G-EYE colonoscopy is superior to standard colonoscopy for increasing adenoma detection rate: an international randomized controlled trial (with videos)

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Background and Aims: Colorectal cancer (CRC) is largely preventable with routine screening and surveillance colonoscopy; however, interval cancers arising from precancerous lesions missed by standard colonoscopy still occur. An increased adenoma detection rate (ADR) has been found to be inversely associated with interval cancers. The G-EYE device includes a reusable balloon integrated at the distal tip of a standard colonoscope, which flattens haustral folds, centralizes the colonoscope's optics, and reduces bowel slippage. The insufflated balloon also aims to enhance visualization of the colon during withdrawal, thereby increasing the ADR.

Methods: In this randomized, controlled, international, multicenter study (11 centers), patients (aged ≥50 years) referred to colonoscopy for screening, surveillance, or changes in bowel habits were randomized to undergo either balloon-assisted colonoscopy by using an insufflated balloon during withdrawal or standard high-definition colonoscopy. The primary endpoint was the ADR.

Results: One thousand patients were enrolled between May 2014 and September 2016 to undergo colonoscopy by experienced endoscopists; 803 were finally analyzed (standard colonoscopy n = 396; balloon-assisted colonoscopy n = 407). Baseline parameters were similar in both groups. Balloon-assisted colonoscopy provided a 48.0% ADR compared with 37.5% in the standard colonoscopy group (28% increase; $P = .0027$). Additionally, balloon-assisted colonoscopy provided for a significant increase in detection of advanced ($P = .0033$) flat adenomas ($P < .0001$) and sessile serrated adenomas/polyps ($P = .0026$).

Conclusion: Balloon-assisted colonoscopy yielded a higher ADR and increased the detection of advanced, flat, and sessile serrated adenomas/polyps when compared with standard colonoscopy. Improved detection by the G-EYE device could impact the quality of CRC screening by reducing miss rates and consequently reducing interval cancer incidence. (Clinical trial registration number: NCT01917513.) (Gastrointest Endosc 2019;89:545-53.)

(footnotes appear on last page of article)

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Colorectal cancer (CRC) is the second-most lethal cancer in the United States, with an annual incidence of approximately 140,000 cases and 50,000 CRC-related deaths.[1-3] Although fatal in its advanced stages, it is, by far, the most preventable cancer when detected at an early stage, in the form of pre-cancerous lesions.[2] The valuable contribution of colonoscopy to the prevention of CRC is ascribed to the early detection and removal of precancerous colon polyps, most frequently adenomas.[4,5] The adenoma detection rate (ADR), defined as the percentage of screened patients in whom at least 1 adenoma is found, has become one of the most important quality indicators for colonoscopy. Indeed, in a large, multicenter study evaluating the association between ADR and the risk of CRC diagnosed 6 months to 10 years after colonoscopy, ADR was inversely related to the risk of interval CRC, as manifested by a 3.0% decrease in risk of CRC with each 1.0% increase in the ADR.[6] The U.S. Multi-Society Task Force on Colorectal cancer established target ADRs of >30% for men and >20% for women undergoing screening colonoscopy.[7] The European Society of Gastrointestinal Endoscopy and the United European Gastroenterology established a minimum ADR standard of 25%.[8]

Back-to-back studies comparing 2 standard colonoscopy procedures have indicated that 20% to 22% of adenomas are still missed,[9,10] whereas similarly designed studies comparing standard colonoscopy with optical or mechanical enhancement technologies for improved polyp detection reported adenoma miss rates by standard colonoscopy between 41% and 48.3%.[11-13] The marked miss rates associated with current technologies are commonly attributed to the location of polyps on the proximal aspects of colon folds and flexures, along with their flat morphology.[14,15] Furthermore, studies have indicated that colonoscopy is less effective in preventing CRC in the proximal colon compared with the distal colon,[16-18] possibly because of the higher prevalence of serrated, flat, and depressed lesions featuring a relatively subtle appearance within the proximal colon.[19-21]

The G-EYE (Smart Medical Systems Ltd, Ra'anana, Israel) is a novel device designed to mechanically enhance the detection of polyps during colonoscopy. It comprises a reusable balloon integrated on a conventional colonoscope (Fig. 1). The balloon does not alter the mechanics or the technical performance of the colonoscope. After cecal intubation, the colonoscope is withdrawn with the balloon partially inflated, thereby straightening colon folds, centralizing the colonoscope's optics, and reducing bowel slippage. The G-EYE device has demonstrated safety and efficacy in previous clinical studies.[12,22] The current randomized, controlled study aimed to directly compare the G-EYE colonoscopy ADR with that of standard high-definition colonoscopy.

MATERIALS AND METHODS

Study design

This study was a randomized, 2-arm, multicenter study. The study received institutional review board approval at each participating site and was registered at clinicaltrials.gov (NCT01917513). Patients scheduled for colonoscopy were randomized to undergo either standard colonoscopy or balloon-assisted colonoscopy by using the G-EYE device. All colonoscopes used were high-definition endoscopes of the same brand and series (Pentax EC-3890i, Pentax, Tokyo, Japan), to eliminate endoscope and optics-related bias. iScan1 was applied during withdrawal of the colonoscope, in both study groups. The study involved 45 experienced endoscopists (most endoscopists had experience of >2500 colonoscopic procedures) from 11 medical centers in Europe, Israel, and India. Physicians with no prior experience with the G-EYE first underwent technical training. Consent was obtained from all study patients. Bowel preparation was performed according to the standard guidelines of each center and was graded according to the Boston Bowel Preparation Quality Scale.[23] Conscious sedation was used (mostly midazolam, fentanyl, propofol, or a combination thereof, according to the center's preference). Device insertion time, net withdrawal time (without intervention time), and total procedure time were measured and recorded.

All detected polyps, except for rectal lesions with endoscopic features of hyperplastic pathology, measuring 2 mm or greater, were endoscopically removed or biopsies and subjected to histologic evaluation. Polyps were classified by size (diminutive, 2-5 mm; small, 6-9 mm or large, ≥10 mm), by location, and according to Paris and Kudo classifications.[24,25] The polyp detection rate was defined as the percentage of patients in whom at least 1 polyp was found. The ADR was defined as the percentage of patients in whom at least 1 adenoma was found. An adenoma was defined as an adenoma and/or sessile serrated adenoma/polyp or traditional serrated adenoma. Advanced adenomas were defined as adenomas that were either ≥10 mm in diameter, included a villous component, harbored high-grade dysplasia, or were cancerous. The proximal colon was defined as the transverse colon, hepatic flexure, ascending colon, and cecum. Safety parameters and adverse events were assessed during the procedure and by phone call interview during the 48 to 72-hour post-procedural follow-up period.

Participants

Patients aged 50 years and older undergoing colonoscopy for screening or after a positive result on a fecal occult blood test, for polyp surveillance, or to assess changes in bowel habits, were recruited to the study.

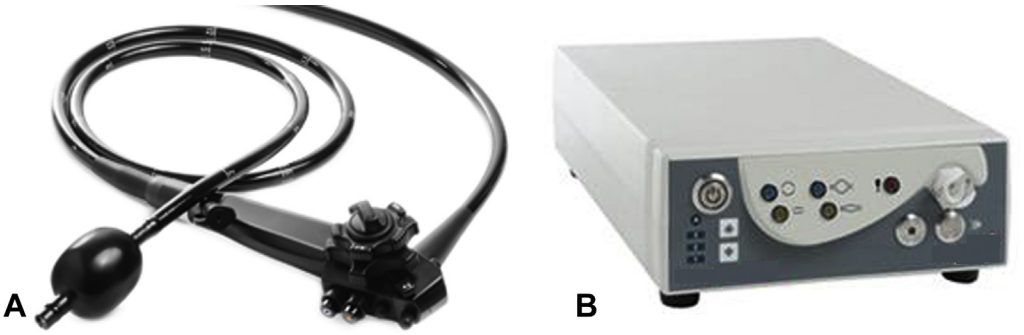

Figure 1. G-EYE system. **A,** G-EYE balloon integrated on a standard colonoscope. **B,** NaviAid SPARK^{2}C inflation system.

Exclusion criteria included previous colon surgery (except for appendectomy), known inflammatory bowel disease, polyposis, suspected colon stricture, diverticulitis or toxic megacolon, a history of radiation therapy to the abdomen or pelvis, pregnancy or lactation, current enrollment in another clinical study, routine use of anticoagulants, and history of coronary ischemia or cardiovascular event within 3 months before the procedure. Patients were withdrawn from the study in cases of inadequate bowel preparation (score <2 in 1 or more colon segments, according to the Boston Bowel Preparation Quality Scale), technical error or device malfunction, non-compliance with the protocol, screening failure, occurrence of serious adverse events or any medical condition revealed during the examination that required cessation of treatment for medical reasons or that may affect the study outcome.

The G-EYE device

The G-EYE is a reusable balloon, integrated onto a standard colonoscope (any brand and model can be used) (Fig. 1). The G-EYE uses a standard interface and standard video processor and can be disinfected by using a regular reprocessing protocol. The balloon is inflated by a dedicated inflation system (NaviAid SPARK^{2}C, Smart Medical Systems Ltd) that provides, aside from anchoring pressure, 3 levels of partial, lower, and non-anchoring pressure to the balloon, applied during withdrawal of the colonoscope (Video 1, available online at www.giejournal.org). The G-EYE is inserted until cecal intubation, with the balloon deflated. Once the cecum is reached and inspected, the balloon is inflated to partial pressure. The G-EYE device is withdrawn with the balloon inflated, eliciting colon fold flattening, optical image centralization, and reduced bowel slippage during withdrawal. The fold-flattening effect of the G-EYE brings mucosal surfaces normally located behind haustral folds into the colonoscope's field of view (Fig. 2, Video 2, available online at www.giejournal.org), enabling immediate and straightforward removal of detected polyps. Additionally, during polypectomy, the balloon can be inflated to anchoring pressure, thereby stabilizing the colonoscope and facilitating controlled intervention.

Study endpoints

The primary endpoint of the study was the ADR in each group (G-EYE vs standard colonoscopy). Secondary endpoints included the number, location, and type of polyps and adenomas detected, procedure times, and safety parameters.

Randomization and blinding

Patients were randomized to the G-EYE or the standard colonoscopy group, in a 1:1 allocation ratio based on randomization scheme blocks, stratified by center, via a computer-generated randomization scheme created with SAS version 9.4 statistical software (SAS Institute, Cary, NC). Physicians were not blinded to the outcome of the randomization; however, physicians were assigned to patients before randomization.

Statistical methods

Sample size calculation: The primary outcome measure of the study was the ADR of G-EYE versus standard high-definition colonoscopy. The null hypothesis was that the ADR is equal in both groups. Based on the medical literature, we assumed an ADR baseline of 24%[26] and calculated that to achieve a 35% increase in the detection rate, with 80% power at a 5% level of significance, 450 patients were required per study group, requiring a total sample size of 900 patients. Assuming a 10% dropout rate, 1000 patients were recruited for the study.

Analysis methods

Continuous variables were summarized by the mean and standard deviation and compared with a 2-sample *t* test or the Wilcoxon rank sum test, as appropriate. Categorical data were summarized by a count and percentage and compared by using the chi-square test. Polyp, adenoma, sessile serrated adenomas/polyps, serrated lesions, and flat lesions detection rate were presented in percentage and compared by using the chi-square test. The ADR also was presented by indication for colonoscopy. Count data, such as number of polyps or adenomas detected, were compared by using Poisson regression models.

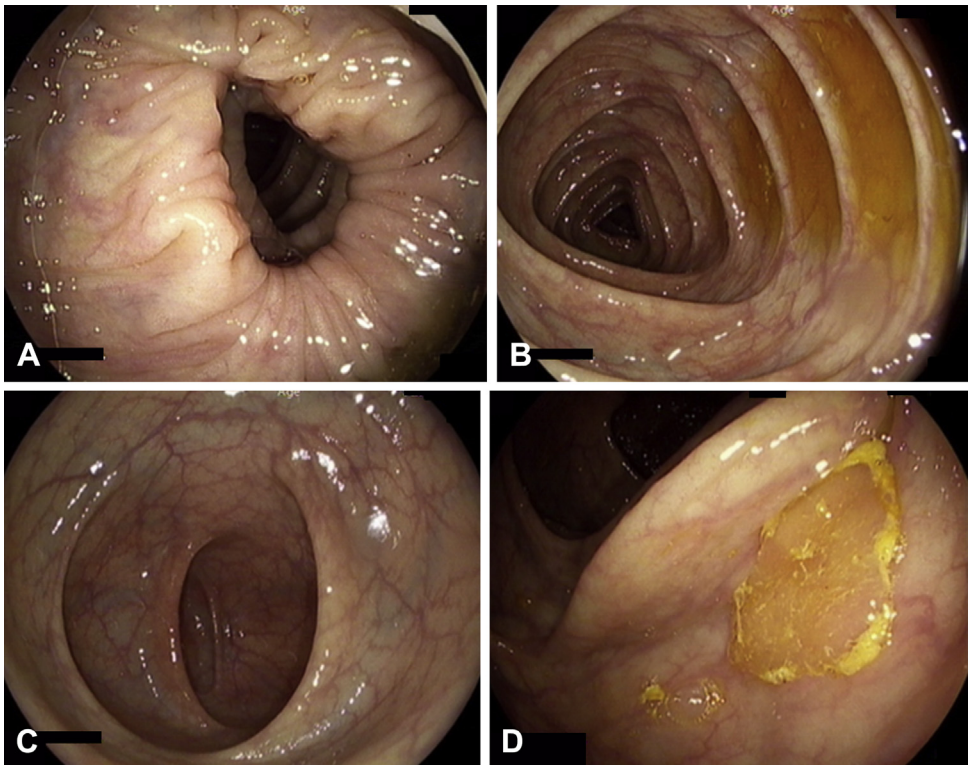

Figure 2. A, Transverse colon without balloon insufflation. **B,** Transverse colon with balloon insufflation. **C,** Sigmoid passage with balloon insufflation. **D,** Diagnosis of a serrated adenoma.

Statistical analyses were performed with SAS V9.4 (SAS Institute). A *P* value of .05 or lower was considered statistically significant. Nominal *P* values are presented.

RESULTS

From May 2014 to September 2016, 1000 patients were enrolled into the study. Of these 1000 patients, 502 were randomized to the balloon-assisted colonoscopy group, and 498 were randomized to the standard colonoscopy group. Results of 396 and 407 patients were analyzed in the standard colonoscopy and G-EYE groups, respectively (Fig. 3). Reasons for exclusion were similar between the 2 groups and are shown in Figure 3. Baseline measures, indications for colonoscopy, and Boston Bowel Preparation Quality Scale scores in both groups were similar and are presented in Table 1. Distribution of experienced and non-experienced physicians between the 2 study groups was similar (Table 1).

Balloon-assisted colonoscopy provided a significant increase in the ADR when compared with standard colonoscopy, with an ADR of 48.0% recorded in the former and 37.5% in the latter cohort ($P = .0027$) (Table 2) (primary endpoint). A similar increment in detection efficacy was observed between balloon-assisted colonoscopy and standard colonoscopy-detected polyps, as manifested by a polyp detection rate of 59.0% in the balloon-assisted colonoscopy arm and 47.7% in the standard colonoscopy arm ($P = .0014$) (Table 2). In line with these findings, balloon-assisted colonoscopy detected a mean of 1.00 adenoma per patient, whereas standard colonoscopy detected a mean of 0.68 adenomas per patient ($P < .0001$; 47.1% increase). Moreover, balloon-assisted colonoscopy detected a higher number of diminutive and small adenomas compared with standard colonoscopy, with 245 versus 160 diminutive adenomas ($P < .0001$; 53.1% increase) and 75 versus 54 small adenomas ($P = .0946$; 38.9% increase), respectively. In addition, the number of large (86 vs 52) and advanced (109 vs 67) adenomas was higher in the balloon-assisted versus standard colonoscopy groups, respectively, representing an increase of 62.3% ($P = .0093$) in large-size adenomas and a 62.7% ($P = .0033$) increase in advanced adenomas. Further, an increase in the number of flat adenomas and sessile serrated adenomas/polyps in the balloon-assisted colonoscopy arm was seen, with 85 and 20, respectively, compared with 35 and 3, respectively, in the standard colonoscopy arm (representing an increase of 142.9% [$P < .0001$] and 566.7% [$P = .0026$], respectively). An even larger difference in the number of flat and serrated adenomas/polyps was detected in the proximal colon, with 65 and 17, respectively, detected by balloon-assisted colonoscopy compared with 21 and 2 detected, respectively, by standard colonoscopy (representing an increase of 209.5% [$P < .0001$] and 750% [$P = .0048$], respectively). Higher detection rates of sessile

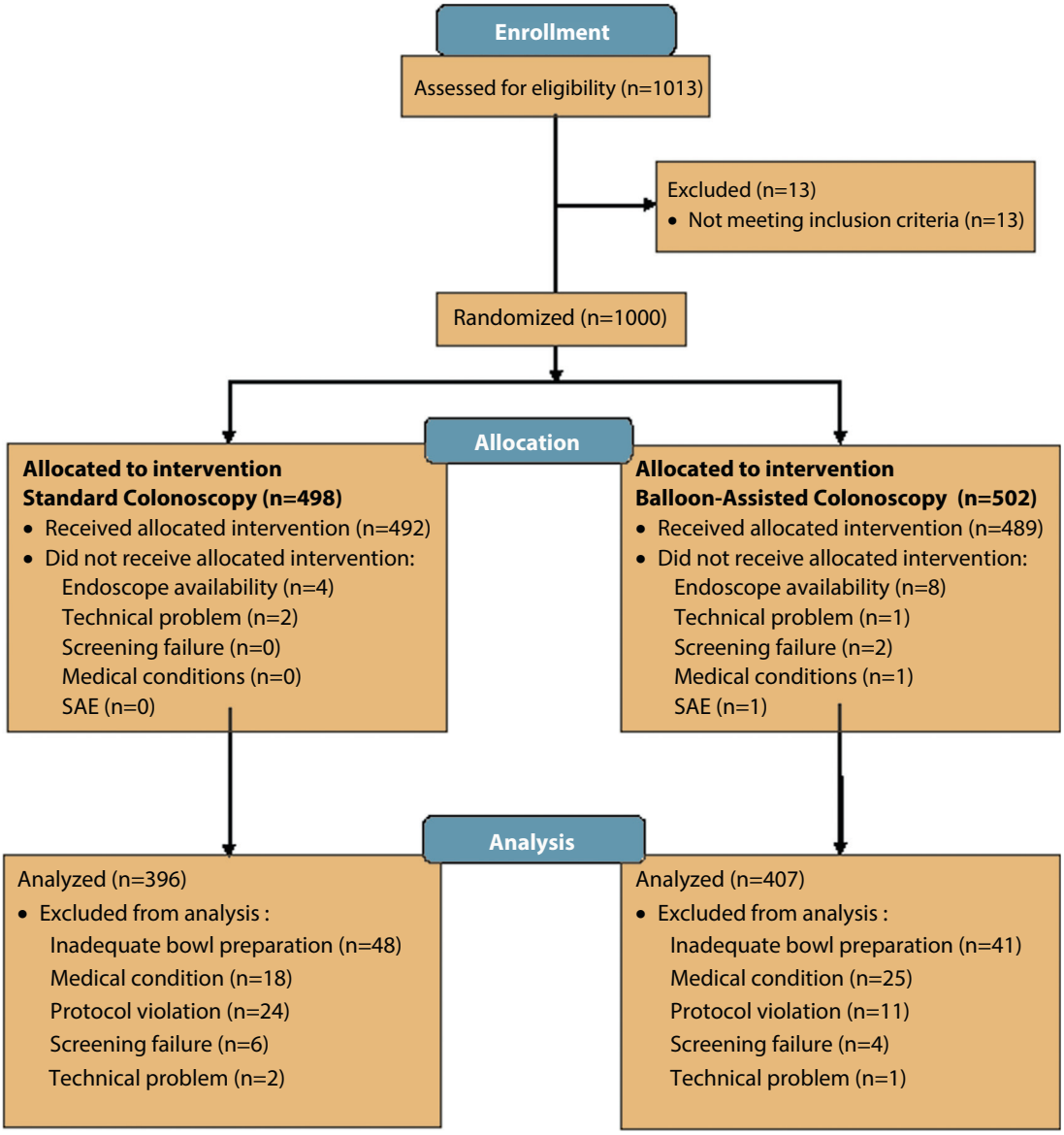

Figure 3. CONSORT flow chart, enrollment, allocation, analysis of study participants and serious adverse events.

serrated adenomas/polyps (2.7%), serrated lesions (14.1%), and flat adenomas (14.9%) by balloon-assisted colonoscopy as compared with the standard colonoscopy group (0.8%, 11.2%, and 6.9%, respectively) also was observed (Table 2). The ADR per each indication for colonoscopy (screening, surveillance, change in bowel habits, and positive fecal occult blood test) presented an increase in the balloon-assisted colonoscopy arm versus standard colonoscopy ($P = .0165$; $P = .4382$; $P = .3882$; $P = .1319$, respectively) (Table 2). The ADR of balloon-assisted colonoscopy performed by physicians having prior experience with the G-EYE device was similar to that of physicians with no prior experience (49.0% vs 47.2%; $P = .7193$). The balloon-assisted colonoscopy ADRs in the initial part and final part of the study were similar—48.6% and 47.1%, respectively ($P = .8657$). Total procedure time of balloon-assisted colonoscopy was approximately 3 minutes longer compared with standard colonoscopy, because of the higher rate of endoscopic interventions consequential of the higher ADR (Table 1). Two serious adverse events were reported in the balloon-assisted colonoscopy arm, both of which occurred before balloon inflation. In the first patient, the colonoscopy procedure was prematurely terminated because of inappropriate bowel preparation. A day later, the patient was diagnosed with an obstructive sigmoid tumor, underwent surgery, and died a few days after as a result of aspiration. In the second case, the patient had an irregular heart rate and bradycardia before the initiation of the procedure. This patient did not undergo colonoscopy and was instead admitted for 24 hours of cardiac

TABLE 1. Baseline parameters, indications for colonoscopy, and procedure times by type of colonoscopy

Baseline characteristics	Standard colonoscopy	G-EYE	*P* value
Age, mean, y	65.2	65.4	.6708*
Sex, % female	43.7	50.1	.0677†
BBPS score, mean ± SD			
Global	2.57 ± 0.42	2.56 ± 0.42	.7854*
Descending colon	2.62 ± 0.49	2.61 ± 0.49	.8412*
Transverse colon	2.62 ± 0.49	2.62 ± 0.49	.8377*
Ascending colon	2.47 ± 0.50	2.46 ± 0.50	.7701*
Indication for colonoscopy, no. (%)			.8488†
Screening	163 (41.2)	165 (40.5)	
Surveillance	76 (19.2)	82 (20.1)	
Change in bowel habits	61 (15.4)	55 (13.5)	
Positive result on fecal occult blood test	96 (24.2)	105 (25.8)	
Endoscopist level of endoscopic experience, no. (%)			.3747†
800-2500 procedures	55 (53.4)	48 (46.6)	
>2500 procedures	341 (48.7)	359 (51.3)	
Procedure time, mean ± SD, min			
Insertion time	8.19 ± 4.83	7.92 ± 4.83	.4935‡
Withdrawal time	7.09 ± 1.37	7.33 ± 1.64	.0157‡
Total procedure time	22.15 ± 10.13	24.93 ± 11.41	< .0001‡

BBPS, Boston Bowel Preparation Quality Scale; *SD*, standard deviation.
**t* test.
†Chi-square.
‡Kruskal-Wallis.

monitoring and was released the next day with no additional complaints.

DISCUSSION

Screening colonoscopy is strongly associated with reduced CRC incidence and mortality; however, the adenoma miss rate remains a concern.[27] A population-based study reported a 6% interval cancer rate after negative colonoscopy results in CRC patients.[28] A large-scale study correlating quality indicators in colonoscopy and interval cancer risk concluded that the endoscopist ADR is a principal predictor for the risk of interval cancer after screening colonoscopy.[29] International efforts have resulted in local screening programs for increasing awareness and quality of CRC screening and monitoring the endoscopist ADR. In addition, novel mechanical (eg, Endocuff, Arc Medical Design Ltd, Leeds, UK) and optical technologies (eg, FUSE, EndoChoice, Alpharetta, Ga) have been introduced recently to increase the ADR and to reduce interval cancer rates. However, these technologies showed no consistent increased efficacy in large randomized trials.[30-35] The current randomized study demonstrated a significant increase in the ADR by balloon-assisted colonoscopy compared with standard colonoscopy. The ADR in the standard colonoscopy group was 37.5%, which exceeds the recommended threshold of 30%.[7] However, use of the insufflated balloon during withdrawal increased the ADR to 48.0%. In addition, balloon-assisted colonoscopy significantly improved the per-patient ADR (1.00 adenoma per patient), both in comparison to the standard colonoscopy group (0.68 adenoma per patient) and relative to published studies reporting a range of 0.42 to 0.5 adenoma per patient.[33,36] Because current U.S. and European Union surveillance guidelines define surveillance intervals by the number of adenomas detected in a single patient,[4,37] this will have direct implications for patient surveillance intervals. A recent study suggested that use of behind-folds visualizing colonoscopy technologies had no advantage in the detection of advanced and large adenomas (≥10 mm).[38] However, in the present study, the number of large and advanced adenomas detected by balloon-assisted colonoscopy was substantially higher (62.3% and 62.7% increase, respectively), compared with standard colonoscopy. This suggests that in previous studies, some advanced lesions were missed, notwithstanding the use of behind-folds visualizing techniques. The G-EYE device seems therefore the first technology that has the potential to increase the general ADR and advanced ADR, in particular. Studies have shown a strong correlation between lesion size and its malignancy potential, with larger lesions considered to be at higher risk for submucosal invasion and lymph node

TABLE 2. PDR, ADR, and adenoma characterization by type of colonoscopy

	Standard colonoscopy	G-EYE	% Difference	*P* value
PDR/ADR and adenoma per patient				
PDR	47.7%	59.0%	23.7%	.0014*
ADR	37.5%	48.0%	28.0%	.0027*
Polyps per patient	0.97	1.42	46.4%	< .0001†
Adenomas per patient	0.68	1.00	47.1%	< .0001†
ADR per indication for colonoscopy				
Screening	30.3%	43.0%	41.9%	.0165*
Surveillance	51.3%	57.5%	12.1%	.4382*
Change in bowel habits	30.5%	38.2%	25.2%	.3882*
Positive fecal occult blood test result	43.2%	53.9%	24.8%	.1319*
Adenoma, distribution according to size, no. (average per patient)				
Diminutive (2-5 mm)	160 (0.41)	245 (0.61)	53.1%	< .0001†
Small (6-9 mm)	54 (0.14)	75 (0.19)	38.9%	.0946†
Large (≥10 mm)	53 (0.14)	86 (0.21)	62.3%	.0093†
Adenoma characterization, no. (average per patient)				
Advanced adenomas	67 (0.17)	109 (0.27)	62.7%	.0033†
Non-advanced adenomas	200 (0.51)	297 (0.74)	48.5%	< .0001†
Serrated lesions	59 (0.15)	90 (0.22)	52.5%	.0192†
SSAs/Ps	3 (0.01)	20 (0.05)	566.7%	.0026†
Hyperplastic polyps	53 (0.14)	67 (0.17)	26.4%	.2665†
Traditional serrated adenomas	3 (0.01)	3 (0.01)	0%	.9705†
Flat adenomas	35 (0.09)	85 (0.21)	142.9%	< .0001†
SSA/P, serrated lesion, and flat lesion detection rates				
SSA/P detection rate	0.8%	2.7%	237.5%	.0357*
Serrated lesion detection rate	11.2%	14.1%	25.9%	.2216*
Flat lesion detection rate	6.9%	14.9%	116.0%	.0003*
Adenoma characterization in the right side of the colon, no. (average per patient)				
Flat adenoma	21 (0.05)	65 (0.16)	209.5%	< .0001†
SSA/P	2 (0.01)	17 (0.04)	750.0%	.0048†

PDR, Polyp detection rate; *ADR,* adenoma detection rate; *SSA/P,* sessile serrated adenoma\polyp.
*Chi-square.
†Poisson model.

involvement.[39] Therefore, detection and removal of such lesions and proper determination of surveillance intervals are critical to CRC prevention.[4,5] The increased rate in detection of advanced adenomas may theoretically represent the risk reduction of advanced adenomas developing into CRC and thus of interval cancer reduction.

Detection rates of sessile serrated adenomas\polyps, serrated lesions, and flat adenomas were higher in the G-EYE group, compared with standard colonoscopy (2.7%, 14.1%, and 14.9% compared with 0.8%, 11.2%, and 6.9%, respectively). In a multicenter study involving 2167 patients evaluating segmental ADR and sessile serrated adenoma\polyp detection rates in average-risk patients, sessile serrated adenoma\polyp detection rates were reported to be 2%, which is lower than the sessile serrated adenoma\polyp detection rates reported in the G-EYE group.[40] In a retrospective analysis of screening colonoscopy with high-definition plus iScan, serrated lesion detection rates and flat adenoma detection rates were reported to be 10%, demonstrating the superiority of G-EYE.[41] Interestingly, a recently published study highlighted the strong overrepresentation of interval cancers in the ascending colon and cecum after negative results on colonoscopies performed less than 3 years before the diagnosis of CRC.[42] Flat and serrated lesions are typically difficult to detect during colonoscopy and are known to be more common in the proximal colon.[20] These lesions are often missed because of their flat architecture and pale appearance.[19-21,43]

United States and European Union guidelines also provide recommendations regarding the appropriate surveillance interval in the event that such lesions are detected during colonoscopy.[4,37] In the present study, the G-EYE detected significantly more flat adenomas and sessile serrated adenomas\polyps in the proximal colon (Table 2). The G-EYE device fold-flattening effect likely enabled exposure of these otherwise hidden lesions, thus demonstrating that this technology both increases general detection efficacy and specifically enables detection of clinically significant lesions that have a direct effect on CRC prevention. The similar balloon-assisted colonoscopy ADR in the initial and final parts of the study may suggest that there is no learning curve associated with the G-EYE device. However, our study was not designed to evaluate the G-EYE learning curve, and additional studies are needed to further establish this point.

This study had several limitations. First, the recruitment rate per site was not equal. Second, the number of procedures performed by each endoscopist was not evenly distributed; endoscopists participated as per on-site availability. Third, the dropout rate was higher than expected, mostly because of insufficient bowel preparation required to maintain high-quality examination. Nevertheless, the outcomes were significant. Fourth, endoscopists were not blinded to the results of randomization. Fifth, the study population included patients with positive results on fecal occult blood tests, for whom baseline ADR is usually higher than in the general screening population. The randomized and international design of this study provides an enhanced attribute to the described results.

In summary, this study showed that the G-EYE device detects considerably more adenomas than does standard colonoscopy, thereby potentially reducing colonoscopy miss rates, with no significant increase in procedural time. Based on our experience, the G-EYE device does not alter the mechanical properties of the colonoscope. The improved ADR, increased number of adenomas per patient, and higher incidence of detected advanced, large, flat, and sessile serrated adenomas\polyps may all have clinical implications in reducing the rate of interval cancer. This new technology has the potential to increase the standard of care in CRC prevention.

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Abbreviations: ADR, adenoma detection rate; CRC, colorectal cancer.

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