Detection of colorectal neoplasms using linked color imaging: A prospective, randomized, tandem colonoscopy trial

Short title: Detection of colorectal neoplasms

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Abbreviations: ADR, adenoma detection rate; AMR, adenoma miss rate; BBPS, Boston Bowel Preparation Scale; BLI, blue laser imaging; CI, confidence interval; eIEE, equipment-based image-enhanced endoscopy; IQR, interquartile range; LCI, linked color imaging; MD, mean difference; NBI, narrow band imaging; RR, risk ratio; SD, standard deviation; SSL, sessile serrated lesion; WLI, white light imaging

What You Need to Know

Background

Colonoscopy using white light imaging (WLI) often overlooks adenomas. Adenoma detection by linked color imaging (LCI) is promising, but the accurate adenoma miss rate (AMR) with LCI remains unclear.

Findings

Both methods provided similar adenoma detection rates (ADR). However, LCI significantly improved AMR even for endoscopists with high ADR. LCI was sufficiently effective, even if bowel preparation was not excellent.

Implications for patient care

LCI had a lower AMR than WLI, specifically for diminutive and non-polypoid adenomas. LCI could help further improve the quality of colonoscopy.

ABSTRACT

Background and aims: A higher adenoma detection rate (ADR) has been shown to be related to a lower incidence and mortality of colorectal cancer. We analyzed the efficacy of linked color imaging (LCI) by assessing the detection, miss, and visibility of various featured adenomas as compared with white light imaging (WLI).

Methods: This was a prospective, randomized, tandem trial. The participants were randomly assigned to two groups: first observation by LCI, then second observation by WLI (LCI group); or both observations by WLI (WLI group). Suspected neoplastic lesions were resected after magnifying image-enhanced endoscopy. The primary outcome was to compare the ADR during the first observation. Secondary outcomes included evaluation of adenoma miss rate (AMR) and visibility score.

Results: Seven-hundred eighty patients were randomized, 700 of whom were included in the final analysis. The ADR was 69.6% and 63.2% in the LCI and WLI groups, respectively, with no significant difference. However, LCI improved the average ADR in low-detectors compared to high-detectors (76.0% vs 55.1%; $P < 0.001$). Total AMR was 20.6% in the LCI group, which was significantly lower than that in the WLI group (31.1%) ($P < 0.001$). AMR in the LCI group was significantly lower, especially for diminutive adenomas (23.4% vs 35.1%; $P < 0.001$) and non-polypoid lesions (25.6% vs 37.9%; $P < 0.001$) compared to the WLI group.

Conclusion: Although both methods provided a similar ADR, LCI had a lower AMR than WLI. LCI

could benefit endoscopists with lower ADR, an observation that warrants additional study.

Trial Registration Number: UMIN000026359

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Keywords: linked color imaging; prospective randomized tandem trial; adenoma detection rate; adenoma miss rate

INTRODUCTION

Early detection of adenomatous lesions is important in colorectal screening, because endoscopic resection of adenomas reduces the incidence and mortality of colorectal cancer[1]. The adenoma detection rate (ADR) is inversely associated with the risk of interval cancer[2]. However, ADR may be an insufficient quality indicator of colonoscopy, as it does not consider the number of polyps. Aniwan et al. reported that the adenoma miss rate (AMR) differed significantly between endoscopists with high ADRs[3]. Moreover, small and flat lesions are often overlooked, even by experienced endoscopists[4].

The high-resolution technique, equipment-based image-enhanced endoscopy (eIEE), does not require adjunct devices and eliminates the need for dye. However, a previous report concluded that narrow band imaging (NBI), a representative of eIEE, did not improve the ADR because of insufficient brightness[5]. Several studies showed positive results that the brighter, next-generation eIEE improved detection of adenomatous lesions[6,7]. However, these new eIEEs also have a darker view than white light imaging (WLI) and may require the operator to move closer to the mucosa for observation, which narrows the field of view.

Linked color imaging (LCI) is a new eIEE designed to enhance slight color differences. LCI enhances the color separation of red blood vessels and white pits, allowing similar visualization to conventional WLI (Figure 1A-D). Furthermore, LCI is brighter than blue laser imaging (BLI)-bright and is expected to enhance visibility to improve polyp detection[8]. Recent studies, including crossover trials and meta-analyses, have suggested that LCI improves the detection of adenomas and sessile

serrated lesions (SSLs)[9,10,11].

We adopted a design in which the second observation was fixed by WLI, to calculate the miss rate in the entire colon more accurately. The present trial aimed to investigate the superiority of LCI over WLI for lesion detection.

METHODS

Study design

This study was a prospective, randomized controlled trial with tandem colonoscopy, conducted at Nagoya University Hospital in Japan from June 2017 to June 2020. The study protocol was approved by the Institutional Review Board of Nagoya University Hospital and was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN 000026359). All authors had access to the study data and have reviewed and approved the final manuscript.

Patients

We enrolled patients aged ≥ 20 years who underwent colonoscopy. The indications for colonoscopy included screening, surveillance, and diagnostic workup of colonic symptoms. Patients with inflammatory bowel disease or polyposis (familial adenomatous polyposis, or other hereditary polyposis syndromes) and those considered high-risk for tandem colonoscopy (including patients with confirmed advanced colorectal cancer, history of difficulty of insertion, or history of poor sedation) or polypectomy (including patients with bloody stool, ongoing antithrombotic therapy, or severe

comorbid illness) were excluded. Additionally, we excluded patients with a history of multiple polyps (> 10), previous colorectal resection, non-standardized preparation methods, inability to provide informed consent, or refusal of the procedure.

Endoscopic equipment and setting

Patients underwent tandem colonoscopy with high-definition colonoscopes (EC-L600ZP, EC-L600ZP7; Fujifilm Co., Tokyo, Japan) using a LASEREO 7000 endoscopic system (Fujifilm Co., Tokyo, Japan). Endoscopic procedures were performed with an endoscopic transparent hood (Disposal distal attachment; Olympus Medical Systems, Tokyo, Japan) to secure the field of view.

Endoscopic procedure

Patients followed a low-residue diet the day before endoscopy and took 10 mL sodium picosulfate before sleeping. On the morning of colonoscopy, 1-2 L of a highly concentrated polyethylene glycol solution (MoviPrep; Ajinomoto Pharma Co., Tokyo, Japan) was administered. Colonoscopies were performed under conscious sedation with intravenous midazolam. Butylscopolamine (20 mg) or glucagon (1 mg) was administered intravenously as a spasmolytic agent immediately before insertion, when there were no contraindications. Procedures in this study were conducted by 14 endoscopists, each with experience in performing ≥ 3000 colonoscopies and ≥ 1000 eIEE examinations including LCI. A previous report was referred to define endoscopists' experience[12]. Patients gave informed consent for participation and publication of the research. Random assignments were performed before the examination in all cases. Eligible patients were stratified according to two factors: constipation

(once every three days, on average) and the presence of previous colonoscopic therapy. Patients were then randomized in a 1:1 ratio by computer-generated random sequences to determine whether they would undergo the first colonoscopy with LCI or with WLI. The random sequence was stored in assignment tables managed by a third party blinded to this trial. The method for the first colonoscopy, LCI or WLI, was decided according to the assignment tables immediately before the procedure, and the endoscopist was made aware of the allocation. Patients were in supine position at each withdrawal. After withdrawal to the rectum with the LCI or WLI, the scope was re-inserted up to the cecum. Then, the second withdrawal was performed using WLI in both groups by another endoscopist who was unaware of the assignment and the results of the first observation. Endoscopic insertion was performed by WLI in both groups. The target for pure withdrawal time was set at six minutes, based on a previous study[13], and using a stopwatch, we spend at least six minutes for withdrawal from the cecum to the dentate line, with as constant a speed as possible. Consequently, the residual suction time, magnified observation time, and treatment time were not measured. All lesions were magnified by BLI and evaluated by Japan NBI Expert Team classification[14]. Chromoendoscopy with indigo carmine and crystal violet was not performed during the diagnostic procedure to avoid any effect on the ADR. Regardless of the first or second observation, neoplastic lesions (adenomas, traditional serrated adenomas, and SSLs) evaluated by optical diagnosis were removed immediately after magnified observations. We contemporaneously recorded the location, size (measured by biopsy forceps or snares), morphology type, and visibility score (range: 1-4) of detected lesions[15]. Lesions were

examined histologically by pathologists who were unaware of the results of the endoscopic diagnosis.

Definition

A diminutive adenoma was defined as an adenoma ≤ 5 mm in diameter, and an advanced adenoma was defined as an adenoma ≥ 10 mm in diameter, and/or with villous histology, and/or with high-grade dysplasia. The morphology was classified as non-polypoid type (0-IIa, IIb, IIc) or polypoid type (0-Ip, Is) according to the Paris classification[16]. We assessed bowel preparation using the Boston Bowel Preparation Scale (BBPS) score[17] and defined a score of 5 or less as "dropout," 6-8 as "adequate," and 9 as "excellent."

Outcomes

The primary endpoint was to compare ADR, defined as the proportion of patients with at least one adenoma found on first observation. The secondary endpoints were the evaluation of AMR and the visibility score. AMR was defined as the number of adenomas identified during the second observation divided by all detected adenomas in first and second colonoscopies.

Sample size

ADR with WLI at our hospital was approximately 60%. We anticipated that an additional 10% of the ADR could be expected with LCI compared to WLI, with reference to previous studies[10]. With a statistical power of 0.80 and a two-sided significance level of 0.05, the minimal sample number was 712 patients. Therefore, assuming potential exclusions or dropouts, 780 patients were recruited to ensure an adequate number of patients.

96 **Statistical analysis**

97 Analyses were performed with SPSS Statistics 26 (IBM, Armonk, NY). Continuous variables are
98 summarized by mean ± standard deviation or median (interquartile range) and were compared using
99 Student's t-test or the Mann-Whitney U test. Categorical variables are expressed as proportions and
100 percentages and were compared using the Chi-squared test. Statistical tests were two-tailed, with
101 significance defined as a *P* value of 0.05 or less. The measurement of intervention effect for continuous
102 outcomes was the mean difference (MD) with 95% confidence interval [CI], and that for dichotomous
103 outcomes was assessed by the risk ratio (RR) with 95% CI. The correlation analysis was evaluated
104 using Spearman's correlation coefficients (rs).

105

106 **RESULTS**

107 **Recruitment and participant flow**

108 Patient recruitment is shown in Supplemental Figure 1. Finally, 349 patients (89.5%) in the LCI
109 group and 351 patients (90.0%) in the WLI group completed the protocol and were analyzed.

110 **Group characteristics**

111 Baseline characteristics of the patients are summarized in Table 1. Age, sex, constipation, previous
112 endoscopic therapy, bowel preparation, antispasmodic drug use, and first/second insertion time did not
113 differ significantly between the groups. The mean withdrawal time was similar between the two groups.
114 No adverse events occurred during the study.

Outcomes

Per patient analysis

During the first observation, polyps were detected in 264 (75.6%) and 247 (70.2%) patients in the LCI and WLI groups, respectively, but no significant difference was found ($P = 0.116$) (Table 2). The ADR was 69.6% in LCI group and 63.2% in the WLI group, with no significant difference (RR 1.10; 95% CI 0.99-1.22; $P = 0.074$). There were also no significant differences in the number of polyps or adenomas per patient between the groups. During the second observation, the proportion of patients with additional polyps (33.8% vs 45.3%; RR 0.75; 95% CI 0.62-0.90; $P = 0.002$) or adenomas (29.8% vs 42.7%; RR 0.70; 95% CI 0.57-0.85; $P < 0.001$) was significantly lower in the LCI than WLI group. There was no significant difference in the proportion of patients with missed advanced adenomas between the two groups. The first observation using LCI resulted in significantly fewer missed polyps ($P = 0.002$) or adenomas ($P < 0.001$) per patient.

In a stratified analysis between high- and low-detectors, according to the median ADR by WLI, no high-detectors with ADR above 60% improved the ADR by LCI, but low-detectors with ADR of 60% or less showed overall improvement (Supplemental Table 1). Moreover, in the correlation analysis of the difference of ADR by WLI, there was a strong negative correlation between the improvement ratio calculated by LCI-ADR/WLI-ADR and ADR using WLI (rs = 0.905, $P < 0.001$) (Supplemental Figure 2).

The learning curves for LCI and WLI were similar (Supplemental Figure 3).

Furthermore, in a subanalysis that evaluated the differences between the surveillance colonoscopy interval recommendation (SCIR) determined only by the first observation and the true SCIR, taking into account missed adenomas in the first and second observations, based on the U.S. guideline[18], the rate of patients with altered SCIR was significantly lower in the LCI group than in the WLI group (12.9% vs 18.8%; RR 0.69; 95% CI 0.48-0.97; $P = 0.032$) (Supplemental Figure 4).

Per lesion analysis

During the first observation, 698 polyps in 349 patients and 632 polyps in 351 patients were detected in the LCI and WLI groups, respectively (Supplemental Table 2). Histopathologically, 547 (78.4%) and 500 (79.1%) polyps were classified as adenomas with low-grade dysplasia and 39 (5.6%) and 33 (5.2%) as adenomas with high-grade dysplasia in the LCI and WLI groups, respectively. In the LCI and WLI groups, 19 (2.7%) and 13 (2.1%) SSLs were detected, respectively. The remaining 111 and 99 polyps in each group contained inflammatory polyps or hyperplastic polyps that were misclassified as neoplastic lesions at optical characterization. No invasive cancer was missed in either group.

The total adenomas found in the first and second observations were 738 and 774 lesions, and the missed adenomas included 152 and 241 lesions in the LCI and WLI groups, respectively (Table 3). The AMR was significantly lower in the LCI group than in the WLI group (20.6% vs 31.1%; RR 0.66; 95% CI 0.55-0.79; $P < 0.001$). In addition, the AMR for < 10 mm lesions was significantly lower in the LCI group than WLI group (≤ 5 mm: 23.4% vs 35.1%; RR 0.67; 95% CI 0.55-0.81; $P < 0.001$, 6-9 mm: 15.8% vs 25.3%; RR 0.62; 95% CI 0.39-0.99; $P = 0.043$). The AMRs for non-polypoid lesions

were 25.6% and 37.9% in the LCI and WLI groups, respectively; the AMR was significantly different between the groups (RR 0.68; 95% CI 0.56-0.81; $P < 0.001$). Significant differences in the AMR were detected in a wide range of locations, including the ascending colon, transverse colon, sigmoid colon, and rectum. In the analysis by location, AMR was higher in the left colon in the WLI group ($P = 0.006$), but there was no significant difference in the LCI group (Supplemental Table 3).

Visibility analysis

During the first observation, the mean visibility scores in the LCI group were significantly better than those in the WLI group (3.31 ± 0.70 vs 3.20 ± 0.74; MD 0.11; 95% CI 0.02-0.19; $P = 0.012$), specifically for diminutive and non-polypoid adenomas (Table 4). In the second observation, the mean visibility scores of adenomas were similar in both groups, except for polypoid lesions (LCI group vs WLI group: 2.93 ± 0.62 vs 3.24 ± 0.60; MD -0.32; 95% CI -0.62 to -0.01; $P = 0.042$). The mean visibility scores of missed adenomas were significantly lower in both groups compared with those of adenomas detected during the first observation.

Furthermore, the LCI group was superior to the WLI group in the visibility score of adequate bowel preparation (3.38 ± 0.65 vs 3.15 ± 0.76; MD 0.23; 95% CI 0.10-0.37; $P < 0.001$) leading to improvement of the AMR (24.0% vs 34.3%; RR 0.69; 95% CI 0.55-0.89; $P = 0.005$) (Table 5).

DISCUSSION

This is a prospective, randomized, tandem colonoscopy trial that directly compared the performance

of LCI with WLI, and evaluated the ADR, AMR, and visibility scores by observing the entire colon.

LCI provides a brighter image than BLI-bright mode, by maintaining a stronger white light spectrum. Yoshida et al. showed that the mean polyp visibility scores for LCI were significantly higher than those for WLI and BLI-bright[19]. Min et al. reported that the ADR was significantly higher for LCI than for WLI using a crossover design[10]. However, they described the sample size as insufficient, and did not mention AMR.

In this study, LCI did not significantly improve the total ADR during the first colonoscopy compared to WLI. Paggi et al. reported that high-detectors with an ADR above 40% using WLI could potentially benefit from using LCI[20]. Our correlation analysis and stratified analysis of endoscopists showed that the superiority of LCI is not guaranteed for endoscopists with very high ADR, above 60% by WLI. Conversely, we expect LCI to be potentially more useful to endoscopists with relatively low ADR using WLI, including general endoscopists.

The AMR varies even for endoscopists with high ADRs[3] and is attracting attention as a secondary quality indicator. Currently, there are no data to support the link between AMR and the risk of interval cancer, but it can be assumed that the AMR partly contributes to the risk. Two previous studies showed that LCI could reduce the rate of missed neoplastic lesions in the right colon[21,22]. Although these results may be clinically significant, because the right colon has a higher rate of missed neoplastic lesions and has flatter lesions with a high malignant potential[23], the studies did not evaluate the detection of neoplastic lesions with LCI in the entire colon. We found that most of the missed lesions were

191 diminutive, and that LCI improved AMR throughout the colon, especially in subcentimetric adenomas.
192 Although a lower AMR for diminutive adenomas with cap-fitted colonoscopy has been reported[24], our
193 results indicate that LCI may further reduce the AMR of diminutive adenomas. It remains unclear
194 whether detection and removal of diminutive adenomas will reduce the incidence of interval cancer.
195 However, according to our subanalysis of SCIR, the lower miss rate of subcentimetric adenomas by
196 LCI enables higher levels of surveillance colonoscopies compared to WLI and may reduce interval
197 cancer. Flat and depressed lesions tend to disappear easily into the surroundings, despite their
198 malignant potential[23]. Suzuki et al. reported that LCI improved the endoscopic visibility of nongranular
199 flat lesions[25]. We further found that LCI significantly reduced the AMR of non-polypoid lesions
200 compared to WLI. LCI could reduce the AMR in wide areas of the colon. LCI may be useful in
201 detecting whole colon adenomas as well as previously reported efficacy in the proximal colon[21,22]. The
202 separate analysis of the right and left colons showed no significant difference in AMR in the LCI group.
203 However, the AMR was lower in the right colon in the WLI group, which may be due to an increased
204 number of adenomas detected because of the hood, especially in the right colon. Despite the high ADR
205 results, it is also true that both modalities still missed more than 20% of adenomas. Determining the
206 best method for optimizing screening colonoscopies remains a matter for future research.
207 In the visibility score analysis, the efficacy of LCI was confirmed in the examination of non-
208 polypoid or diminutive adenomas. In the second observation, the polypoid adenomas missed in the
209 first observation with LCI had a significantly lower visibility score than those observed with WLI.

Although the polypoid adenomas are relatively easy to see, this result suggests that LCI facilitates easier detection of slightly red or non-reddish polypoid adenomas.

Optimal bowel cleansing is crucial for viewing, and it is true that even a small amount of residual stool diminishes polyp detection[6]. Atkinson et al. reported that patients with the best bowel preparation showed significant differences in ADR compared to those with adequate bowel preparation using NBI and WLI[6]. In this study, we assessed the efficacy of LCI for each dichotomized BBPS score. In patients with excellent preparation, differences between high ADRs or high visibility scores in both groups are likely to be small, making it difficult to detect significant differences; however, the AMR was significantly different. LCI was considered to have improved the adenoma visibility in patients with adequate preparation, resulting in a lower AMR.

This study has some limitations. First, this was a single-center study. In this setting, a single-center study allowed all conditions to be uniform; however, assessment of the utility of LCI in detecting adenomas requires an external validation study with a multi-center trial. Second, many endoscopists served as experts in this study. This may lead to potential bias in that differences in endoscopist characteristics can be reflected in the results of adenoma detection. Third, although AMR was often evaluated in the tandem studies, it did not always reflect the true miss rate with consideration for missed lesions in both observations. However, there is no way to actually recognize the number of missed lesions. Fourth, WLI was used during the insertion phase in each group. Insertion using LCI could have led to a more accurate evaluation of LCI performance. Fifth, this study focused primarily

on average-risk patients, who make up most of the population, therefore, our findings may not be clinically significant for high-risk patients. Sixth, the usefulness of LCI for SSLs has been reported[9], but we did not evaluate SSLs in this study because of their small number and the difference of visibility from adenoma with LCI. Finally, we chose WLI, the standard modality for screening colonoscopy, as the reference to examine the efficacy of LCI in this study. Leung et al. compared next-generation NBI with LCI and its findings indicated that NBI had a higher ADR than LCI[26]. However, data remain insufficient. We believe the current research provides direction for additional studies such as including trainees, focusing on high-risk patients, and head-to-head comparison studies of LCI with other eIEEs.

In conclusion, we did not find a significant difference for ADR between the WLI and LCI groups; however, the LCI improved the ADR in lower detectors. Our data suggest that LCI makes a significant difference in AMR, particularly in detecting diminutive or non-polypoid adenomas, even for expert endoscopists with a high ADR.

FIGURE LEGENDS

Figure 1. Representative cases of white light (A, C) and linked color images (B, D) of a non-polypoid, diminutive adenoma according to excellent (A, B) or adequate (C, D) bowel preparation.

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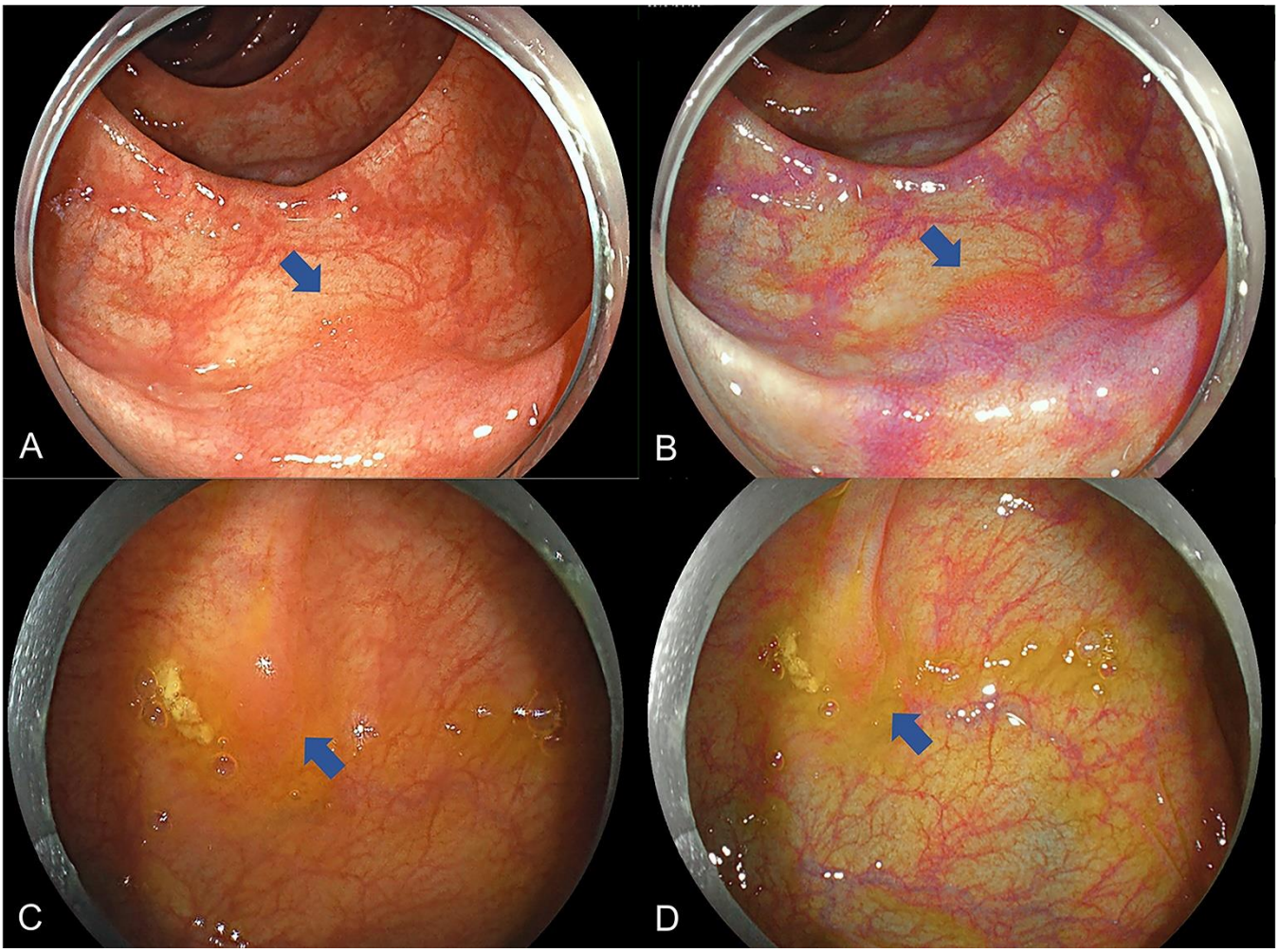

Figure 1

Table 1. Demographic characteristics

	LCI group (N = 349)	WLI group (N = 351)	*P* value
Age, mean ± SD, years	66.5 ± 10.8	65.8 ± 12.3	0.455
Sex, male, n (%)	218 (62.5)	222 (63.2)	0.830
Indication for colonoscopy, n (%)			
Screening	169 (48.4)	167 (47.6)	0.823
Surveillance	168 (48.1)	170 (48.4)	0.938
Symptoms	12 (3.5)	14 (4.0)	0.700
Constipation, n (%)	62 (17.8)	55 (15.7)	0.457
Previous colonoscopic therapy, n (%)	155 (44.4)	162 (46.2)	0.644
BBPS score, mean ± SD	8.3 ± 1.1	8.4 ± 1.0	0.206
Antispasmodic drug, n (%)	219 (62.8)	217 (61.8)	0.800
1st insertion time, mean ± SD, second	371 ± 170	375 ± 194	0.788
2nd insertion time, mean ± SD, second	244 ± 139	253 ± 150	0.441
1st withdrawal time, mean ± SD, second	367 ± 39	369 ± 33	0.479
2nd withdrawal time, mean ± SD, second	363 ± 22	359 ± 30	0.069

LCI, linked color imaging; WLI, white light imaging; BBPS, Boston Bowel Preparation Scale; SD, standard deviation

Table 2. Tandem colonoscopy findings of LCI and WLI groups

First colonoscopy	LCI group (N = 349)	WLI group (N = 351)	*P* value	RR/MD (95% CI)
Patients with polyps, % (n)	75.6 (264)	70.2 (247)	0.116	1.08[a] (0.98 to 1.18)
Patients with adenomas, % (n)	69.6 (243)	63.2 (222)	0.074	1.10[a] (0.99 to 1.22)
Patients with advanced adenomas, % (n)	14.3 (50)	14.0 (49)	0.889	1.03[a] (0.71 to 1.48)
Number of polyps per patient, median (IQR)	2 (1-3)	1 (0-3)	0.114	-
mean ± SD	2.00 ± 1.96	1.80 ± 1.91	-	0.20[b] (-0.09 to 0.49)
Number of adenomas per patient, median (IQR)	1 (0-3)	1 (0-2)	0.132	-
mean ± SD	1.68 ± 1.76	1.52 ± 1.72	-	0.16[b] (-0.10 to 0.42)
Second colonoscopy				
Patients with polyps, % (n)	33.8 (118)	45.3 (159)	0.002	0.75[a] (0.62 to 0.90)
Patients with adenomas, % (n)	29.8 (104)	42.7 (150)	< 0.001	0.70[a] (0.57 to 0.85)
Patients with advanced adenomas, % (n)	0.86 (3)	1.71 (6)	0.318	0.50[a] (0.14 to 1.82)
Number of polyps per patient, median (IQR)	0 (0-1)	1 (0-1)	0.002	-
mean ± SD	0.52 ± 0.89	0.77 ± 1.19	-	-0.25[b] (-0.40 to -0.09)
Number of adenomas per patient, median (IQR)	0 (0-1)	0 (0-1)	< 0.001	-
mean ± SD	0.44 ± 0.79	0.69 ± 1.10	-	-0.25[b] (-0.39 to -0.11)

LCI, linked color imaging; WLI, white light imaging; IQR, interquartile range; SD, standard deviation; RR, risk ratio; MD, mean difference; CI, confidence interval

[a] The intervention effect for dichotomous outcomes was assessed by the RR.

[b] The intervention effect for continuous outcomes was assessed by the MD.

Table 3. Miss rate analysis of adenomas in the LCI and WLI groups

	Adenoma miss rate			
	LCI group, % (n/N)	WLI group, % (n/N)	*P* value	RR (95% CI)
All	20.6 (152/738)	31.1 (241/774)	< 0.001	0.66 (0.55 to 0.79)
Size (mm)				
≤ 5	23.4 (127/542)	35.1 (198/564)	< 0.001	0.67 (0.55 to 0.81)
6-9	15.8 (23/146)	25.3 (37/146)	0.043	0.62 (0.39 to 0.99)
≥ 10	4.0 (2/50)	9.4 (6/64)	0.265	0.43 (0.10 to 1.77)
Morphology				
Non-polypoid	25.6 (125/488)	37.9 (204/538)	< 0.001	0.68 (0.56 to 0.81)
Polypoid	10.8 (27/250)	15.7 (37/236)	0.112	0.69 (0.43 to 1.09)
Location				
Cecum	14.0 (7/50)	16.4 (10/61)	0.728	0.85 (0.34 to 2.03)
Ascending colon	16.6 (32/193)	25.7 (53/206)	0.026	0.64 (0.44 to 0.95)
Transverse colon	22.3 (47/211)	32.5 (68/209)	0.018	0.69 (0.50 to 0.94)
Descending colon	26.3 (20/76)	35.0 (28/80)	0.240	0.75 (0.46 to 1.21)
Sigmoid colon	26.8 (41/153)	39.3 (70/178)	0.019	0.68 (0.49 to 0.93)

Rectum	9.1 (5/55)	30.0 (12/40)	0.009	0.31 (0.12 to 0.75)

LCI, linked color imaging; WLI, white light imaging; RR, risk ratio; CI, confidence interval

Morphology was described according to the Paris classification[16]

Table 4. Mean visibility scores of adenomas classified by each observation

	First observation, mean ± SD			Second observation, mean ± SD			First vs second observation, *P* value	
	LCI group (LCI mode)	WLI group (WLI mode)	*P* value	LCI group (WLI mode)	WLI group (WLI mode)	*P* value	LCI group	WLI group
All	3.31 ± 0.70	3.20 ± 0.74	0.012	2.75 ± 0.63	2.78 ± 0.68	0.706	< 0.001	< .0001
Size (mm)								
≤ 5	3.21 ± 0.70	3.04 ± 0.70	< 0.001	2.76 ± 0.61	2.76 ± 0.68	0.988	< 0.001	< 0.001
6-9	3.52 ± 0.67	3.55 ± 0.67	0.718	2.70 ± 0.77	2.84 ± 0.65	0.443	< 0.001	< 0.001
≥ 10	3.65 ± 0.57	3.58 ± 0.72	0.599	2.50 ± 0.71	2.83 ± 0.98	0.680	0.007	0.025
Morphology								

Non-polypoid	3.11 ± 0.70	2.94 ± 0.71	0.002	2.72 ± 0.63	2.69 ± 0.67	0.764	< 0.001	< 0.001
Polypoid	3.63 ± 0.55	3.65 ± 0.53	0.789	2.93 ± 0.62	3.24 ± 0.60	0.042	< 0.001	< 0.001

LCI, linked color imaging; WLI, white light imaging; SD, standard deviation

Morphology was described according to the Paris classification[16]

Table 5. Detection of colorectal adenomas classified by bowel preparation scale

	Adenoma detection rate, % (n/N)				**Adenoma miss rate, % (n/N)**				**Visibility score, mean ± SD**			
	First observation				First → Second observation				First observation			
	LCI group	WLI group	*P* value	RR (95% CI)	LCI group	WLI group	*P* value	RR (95% CI)	LCI mode	WLI mode	*P* value	MD (95% CI)
Excellent preparation (BBPS score 9)	70.0 (159/227)	66.7 (150/225)	0.440	1.05 (0.93 to 1.19)	18.1 (78/430)	29.2 (143/489)	< 0.001	0.62 (0.49 to 0.79)	3.26 ± 0.72	3.23 ± 0.72	0.590	0.03 (-0.08 to 0.14)
Adequate preparation (BBPS score 6-8)	68.9 (84/122)	56.1 (71/126)	0.056	1.21 (1.00 to 1.45)	24.0 (74/308)	34.3 (98/286)	0.005	0.69 (0.54 to 0.89)	3.38 ± 0.65	3.15 ± 0.76	< 0.001	0.23 (0.10 to 0.37)

LCI, linked color imaging; WLI, white light imaging; BBPS, Boston Bowel Preparation Scale; SD, standard deviation; RR, risk ratio; MD, mean difference; CI, confidence interval