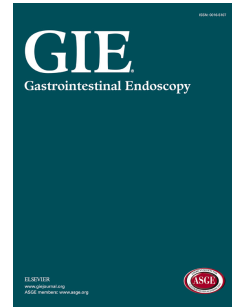


# Accepted Manuscript



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

Haim Shirin, Acquisition of data, critical revision of the manuscript for important intellectual content, Beni Shpak, Acquisition of data, Julia Epshtein, Acquisition of data, John Gásdal Karstensen, Acquisition of data, administrative support, Arthur Hoffman, Acquisition of data, Rogier de Ridder, Acquisition of data, Pier Alberto Testoni, Acquisition of data, Saud Ishaq, Acquisition of data, D. Nageshwar Reddy, Acquisition of data, Seth A. Gross, Study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, Helmut Neumann, Acquisition of data, Martin Goetz, Acquisition of data, Dov Abramowich, Acquisition of data, Menachem Moshkowitz, Acquisition of data, Meir Mizrahi, Acquisition of data, Peter Vilmann, Acquisition of data, critical revision of the manuscript for important intellectual content, Johannes Wilhelm Rey, Acquisition of data, Silvia Sanduleanu-Dascalescu, Acquisition of data, Edi Viale, Acquisition of data, Hrushikesh Chaudhari, Acquisition of data, Mark B. Pochapin, Study concept and design, Michael Yair, Acquisition of data, Mati Shnell, Acquisition of data, Shaul Yaari, Acquisition of data, Jakob Westergren Hendel, Acquisition of data, Daniel Teubner, Administrative support, Roel M.M. Bogie, Administrative support, Chiara Notaristefano, Acquisition of data, Roman Simantov, Acquisition of data, Nathan Gluck, Acquisition of data, Eran Israeli, Acquisition of data, Trine Stigaard, Acquisition of data, Shay Matalon, Acquisition of data, Alexander Vilkin, Acquisition of data, Ariel Benson, Acquisition of data, Stine Sloth, Acquisition of data, Amit Maliar, Acquisition of data, Amir Waizbard, Acquisition of data, Harold Jacob, Acquisition of data, Peter Thielsen, Acquisition of data, Eyal Shachar, Acquisition of data, Shmuel Rochberger, Acquisition of data, Tiberiu Hershcovici, Acquisition of data, Julie Isabelle Plougmann, Administrative support, Michal Braverman, Acquisition of data, Eduard Tsvang, Acquisition of data, Armita Armina Abedi, Administrative support, Yuri Brachman, Acquisition of data, Peter D. Siersema, Acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, Ralf Kiesslich, Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content

PII: S0016-5107(18)33138-9

DOI: [10.1016/j.gie.2018.09.028](https://doi.org/10.1016/j.gie.2018.09.028)

Reference: YMGE 11258

To appear in: *Gastrointestinal Endoscopy*

Received Date: 14 March 2018

Accepted Date: 20 September 2018

Please cite this article as: Shirin H, Shpak B, Epshtein J, Karstensen JG, Hoffman A, de Ridder R, Testoni PA, Ishaq S, Acquisition of data Reddy DN, Gross SA, Neumann H, Goetz M, Abramowich D, Moshkowitz M, Mizrahi M, Vilmann P, Rey JW, Sanduleanu-Dascalescu S, Viale E, Chaudhari H, Pochapin MB, Yair M, Shnell M, Yaari S, Hendel JW, Teubner D, Bogie RMM, Notaristefano C, Simantov R, Gluck N, Israeli E, Stigaard T, Matalon S, Vilkin A, Benson A, Sloth S, Maliar A, Waizbard A, Jacob H, Thielsen P, Shachar E, Rochberger S, Hershcovici T, Plougmann JI, Braverman M, Tsvang E, Abedi AA, Brachman Y, Siersema PD, Kiesslich R, G-EYE colonoscopy is superior to standard colonoscopy for increasing adenoma detection rate: an international randomized controlled trial (with videos), *Gastrointestinal Endoscopy* (2018), doi: <https://doi.org/10.1016/j.gie.2018.09.028>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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

Ralf Kiesslich, MD

HELIOS Dr. Horst Schmidt Kliniken Wiesbaden

Ludwig-Erhard- Straße 100

65199 Wiesbaden, Germany

Tel.: +49-0611-432420

Fax: +49-0611-432418

[info@ralf-kiesslich.de](mailto:info@ralf-kiesslich.de)

**Co-authors & Contributions:**

1. Haim Shirin,
  - a. Assaf Harofeh Medical Center, Tzrifin, Israel.
  - b. Tel Aviv University, Tel Aviv, Israel

Acquisition of data, critical revision of the manuscript for important intellectual content.

2. Beni Shpak, Laniado Hospital, Netanya, Israel. Acquisition of data.

3. Julia Epshtein, Hadassah Medical Center, Jerusalem, Israel. Acquisition of data.
4. John Gásdal Karstensen, Copenhagen University Hospital Herlev, Herlev, Denmark. Acquisition of data, administrative support.
5. Arthur Hoffman, Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany. Acquisition of data.
6. Rogier de Ridder, UMC Maastricht, Maastricht. Acquisition of data.
7. Pier Alberto Testoni, Vita Salute San Raffaele University – Scientific Institute San Raffaele, Milan, Italy. Acquisition of data.
8. Sauid Ishaq.
  - a. Russells Hall Hospital, Dudley, United Kingdom
  - b. Birmingham City University, Birmingham, United KingdomAcquisition of data.
9. D. Nageshwar Reddy, Asian Institute of Gastroenterology, Hyderabad, India. Acquisition of data.
10. Seth A. Gross, NYU Langone Medical Center, New York, NY, USA. Study concept and design , acquisition of data, critical revision of the manuscript for important intellectual content
11. Helmut Neumann, Universitätsmedizin Johannes Gutenberg University Mainz, Mainz, Germany. Acquisition of data.
12. Martin Goetz, Universitätsklinikum Tübingen, Tübingen, Germany. Acquisition of data.

13. Dov Abramowich, Assaf Harofeh Medical Center, Tzrifin, Israel.

Acquisition of data.

14. Menachem Moshkowitz, Laniado Hospital, Netanya, Israel.

Acquisition of data.

15. Meir Mizrahi.

a. Hadassah Medical Center, Jerusalem, Israel

b. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston,  
MA, USA

Acquisition of data.

16. Peter Vilmann, Copenhagen University Hospital Herlev, Herlev, Denmark.

Acquisition of data, critical revision of the manuscript for important intellectual  
content

17. Johannes Wilhelm Rey, Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany.

Acquisition of data.

18. Silvia Sanduleanu-Dascalescu, UMC Maastricht, Maastricht, The Netherlands.

Acquisition of data.

19. Edi Viale, Vita Salute San Raffaele University – Scientific Institute San Raffaele,  
Milan, Italy. Acquisition of data.

20. Hrushikesh Chaudhari, Asian Institute of Gastroenterology, Hyderabad, India.

Acquisition of data.

21. Mark B. Pochapin, NYU Langone Medical Center, New York, NY, USA.

Study concept and design

22. Michael Yair, Assaf Harofeh Medical Center, Tzrifin, Israel.  
Acquisition of data.
23. Mati Shnell, Laniado Hospital, Netanya, Israel. Acquisition of data.
24. Shaul Yaari, Hadassah Medical Center, Jerusalem, Israel. Acquisition of data.
25. Jakob Westergren Hendel, Copenhagen University Hospital Herlev, Herlev, Denmark. Acquisition of data.
26. Daniel Teubner, Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany.  
Administrative support.
27. Roel M. M. Bogie, UMC Maastricht, Maastricht, The Netherlands Administrative support.
28. Chiara Notaristefano, Vita Salute San Raffaele University – Scientific Institute San Raffaele, Milan, Italy. Acquisition of data.
29. Roman Simantov, Assaf Harofeh Medical Center, Tzrifin, Israel.  
Acquisition of data.
30. Nathan Gluck,
  - a. Laniado Hospital, Netanya, Israel. Acquisition of data.
  - b. Tel Aviv Sourasky Medical Center, affiliated to Sackler Medical School, Tel Aviv University, Israel
31. Eran Israeli, Hadassah Medical Center, Jerusalem, Israel. Acquisition of data.
32. Trine Stigaard, Copenhagen University Hospital Herlev, Herlev, Denmark.  
Acquisition of data.

33. Shay Matalon, Assaf Harofeh Medical Center, Tzrifin, Israel.

Acquisition of data.

34. Alexander Vilkin, Laniado Hospital, Netanya, Israel. Acquisition of data.

35. Ariel Benson, Hadassah Medical Center, Jerusalem, Israel. Acquisition of data.

36. Stine Sloth, Copenhagen University Hospital Herlev, Herlev, Denmark.

Acquisition of data.

37. Amit Maliar, Assaf Harofeh Medical Center, Tzrifin, Israel. Acquisition of data.

38. Amir Waizbard, Laniado Hospital, Netanya, Israel. Acquisition of data.

39. Harold Jacob, Hadassah Medical Center, Jerusalem, Israel.

Acquisition of data.

40. Peter Thielsen, Copenhagen University Hospital Herlev, Herlev, Denmark

Acquisition of data.

41. Eyal Shachar, Assaf Harofeh Medical Center, Tzrifin, Israel.

Acquisition of data.

42. Shmuel Rochberger, Laniado Hospital, Netanya, Israel. Acquisition of data.

43. Tiberiu Hershcovici, Hadassah Medical Center, Jerusalem, Israel.

Acquisition of data.

44. Julie Isabelle Plougmann, Copenhagen University Hospital Herlev, Herlev,  
Denmark. Administrative support.

45. Michal Braverman, Assaf Harofeh Medical Center, Tzrifin, Israel.

Acquisition of data.

46. Eduard Tsvang, Hadassah Medical Center, Jerusalem, Israel.

Acquisition of data.

47. Armita Armina Abedi, Copenhagen University Hospital Herlev, Herlev, Denmark.

Administrative support

48. Yuri Brachman, Assaf Harofeh Medical Center, Tzrifin, Israel.

Acquisition of data.

49. Peter D. Siersema, UMC Radboud, Nijmegen, Netherlands.

Acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

50. Ralf Kiesslich, Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany.

Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content

**Acknowledgment:** Study was sponsored by Smart Medical Systems Ltd. Ra'anana Israel: study coordinator, and analysis support.



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

## **ABSTRACT**

**Background:** Colorectal cancer (CRC) is largely preventable with routine screening and surveillance colonoscopy; however, interval cancers arising from precancerous lesions missed by standard colonoscopy (SC) still occur. Increased adenoma detection rate (ADR) has been found to be inversely associated with interval cancers. The G-EYE device comprises 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 ADR.

**Methods:** In this randomized, controlled, international, multicenter study (11 centers), subjects (age  $\geq 50$ ) referred to colonoscopy for screening, surveillance, or due to changes in bowel habits, were randomized to undergo either balloon-assisted colonoscopy using an insufflated balloon during withdrawal or standard high-definition colonoscopy. Primary endpoint was ADR.

**Results:** One thousand subjects were enrolled between May 2014 and September 2016 to undergo colonoscopy by experienced endoscopists; 803 were finally analyzed (SC: 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 SC group (28% increase,  $p=0.0027$ ). Additionally, balloon-assisted colonoscopy provided for a significant increase in detection of advanced ( $p=0.0033$ ), flat adenomas ( $p<0.0001$ ), and sessile serrated adenoma/polyp (SSA/Ps) ( $p=0.0026$ ).

**Conclusions:** Balloon-assisted colonoscopy yielded a higher ADR and increased the detection of advanced, flat and SSA/Ps when compared with SC. Improved detection by the G-EYE device could impact the quality of CRC screening by reducing miss rates, and consequently reducing of interval cancers incidence; [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01917513) (NCT01917513).

## INTRODUCTION

Colorectal cancer (CRC) is the second-most lethal cancer in the USA, with an annual incidence of approximately 140,000 cases and 50,000 CRC-related deaths<sup>1-3</sup>. 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<sup>2</sup>. The valuable contribution of colonoscopy to the prevention of CRC is ascribed to the early detection and removal of precancerous colonic polyps, most frequently adenomas<sup>4,5</sup>. The adenoma detection rate (ADR), defined as the percentage of screened patients in whom at least one 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 ADR<sup>6</sup>. The United States (U.S.) Multi-Society Task Force on CRC established target ADRs of >30% for

men and >20% for women undergoing screening colonoscopy<sup>7</sup>. The European Society of Gastrointestinal Endoscopy (ESGE) and the United European Gastroenterology (UEG) established a minimum ADR standard of 25%<sup>8</sup>.

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

The G-EYE (Smart Medical Systems Ltd, 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 (Figure 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 colonoscope's optics, and reducing bowel slippage. The G-EYE device has demonstrated safety and efficacy in previous clinical studies<sup>12,22</sup>. The current randomized, controlled study aimed to directly compare the G-EYE colonoscopy ADR with that of standard high-definition (HD) colonoscopy.

## **MATERIALS AND METHODS**

Study Design:

This study was a randomized, 2-arm, multicenter study. The study received IRB approval at each participating site and was registered at clinicaltrials.gov (NCT01917513). Patients scheduled for colonoscopy were randomized to undergo either SC or balloon-assisted colonoscopy using the G-EYE device. All colonoscopes used were high definition (HD) endoscopes of the same brand and series (Pentax EC-3890i), 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 subjects. Bowel preparation was performed according to the standard guidelines of each center and was graded according to the Boston Bowel Preparation Quality Scale Score (BBPS)<sup>23</sup>. 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 2mm or greater, were endoscopically removed or biopsied and subjected to histological evaluation. Polyps were classified by size ("diminutive" (2-5 mm), "small" (6-9 mm) or "large" ( $\geq 10$  mm)), by location, and according to Paris and Kudo classification<sup>24,25</sup>. Polyp detection rate (PDR) was defined as the percentage of subjects in whom at least one polyp was found. ADR was defined as the percentage of subjects in whom at least one adenoma was found. Adenoma was defined as adenoma and/or sessile serrated adenomas/polyp (SSA/P) or traditional serrated adenomas. Advanced adenomas

were defined as adenomas which were either  $\geq 10$  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 postprocedural follow-up period.

#### Participants:

Subjects of ages 50 and older, undergoing colonoscopy for screening or after a positive fecal occult blood test (FOBT), for polyp surveillance, or to assess changes in bowel habits, were recruited to the study. Exclusion criteria included previous colonic surgery (except for appendectomy), known inflammatory bowel disease, polyposis, suspected colonic stricture, diverticulitis or toxic megacolon, 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 a coronary ischemia or cardiovascular event within 3 months before the procedure. Subjects were withdrawn from the study in cases of inadequate bowel preparation (score  $< 2$  in one or more colon segments, according to BBPS), 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) (Figure 1). The G-EYE uses a standard interface and standard video

processor and can be disinfected using a regular reprocessing protocol. The balloon is inflated by a dedicated inflation system (NaviAid SPARK<sup>2</sup>C, Smart Medical Systems Ltd, Israel), that provides, aside from anchoring pressure, three levels of partial, lower, non-anchoring pressure to the balloon, applied during withdrawal of the colonoscope. The G-EYE is inserted until cecal intubation, with the balloon deflated. Once the cecum is reached and inspected, the balloon is inflated to this 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 (Figure 2), 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 ADR in each group (G-EYE versus SC). Secondary endpoints included the number, location, and type of polyps and adenomas detected, procedure times, and safety parameters.

#### Randomization and Blinding:

Subjects were randomized to the G-EYE or the SC 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, USA). Physicians were not blinded to the outcome of the randomization; however, physicians were assigned to subjects before randomization.

#### Statistical Methods:

Sample size calculation: The primary outcome measure of the study was the ADR of G-EYE versus standard HD 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%<sup>26</sup>, and calculated that to achieve 35% increase in the detection rate, with 80% power at a 5% level of significance, 450 subjects were required per study group, requiring a total sample size of 900 subjects. Assuming a 10% dropout rate, 1000 subjects were recruited for the study.

#### Analysis methods:

Continuous variables were summarized by the mean and standard deviation and compared with a two-sample T-test or the Wilcoxon rank sum test, as appropriate. Categorical data were summarized by a count and percentage and compared using the Chi-squared test. Polyp, adenoma, SSA/P, SL, and FL detection rate were presented in percentage and compared using the Chi-squared test. ADR is also presented by indication for colonoscopy. Count data, such as number of polyps or adenomas detected, was compared using Poisson regression models. Statistical analyses were performed with SAS V9.4 (SAS Institute, Cary, NC, USA). A *P* value of .05 or lower was considered statistically significant. Nominal *P* values are presented.

## **RESULTS**

From May 2014 to September 2016, 1000 subjects were enrolled into the study. Of these 1000 subjects, 502 were randomized to the balloon-assisted colonoscopy group and 498 were randomized to the SC group. Results of 396 and 407 subjects were analyzed in the SC and G-EYE groups, respectively (Figure 3). Reasons for exclusion were similar between the two groups and are shown in Figure 3. Baseline measures, indications for colonoscopy and BBPS score 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 SC, with an ADR of 48.0% recorded in the former and 37.5% in the latter cohort ( $p=0.0027$ ; Table 2, primary endpoint). A similar increment in detection efficacy was observed between balloon-assisted colonoscopy and SC-detected polyps, as manifested by a PDR of 59.0% in the balloon-assisted colonoscopy arm and 47.7% in the SC arm ( $p=0.0014$ ; Table 2). In line with these findings, balloon-assisted colonoscopy detected a mean 1.00 adenoma per patient whereas SC detected a mean 0.68 adenoma per patient ( $p<0.0001$ , 47.1% increase). Moreover, balloon-assisted colonoscopy detected a higher number of diminutive and small adenomas compared with SC, with 245 versus 160 diminutive adenomas ( $p<0.0001$ , 53.1% increase) and 75 versus 54 small adenomas ( $p=0.0946$ , 38.9% increase), respectively. In addition, the number of large (86 versus 52) and advanced adenomas (109 versus 67) was higher in the balloon-assisted versus SC colonoscopy groups, respectively, representing an increase of 62.3% ( $p=0.0093$ ) in large-size adenomas and a 62.7% ( $p=0.0033$ ) increase in advanced adenomas. Further, an increase in the number of flat adenomas and SSA/Ps in the balloon-assisted colonoscopy arm was seen, with 85 and 20, respectively, compared with 35 and 3, respectively, in the



SC arm (representing an increase of 142.9% ( $p < 0.0001$ ) and 566.7% ( $p = 0.0026$ ), respectively). An even larger difference in the number of flat and SSA/Ps was detected in the proximal colon, with 65 and 17, respectively, detected by balloon-assisted colonoscopy compared with 21 and 2 detected, respectively, by SC (representing an increase of 209.5% ( $p < 0.0001$ ) and 750% ( $p = 0.0048$ ), respectively). Higher detection rates of SSA/Ps (2.7%), serrated lesions (14.1%) and flat adenomas (14.9%) by balloon-assisted colonoscopy as compared with SC group (0.8%, 11.2% and 6.9%, respectively), was also observed (Table 2). ADR per each indication for colonoscopy (screening, surveillance, change in bowel habits and positive FOBT) presented an increase in the balloon-assisted colonoscopy arm versus SC ( $p = 0.0165$ ,  $p = 0.4382$ ,  $p = 0.3882$ ,  $p = 0.1319$ , respectively, Table 2). 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% versus 47.2%,  $p = 0.7193$ ). Balloon-assisted colonoscopy ADR in the initial part and final part of the study was similar, 48.6% and 47.1%, respectively ( $p = 0.8657$ ). Total procedure time of balloon-assisted colonoscopy was approximately 3 min longer compared with SC, due to 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 subject, the colonoscopy procedure was prematurely terminated due to inappropriate bowel preparation. A day later, the subject was diagnosed with obstructive sigmoid tumor, underwent surgery and passed away a few days thereafter as a result of aspiration. In the second case, the subject had an irregular heart rate and bradycardia before the initiation of the procedure. This subject did not undergo colonoscopy and was instead admitted for 24 hours of cardiac monitoring and 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<sup>27</sup>. A population-based study reported a 6% interval cancer rate after negative colonoscopy in CRC patients<sup>28</sup>. A large-scale study correlating quality indicators in colonoscopy and interval cancer risk, concluded that the endoscopists' ADR is a principal predictor for the risk of interval cancer after screening colonoscopy<sup>29</sup>. International efforts have resulted in local screening programs for increasing awareness and quality of CRC screening, and monitoring endoscopists' ADR. In addition, novel mechanical (eg, Endocuff) and optical technologies (eg, FUSE) have recently been introduced to increase ADR and to reduce interval cancer rates; however, these techniques showed no consistent increased efficacy in large randomized trials<sup>30-35</sup>. The current randomized study demonstrated a significant increase in ADR by balloon-assisted colonoscopy compared with SC. The ADR in the SC group was 37.5%, which exceeds the recommended threshold of 30%.<sup>7</sup> However, use of the insufflated balloon during withdrawal increased the ADR to 48.0%. In addition, balloon-assisted colonoscopy significantly improved the per patient adenoma detection rate (1.00 adenoma per patient), both in comparison to the SC group (0.68 adenoma per patient) and relative to published studies reporting a range of 0.42-0.5 adenoma per patient<sup>33,36</sup>. As current U.S. and EU surveillance guidelines define surveillance intervals by the number of adenomas detected in a single patient<sup>4,37</sup>, this will have direct implications on 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-size adenomas ( $\geq 10$  mm)<sup>38</sup>. 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 SC. This suggests that in previous studies, some advanced lesions were missed, notwithstanding the use of behind-folds visualizing technologies. 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 involvement<sup>39</sup>. Therefore, detection and removal of such lesions and proper determination of surveillance intervals, are critical to CRC prevention<sup>4,5</sup>. The increased rate in detection of advanced adenomas may theoretically represent the risk reduction of advanced adenoma developing into CRC and thus of interval cancer reduction.

Detection rates (DR) of SSA/P, SL and FA were also higher in the G-EYE group, compared with SC (2.7%, 14.1% and 14.9%, compared with 0.8%, 11.2% and 6.9% respectively). In a multicenter study involving 2167 subjects evaluating segmental ADR and SSA/P-DR in average-risk subjects, SSA/P-DR was reported to be 2%, which is lower than the SSA/P-DR reported in the G-EYE group<sup>40</sup>. In a retrospective analysis of screening colonoscopy with HD+iScan, SL-DR and FA-DR were reported to be 10%, demonstrating the superiority of G-EYE<sup>41</sup>. Interestingly, a recently published study highlighted the strong over-representation of interval cancers in the ascending colon and cecum after negative colonoscopy performed less than 3 years before the diagnosis of CRC<sup>42</sup>. Flat and serrated lesions are typically difficult to detect during colonoscopy and are known to be more common in the proximal colon<sup>20</sup>. These lesions are often missed due to their flat architecture and pale appearance<sup>19-21,43</sup>. US and EU guidelines also provide recommendations regarding the appropriate surveillance interval in the event that such lesions are detected during

colonoscopy<sup>4,37</sup>. In the present study, the G-EYE detected significantly more flat and SSA/Ps 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 which have a direct effect on colorectal cancer 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 in order to further establish this point.

This study had several limitations. First, 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 due to insufficient bowel preparation required to maintain high-quality examination; nevertheless, the outcomes were significant. Fourth, endoscopists were not blinded to the results of the randomization. Fifth, the study population included positive FOBT subjects 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 SC, 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 SSA/Ps 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.

ACCEPTED MANUSCRIPT

**FIGURE LEGENDS**

Figure 1: G-EYE System. A, G-EYE balloon integrated on a standard colonoscope. B, NaviAid SPARK<sup>2</sup>C inflation system

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

Figure 3: CONSORT flow chart, enrollment, allocation, and analysis of study subjects

## TABLES

**Table 1:** Baseline parameters, indications for colonoscopy and procedural times, by type of colonoscopy

	SC	G-EYE	P value
<b>Baseline characteristics</b>			
Age (years), mean	65.2	65.4	0.6708(*)
Gender (% female)	43.7	50.1	0.0677(#)
<b>BBPS score, mean <math>\pm</math>SD</b>			
Global BBPS score	2.57 $\pm$ 0.42	2.56 $\pm$ 0.42	0.7854(*)
Descending colon, BBPS score	2.62 $\pm$ 0.49	2.61 $\pm$ 0.49	0.8412(*)
Transverse colon, BBPS score	2.62 $\pm$ 0.49	2.62 $\pm$ 0.49	0.8377(*)
Ascending colon, BBPS score	2.47 $\pm$ 0.50	2.46 $\pm$ 0.50	0.7701(*)
<b>Indication for colonoscopy, n (%)</b>			
Screening	163 (41.2)	165 (40.5)	0.8488(#)
Surveillance	76 (19.2)	82 (20.1)	
Change in bowel habits	61 (15.4)	55 (13.5)	
Positive FOBT	96 (24.2)	105 (25.8)	
<b>Level of endoscopic experience, n (%)</b>			
800-2500 procedures	55 (53.4%)	48 (46.6%)	0.3747(#)
>2500 procedures	341 (48.7%)	359 (51.3%)	

Procedural times [min], mean (SD)			
Insertion time	8.19 (4.83)	7.92 (4.83)	0.4935(&)
Withdrawal time	7.09 (1.37)	7.33 (1.64)	0.0157(&)
Total procedure time	22.15 (10.13)	24.93 (11.41)	<0.0001(&)

\* t-test

# chi-square

& Kruskal-Wallis



Table 2: PDR/ADR and adenoma characterization, by type of colonoscopy

	SC	G-EYE	% Difference	P value
<b>PDR/ADR and adenoma per patient</b>				
Polyp detection rate (PDR)	47.7%	59.0%	23.7%	0.0014(#)
Adenoma detection rate (ADR)	37.5%	48.0%	28.0%	0.0027(#)
Polyps per patient	0.97	1.42	46.4%	<0.0001(+)
Adenomas per patient	0.68	1.00	47.1%	<0.0001(+)
<b>ADR per indication for colonoscopy</b>				
Screening	30.3%	43.0%	41.9%	0.0165(#)
Surveillance	51.3%	57.5%	12.1%	0.4382(#)
Change in bowel habits	30.5%	38.2%	25.2%	0.3882(#)
Positive FOBT	43.2%	53.9%	24.8%	0.1319(#)
<b>Adenoma, distribution according to size, n (average per subject)</b>				
Diminutive (2-5mm)	160 (0.41)	245 (0.61)	53.1%	<.0001(+)
Small (6-9mm)	54 (0.14)	75 (0.19)	38.9%	0.0946(+)
Large (≥10mm)	53 (0.14)	86 (0.21)	62.3%	0.0093(+)
<b>Adenoma characterization, n (average per subject)</b>				
Advanced adenoma	67 (0.17)	109 (0.27)	62.7%	0.0033(+)
Non-advanced adenoma	200 (0.51)	297 (0.74)	48.5%	<.0001(+)
Serrated lesions	59 (0.15)	90 (0.22)	52.5%	0.0192(+)
Sessile serrated adenoma/polyp (SSA/P)	3 (0.01)	20 (0.05)	566.7%	0.0026(+)
Hyperplastic polyps (HP)	53 (0.14)	67 (0.17)	26.4%	0.2665(+)
Traditional serrated adenoma (TSA)	3 (0.01)	3 (0.01)	0%	0.9705(+)
Flat adenoma	35 (0.09)	85 (0.21)	142.9%	<.0001(+)
<b>SSA/P, SL and FL detection rates</b>				

SSA/P-DR	0.8%	2.7%	237.5%	0.0357(#)
SL-DR	11.2%	14.1%	25.9%	0.2216(#)
FL-DR	6.9%	14.9%	116.0%	0.0003(#)
<b>Adenoma characterization in the right colon, n (average per subject)</b>				
Flat adenoma	21 (0.05)	65 (0.16)	209.5%	<.0001(+)
Sessile serrated adenoma/polyp (SSA/P)	2 (0.01)	17 (0.04)	750.0%	0.0048(+)

# chi-square

+Poisson model

## REFERENCES

- [1] Cancer facts & figures 2016. Atlanta: American Cancer Society, 2016  
(<http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf>)
- [2] Levin B, Lieberman DA, McFarland B, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the; American College of Radiology, CA Cancer J Clin. 2008;58:130-60.
- [3] Cooper GS, Chak A, Koroukian A. The Polyp Detection Rate of Colonoscopy: A National Study of Medicare Beneficiaries. The Am J Med 2005;118:1413
- [4] Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-57.
- [5] Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
- [6] Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-306.
- [7] Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-

- Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2017; 112:1016–1030.
- [8] Kaminski MF, Thomas-Gibson S, Bugajski M, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy* 2017;49:378-97.
- [9] Van Rijn JC, Reitsma JB, Stoker J, et al. Polyp Miss Rate Determined by Tandem Colonoscopy: A Systematic Review. *Am J Gastroenterol* 2006;101:343–350
- [10] Heresbach D, Barrioz T, Lapalus MG, et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. *Endoscopy* 2008;40:284-90.
- [11] Gralnek IM, Siersema PD, Halpern Z, et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. *Lancet Oncol* 2014;15:353-60.
- [12] Halpern Z, Gross SA, Gralnek IM, et al. Comparison of adenoma detection and miss rates between a novel balloon colonoscope and standard colonoscopy: a randomized tandem study. *Endoscopy* 2015;47:238-44.
- [13] Dik VK, Gralnek IM, Segol O, et al. Multicenter, randomized, tandem evaluation of EndoRings colonoscopy: results of the CLEVER study. *Endoscopy* 2015;47:1151-8.

- [14] Pickhardt PJ, Nugent PA, Mysliwiec PA, et al. Location of adenomas missed by optical colonoscopy. *Ann Intern Med* 2004;141:352-9.
- [15] Iannaccone R, Catalano C, Mangiapane F, et al. Colorectal polyps: detection with low-dose multi-detector row helical CT colonography versus two sequential colonoscopies. *Radiology* 2005;237:927-37.
- [16] Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150:1-8
- [17] Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369:1095-105
- [18] Baxter NN, Warren JL, Barrett MJ et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol* 2012;30:266-9.
- [19] East JE, Vieth M, Rex DK. Serrated lesions in colorectal cancer screening: detection, resection, pathology and surveillance. *Gut* 2015;64:991-1000
- [20] Singh H, Turner D, Xue L, et al. Risk of Developing Colorectal Cancer Following a Negative Colonoscopy Examination Evidence for a 10-Year Interval Between Colonoscopies. *JAMA*.2006;295(20):2366–2373.
- [21] Lasisi F, Rex DK. Improving protection against proximal colon cancer by colonoscopy. *Expert Rev Gastroenterol Hepatol* 2011;5:745-54.

- [22] Gralnek IM, Suissa A, Domanov S. Safety and efficacy of a novel balloon colonoscope: a prospective cohort study. *Endoscopy* 2014;46:883-7
- [23] Lai EJ, Calderwood AH, Doros G, et al. The Boston Bowel Preparation Scale: a valid and reliable instrument for colonoscopy-oriented research. *Gastrointest Endosc* 2009;69:620-5.
- [24] Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* 2005;37:570-8.
- [25] Kudo S, Tamura S, Nakajima T, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc* 1996;44:8-14.
- [26] De Jonge V, Sint Nicolaas J, Cahen DL, et al. Quality evaluation of colonoscopy reporting and colonoscopy performance in daily clinical practice. *Gastrointestinal Endoscopy* 2012;75:98-106
- [27] Pan J, Xin L, Ma YF, et al. Colonoscopy reduces colorectal cancer incidence and mortality in patients with non-malignant findings: a meta-analysis. *Am J Gastroenterol* 2016;111:355-65.
- [28] Samadder NJ, Curtin K, Tuohy TMF, et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. *Gastroenterology* 2014;146:950-60.
- [29] Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. *New Engl J Med* 2010;362:1795-1803

- [30] Hassan C, Senore C, Radaelli F, et al. Full-spectrum (FUSE) versus standard forward-viewing colonoscopy in an organized colorectal cancer screening programme. *Gut* Published Online 2016.
- [31] Lenze F, Beyna T, Lenz P, Heinzow HS, Hengst K, Ullerich H. Endocuff-assisted colonoscopy: a new accessory to improve adenoma detection rate? Technical aspects and first clinical experiences. *Endoscopy* 2014;46:610-13.
- [32] de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Adenoma detection with cap-assisted colonoscopy versus regular colonoscopy: a randomised controlled trial. *Gut* 2012;61:1426-34.
- [33] Bhattacharyya R, Chedgy F, Kandiah K, Endocuff-assisted vs. standard colonoscopy in the fecal occult blood test-based UK Bowel Cancer Screening Programme (E-cap study): a randomized trial. *Endoscopy*. 2017 Nov;49(11):1043-1050.
- [34] Biecker E, Floer M, Heinecke A, et al. Novel endocuff-assisted colonoscopy significantly increases the polyp detection rate. *J Clin Gastroenterol* 2015;49:413-8.
- [35] Omata F, Ohde S, Deshpande GA. Image-enhanced, chromo, and cap-assisted colonoscopy for improving adenoma/neoplasia detection rate: a systematic review and meta-analysis. *Scandinavian Journal of Gastroenterology* 2014; 49(2): 222-237
- [36] Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med* 2006;355:2533-41.

- [37] Atkin WS, Valori R, Kuipers EJ, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition: colonoscopic surveillance following adenoma removal. *Endoscopy* 2012;44 Suppl 3:SE151-63.
- [38] Brand EC, Dik VK, Van Oijen MGH, et al. missed adenoma with behind-folds visualizing colonoscopy technologies compared with standard colonoscopy: a pooled analysis of 3 randomized back-to-back tandem colonoscopy. *Gastrointestinal Endoscopy* 2017;86:376-385.
- [39] Dos Santos CEO, Pereira-Lima JC, de Quadros Onofrio F. Large colorectal lesions: Evaluation and management. *GE Port J Gastroenterol* 2016;23:197-207.
- [40] Sanaka MR, Gohel T, Podugu A, Adenoma and sessile serrated polyp detection rates: variation by patient sex and colonic segment but not specialty of the endoscopist. *Dis Colon Rectum*. 2014 Sep;57(9):1113-9
- [41] Rodriguez-D'Jesus AND Saperas E, Enhanced flat adenoma detection rate with high definition colonoscopy plus iScan for average-risk colorectal cancer screening. *Rev Esp Enferm Dig*, 2016;108:257-262
- [42] Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative colonoscopy: population-based case-control study. *Gut* 2012;61:1576-82.
- [43] Feihel D, Kolb JM, Aisenberg J. Identification and resection of sessile serrated adenomas/polyps during routine colonoscopy. *Video Journal and Encyclopedia of GI Endoscopy* 2013;1:372-4.

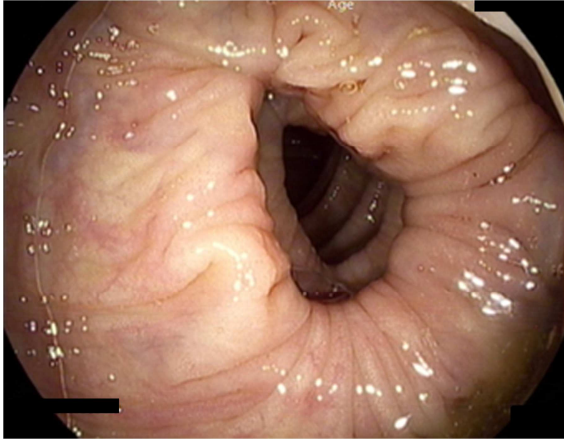




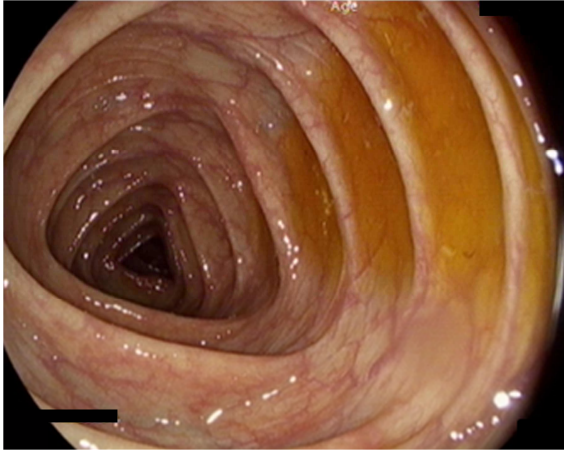
ACCEPTED MANUSCRIPT



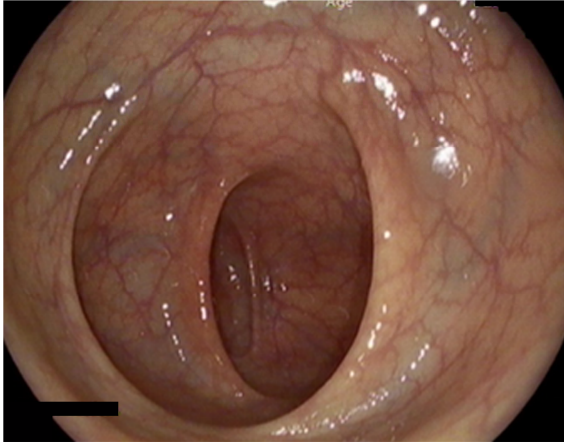
ACCEPTED MANUSCRIPT



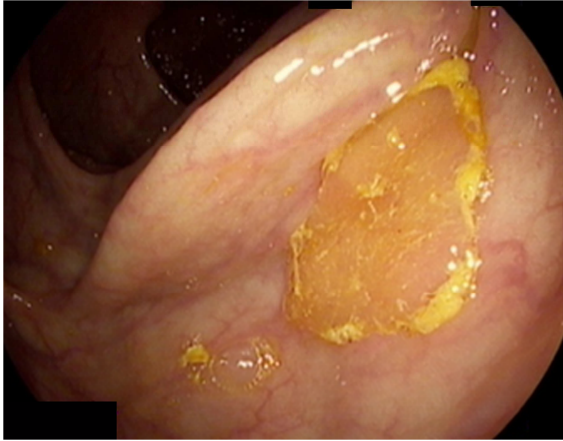
ACCEPTED MANUSCRIPT



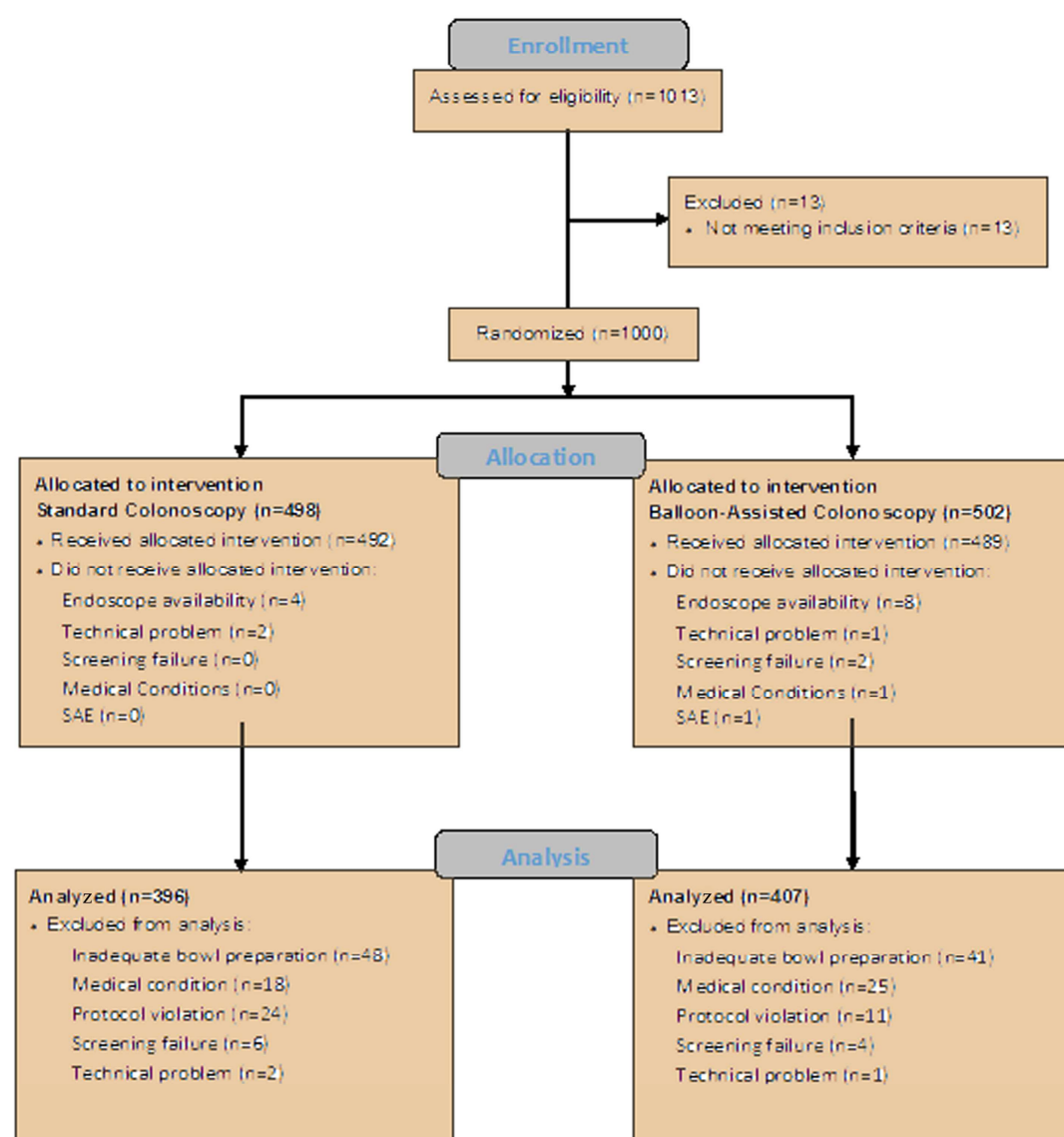
ACCEPTED MANUSCRIPT



ACCEPTED MANUSCRIPT



ACCEPTED MANUSCRIPT



**Acronyms:**

CRC = Colorectal Cancer

SC = Standard Colonoscopy

DR= Detection Rate

ADR = Adenoma Detection Rate

SSA\Ps = Sessile Serrated Adenoma\Polyp

SSA\P-DR= Sessile Serrated Adenoma\Polyp Detection Rate

SL= Serrated Lesions

SL-DR= Serrated Lesions Detection Rate

FA= Flat Adenoma

FA-DR= Flat Adenoma Detection Rate

ESGE = European Society of Gastrointestinal Endoscopy

UEG = United European Gastroenterology

IRB = Institutional Review Board

HD = High Definition

PDR = Polyp Detection Rate

FOBT = Fecal Occult Blood Test

BBPS = Boston Bowel Preparation Scale