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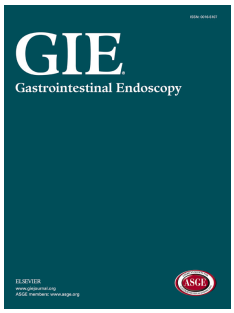

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Linked-color imaging versus narrow-band imaging for colorectal polyp detection: a prospective randomized tandem colonoscopy study

(running title: Linked-color imaging vs NBI for colorectal polyp)

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Specific author contributions: WKL and CGG were involved in the design of the trial, data analysis and writing of the manuscript. TT and LJC assisted in patient's recruitment and trial logistics. MKLK, ET, LYM, DYKB, SYW, KSHL, VT, FYFL, TKLL, KSC, SHL and IFNH were involved in patient's recruitment, performance of colonoscopy and provided critical comments on the manuscript.

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ABSTRACT

Background and Aims: Linked-color imaging (LCI) is a newly available image enhanced endoscopy (IEE) system, which emphasizes the red mucosal color. No study has yet compared LCI with other available IEE systems.

Aim: To compare the polyp detection rates of LCI with narrow band imaging (NBI).

Methods: This is a prospective randomized tandem colonoscopy study. Eligible patients who underwent colonoscopy for symptoms or screening/surveillance were randomized in a 1:1 ratio to receive tandem colonoscopy with both colonoscope withdrawals using LCI or NBI. The primary outcome was polyp detection rate.

Results: Two hundred seventy-two patients were randomized (mean age 62 years; 48.2% male; colonoscopy for symptoms: 72.8%) with 136 in each arm. During first colonoscopy, the NBI group had significantly higher polyp detection rate (71.3% vs 55.9%; P = 0.008), serrated lesion detection rate (34.6% vs 22.1%; P = 0.02), and mean number of polyps detected (2.04 vs 1.35; P = 0.02) than the LCI group. There was also a trend of higher adenoma detection rate in the NBI group (51.5% vs 39.7% in LCI; P = 0.05). Multivariable analysis confirmed that use of NBI (adjusted OR, 1.99; 95% CI, 1.09-3.68) and withdrawal time >8 minutes (aOR, 5.11; 95% CI, 2.79-9.67) were associated with polyp detection. Overall, 20.5% of polyps and 18.1% of adenoma were missed by first colonoscopy, but there was no significant difference in the miss rates between the 2 groups.

Conclusion: NBI was significantly better than LCI for colorectal polyp detection. However, both LCI and NBI missed 20.5% of polyps.

INTRODUCTION

Early detection of colorectal polyp and the subsequent removal by polypectomy are the capstone of colorectal cancer (CRC) prevention.[1] Colonoscopy is therefore generally considered as the gold standard for the detection and treatment of colorectal polyps. However, several studies have found that up to 32% of adenomas could be missed during colonoscopy.[2-4] The missed adenomas are of great concern and is usually believed to be one of the important causes for the development of interval colorectal cancer, which is cancer detected before the expected surveillance interval.

Image-enhanced endoscopy (IEE) has been frequently used in clinical practices for polyp detection and characterization. Among various IEE modalities, narrow-band imaging (NBI) by Olympus (Tokyo, Japan) is one of the most widely used. As yet, there are conflicting data on whether NBI could actually increase the adenoma detection rate based on results of the 3 previous meta-analyses published in 2015.[5-7] With the improvement in light source and image resolution, the new generation of NBI can achieve brighter and sharper endoscopic images. We have previously shown that the use of the new generation of NBI were found to have significantly higher adenoma detection rate than conventional white-light colonoscopy.[8]

Linked-color imaging (LCI) is a new mode of IEE, which is produced by Fujifilm (Tokyo, Japan), with a different mode of wavelength optimization by using all 3 primary colors of red, blue, and green. It is designed to detect subtle color differences

of the red GI mucosa and enhancing the contrast of hemoglobin for detection of mucosal vascular pattern. Further signal processing enhances the red color and make the white color whiter (Figure 1). In a recent study[9], the adenoma miss rate of LCI was 8%, which was significantly lower than that of white-light endoscopy. Other studies also suggested that LCI increased the detection rate of sessile serrated polyps[10] and proximal colonic polyps[11] when compared with white-light colonoscopy. There is yet a direct head-to-head comparison between LCI and other imaging modalities for colorectal polyp detection. In this prospective randomized tandem colonoscopy study, we aimed to compare the polyp detection rates of the newly available LCI with the NBI, a commonly used IEE system.

METHOD

Study design

This was a prospective randomized tandem colonoscopy study conducted in the Integrated Endoscopy Centre of the Queen Mary Hospital in Hong Kong, which is a major regional hospital as well as a university teaching hospital. This study was initiated by the investigators and was registered in the ClinicalTrials.gov (NCT03336359).

Study subjects

Consecutive adult patients, aged between 40 and 80, undergoing colonoscopy in the

Queen Mary Hospital were invited to participate in this study. The indications of colonoscopy included diagnostic work up for bowel symptoms, screening, and surveillance (ie, patients with prior colonoscopy or colorectal polyps). Patients were excluded if they were unable to provide informed consent, had undergone previous colorectal resection, had personal history of colorectal cancer, inflammatory bowel disease, familial adenomatous polyposis, Peutz-Jeghers syndrome, or other hereditary polyposis syndromes. However, patients with family history of colorectal cancer or adenoma were not excluded. Patients who were considered unsafe for polypectomy, including patients with bleeding tendency and severe comorbid illnesses, were excluded. All patients provided written informed consent for participation in this study. The study protocol was approved by the Institutional Review Board of the University of Hong Kong-Hospital Authority Hong Kong West Cluster (UW17-370).

Randomization and Blinding

Eligible subjects were randomly allocated in a 1:1 ratio to undergo tandem colonoscopy with LCI or NBI. Randomization was carried out by computer generated random sequences in blocks of 4. Randomization sequences were stored in opaque envelope and were opened by an independent research staff after obtaining consent from the patient. The patients were blinded to the assigned colonoscopic methods.

Tandem Colonoscopy

All patients were instructed to take low-residue diet 2 days before colonoscopy. Oral

polyethylene glycol lavage solution (3 liters in split dose) was used for bowel preparation as usual practice. Patients assigned to the LCI group would undergo colonoscopy with the ELUXEO 7000 endoscopic system (Fujifilm), whereas patients assigned to the NBI group would undergo colonoscopy with EVIS- EXERA 290 video system (Olympus). All procedures were performed with the patient under conscious sedation with intravenous midazolam and pethidine.

We included both experienced endoscopists as well as junior fellows in this study. Fellows were under direct supervision by experienced endoscopists during each procedure. None of them had red-green color blindness because this may potentially interfere with interpretation of LCI images. Although NBI is used as a supplementary technique for rountine colonoscopy examination in our center, all experienced endoscopists had prior experiences with IEE, particularly with NBI as in our previous study[8]. All endoscopy fellows had performed at least 100 colonoscopies with NBI examination. Because LCI was only recently available, all endoscopists had performed at least 50 LCI examinations.

For all procedures, the colonoscope was first advanced to the cecum under white light. Cecal intubation was confirmed by the identification of the appendiceal orifice and ileocecal valve or by intubation of the ileum. Once cecal intubation was confirmed, the colonoscope was withdrawn to the anus under the assigned method, LCI, or NBI. The Boston Bowel Preparation Scale (BBPS) was used to evaluate the bowel

cleanliness during the first examination.[12] The colonoscope withdrawal time of the first pass (minus the polypectomy time) was measured by an independent observer. The first withdrawal time had to be longer than 6 minutes in all cases. Polyps detected on first withdrawal were estimated for size (measured by open biopsy forceps), location, and then removed. For standardization purpose, polyps were not removed during insertion and would leave till scope withdrawal for fair comparison of polyp detection rate. Removed polyps were labelled clearly and sent for histological examination. Tandem colonoscopy was not performed in patients who were found to have colorectal cancer or very poor bowel preparation during first colonoscopy (Figure 2). Although total withdrawal time cannot be determined in patients with incomplete colonoscopy, all polyps detected in incomplete examination would be removed and included in the estimation of polyp or adenoma detection rate.

Immediately after the first withdrawal examination, the colonoscope was reintroduced to the cecum under white light by the same endoscopist. A second colonoscope withdrawal was performed by the original assigned mode (ie, LCI followed by LCI or NBI followed by NBI). The withdrawal time of the second examination (minus the polypectomy time) was also recorded, but there was no restriction on the second withdrawal time because there is no current recommendation on the optimal second colonoscopy withdrawal time. Any polyps detected on second pass examination were again removed, labeled, and sent for histological examination as in the first examination.

Histologic examination

All resected or biopsy specimens were fixed in 10% buffered formalin solution, and examined histologically by experienced pathologists, who were blinded to the assigned examination mode, according to the World Health Organization (WHO) criteria.[13] Advanced adenoma was defined as adenoma ≥10 mm in diameter or with villous histology in 25% or high-grade dysplasia, or carcinoma. Serrated lesions included traditional serrated adenoma, sessile serrated adenoma with or without cytological dysplasia, and hyperplastic polyp.[14]

Outcomes

The primary outcome of this study was the polyp detection rate during the first examination. Polyp detection rate was defined as the proportion of patients with at least one polyp detected during the first pass examimation. Other outcomes included adenoma detection rate, serrated lesions detection rate, proximal polyp detection rate, proximal adenoma detection rate, and advanced adenoma detection rate on first and second colonoscopy, respectively. The miss rate of polyps or adenomas was based on per-lesion analysis, which was calculated on the numbers of additional polyps/adenomas detected on second examination divided by the total numbers of polyps/adenomas detected on both examinations.

Sample size estimation

We hypothesize that LCI is superior to NBI for colorectal polyp detection. Based on previous studies, the lower end of polyp detection rate of NBI is about 35%[15-18]. For LCI, the only reported polyp detection rate in randomized study was 68%[9]. With a very conservative estimate of about half of the reported difference between LCI and NBI (ie, 17%), a total of 266 patients would be enrolled to achieve a power of 80% and a 2-sided significance level of 0.05.

Statistical analysis

Analysis of lesion detection rates were based on intention-to-treat analysis. Continuous variables were presented as the mean (with standard deviation) and were compared using the Student t-test. Non-parametric variables were expressed as median and interquartile range (IQR). The Mann Whitney U test was used to calculate the differences in the number of polyps and adenomas between 2 groups. Categorical variables were presented as frequencies and percentages and were compared by the chi-squared test or the Fisher exact test where applicable. Subgroup analyses were performed according to bowel preparation quality, experiences of endoscopists and withdrawal time. Multivariable logistic regression analysis was performed to identify for factors associated with polyp detection including the use of NBI, withdrawal time, indications of colonsocopy, endoscopist's experiences, bowel preparaton quality, and baseline demographic of the patients. These variables were either found to be associated with polyp detection on univariable analysis or suspected to be associated with polyp detection. The multivariable logistic regression analysis determined those

factors independently associated with polyp detection, after adjusting for the contributions of the other variables in the model. The adjusted odds ratio (aOR) and 95% confidence intervvals (CI) were presented. A 2-sided *P* value of .05 or less was considered statistically significant. It is recognized that there was multiple testing of outcome data arising from individual patients. Consequently, the definitive analysis of the primary outcome area, the multivariate logistic regression analysis of fractions of patients in whom polyps were detected, was taken as the main result without correction of *P* values. All other *P* values related to outcomes should be taken as confirmatory or secondary, with no correction for multiple testing, and should be taken as descriptive only.

RESULTS

Patients

Between Oct 2017 and Jun 2018, 547 patients were screened for eligibility. After excluding illegible patients, 272 patients were enrolled with 136 patients in each arm (**Figure 2**). The baseline characteristics of the enrolled patients were shown in **Table 1**. The indications for colonoscopy were for work up of bowel symptoms in 72.8% whereas screening and surveillance colonoscopy accounted for 11.4% and 15.8%, respectively. There were more symptomatic patients in the LCI group than in the NBI group (78.7% vs 66.9%; $P = 0.04$). The median withdrawal time was significantly longer in the NBI group for both first (9 vs 8 minutes in LCI; $P = 0.01$) and second

examination (6 vs 5 minutes in LCI; *P* = 0.002).

Tandem Colonoscopy Findings

During first examination, 76 (55.9%) patients in the LCI group and 97 (71.3%) patients in NBI group were found to have colorectal polyps (*P* = 0.008, Table 2). The adenoma detection rate of the first pass examination in the LCI and NBI groups was 39.7% and 51.5%, respectively (*P* = 0.05). The proportion of patients with serrated lesions was also significantly lower in the LCI group than NBI group (22.1 % vs 34.6%; *P* = 0.02). Although the median number of polyps detected in the LCI group was significantly lower than the NBI group (*P* = 0.02), there was no significant difference in the median number of adenoma between the 2 groups (*P* = 0.11).

During second colonoscopy, there was no significant difference in the proportion of patients who were found to have additional polyps and adenomas between the 2 groups (**Table 2**). The proportion of patients with polyps on second examination was 27.9% for LCI and 35.3% for NBI (*P* = 0.19), whereas the corresponding proportion with adenomas was 15.4% and 20.6% (*P* = 0.27), respectively. However, the proportion of patients with proximal polyps (9.6% vs 19.9%; *P* = 0.017) and proximal adenoma (5.9% vs 13.2%; *P* = 0.04) detected on second examination were still significantly lower in the LCI group than the NBI group. The median number of proximal polyps (*P* = 0.02) and proximal adenoma (*P* = 0.05) detected on second colonoscopy were also significantly lower in the LCI group than the NBI group.

When the findings of the 2 tandem colonoscopies were combined, a total of 191 (70.2%) and 137 (50.4%) patients were found to have colorectal polyps and adenomas on both examinations, respectively. The NBI group has a significantly higher overall polyp detection rate (75.7% vs 64.7%; *P* = 0.047), serrated lesion detection rate (41.2% vs 27.9%; *P* = 0.02) and mean number of polyps detected per patient (2.54 ± 3.38 vs 1.72 ± 2.17; *P* = 0.02) than the LCI group. The combined adenoma detection rate was also numerically higher in the NBI group than the LCI group (55.1% vs 45.6%; *P* = 0.12)

Subgroup analysis showed that the polyp detection rate was signficantly higher in the NBI group among patients with good bowel preparation (defined as BBPS ≥6), and in those with colonoscope withdrawal time >6 minutes in both examinations (**Supplementary Table 1**). A total of 11 endoscopists including 6 experienced endoscopists and 5 junior fellows participated in this study. The adenoma and polyp detection rates of individual endoscopists were shown in **Supplementary Figure 1**. There was no significant difference in the polyp (63.8% vs 63.4%; *P* = 1.0) or adenoma (42.6% vs 48.9%, *P* = 0.33) detection rates between experienced and junior endoscopists. However, the adenoma detection rate of junior fellows was significantly lower with the use of LCI than NBI (40.3% vs 61.1%; *P* = 0.03). There was also no significant difference in polyp or adenoma detection rate between first half and second half of patients enrolled in this study (**Supplementary Figure 2**).

Multivariable logistic regression analysis was performed to identify those factors independently associated with polyp detection on first colonoscopy after adjusting for the other variables in the model (**Table 3**). The use of NBI (adjusted OR, 1.99; 95% CI, 1.04 -3.20) and the longer withdrawal time of >8 mins (aOR, 5.11; 95% CI, 2.79–9.67) were independently associated with polyp detection. Patients' characteristics including men (aOR, 2.17; 95% CI, 1.19 – 4.0) and age (aOR, 1.07; 95% CI, 1.04 – 1.11) were the other 2 factors associated with adenoma detection. For indications, colonoscopy performed for bowel symptoms were associated with a lower risk of polyp detection than screening colonoscopy (aOR, 0.31; 95% CI, 0.10-0.86). However, the experience of endoscopists and bowel preparation quality were not found to be signficiant factors. Factors independently associated with adenoma detection was shown in Supplementary Table 2.

Missed Lesions

Based on per lesion analysis, 20.5% of polyps and 18.1% of adenomas were missed by first colonoscopy. Majority of these lesions were <5 mm in diameter, but 9.4% of ≥5 mm adenomas and 14.1% of ≥5mm polyps were missed. More importantly, 9 (26.5%) advanced adenoma were missed by first colonoscpy, including 7 in the LCI group and 2 in the NBI group (P = 0.05). Although there was no significant difference in the overall miss rates between proximal and distal lesions, the miss rate of LCI group was significantly higher in the distal than in the proximal colon (polyp miss rate:

28.1% vs 15%, *P* = 0.02; adenoma miss rate: 28.4% vs 13.8%, *P* = 0.04), particularly for small <5 mm lesions (<5 mm polyp miss rate: 31.1% vs 15%, *P* = 0.008; <5 mm adenoma miss rate 32.1% vs 13.3%, *P* = 0.02; **Supplementary Table 3**).

Tandem colonoscopy increased the overall polyp detection rate by 10.4% (from 63.6% to 70.2%) and the overall adenoma detection rate by 10.5% (from 45.6% to 50.4%; **Table 4**), when compared to single examination only. The increase in the polyp (LCI: 15.7% vs NBI: 6.2%; *P* = 0.03) and adenoma (14.9% vs 7.0%; *P* = 0.07) detection rates by repeated examination were higher in the LCI group than the NBI group. Based on per lesion analysis, the overall percentage increase in number of polyps and adenoma detected by repeated colonoscopy was 25.8% (119/461) and 22.1% (65/294), respectively. There was no signficant difference in the increase in number of polyps or adenoma detected by repeated examination between LCI and NBI.

DISCUSSION

This was the first prospective randomized tandem colonoscopy study that directly compared the newly available LCI with NBI for colorectal polyps detection. Although the newly developed LCI aims to enhance mucosal red color and facilitate polyp detection, we found that polyp detection rate, serrated lesion detection rate and the median number of polyps detected on first colonoscopy were all significantly lower in

the LCI group than the NBI group. There was also a borderline trend of higher adenoma detection rate in the NBI group than the LCI group. Although there was no significant difference in the proportion of patients with polyps or adenomas detected on second examination, more proximal polyps and adenomas were detected by NBI on the second examination. When 2 examinations were combined, NBI was significantly better than LCI in terms of polyp detection rate, serrated lesion detection rate, and number of polyps detected.

Based on early trials that LCI was superior to white light for detection of polyps[9] and sessile serrated polyps[10], we hypothesized that LCI could be better than NBI for polyp detection. Although the available data on whether IEE actually enhance colorectal polyp or adenoma detection remain confliciting, the current study could shed new insight onto the role of IEE on colorectal polyp detection. In a previous meta-analysis, IEE appears to modestly increase adenoma detection rate (OR, 1.25; 95% CI, 1.12 – 1.40) but not polyp detection rate (OR, 1.10; 95% CI, 0.88 – 1.38) when compared with conventional white-light colonoscopy.[19] In the current study, we showed that the filtering of blue and green wavelength may be better than the enhancement of red color for polyp detection. With the direct comparison between NBI and LCI, it may be able to conclude that the IEE, particularly with the use of specific optical filters, do play a role on polyp detection. It should also be noted that red-green color blindness may potentially have a negative impact on the use of LCI due to the inability to differentiate red color.

In this study, the protocol stipulated that the first withdrawal time to be not less than 6 minutes. Because the second colonoscopy aimed for missed lesions and there was no current recommendation on the withdrawal time for the second colonoscopy, we did not pose any limit on the second colonoscopy withdrawal time. It is however interesting to note that both the first and second withdrawal time were significantly longer in the NBI group than LCI group. NBI generally requires a better bowel preparation and residual debris would severely hinder the visualization of colonic mucosa. Hence, repeated irrigation of the colonic mucosa may lengthen the examination time. Our mutivariable logistic regression analysis also confirmed that withdrawal time of >8 minutes in the first colonoscopy was independently associated with polyp detection.

We included both experienced endoscopists and fellows in this study but there was no significant difference in the overall polyp and adenoma detection rate between them (**Supplementary Figure 1**). In contrast to NBI, LCI is a relatively new technology and both experienced and fellow endoscopists had received training and practices on LCI before actual participation in this study. Notably, the adenoma detection rate of the fellows was actually higher with use of NBI than LCI (61.1% vs 40.3%). Our finding may therefore suggest that NBI is more useful for endoscopy trainees in polyp detection and the training on LCI by experienced endoscopists may be shorter than fellows. Nonetheless, we did not find any significant increase in the polyp or adenoma

detection rate in the second half of study, suggesting that learning curve for LCI may not play an important role on our results. The current sample size, however, may be underpowered to detect any significant difference in the detection rates between experienced endoscopists and fellows. As yet, the role of including fellows on colonoscopy study remains controversial. It was observed that trainee participation actually increased the adenoma, particularly diminutive adenoma, detection.[20] A previous retrospective study found that the adenoma detection rate of fellows increased after 140 colonoscopies under attending supervision and then even surpassed the supervising attending.[21] Munroe et al showed that the adenoma miss rate would decrease with experiences of trainees during tandem colonoscopy examination.[22] In a randomized study involving 401 patients, it was shown that NBI was significantly better than WLI for adenoma detection in the initial 100 study patients only.[23] The difference could not be maintained in the last 100 patients, implying the learning curve for adenoma detection was faster with NBI than with WLI. There were, however, no data on the learning curve of LCI for polyp/adenoma detection.

Despite the use of 2 different IEE modes, the missing rates in this study were up to 20.5% for polyps or 18.1% for adenomas. More importantly, up to 26.5% advanced adenomas were missed on first examination, particularly for LCI where 43.8% advanced adenoms were missed. It is also interesting to note that both proximal and distal polyps were missed in this study but LCI was found to miss more distal than

proximal lesions. Our findings are consistent with a recent meta-analysis that IEE failed to reduce adenoma miss rate when compared to conventional colonoscopy.[19] Notably, the use of tandem colonoscopy or repeated examination could increase the polyp and adenoma detection rates by about 10.5% in this study. The increase in polyp or adenoma detection by repeated examination were particularly high in the LCI group, which could be up to 15%. Hence, repeated examination may be another simple way to boost the polyp or adenoma detection rate.

Due to the potential difference in baseline characteristics, indications for colonoscopy and withdrawal time of this randomized study, we have performed multivariable logistic regresion to identify those factors associated with polyp detection on first colonoscopy after adjusting for the other variables in the model. Even after adjusting for various potential confounding factors, we found that the use of NBI (adjusted OR, 1.99; 95% CI, 1.09-3.68) were still independently associated with polyp detection. Moreover, withdrawal time >8 minutes appeared to be a stronger predictor of polyp detection with adjusted OR of 5.11. Other factors such as history of colonoscopy or colorectal polyps (in the surveillance colonoscopy group) and experiences of endoscopists were not associated with polyp or adenoma detection.

This study has several limitations. This study included mostly symptomatic patients and patients who had prior colonoscopy because routine screening colonoscopy was not supported in public hospitals in Hong Kong. The mean age of our patients was 62

years, which was older than usual screening population. These could account for the high adenoma detection rate in this study, which was 45.6% for the first colonoscopy examination in the whole group. In our previous NBI study[8], the adenoma detection rate of the NBI group was also 48%. Second, there were significantly more symptomatic patients in the LCI than NBI group (78.7% vs 66.9%, P = 0.04). Intutively, this could potentially favor a higher polyp or adenoma detection rate in the LCI group. In contrast, it was shown that colonoscopy performed for bowel symptoms were associated with a lower risk of detecting polyp than screening colonoscopy (OR, 0.31; 95% CI, 0.10-0.86). Third, because the aim of this study was to compare the newly available LCI with the NBI, we had not included another group of patients with white-light colonoscopy only. This design was based on the findings of our previous study on the new NBI[8] and the recent study on LCI[9], which all suggested a better performance of IEE than white-light imaging for polyp or adenoma detection. The recently published meta-analysis of individual patient's data also confirmed the superiority of NBI over white-light endoscopy for adenoma detection[24]. It would therefore be more logical to have a head-to-head comparison of 2 imaging modalities rather than comparing with conventional white light again. Last, the actual miss rate, which was based on per-lesion analysis, could be underestimated in this study because the patients with incomplete second colonoscopy could not be assessed.

In conclusion, this propective randomized tandem colonoscopy study showed that NBI was significantly better than LCI for colorectal polyp detection, including

serrated lesions. Apart from the difference in modes of image enhancement, the longer examination time of the NBI group could also account for the difference in polyp detection rates. As yet, both imaging modalities still had unacceptably higher adenoma miss rates of >20%. Repeat colonoscopic examination could boost up the polyp and adenoma detection rate, particularly for LCI.

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Table 1 Patients' baseline characteristics

	LCI (n=136)	NBI (n=136)	*P* value
Age in year, mean ± SD	62.0 ± 10.0	62.0 ± 9.3	0.96
Sex, female (%)	72 (52.9)	69 (50.7)	0.81
Indications:			
Screening	14 (10.3)	17 (12.5)	0.71
Surveillance	15 (11.0)	28 (20.6)	0.05
Bowel symptoms	107 (78.7)	91 (66.9)	0.04
Incomplete first colonoscopy	2 (0.7)	0	0.50
Incomplete second colonoscopy	8* (5.9)*	7 (5.1)	1.0
BBPS			
Median BBPS, median (IQR)	7.5 (6.0, 8.0)	7.0 (6.0, 9.0)	0.75
<6 (%)	29 (21.3)	31 (22.8)	0.62
≥6 (%)	107 (78.7)	105 (77.2)	-
Intubation time of first colonoscopy in minutes,			
Mean ± SD	9.1 ± 5.1	8.8 ± 6.2	0.62
Median and IQR	8 (6-11)	7 (5-10)	0.14
Withdrawal time of first colonoscopy in minutes,			
Mean ± SD	8.6 ± 3.1	10.0 ± 4.1	0.003
Median and IQR	8 (6-10)	9 (7-12)	0.01
Intubation time of second colonoscopy in minutes,			
Mean ± SD	5.3 ± 3.5	5.3 ± 4.8	0.91
Median and IQR	5 (3-6)	4 (3-6)	0.32
Withdrawal time of second colonoscopy in minutes			
Mean ± SD	5.1 ± 1.4	5.7 ± 1.7	0.003
Median and IQR	5 (4-6)	6 (5-6)	0.002

*including 2 patients with incomplete first colonoscopy. Details in Figure 1

SD = standard deviation; IQR = interquartile range

Table 2 Findings on tandem colonosopy (per patient analysis)

	LCI (n = 136)	NBI (n = 136)	*P* value
First colonoscopy			
Patients with polyps	76 (55.9)	97 (71.3)	0.008
Patients with adenomas	54 (39.7)	70 (51.5)	0.05
Patients with advanced adenomas	9 (6.6)	9 (6.6)	1.0
Patients with serrated polyps	30 (22.1)	47 (34.6)	0.02
Patients with proximal polyps	56 (41.2)	56 (41.2)	1.0
Patients with proximal adenomas	43 (31.6)	48 (35.3)	0.52
Number of polyps per patient, median (IQR)	1 (0-2)	1 (0-3)	0.02*
Mean number of polyps per patient (SD)	1.35 ± 1.80	2.04 ± 2.91	-
Number of adenomas per patient, median (IQR)	0 (0-1)	1 (0-2)	0.11*
Mean number of adenomas per patient (SD)	0.90 ± 1.48	1.26 ± 2.25	-
Second colonoscopy			
Patients with polyps	38 (27.9)	48 (35.3)	0.19
Patients with adenoma	21 (15.4)	28 (20.6)	0.27
Patients with advanced adenoma	4 (2.9)	2 (1.5)	0.68
Patients with serrated polyps	13 (9.6)	20 (14.7)	0.19
Patients with proximal polyps	13 (9.6)	27 (19.9)	0.02
Patients with proximal adenoma	8 (5.9)	18 (13.2)	0.04
Mean number of polyps per patient (SD)	0.38 ± 0.70	0.50 ± 0.82	0.17*
Mean number of adenomas per patient (SD)	0.23 ± 0.61	0.25 ± 0.54	0.33*

* Man-Whitney U test comparing the distributions, not the means specifically.

SD = standard deviation

Table 3: Factors associated with polyp detection on first colonoscopy based on multivariable logistic regression analysis

Variables (Reference)	Adjusted OR (95% CI)	*P* value
NBI	1.99 (1.09-3.68)	0.03
LCI	-	
*BBPS < 6	1.66 (0.79-3.60)	0.19
BBPS≥6	-	
Withdrawal time of first colonoscopy		
>8 mins	5.11 (2.79-9.67)	< 0.001
≤ 8 mins	-	
Age (in years)	1.07 (1.04-1.11)	< 0.001
Male	2.17 (1.19-4.00)	0.01
Female	-	
Indications of colonoscopy:		
Surveillance	0.46 (0.12- 1.57)	0.23
Bowel symptoms	0.31 (0.10-0.86)	0.03
Screening	-	
Endoscopist:		
Specialists	0.89 (0.49-1.64)	0.72
Fellows	-	

*BBPS Boston bowel preparation scale

Table 4: Increased Detection Rates by Repeat Tandem Colonoscopy

	Combined first and second colonoscopy	First colonoscopy only	% Increase in detection rate*	*P* value**
Polyp detection rate (%)				
LCI	64.7	55.9	15.7	0.03
NBI	75.7	71.3	6.2	
Total	70.2	63.6	10.4	
Adenoma detection rate (%)				
LCI	45.6	39.7	14.9	0.07
NBI	55.1	51.5	7.0	
Total	50.4	45.6	10.5	

*% increase in detection rate is calculated as

$$\frac{Combined\ colonoscopy\ finding - first\ colonoscopy\ finding}{First\ colonoscopy\ finding} \times 100\%$$

"Finding" refer to "polyp" in polyp detection rate and "adenoma" in adenoma detection rate

**LCI vs NBI

Figure Legend

Figure 1: A small colonic adenoma under white-light endoscopy, narrow-band imaging (NBI), and linked-color imaging (LCI).

Figure 2: Trial profile.

Supplementary Tables and Figures

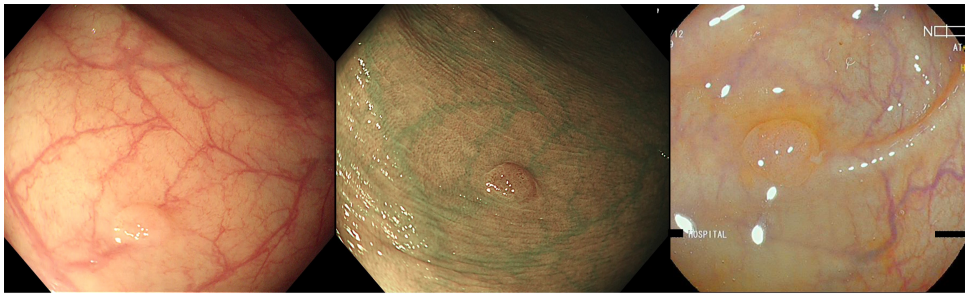
Supplementary Table 1: First colonoscopy findings according to bowel preparation quality, endoscopist's experiences, and withdralwal time.

Supplementary Table 2: Factors associated with adenoma detection on first colonoscopy based on multivariable logistic regression analysis.

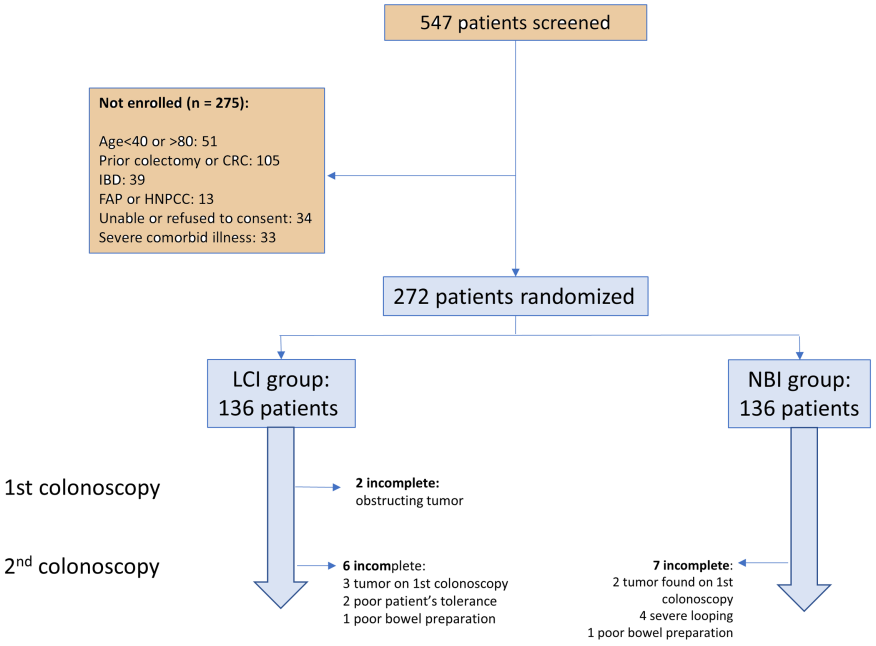
Supplementary Table 3: Number of missed lesions (per lesion analysis).

Supplementary Figure 1: Individual endoscopist's adenoma (A) and polyp (B) detection rates.

Supplementary Figure 2: Comparison of polyp/adenoma detection rates between first and second half of patients recruited.



White light NBI LCI



Abbreviations

BBPS, Boston bowel preparation scale

CRC, colorectal cancer

IEE, image enhanced endoscopy

LCI, linked color imaging

NBI, narrow band imaging

WHO, World Health Organization

Supplementary Table 1: First colonoscopy findings according to bowel preparation quality, endoscopist's experiences and withdrawal time

	LCI (n = 136)	NBI (n = 136)	*P* value
Quality of bowel preparation:			
BBPS ≥6			
Patients with polyps	59 (55.1)	72 (68.6)	0.04
Patients with adenoma	42 (39.3)	55 (52.4)	0.06
Mean number of polyps per patient	1.35 ± 1.84	2.10 ± 3.03	0.03
Mean number of adenomas per patient	0.91 ± 1.54	1.31 ± 2.31	0.13
BBPS <6			
Patients with polyps	17 (58.6)	25 (80.6)	0.11
Patients with adenoma	12 (41.4)	15 (48.4)	0.78
Mean number of polyps per patient	1.34 ± 1.67	1.87 ± 2.49	0.34
Mean number of adenomas per patient	0.90 ± 1.26	1.06 ± 2.05	0.71
Experiences of Endoscopists:			
Junior Fellows			
Patients with polyps	44 (57.1)	39 (72.2)	0.11
Patients with adenoma	31 (40.3)	33 (61.1)	0.03
Mean number of polyps per patient	1.21 ± 1.43	2.33 ± 3.09	0.006
Mean number of adenomas per patient	0.86 ± 1.33	1.59 ± 2.85	0.05
Specialists			
Patients with polyps	32 (54.2)	58 (70.7)	0.07
Patients with adenoma	23 (39.0)	37 (45.1)	0.58
Mean number of polyps per patient	1.53 ± 2.19	1.85 ± 2.78	0.45
Mean number of adenomas per patient	0.97 ± 1.67	1.04 ± 1.72	0.81
Both first and second colonoscopy withdrawal time >6 minutes			
Patients with polyps	30 (63.8)	57 (82.6)	0.02
Patients with adenoma	21 (44.7)	43 (62.3)	0.06
Mean number of polyps per patient	1.66 ± 2.07	2.72 ± 3.56	0.07

Mean number of adenomas per patient	1.11 ± 1.73	1.77 ± 2.83	0.16

Supplementary Table 2: Factors associated with adenoma detection on first colonoscopy based on multivariable logistic regression analysis

Variables (Reference)	Adjusted OR (95% CI)	*P* value
NBI	1.81 (1.04-3.20)	0.037
LCI	-	
*BBPS < 6	1.00 (0.52-1.94)	0.99
BBPS≥6	-	
Withdrawal time of first colonoscopy		
>8 mins	2.78 (1.62-4.82)	< 0.001
≤ 8 mins	-	
Age (in years)	1.08 (1.04-1.11)	< 0.001
Male	2.27 (1.30-4.00)	0.004
Female	-	
Indications of colonoscopy:		
Surveillance	0.66 (0.23-1.88)	0.44
Bowel symptoms	0.82 (0.34-1.98)	0.66
Screening	-	
Endoscopist:		
Specialists	0.64 (0.37-1.12)	0.12
Fellows	-	

*BBPS Boston bowel preparation scale

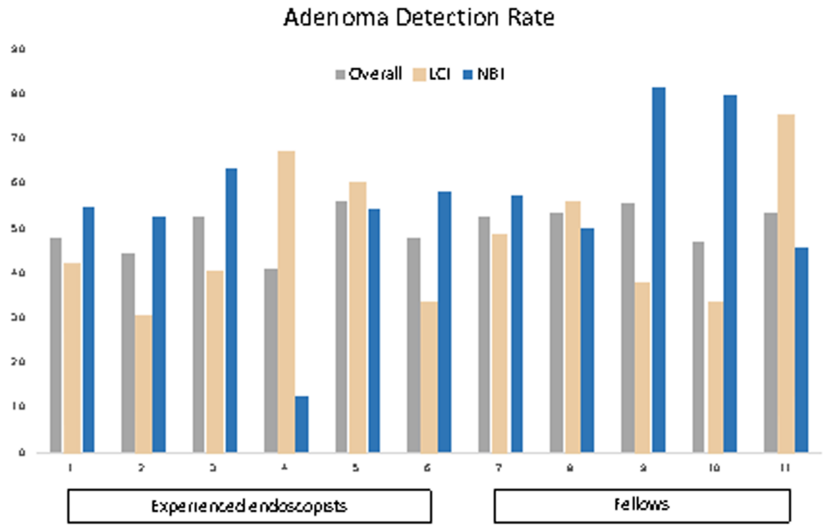
Supplementary Table 3: Number of missed lesions (per lesion analysis)

	Polyps				Adenoma			
	Total	**First**	**Second**	**Miss rate****	**Total**	**First**	**Second**	**Miss rate****
All	580	461	119	20.5%	359	294	65	18.1%
LCI	234	183	51	21.8%	154	123	31	20.1%
NBI	346	278	68	19.7%	205	171	34	16.6%
*P**				0.53	*P**			0.39
≥5 mm					≥5 mm			
All	99	85	14	14.1%	74	67	7	9.4%
LCI	31	27	4	12.9%	26	22	4	15.4%
NBI	68	58	10	14.7%	48	45	3	6.3%
*P**				1.0	*P**			0.23
<5 mm					<5 mm			
All	481	376	105	21.8%	285	227	58	20.3%
LCI	203	156	47	23.2%	128	101	27	21.1%
NBI	278	220	58	20.9%	157	126	31	19.7%
*P**				0.55	*P**			0.78
	Proximal polyps				**Proximal adenoma**			
	Total	**First**	**Second**	**Miss rate**	**Total**	**First**	**Second**	**Miss rate**
All	278	229	49	17.6%	213	180	33	15.5%
LCI	113	96	17	15.0%	87	75	12	13.8%
NBI	165	133	32	19.4%	126	105	21	16.7%
*P**				0.35	*P**			0.57
≥5 mm					≥5 mm			
All	50	44	6	12.0%	40	36	4	10.0%
LCI	13	11	2	15.4%	12	10	2	16.7%
NBI	37	33	4	10.8%	28	26	2	7.1%
*P**				0.62	*P**			0.57
<5 mm					<5 mm			
All	228	185	43	18.9%	173	144	29	16.8%
LCI	100	85	15	15.0%	75	65	10	13.3%
NBI	128	100	28	21.9%	98	79	19	19.4%
*P**				0.19	*P**			0.29
	Distal polyps				**Proximal adenoma**			
	Total	**First**	**Second**	**Miss rate**	**Total**	**First**	**Second**	**Miss rate**
All					All			
All	302	232	70	23.2%	146	114	32	21.9%
LCI	121	87	34	28.1%	67	48	19	28.4%
NBI	181	145	36	19.9%	79	66	13	16.5%
*P**				0.13	*P**			0.11
≥5 mm					≥5 mm			
All	49	41	8	16.3%	34	31	3	8.8%
LCI	18	16	2	11.1%	14	12	2	14.3%
NBI	31	25	6	19.4%	20	19	1	5.0%
*P**				0.69	*P**			0.56
<5 mm					<5 mm			

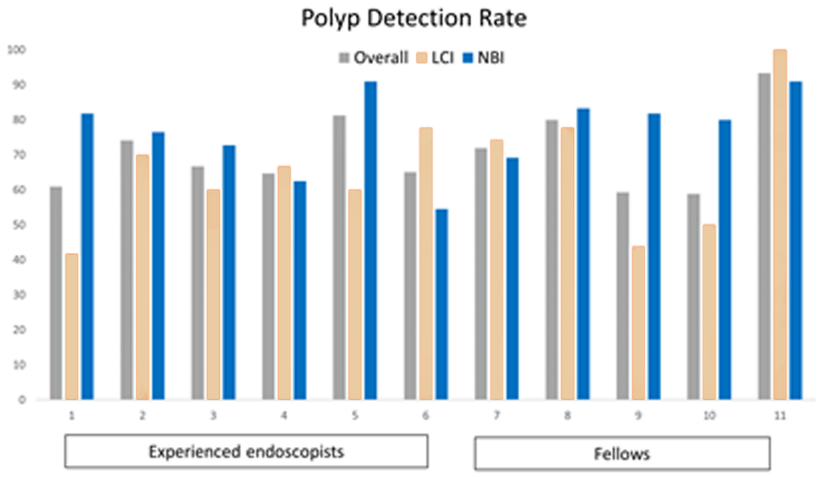
All	253	191	62	24.5%	112	83	29	25.9%
LCI	103	71	32	31.1%	53	36	17	32.1%
NBI	150	120	30	20%	59	47	12	20.3%
*P**				0.05	*P**			0.20
	Serrated lesions				**Advanced adenoma**			
	Total	**First**	**Second**	**Miss rate**	**Total**	**First**	**Second**	**Miss rate**
All	154	114	40	25.8%	34	25	9	26.5%
LCI	49	35	14	28.6%	16	9	7	43.8%
NBI	105	79	26	24.8%	18	16	2	11.1%
*P**				0.62	*P**			0.05
≥5 mm								
All	17	12	5	29.4%				
LCI	3	3	0	0				
NBI	14	9	5	35.7%				
*P**				0.52				
<5 mm								
All	137	102	35	25.5%				
LCI	46	32	14	30.4%				
NBI	91	70	21	23.1%				
*P**				0.35				

* LCI vs NBI;

** Miss rate = number of lesions detected on second colonoscopy/total number of lesions detected on both colonoscopy



Difference in ADR between Experienced endoscopists and Fellows
Overall, P = .33, LCI, P = 1.0, NBI, P = .08



Difference in PDR between Experienced endoscopists and Fellows
Overall: $P = 1.0$; LCI: $P = .86$; NBI: $P = 1.0$