High-definition colonoscopy versus Endocuff versus EndoRings versus full-spectrum endoscopy for adenoma detection at colonoscopy: a multicenter randomized trial CME

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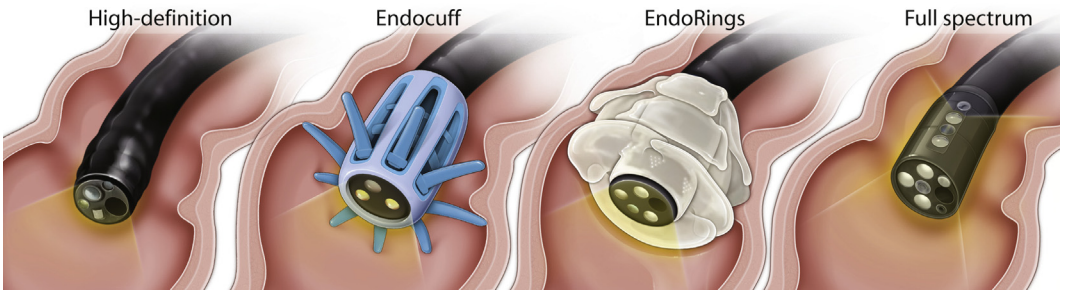
GRAPHICAL ABSTRACT



Background and Aims: Devices used to improve polyp detection during colonoscopy have seldom been compared with each other.

Methods: We performed a 3-center prospective randomized trial comparing high-definition (HD) forward-viewing colonoscopy alone to HD with Endocuff to HD with EndoRings to the full spectrum endoscopy (FUSE) system. Patients were age ≥50 years and had routine indications and intact colons. The study colonoscopists were all proven high-level detectors. The primary endpoint was adenomas per colonoscopy (APC).

Results: Among 1188 patients who completed the study, APC with Endocuff (APC mean ± standard deviation: 1.82 ± 2.58), EndoRings (1.55 ± 2.42), and standard HD colonoscopy (1.53 ± 2.33) were all higher than FUSE (1.30 ± 1.96; $P < .001$ for APC). The APC for Endocuff was higher than standard HD colonoscopy ($P = .014$). Mean cecal insertion times with FUSE (468 ± 311 seconds) and EndoRings (403 ± 263 seconds) were both longer than with Endocuff (354 ± 216 seconds; $P = .006$ and .018, respectively).

Conclusions: For high-level detectors at colonoscopy, forward-viewing HD instruments dominate the FUSE system, indicating that for these examiners image resolution trumps angle of view. Further, Endocuff is a dominant strategy over EndoRings and no mucosal exposure device on a forward-viewing HD colonoscope. (Clinical trial registration number: NCT02345889.) (Gastrointest Endosc 2018;88:335-44.)

(footnotes appear on last page of article)

Colonoscopy prevents colon cancer through detection and removal of precancerous lesions.[1] More effective detection of adenomas is associated with better prevention of postcolonoscopy cancer.[2,3] Critical elements of effective detection include optimal maneuvering of the colonoscope to expose mucosa behind folds, adequate distension, clean colon, and sufficient inspection time to visually process the exposed mucosa.[4] The use of high-definition (HD) colonoscopes aids in detection[5] and is now widely considered fundamental to detection and effective therapeutics.

Although optimal maneuvers and lesion recognition ability during colonoscopy examination are the core of effective detection and can be taught to colonoscopists,[6,7] adjunctive devices and techniques have also been widely investigated. These include tools to highlight flat and subtle precancerous lesions such as chromoendoscopy[8,9] and electronic chromoendoscopy[10,11] and mucosal exposure devices such as Endocuff,[12] EndoRings,[13] and ultra-wide-angle endoscopes such as full spectrum endoscopy (FUSE).[14]

Available data with mucosal exposure devices have often compared such devices with standard colonoscopy in 2-arm studies. The most robust data are available for Endocuff[12,15-18] and indicate that Endocuff produces an average 7% gain in the adenoma detection rate (ADR).[12] Data are more limited with EndoRings and are largely from a single randomized tandem study showing that EndoRings reduced the miss rate for adenomas.[14] Data on the value of the FUSE system have been mixed, with FUSE resulting in a lower miss rate in an initial tandem study[14] but no improvement in a subsequent randomized trial in patients with positive fecal immunochemical tests.[19] To the extent that mucosal exposure devices are effective, it remains uncertain which colonoscopists can improve detection with these devices. That is, do all endoscopists improve detection by use of mucosal exposure devices or are the benefits confined or result predominantly for colonoscopists with low baseline ADRs?

In this study, we sought to evaluate the utility of mucosal exposure devices in the hands of colonoscopists with known high ADRs when using standard equipment. In addition, we sought to directly compare 3 mucosal exposure devices with each other, namely Endocuff versus EndoRings versus FUSE.

METHODS

We conducted a prospective randomized controlled trial comparing HD forward-viewing white-light colonoscopy (referred to as the standard or control arm), versus HD forward-viewing white-light colonoscopy plus Endocuff, versus HD forward-viewing white-light colonoscopy with EndoRings, versus the FUSE system. Patients were randomized in a 1:1:1:1 ratio. The study was conducted at 3 academic endoscopy units in Indianapolis, Indiana; Milan, Italy; and New York, New York. The study was reviewed and approved by the Institutional Review Board at Indiana University on January 14, 2015, and all subjects gave informed consent. The trial was registered at Clinicaltrials.gov (NCT02345889).

Participants were aged ≥50 years and undergoing colonoscopy for colorectal cancer screening, surveillance of polyps, or symptoms. Patients were excluded if there was any previous surgical resection of the colon, if there was a known colonic stricture or severe diverticular disease that might impede passage of the colonoscope with Endocuff or EndoRings, if there was a known coagulopathy, for inability to provide informed consent, for any known polyp syndrome or inflammatory bowel disease or Lynch syndrome, or if the indication was a known therapeutic procedure including polypectomy (Table 1). Patients were excluded after randomization if their bowel preparation was considered inadequate for polyp examination, if the patient was found to have a polyp syndrome (World Health Organization criteria were used to classify patients with serrated polyposis syndrome[20]) based on the findings of the colonoscopy, or if the patient was diagnosed with inflammatory bowel disease during the study colonoscopy. As part of this intent-to-treat analysis, patients remained in the analysis if Endocuff or EndoRings on a pediatric colonoscope could not pass the sigmoid colon.

Interventions

The study was performed at 3 sites, 2 in the United States and 1 in Italy. The original plan was to conduct the study at 4 sites, but the fourth site never initiated the trial. At each site one endoscopist with a proven high (≥40% in screening colonoscopy) baseline ADR (D.K.R., A.R., and S.A.G.) performed every withdrawal. All 3 sites had extensive experience with control arm equipment, FUSE, and Endocuff before initiation. Two sites were less familiar with EndoRings, and the endoscopists performed enough procedures with EndoRings before study initiation to be very familiar with its use. Fellows were allowed to insert the colonoscope, but cecal insertion times were evaluated separately when fellows participated in insertion.

A computer-generated sequence was used to randomize the patients. Each site was provided with a series of opaque envelopes numbered sequentially with the concealed randomization. Enrollment and assignment of patients to study arms occurred at the individual sites. The randomization was revealed only after the patient provided informed consent.

At all 3 sites, Olympus HD colonoscopes (Olympus, Tokyo, Japan) were used for the control arm and the arms with Endocuff and EndoRings. These were 190 series or H180 series colonoscopes, and the colonoscopists had the discretion to select an adult or pediatric instrument. If an adult instrument could not pass an angulated sigmoid, the protocol required an attempt with a pediatric instrument in the same randomization arm. Thus, patients randomized to Endocuff were required to have an attempt using the pediatric colonoscope with the pediatric Endocuff device.

The resolution of the FUSE system was improved by the manufacturer while the study was in progress. All 3 sites had access and incorporated the most up to date FUSE colonoscopes as they became available. Both adult and pediatric FUSE colonoscopes were available at each site.

The Endocuff device used was the original device with 2 rows of fingers (Arc Medical Design, Leeds, UK). The EndoRings device was manufactured in Israel by EndoAid

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria
• Screening, surveillance, or diagnostic colonoscopy
• Age ≥50 years
Exclusion criteria
• Any large-bowel resection
• Inflammatory bowel disease
• Any polyposis syndrome
• Any family history of polyposis syndromes
• Referral for a previous incomplete colonoscopy
• Referral for removal of a polyp
• Referral for positive fecal blood test
• Anticipated severe sigmoid angulation

Ltd (Caesarea, Israel). During the study, the device was modified from a 3-ring device to a 2-ring device, and the EndoRings used were changed as soon as the new device was available.

The FUSE system and colonoscopes were provided by Endochoice (Marrietta, Ga). The EndoRings devices were provided by EndoAid. The Endocuff devices were provided by the U.S. Endocuff distributor (Medivators Inc, Minneapolis, Minn). No other industry support was provided for the trial. There was no industry involvement in the design of the trial or its conduct, and no industry had access to or reviewed the study data or the manuscript before publication.

Each of the study endoscopists was asked to force the inspection time during withdrawal to approximately 8 minutes to remove inspection time as a variable that could affect the detection results. Inspection time was measured during withdrawal by an assistant using a stopwatch. The stopwatch was started as soon as the cecum was cleaned and cecal inspection initiated. It was stopped for all maneuvers, including polypectomy and biopsy sampling, and during all washing and suctioning of the colon. For the FUSE device, the endoscopist tried to observe all 3 screens, but 2 individuals (usually the technician and the registered nurse in the room) were assigned to watch the 2 lateral images (1 assistant assigned to each screen) to help ensure that any exposed polyp was recognized.

Outcomes

The primary outcome was the rate of conventional adenomas per colonoscopy (APC). Secondary outcomes included the ADR (percent of patients with ≥1 conventional adenoma), number of sessile serrated polyps per colonoscopy, the sessile serrated detection rate (number of patients with ≥1 sessile serrated polyp), the colonoscope insertion times, the failure rate of insertion, and the detection targets noted above for the right side of the colon (cecum, ascending, and hepatic flexure). No interim analysis was performed.

Conventional adenomas were uniformly dysplastic lesions that were characterized as tubular, tubulovillous, or villous with dysplasia as low grade or high grade. Serrated class lesions included hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas.

Because of the failure to initiate the study at 1 planned site and slow randomization at another, randomization was continued beyond the initial planned number at 2 sites (see Results). Proximal colon refers to the cecum, ascending colon, and hepatic flexure.

Sample size and statistical analysis

Based on previous studies at Indiana University, we estimated that the baseline APC in the standard colonoscopy group would be 1.7 with a coefficient of variation of 1.5. To demonstrate an increase in APC to 2.2 (an absolute increase of .5 or a 29% increase) in any of the 3 increased mucosal exposure groups, a sample size of 287 patients per group, or total sample of 1148 subjects was needed, assuming 80% power, and 2-sided 5% significance level.

Generalized estimating equation methods were used to analyze the combined data across all 3 sites, using site as the cluster effect. Age and Boston Bowel Preparation Score assumed normal distributions, insertion and withdrawal times assumed log-normal distributions, count data used a negative binomial model, and binary data used logistic regression. Similar analyses, without using generalized estimating equation for clustering, were performed for analyses of each site separately. Pair-wise tests between all groups were performed when the overall group effect was significant. A 5% significance level was used for all tests, with no adjustment for multiple comparisons. Analyses were performed using SAS, version 9.4 (SAS institute, Inc, Cary, NC). To assess the effect of changing the FUSE and EndoRings technology during the study, APC was plotted against time for the EndoRings and FUSE groups, with a spline added to the plot to evaluate trends.

RESULTS

Data on patients screened, deemed ineligible, and refusal to participate were collected only in Indianapolis. The flow of patients through the study, including those excluded after randomization at all 3 sties, are described in Figure 1.

Exclusions after screening and before randomization were tracked at Indianapolis only. Subjects who passed initial screening at Indianapolis but were excluded before randomization included 17 identified to have some degree of prior colon resection, 4 referred for a previous incomplete colonoscopy (this reason for referral was not evident to screeners in the initial portion of the study), 9 with evidence of inflammatory bowel disease, 4 with serrated polyposis syndrome, 1 with familial adenomatous polyposis, 1 with a positive fecal blood test, and 6 considered unable to

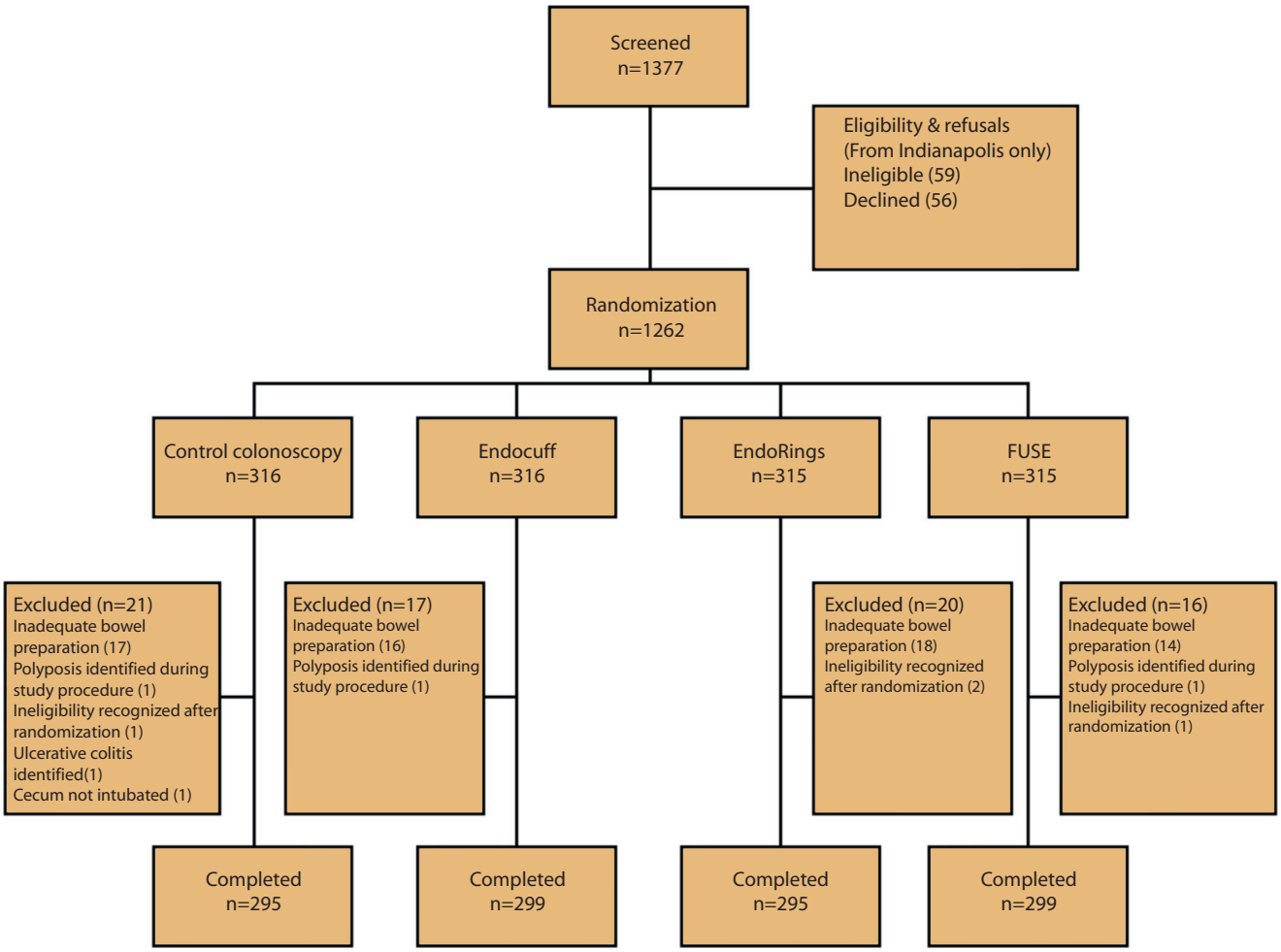


Figure 1. Flow of patients through the study. *FUSE,* Full spectrum endoscopy.

give informed consent by the investigator for reasons including dementia, anxiety, and inadequate English language skill. Seventeen were excluded by the investigator based on evidence of severe sigmoid diverticular disease in prior colonoscopy reports (considered to make passage of the colonoscope with Endocuff or EndorRings likely to fail) or recent diverticulitis.

There were 1262 patients randomized, of whom 74 were excluded after randomization (Fig. 1). One patient was excluded from the control arm for failure to intubate the cecum (Fig. 1). Three patients were excluded when they were recognized to have serrated polyposis syndrome during the study colonoscopy. Six patients were randomized to EndoRings and 4 to Endocuff and included in the intent to treat analysis in whom the instrument could not pass the sigmoid with either adult or pediatric versions. There were 3 patients in the EndoRings arm and 1 in the Endocuff arm in whom the adult scope with device could not pass the sigmoid colon, but the pediatric colonoscope and device were successfully passed to the cecum. In 1 patient the FUSE processor failed during the procedure and could not be promptly repaired. The procedure was completed using a standard Olympus colonoscope, and the patient was included in the study.

There were 1188 subjects who completed the study, of whom 299 were randomized to Endocuff, 295 (Fig. 2) to EndoRings, 299 to FUSE, and 295 to the control arm colonoscopy. The mean age of all subjects who completed the study was 62.6 years (standard deviation, 8.3), and there were 582 women (49%). There were 784 subjects who completed the study at Indianapolis, 302 at Milan, and 102 at New York. Table 2 shows demographic features and procedure indications for the 4 colonoscopy groups. There were no significant differences in these factors between groups, either overall or at the individual study sites. More than 90% of patients had polyp surveillance or screening as their indication.

Detection

Considering only patients with the indication screening and who were randomized to the control arm, the fraction of subjects with at least 1 conventional adenoma (the ADR using standard forward-viewing HD instruments) was 39 of

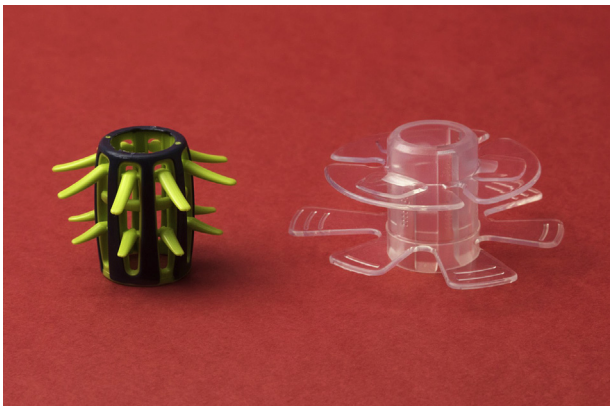


Figure 2. The Endocuff (*left*) and the revised EndoRings (*right*) devices used in the study.

64 subjects (61%) at Indianapolis, 19 of 44 (43%) at Milan, and 16 of 19 (84%) at New York, consistent with previous internal data at each site that the study endoscopists were high-level detectors.

Table 3 summarizes detection in each study arm for all sites combined and individual sites. The control colonoscopy arm, Endocuff, and EndoRings were all superior to FUSE for the primary endpoint ($P < .001$). Overall, the highest APC was achieved with Endocuff at 1.82 (2.58). Endocuff was superior to control colonoscopy (.014). The most marked differences in detection with Endocuff were in New York, where the APC was 2.00 (standard deviation, 2.34) with Endocuff and <1 with the other 3 modalities (.75 ± .94 for EndoRings, .80 ± 1.37 for FUSE, .92 ± 1.15 for control). There were no differences in Indianapolis ($P = .151$) or Milan ($P = .848$) between the modalities for the primary endpoint.

The ADR was also significantly higher with Endocuff, EndoRings, and control colonoscopy compared with FUSE ($P \leq .006$). Further, Endocuff was superior to EndoRings ($P < .001$) and control colonoscopy ($P = .003$). There were no significant differences between study arms in ADR within sites. Similar findings were observed for the polyp detection rate as were seen with ADR.

Evaluation by location in the colon showed that APCs were higher in the right side of the colon (cecum, ascending, and hepatic flexure) for Endocuff ($P < .001$), EndoRings ($P = .043$), and control ($P = .003$) compared with FUSE (Supplementary Table 1, available online at www.giejournal.org). APC for Endocuff in the right side of the colon was higher than control colonoscopy ($P = .034$). When analyzed by site, APC with Endocuff was higher in the right side of the colon in New York when compared with EndoRings ($P = .005$) and control ($P = .030$), but there were no differences in right-sided colon ADR between modalities in Indianapolis ($P = .563$) or in Milan ($P = .966$). Very similar differences between modalities were seen in right-sided colon ADR at New York specifically; however, these differences in right-sided colon ADR between modalities were again not seen in Indianapolis ($P = .382$) or Milan ($P = .805$).

The detection endpoints in a per protocol analysis are shown in Supplementary Table 2, available online at www.giejournal.org. Compared with the intention to treat analysis shown in Table 3, the per protocol analysis does not include the 10 patients in whom the colonoscope could not be passed through the sigmoid colon with a device on the tip and the 1 patient in whom the FUSE system failed. Differences in results between the intention to treat and per protocol analyses were minor.

There were no differences between modalities in APC for conventional adenomas ≥10 mm either overall ($P = .306$) or at any of the study sites. Supplementary Table 1 shows the actual numbers of histologically identified conventional adenomas and sessile serrated polyps according to lesion size and location in the colon (right side of colon including cecum, ascending flexure, and hepatic flexure vs distal to the hepatic flexure).

There were some statistically significant differences in the detection of sessile serrated polyps between modalities (Table 3), but the trends were not consistent and, although statistically significant, were numerically minor. Because the technology for FUSE and EndoRings were changed during the study, APC was plotted against time for each technology, and no significant trends over time were observed for FUSE ($P = .46$) or EndoRings ($P = .83$).

Procedure times

For the entire study, cecal insertion time was longer with FUSE compared with Endocuff ($P = .006$) and control colonoscopy ($P = .016$) (Table 4). Further, EndoRings insertion time was longer than that for Endocuff ($P = .020$). A gastroenterology fellow was involved in the insertion phase in 39% of colonoscopies at Indianapolis, 61% of colonoscopies in Milan, and none of the colonoscopies in New York. When only colonoscopies in which no fellow participated in insertion were considered, the cecal insertion time was still longer with FUSE than the other 3 arms ($P \leq .017$), and EndoRings insertion time was longer than Endocuff insertion time ($P = .014$). When insertion times by site were evaluated, FUSE was longer than Endocuff ($P \leq .02$) and standard ($P \leq .03$) at all sites, FUSE was longer than EndoRings in Indianapolis, EndoRings was longer than Endocuff ($P = .023$) and standard ($P = .003$) in New York, and FUSE was longer than EndoRings ($P = .004$) and standard was longer than Endocuff ($P = .050$) in Milan.

The mean Boston Bowel Preparation Score overall was 8.12 (standard deviation, 1.33), with no significant difference between the study arms, but was higher at Indianapolis (8.75 ± .84) and New York (8.47 ± 1.23) than at Milan (6.39 ± .76). There were no colorectal perforations in any of the study patients.

DISCUSSION

In this prospective randomized controlled trial we compared adenoma detection with a control arm of HD

TABLE 2. Demographics and procedure indications

	Study arm			
	Control* (n = 295)	Endocuff† (n = 299)	EndoRings‡ (n = 295)	Full spectrum endoscopy (n = 299)
Mean age, y (SD)	62.6 (8.3)	63.2 (8.2)	62.3 (7.9)	62.3 (8.7)
Female	139 (47%)	141 (47%)	156 (53%)	146 (49%)
Race				
White	272 (92%)	276 (92%)	276 (94%)	269 (90%)
Black	13 (4%)	15 (5%)	13 (4%)	20 (7%)
Hispanic	5 (2%)	6 (2%)	5 (2%)	4 (1%)
Asian	4 (1%)	2 (1%)	1 (<1%)	5 (2%)
Other	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Indication				
Screening	127 (43%)	126 (42%)	123 (42%)	128 (43%)
Surveillance	151 (51%)	150 (50%)	152 (52%)	154 (52%)
Diagnostic	16 (5%)	23 (8%)	20 (7%)	16 (5%)

SD, Standard deviation.
*Control: high-definition forward-viewing Olympus 190 or H180 colonoscope.
†Control instrument with Endocuff.
‡Control instrument with EndoRings.

forward-viewing colonoscopy to HD forward-viewing colonoscopy with the adjunctive mucosal exposure devices Endocuff and EndoRings and with the FUSE colonoscopy system. Although a number of studies have compared individual mucosal exposure devices with standard colonoscopy, to our knowledge this is the first study to compare mucosal exposure devices with each other.

A principal finding of our study was that the FUSE colonoscope system was inferior to HD forward-viewing Olympus colonoscopes with or without adjunctive devices. Thus, APCs and the ADR were higher with Olympus colonoscopes compared with the FUSE system. This result is different from that obtained in the initial tandem colonoscopy study comparing the FUSE system with standard-definition colonoscopes,[14] which found that FUSE was superior for detection. Further, the result is different from a prospective randomized trial comparing an early generation of FUSE colonoscopes with standard-definition forward-viewing colonoscopes in a fecal immunochemical test–positive population in Italy.[19] In that study, there was no difference in detection between the very-wide-angle FUSE system and the forward-viewing standard-definition colonoscopes. However, there was a nonsignificant trend in that study toward better detection of large adenomas by standard endoscopy. In our study, we used HD Olympus colonoscopes and state-of-the-art FUSE instruments as they became available during the study interval. Although the FUSE colonoscopes were also considered HD, our subjective impression is that the resolution of the Olympus instruments was superior to FUSE. Our results indicate that in the hands of high-level detectors, high image resolution is more important to detection than angle of view. Thus, skilled examiners appear to be able to compensate for a more limited angle of view by their manipulation and deflection of the instrument tip to expose mucosal surfaces on the proximal sides of the haustral folds and flexures. Because we found that the FUSE colonoscope was also inferior with regard to the time for cecal insertion (possibly because the FUSE insertion tubes are "floppier" than Olympus instruments), we conclude that in the hands of careful examiners, HD forward-viewing colonoscopes have superior performance to the FUSE colonoscopes. It is possible that a wide-angle instrument with image resolution comparable with Olympus HD colonoscopes might provide superior detection. However, to our knowledge, no such device exists at the present time, and the FUSE colonoscope is being withdrawn from the commercial market after purchase of EndoChoice by Boston Scientific. Thus, whether a super wide-angle colonoscope can outperform a 170-degree angle of view HD instrument is uncertain and must await development of new technology and further investigation.

Our data indicate that with regard to adjunctive devices that fit over the tip of an HD forward-viewing colonoscope, Endocuff is a dominant strategy over EndoRings and no device. First, there was a significant increase of APC with Endocuff compared with control colonoscopy, and ADR was higher with Endocuff compared with EndoRings and control colonoscopy. A marked difference in detection with Endocuff at one center, which contributed the smallest group of patients to the overall study, had an important effect on this conclusion, although a numerical increase with a trend toward statistical significance was also seen at the largest participating site. There was no disadvantage with Endocuff with regard to insertion. Thus, overall Endocuff produced improved detection with no detriment to

TABLE 3. Detection endpoints in the intent to treat analysis

	Study arm			
	Control (n = 295)	Endocuff (n = 299)	EndoRings (n = 295)	Full spectrum endoscopy (n = 299)
Adenomas per colonoscopy				
All sites*	1.53 (2.33)†	1.82 (2.58)	1.55 (2.42)	1.30 (1.96)
Indianapolis	1.89 (2.69)	2.17 (2.88)	1.97 (2.77)	1.59 (2.18)
Milan	.83 (1.18)	.80 (1.25)	.72 (1.17)	.68 (1.19)
New York‡	.92 (1.15)	2.00 (2.34)	.75 (.94)	.80 (1.32)
Adenoma detection rate				
All sites§	166 (56%)¶	191 (64%)	167 (57%)	154 (52%)
Indianapolis	117 (61%)	137 (70%)	127 (65%)	115 (58%)
Milan	37 (47%)	35 (47%)	29 (39%)	28 (37%)
New York	12 (48%)	19 (68%)	11 (46%)	11 (44%)
Sessile serrated polyp per colonoscopy				
All sites‖	.17 (.54)†	.17 (.54)	.20 (.81)	.18 (.74)
Indianapolis	.24 (.64)	.23 (.63)	.29 (.98)	.25 (.89)
Milan	.03 (.16)	.04 (.26)	.01 (.12)	.03 (.16)
New York	.04 (.20)	.07 (.26)	.04 (.20)	.04 (.20)
Sessile serrated polyp detection rate				
All sites**	36 (12%)¶	33 (11%)	33 (11%)	30 (10%)
Indianapolis	33 (17%)	29 (15%)	31 (16%)	27 (14%)
Milan	2 (3%)	2 (3%)	1 (1%)	2 (3%)
New York	1 (4%)	2 (7%)	1 (4%)	1 (4%)
Polyp detection rate				
All sites††	226 (77%)¶	247 (83%)	231 (78%)	212 (71%)
Indianapolis‡‡	162 (84%)	175 (89%)	171 (87%)	155 (78%)
Milan	46 (59%)	50 (68%)	42 (56%)	38 (51%)
New York	18 (72%)	22 (79%)	18 (75%)	19 (76%)

*Control, Endocuff, and EndoRings higher than FUSE (all $P < .001$). Endocuff > control ($P = .014$).
†Designated polyp type per colonoscopy (standard deviation).
‡Endocuff > EndoRings ($P = .008$), FUSE ($P = .011$), and control ($P = .027$) in New York; no difference in study arms for APC at Indianapolis ($P = .137$) or Milan ($P = .848$).
§Endocuff ($P < .001$), EndoRings ($P = .001$), and control ($P = .006$) all higher than FUSE. Endocuff higher than EndoRings ($P < .001$) and control ($P = .003$). No differences in ADR by site.
¶Number of patients with designated polyp type (%).
‖EndoRings higher than FUSE ($P < .001$) and control ($P < .001$). FUSE higher than control ($P < .001$).
**Endocuff ($P = .009$) and control ($P < .001$) higher than FUSE. Control higher than Endocuff ($P = .047$) and EndoRings ($P = .004$).
††Endocuff ($P < .001$), EndoRings ($P = .002$), and control ($P < .001$) higher than FUSE. Endocuff higher than EndoRings ($P = .008$) and control ($P < .001$).
‡‡At Indianapolis Endocuff ($P = .004$) and EndoRings ($P = .015$) were higher than FUSE.

insertion except for an occasional patient with an angulated sigmoid colon in which passage of the colonoscope required removal of the cuff. Further, the finding that Endocuff resulted in gains in detection even in high-level detectors, who would be expected to have superior technique with standard instruments, suggests that Endocuff could potentially produce detection gains for examiners with any baseline level of detection. Thus, Endocuff may overcome mucosal exposure problems that cannot be overcome with an HD forward-viewing colonoscope alone.

In this study, Endocuff allowed an ADR that was at least 7 percentage points higher (95% confidence interval, 3%-16%) than the other 3 arms of the study. A study found that each 1% gain in ADR resulted in a 3% drop in the risk of interval cancer and a 5% drop in the risk of fatal interval cancer.[3] Whether such impacts on interval cancer will occur in very high-level detectors is uncertain, but our results indicate that potentially important gains in ADR are achievable with Endocuff even by detectors with very high ADRs using standard instruments. Endocuff was associated with gains in APC of 17% to 40% compared with the other 3 arms. This difference in overall adenoma detection could also result in important protective effects against interval cancer, although the relationship of APC to interval cancer protection has not yet been described. Although we did not formally address the cost-effectiveness of Endocuff,

TABLE 4. Procedure times

	Study arm			
	Control	**Endocuff**	**EndoRings**	**Full spectrum endoscopy**
Cecal insertion time, sec	n = 295	n = 299	n = 295	n = 299
All sites*	422 (319)	354 (216)	403 (263)	468 (311)
Indianapolis	366 (243)	320 (179)	352 (191)	395 (225)
Milan	642 (405)	503 (254)	581 (356)	731 (385)
New York	170 (62)	193 (93)	251 (110)	242 (80)
Cecal insertion time when no fellow was involved, sec	n = 173	n = 169	n = 172	n = 176
All sites†	320 (256)	265 (173)	331 (222)	380 (252)
Indianapolis	283 (185)	239 (127)	277 (127)	340 (169)
Milan	556 (378)	438 (269)	588 (345)	718 (401)
Inspection time, sec	n = 295	n = 299	n = 295	n = 299
All sites‡	444 (103)	419 (95)	417 (147)	421 (112)
Indianapolis	418 (91)	392 (89)	388 (160)	378 (83)
Milan	501 (109)	492 (78)	484 (92)	522 (120)
New York	467 (95)	414 (84)	438 (96)	454 (81)

Values in parentheses are standard deviations. *n*, Number of insertions in designated group performed with no participation by a fellow.
*FUSE longer than Endocuff ($P = .006$) and control ($P = .016$), EndoRings longer than Endocuff ($P = .020$) (site difference similar but not shown).
†When no fellow was involved in insertion FUSE was longer than Endocuff ($P < .001$), EndoRings ($P = .017$), and control ($P = .001$); EndoRings longer than Endocuff ($P = .014$). By site: FUSE longer than Endocuff and control at all sites; EndoRings longer than Endocuff and control in New York, FUSE longer than EndoRings in Milan, and control longer than Endocuff in Milan.
‡No significant difference overall. By site, control significantly longer than Endocuff, EndoRings, and FUSE in Indianapolis.

the cost of Endocuff is low in the United States compared with the cost of colonoscopy and would be unlikely to adversely affect the cost-effectiveness of improving the quality of adenoma detection.[21,22]

The reasons EndoRings did not match Endocuff with regard to detection are not clear. From a mucosal exposure perspective, the ability of EndoRings to deflect folds seems comparable with Endocuff. In the left side of the colon, EndoRings seems to have even more of a tendency than Endocuff to straighten the lumen and flatten the haustral folds. However, the mucosal gripping properties of EndoRings seem to cause it to jump back 2 or 3 folds at times during withdrawal through the sigmoid, and it can be difficult to reinsert the instrument to the point where slippage began. In any case, our data suggest that EndoRings creates greater problems for colonoscope insertion than Endocuff, which certainly relates to its larger diameter and bulkier profile. Taken together, our data suggest that Endocuff is a more effective and easier to use device than EndoRings.

Strengths of our study include large size, the use of multiple centers, and the testing of multiple devices. This design allowed a comparison of available devices in a fashion not previously available to practicing colonoscopists. Further, we used the best available versions of each technology throughout the study. We did not see evidence that successive generations of FUSE or EndoRings were associated with increasing detection, suggesting that our results apply to the latest generations of these devices. Next, we actively forced the inspection times in the 4 study arms to be equal, because withdrawal time is well known to influence detection,[23] and failure to control inspection time can disrupt the interpretation of a detection trial.[23]

Limitations of our study were primarily that the recruitment was uneven across the sites, and there were some differences between sites with regard to detection. These differences suggest some operator dependence applies to these devices, such as the very large increase in APCs with Endocuff relative to other devices in New York. However, many of the trends seen in the overall study were consistent across the individual sites, including the detection of adenomas and serrated lesions and insertion times. Certainly, direct comparisons between mucosal exposure devices by other investigators could be informative. However, we acknowledge that the operator dependence demonstrated in the study indicates that some caution is appropriate in concluding generalizability. Finally, endoscopists were not blinded to which device was in use. This is a consistent problem with colonoscopy detection studies, and these studies depend on the investigating endoscopists approaching the use of each device without bias.

The version of Endocuff that we used is no longer commercially available and has been replaced by Endocuff Vision (Arc Medical Design). Endocuff Vision has fingers that are 3 mm longer than those on Endocuff, and there is only 1 ring of fingers. There are no direct comparative studies of Endocuff Vision and Endocuff. Our anecdotal impression of the fold flattening achieved with Endocuff

Vision is that it is as or more effective than Endocuff, with no reduction of insertability. We upgraded the EndoRings and FUSE colonoscopes as upgrades became available during the study. Although the use of upgraded devices makes study interpretation more challenging, we considered that failure to upgrade and using only older devices would also subject the study to criticism. Again, we saw no significant improvement in ADRs over the course of the study within the EndoRings or FUSE arms, suggesting that our conclusions regarding detection remain valid with the latest generations of these devices.

To the extent that our results endorse the routine use of Endocuff in clinical practice, practitioners might be interested in our impressions of how the device affects actual colonoscopy performance. Our collective impression is that the use of Endocuff in routine colonoscopic examination is easy for experienced endoscopists to learn and does not adversely affect the performance of routine polypectomies. We suspect it may have the potential to make the process of examining the proximal sides of folds faster, as has been suggested in retrospective uncontrolled evaluations[24] but which has not been tested as a primary endpoint of randomized trials. We did not routinely or systematically attempt terminal intubation during the study, but our impression was that Endocuff does reduce the ease and success rate of terminal ileal intubation, consistent with the results of other studies.[25] Finally, attention to difficult sigmoid colons is needed in considering use of Endocuff. In the current study, about 1.5% of subjects had sigmoid colons that did not allow passage of Endocuff, and at Indianapolis about 2% of screened subjects were excluded before randomization because of known diverticular disease that might have made sigmoid passage with Endocuff or EndoRings difficult or impossible. We note that the detection gains found in this study with Endocuff were largely in diminutive lesions (Supplementary Table 1), and the clinical significance of detection gains in diminutive lesions remains uncertain. Improved detection of diminutive lesions may be generally associated with improved detections of large lesions, but that suggestion is not proven true by these data. Further, we did not perform a formal cost analysis of Endocuff use and have not evaluated the cost-effectiveness of using Endocuff routinely in colonoscopy.

In conclusion, in a prospective randomized controlled trial we demonstrated that detection with HD forward-viewing colonoscopes is superior to a very-wide-angle colonoscope system, which in all in its iterations had what seemed to be recognizably inferior image resolution. Thus, in the hands of high-level detectors, image resolution trumps angle of view for adenoma detection during colonoscopy. Next, we showed that use of an adjunct (Endocuff) on the end of an HD forward-viewing colonoscope produced gains in adenoma detection even in the hands of examiners who are very skilled with standard instruments lacking adjunctive devices. Further, Endocuff produced no reduction of insertion capability that was clinically important. Finally, our results indicate that the design of Endocuff is superior to the design of EndoRings as a mucosal exposure device for colonoscopy.

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Abbreviations: ADR, adenoma detection rate; APC, adenoma per colonoscopy; FUSE, full spectrum endoscopy; HD, high definition.

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See CME section; p. 397.

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SUPPLEMENTARY TABLE 1. Numbers of histologically proven conventional adenomas and sessile serrated polyps by size and location in the 4 study arms

Location	Size	Study arm			
		Control (n = 295)	Endocuff (n = 299)	EndoRings (n = 295)	Full spectrum endoscopy (n = 299)
			Conventional adenomas		
All	All	445	543	463	385
	1-5 mm	336 (76)	424 (78)	342 (74)	299 (78)
	6-9 mm	73 (16)	83 (15)	79 (17)	63 (16)
	≥10 mm	36 (8)	36 (7)	42 (9)	23 (6)
Distal to the hepatic flexure	All	240	290	250	191
	1-5 mm	176 (73)	225 (76)	180 (72)	154 (81)
	6-9 mm	45 (19)	46 (16)	48 (19)	28 (15)
	≥10 mm	19 (8)	19 (7)	22 (9)	9 (5)
Right side of the colon	All	205	253	213	194
	1-5 mm	160 (78)	199 (79)	162 (76)	145 (75)
	6-9 mm	28 (14)	37 (15)	31 (15)	35 (18)
	≥10 mm	17 (7)	17 (7)	20 (9)	14 (7)
			Sessile serrated polyps		
All	All	51	50	57	53
	1-5 mm	28 (55)	20 (40)	21 (37)	21 (43)
	6-9 mm	14 (27)	13 (26)	16 (28)	13 (32)
	≥10 mm	9 (18)	17 (34)	20 (35)	19 (36)
Distal to the hepatic flexure	All	31	18	28	28
	1-5 mm	19 (49)	9 (50)	13 (46)	12 (43)
	6-9 mm	8 (26)	3 (17)	8 (29)	9 (32)
	≥10 mm	4 (13)	6 (33)	7 (25)	7 (25)
Right side of the colon	All	20	32	29	25
	1-5 mm	9 (45)	11 (34)	8 (28)	9 (36)
	6-9 mm	6 (30)	10 (31)	8 (28)	4 (16)
	≥10 mm	5 (25)	11 (34)	13 (45)	12 (48)

Values are number of polyps with percent of all polyps in this location that are in this size group in parentheses. Right side of the colon includes the cecum, ascending colon, and hepatic flexure.

SUPPLEMENTARY TABLE 2. Detection endpoints in the per protocol analysis

	Study arm			
	Control (n = 295)	**Endocuff (n = 299)**	**EndoRings (n = 295)**	**Full spectrum endoscopy (n = 299)**
Adenomas per colonoscopy				
All sites*	1.53 (2.33)†	1.84 (2.59)	1.57 (2.43)	1.30 (1.96)
Indianapolis	1.89 (2.69)	2.21 (2.88)	1.98 (2.78)	1.59 (2.18)
Milan	.83 (1.18)	.80 (1.25)	.72 (1.18)	.68 (1.19)
New York‡	.92 (1.15)	2.07 (2.35)	.82 (0.96)	.83 (1.34)
Adenoma detection rate				
All sites§	166 (56%)¶	191 (65%)	165 (57%)	154 (52%)
Indianapolis	117 (61%)	137 (71%)	126 (65%)	115 (58%)
Milan	37 (47%)	35 (47%)	28 (38%)	28 (37%)
New York	12 (48%)	19 (70%)	11 (50%)	11 (46%)
Sessile serrated polyp per colonoscopy				
All sites‖	.17 (.54)†	.17 (.54)	.20 (.82)	.18 (.54)
Indianapolis	.24 (.64)	.23 (.63)	.30 (.98)	.25 (.89)
Milan	.03 (.16)	.04 (.26)	.01 (.12)	.03 (.16)
New York	.04 (.20)	.07 (.27)	.05 (.21)	.04 (.20)
Sessile serrated polyp detection rate				
All sites**	36 (12%)¶	33 (11%)	33 (11%)	30 (10%)
Indianapolis	33 (17%)	29 (15%)	31 (16%)	27 (14%)
Milan	2 (3%)	2 (3%)	1 (1%)	2 (3%)
New York	1 (4%)	2 (7%)	1 (5%)	1 (4%)
Polyp detection rate				
All sites††	22 (77%)†	247 (84%)	229 (79%)	213 (71%)
Indianapolis‡‡	163 (85%)	174 (90%)	171 (89%)	156 (78%)
Milan	46 (59%)	50 (68%)	41 (55%)	38 (51%)
New York	19 (76%)	23 (85%)	17 (77%)	19 (79%)

*Standard, Endocuff, and EndoRings higher than FUSE (all $P < .001$). Endocuff > EndoRings ($P = .048$) and standard ($P = .004$).
†Designated polyp type per colonoscopy (standard deviation).
‡Endocuff > EndoRings ($P = .011$), FUSE ($P = .010$), and standard ($P = .018$) in New York; no difference in study arms for APCa at Indianapolis ($P = .16$) or Milan ($P = .845$).
§Endocuff ($P < .001$), EndoRings ($P = .004$), and standard ($P = .007$) all higher than FUSE. Endocuff higher than EndoRings ($P < .001$) and standard ($P = .004$). No differences in ADR by site.
¶Number of patients with designated polyp type (%).
‖EndoRings higher than FUSE ($P < .001$) and standard ($P < .001$); FUSE higher than standard ($P < .001$).
**Endocuff ($P = .002$), EndoRings ($P = .041$), and standard ($P < .001$) higher than FUSE. Standard higher than EndoRings ($P = .015$).
††Endocuff ($P < .001$), EndoRings ($P = .009$), and standard ($P < .001$) higher than FUSE. Endocuff higher than EndoRings ($P = 0.16$) and standard ($P < .001$).
‡‡At Indianapolis Endocuff ($P = .003$) and EndoRings ($P = .007$) higher than FUSE.