Based on this analysis, it was decided to stop recruitment, because increasing the study size would have required substantial additional resources and time with a limited expected gain in the precision of the estimates.

RESULTS

Study population

Overall, 222 screenees with a positive FIT result were enrolled (125 males and 97 females, mean age 61 years)

TABLE 2. Overall findings for all enrolled patients

	Number of patients	TC completed		Advanced adenoma		CRC	Advanced neoplasia	
		Number	%	Number	DR (%)	Number	DR (%)	95% CI
CCE-2 not swallowed	19	15	78.9	5	26.3	1	31.6	13.6-56.5
CCE-2 not excreted	25*	25	100.0	3	12.0	1	16.0	5.3-36.9
Total (no CCE-2 examination)	44	40	90.9	8	18.2	2	22.7	12.0-38.2
CCE-2 excreted	178	174	97.8	49	27.5	11	33.7	26.9-41.2
Total intention to treat	222	214	96.4	57	25.7	13	31.5	25.6-38.2

TC, Traditional colonoscopy; *CRC*, colorectal cancer; *DR*, detection rate; *CI*, confidence interval; *CCE-2*, second-generation colon capsule endoscopy.
*24 capsules reached the left colon due to slow transit, 1 not functioning at the cecum but excreted.

in 4 participating screening centers. Of these 222 patients, 19 (8.6%) refused to swallow the capsule, and when the AdvanCE system was used to position it in the stomach, the CCE-2 examination was interrupted; the CCE-2 was still in the left colon segment in 25 (11.3%) cases, due to slow transit. The remaining 178 (80.2%) screenees completed both CCE-2 and TC examinations and were included in the per-protocol analysis. The detection rate of advanced adenomas and CRC was similar among patients who did not undergo both examinations as among those who underwent both CCE-2 and TC (Table 2). Of the 178 patients who underwent both the CCE and the TC examinations, at least 1 polyp at post-CCE-2 TC was detected in 123 (69.7%) (Table 2). The most-advanced lesion was a CRC in 11 (6.2%) patients, an advanced adenoma in 49 (27.5%) patients, a low-risk adenoma in 49 (28%) patients, and a hyperplastic polyp (n = 11, 9.0%), or inflammatory polyp (n = 3, 1.7%) in the remaining patients.

Per-patient analysis

A 6-mm cut-off. *Advanced neoplasia.* When adopting a 6-mm threshold for TC referral (Table 3), CCE-2 detected 54 (90.0%) of 60 cases of AN in 178 screenees. CCE-2 was truly negative in 78 of 118 (66.1%) cases, whereas it was false positive in 40 patients not diagnosed with AN at TC. This leads to a post-CCE-2 TC referral rate of 52.8% (94 of 178). Of 40 false-positive cases, 33 (82.5%) were diagnosed with a nonadvanced adenoma. The sensitivity and specificity of CCE-2 for AN (Table 4) were 90.0% (95% CI, 78.8-95.9) and 66.1% (95% CI, 56.7-74.4), respectively, with a PPV and NPV of 57.4% (95% CI, 46.8-67.5) and 92.9% (95% CI 84.5-97.1).

When the analysis was restricted to patients with adequate bowel preparation at CCE-2, the results did not change. When considering per-patient sensitivity and NPV for AN by colonic site, CCE-2 examination would have detected 11 of 18 AN (sensitivity, 61.1%; 95% CI, 36.1-81.7) in the proximal colon (1 polyp or mass >5 mm at CCE-2 examination in patients with AN proximal to the descending colon) with NPV of 95.2% (95% CI, 89.9-97.8); the corresponding sensitivity and NPV for AN located in the distal

colon (descending colon, sigmoid, and rectum) were 91.7% (95% CI,79.1-97.3) and 96.0% (95% CI, 89.3-98.7).

Any adenoma and any adenoma >6 mm. When the 6-mm size threshold was used, CCE-2 detected at least 1 adenoma in 123 (69.7%) patients; 10 of 11 of those with CRC, and 90 (10 CRCs) of 123 (73.2%) with 1 or more polyps (any type and size). Sensitivity was 80.6% (95% CI, 71.1%-87.6%) for any adenoma and 90.9% (95% CI, 57.1%-99.5%) for CRC; the NPV was 98.8% (95% CI, 92.6%-99.9%) for CRC and 76.2% (95% CI, 65.4%-84.5%) for any adenoma. When restricting the analysis to patients with at least 1 adenoma or CRC ≥6 mm, CCE-2 detected 73 of 81 cases, corresponding to a sensitivity of 90.1% (95% CI, 81.0-95.3). The size of all CRCs was ≥10 mm, but CCE-2 misjudged the size in 1 case (10-mm malignant polyp), classifying it as a diminutive polyp.

A 10-mm cut-off. *Advanced neoplasia and any (advanced) adenoma ≥10 mm.* CCE-2 detected 46 of 60 (76.7%) cases of AN in 178 screenees when a 10-mm threshold was adopted (Table 3). In addition to the 6 lesions missed when using the 6-mm cut-off, 8 additional advanced adenomas were missed (4 advanced adenomas <10 mm and 4 adenomas ≥10 mm misjudged by CCE-2 as <10 mm). CCE-2 was truly negative in 107 of 118 cases, whereas it was false positive in 11 patients not diagnosed with AN at TC, resulting in a post-CCE-2 TC referral rate of 32.0% (57 of 178): 7 (63.6%) of 11 patients with a false-positive CCE-2 result were diagnosed with a nonadvanced adenoma, 3 with hyperplastic polyps, and 1 with a submucosal lipoma.

The sensitivity and specificity of CCE-2 for AN were 76.7% (95% CI, 66.7-86.2) and 90.7% (95% CI, 83.6-95.0), respectively, with a PPV and NPV of 80.7% (95% CI, 67.7-89.5) and 88.4% (95% CI, 81.0-93.3). When limiting the analysis to patients with at least 1 adenoma ≥10 mm, CCE-2 detected the adenoma in 34 of 40 patients, corresponding to a sensitivity of 85% (95% CI, 73.9%-96.1%).

A second TC was indicated in only 1 case after the CCE-2 report of a polyp ≥10 mm not detected at the initial TC, and the second examination confirmed the presence of an advanced adenoma.

TABLE 3. Distribution of cases of advance neoplasia (advance adenoma and CRC) between CCE-2 and colonoscopy (TC)

	With TC	Without TC	Total
With CCE (>6 mm)	54	40	94
Without CCE	6*	78	84
Total	60	118	178
With CCE (≥10 mm)	46	11	57
Without CCE	14	107	121
Total	60	118	178

CRC, Colorectal cancer; *TC*, traditional colonoscopy; *CCE*, colon capsule endoscopy.
*CCE detected 3 lesions judged to be <6 mm when TC detected advanced neoplasia: 1 CRC, 2 high-risk adenomas <10 mm. CCE missed 3 advanced neoplasia: 2 tubular adenomas >9 mm and 1 high-risk adenoma <10 mm.

TABLE 4. Accuracy of CCE-2 for advanced neoplasia at different cut-offs

CCE-2 accuracy for advanced neoplasia	6-mm cut-off, % (95% CI)	10-mm cut-off, % (95% CI)
Sensitivity	90.0 (78.8-95.9)	76.7 (63.7-86.2)
Specificity	66.1 (56.7-74.4)	90.7 (83.6-95.0)
Positive predictive value	57.4 (46.8-67.5)	80.7 (67.7-89.5)
Negative predictive value	92.9 (84.5-97.1)	88.4 (81.0-93.3)

CCE-2, Second-generation colon capsule endoscopy; *CI*, confidence interval.

Per-polyp analysis

Among the 178 patients who underwent a TC after a complete CCE-2 examination, CCE-2 detected 157 colorectal lesions (148 polyps and 9 lesions reported as masses) ≥6 mm in 93 patients; in addition, CCE-2 detected 125 polyps in 66 patients, but they were not included in the per-polyp analysis because they were judged to be ≤5 mm, ie, below the positivity threshold stipulated in our study protocol. The CCE-2 examination was negative in 19 patients in whom 31 polyps were detected at the TC examination (27 polyps ≤5 mm, 2 polys 6-9 mm, 2 polyps ≥10 mm), whereas the TC examination was negative in 3 patients in whom 1 polyp of 6 to 9 mm was found at the CCE-2 examination.

Therefore, in the per-polyp analysis, we included 90 patients in whom 154 polyps ≥6 mm were detected at the CCE-2 examination and 281 polyps (121 ≥6 mm) at TC. Of 154 polyps detected at CCE-2 in these 90 patients, 107 (69.5%) could be matched for site, morphology, and size, 11 (7.1%) for site and morphology but not for size, 21 (13.6%) were matched for site and size but not for morphology; 15 (9.7%) could not be matched for site, for morphology, or for size (Table 3). These 15 polyps have been reported in 13 patients in whom 35 polyps (5 low-risk adenomas 6-9 mm; 2 diminutive advanced adenomas and 5 advanced adenomas 6 mm) were found at TC (Table 5, Figures 1-4).

When adopting the 6-mm cut-off and considering only those polyps matched with lesions detected at TC, the per-polyp CCE-2 sensitivity was 90.3% (139 of 154). If we consider all polyps ≥6 mm detected at TC, including those cases with a negative CCE-2 examination, the per-polyp CCE-2 sensitivity was 84.8% (139 of 164).

Bowel preparation, transit time, and safety

The overall bowel preparation was considered adequate in 157 patients (88.2%) and inadequate in 19 patients (10.7%); in 2 cases, the quality of preparation was not reported (Supplementary Table 1, available online at www.giejournal.org). The mean transit time of the capsule was 4 hours and 4 minutes and > 0% of patients excreted the capsule within 5 hours (Supplementary Table 2, available online at www.giejournal.org). The sensitivity for AN when using the 6-mm referral threshold was 90.0% (18 of 20) when the capsule was excreted within 3 hours, 100% (26 of 26) when the transit time was between 3 and 5 hours, and 71.4% (10 of 14) when the transit time had exceeded 5 hours.

Reading time was recorded in 76% of the cases. The mean time was 61.6 minutes, and in 78 patients (57%), reading sessions were completed within 40 minutes. Sensitivity for AN when using the 6-mm referral threshold was 100% (21 of 21) for reading times in the range 20 to 40 minutes and 75% (12 of 16) when the reading time was shorter than 20 minutes or longer than 40 minutes.

With regard to safety, 2 patients had discomfort on swallowing the capsule, which was then placed directly in the stomach with the AdvanCE system (US Endoscopy, Mentor, Ohio, USA) under endoscopy guidance. Overall, 25% of patients experienced adverse events that were considered related to colon preparation (nausea, headache, abdominal pain). All events were classified as mild and resolved spontaneously within the same day. No serious adverse events or cases of capsule retention occurred.

**TABLE 5. Per-polyp analysis and matching of polyps detected by CCE and TC**

	Number	%
Not matched	15	9.7
Matched for site,* morphology, and size	107	69.5
Matched for site,* morphology, but not for size	11	7.1
Matched for site,* size, but not morphology	21	13.6
Total	154	100.0

CCE, Colon capsule endoscopy; *TC*, traditional colonoscopy.
*Left colon segment (rectum, sigmoid colon, descending colon and splenic flexure), right colon segment (cecum, ascending colon, hepatic flexure), transverse colon.
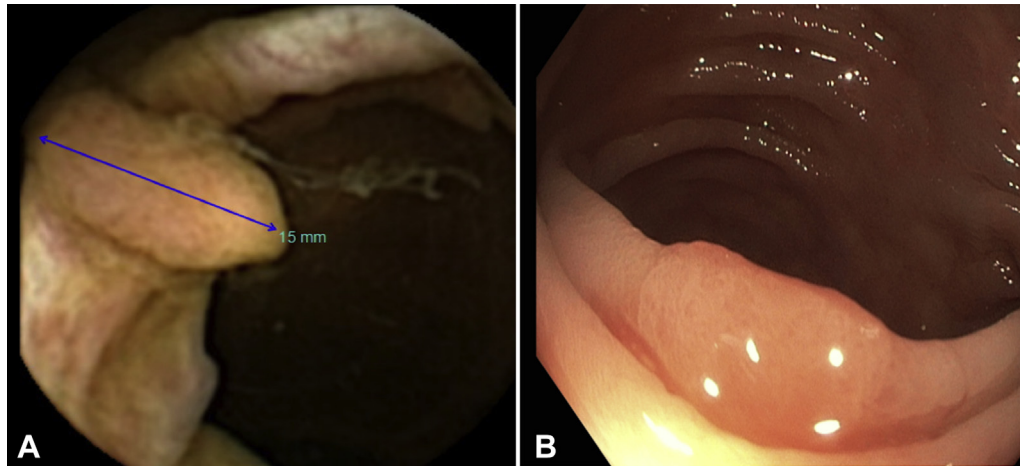
Figure 1. Sessile and pedunculated polyps visualized at colon capsule endoscopy (**A**) and traditional colonoscopy (**B**).
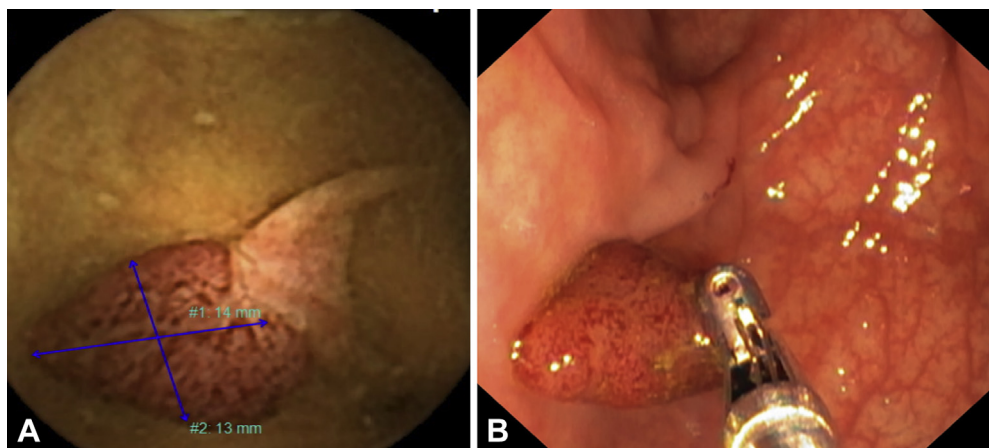

Figure 2. Sessile and pedunculated polyps visualized at colon capsule endoscopy (**A**) and traditional colonoscopy (**B**).

DISCUSSION

In patients with a positive FIT result, we showed a high sensitivity of CCE-2 for AN with a 6-mm cut-off that resulted in a 92.9% NPV for the per-patient analysis, marginalizing the risk of false-negative results after CCE-2 examination. This was offset by a high rate of post-CCE-2 referral for TC (ie, 52.8%) related to an apparently low specificity of CCE-2 for AN, mainly due to a substantial proportion of non-advanced adenomas measuring 6 to 9 mm. On the other hand, we excluded the feasibility of a 10-mm cut-off for post-CCE-2 referral to TC as being associated with a suboptimal sensitivity for AN.
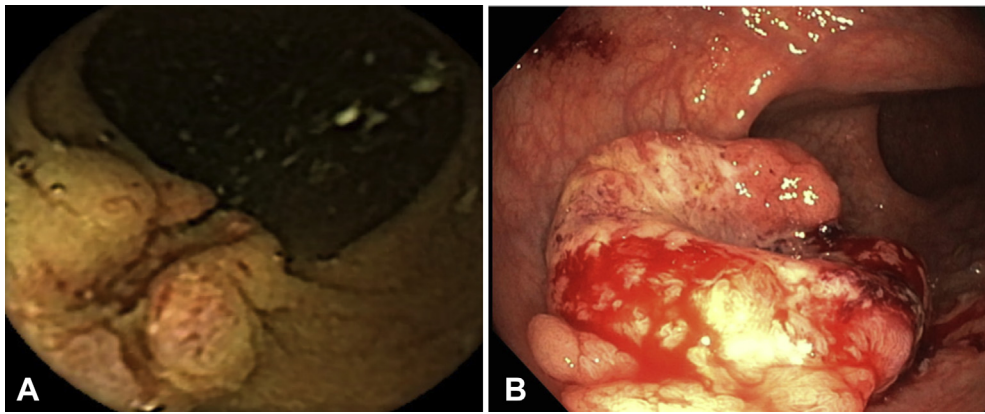
Figure 3. Colon cancers at colon capsule endoscopy (**A**) and traditional colonoscopy (**B**).
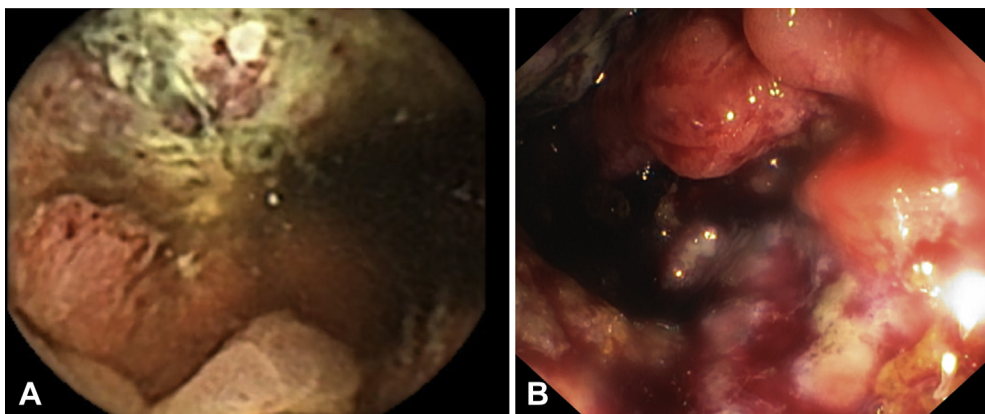
Figure 4. Colon cancers at colon capsule endoscopy (**A**) and traditional colonoscopy (**B**).

The clinical relevance of this analysis is directly related to the precision of our estimate of the sensitivity of CCE-2 for AN, which represents the main target of FIT-based screening. Previous studies were underpowered for this aim as a result of the low prevalence of AN in a primary CRC screening or unselected endoscopic population.[15,19-21] Thus, only accuracy data for overall neoplasia (polyp detection rate) at different cut-offs were reported without focusing on the detection rate of AN.[22] Based on 59 cases of AN, our 90.0% estimate of CCE-2 sensitivity is equivalent or superior to the corresponding values shown for other CRC screening imaging modalities, such as colonoscopy, sigmoidoscopy, and CT colonography; CCE-2 appears remarkably more accurate than FIT or the guaiac-based fecal occult blood test. In addition, such an estimate is in line with the 86% sensitivity value assessed for adenomas ≥6 mm in a previous meta-analysis. We also showed a reassuring CCE-2 sensitivity in detecting already-developed CRC, because only 1 of 9 CRC false-negative cases was actually a 10-mm malignant polyp misjudged as ≤5 mm.

The clinical relevance of the high sensitivity of CCE-2 for AN is demonstrated by the high NPV shown in our study.

Despite the high prevalence of AN in a disease-enriched FIT positive setting, CCE-2 was able to maintain the NPV over 90% when adopting a 6-mm cut-off. Overall, our data support the use of CCE-2 as a possible alternative to CT colonography in patients with a positive FIT result who are unwilling to or cannot undergo colonoscopy. In a previous head-to-head study on patients with incomplete colonoscopy, CCE-2 showed a statistically significantly higher diagnostic yield than CT colonography for neoplasia ≥6 mm.[23,24]

However, our study also confirmed the well-known limitations of CCE-2. First, approximately 1 of every 5 patients was excluded from the final study analysis because of failure to swallow the capsule (9%) or incomplete CCE-2 examination (11%) due to delayed transit. The finding of a similar prevalence of AN among patients who did not undergo or did not complete both examinations as among patient with complete CCE-2 examination would suggest that the patients included in our analysis are representative of screenees with a positive FIT result in our screening population. Also, the proportion of refusals might be lower if the CCE-2 procedure could be offered as a triage or as a

primary screening test, restricting TC referral only to patients with polyps (ie, outside the experimental setting). However, when considering the heavy bowel preparation required for CCE-2, the observed proportion of incomplete examinations may limit the acceptance of CCE-2.

Second, the 57.4% PPV for AN at the 6-mm cut-off was disappointingly only slightly higher than the 25% to 30% for the initial FITs. This was not related primarily to size mismatching between the CCE-2 and colonoscopy techniques (ie, ≥6 mm at CCE-2 shown to be ≤5 mm at colonoscopy) but rather with a somewhat expected low prevalence of advanced features among polyps measuring 6 to 9 mm. On the other hand, it could be argued that most of the apparently false positives at 6 mm actually ended up with the removal of a nonadvanced adenoma, which could be considered as a clinically relevant (albeit not optimal) target of a CRC screening intervention. Overall, the 52.8% post-CCE-2 referral to TC indicates that, for CCE-2 to be a cost-effective triage for patients with a positive FIT result, its cost should be roughly half than that of colonoscopy.

Our analysis provides the most reliable estimate of CCE-2 accuracy for AN. However, there are limitations. We were forced to close the study prematurely because of the low attractiveness of the study protocol to potential screenees. This was somewhat unexpected due to the potential appeal of CCE-2 as a noninvasive test, despite the fact that same-day colonoscopy was also required. A recent Spanish study[25] unexpectedly showed a reduced acceptance of CCE-2 compared with colonoscopy in the screening setting of patients with positive family history. Moreover, we included only those with a complete CCE-2 in the final analysis, assuming that any incomplete CCE-2 would be completed in real life by an additional test such as colonoscopy. If this was not the case, the accuracy of CCE-2 would be reduced detrimentally. Finally, a central reader was not included in the study; CCE-2 reading was centralized in highly trained tertiary centers, without data on interrater reliability among readers, reducing the generalizability of our findings.

In conclusion, our study showed reassuring values for the sensitivity of CCE-2 for AN, further supporting its use in primary or secondary screening settings. On the other hand, the excessive post-CCE-2 referral rate to colonoscopy argues against its routine use in an enriched disease setting, suggesting its use should be reserved for those cases in whom colonoscopy cannot be performed due to the patient's unwillingness or contraindications.

ACKNOWLEDGMENTS

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APPENDIX 1

In addition to the exclusion criteria already adopted by the population screening programs (ie, personal history of colorectal cancer or adenomas, or inflammatory bowel disease, hereditary syndromes such as familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, inability to provide informed consent, severe life-threatening disease), the presence of any of the following excluded an individual from study enrollment:

- Patients unable or unwilling to sign a written informed consent form
- Dysphagia or any swallowing disorder
- Congestive heart failure
- Kidney disease with pre-existing electrolyte disturbances, high level of serum creatinine, inadequate glomerular filtration rate, or renal dialysis
- Previous abdominal surgery of the GI tract, other than uncomplicated procedures that would be unlikely to lead to bowel obstruction based on the clinical judgment of the investigator
- Clinical symptoms suggestive of subocclusion (acute abdominal pain with severe constipation or vomiting)
- History of negative large-bowel endoscopy within the previous 5 years
- Any allergy or other known contraindication to the medications used in the study; in particular, a history of allergic reactions after administration of iodine contrast medium and history of thyroid disorders
- The patient is expected to undergo a magnetic resonance imaging examination within 7 days after ingestion of the capsule
- Any condition believed to have an increased risk for capsule retention, such as intestinal tumors, previous history of abdominal or pelvic radiotherapy, or nonsteroidal anti-inflammatory drug enteropathy
- Any condition that precludes compliance with the study and/or device instructions
- Patient currently participating in another clinical study

SUPPLEMENTARY TABLE 1. Quality of bowel preparation at colon capsule endoscopy

Quality	Number of patients	%
Not recorded	2	1.1
Inadequate	19	10.7
Adequate	157	88.2
Total	179	

SUPPLEMENTARY TABLE 2. Colon capsule transit time

Hours	No. of patients	%
Not recorded	10	5.6
1-2	18	10.1
2-3	38	21.3
3-4	28	15.7
4-5	46	25.8
5-7	28	15.7
>7	10	5.6
Total	178	

The *red line* indicates mean transit time that was 4 hours and 4 minutes. According to these data, >70% of patients excreted the capsule within 5 hours.