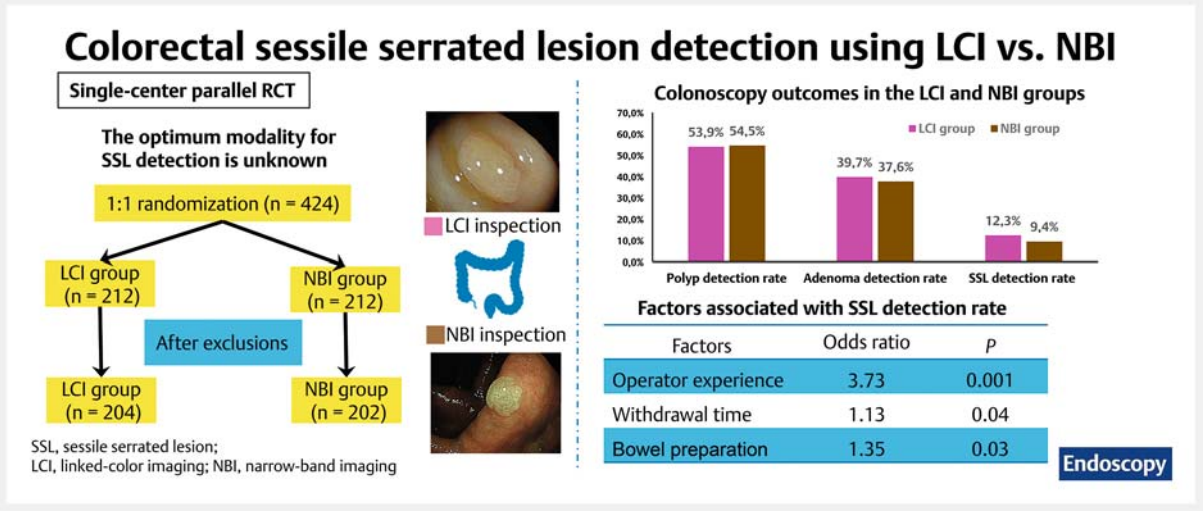
Colorectal sessile serrated lesion detection using linked-color imaging versus narrow-band imaging: a parallel randomized controlled trial

GRAPHICAL ABSTRACT



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submitted 3.8.2022
accepted after revision 8.12.2022
accepted manuscript online 9.12.2022
published online 22.02.2023

Bibliography
Endoscopy 2023; 55: 546–554
DOI 10.1055/a-1995-2685
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Supplementary material
Supplementary material is available under https://doi.org/10.1055/a-1995-2685

ABSTRACT

Background Previous studies have reported the effectiveness of narrow-band imaging (NBI) and linked-color imaging (LCI) in improving the detection of colorectal neoplasms. There has however been no direct comparison between LCI and NBI in the detection of colorectal sessile serrated lesions (SSLs). The present study aimed to compare the effectiveness of LCI and NBI in detecting colorectal SSLs.
Methods A prospective, parallel, randomized controlled trial was conducted. The participants were randomly assigned to the LCI or NBI arms. The primary end point was the SSL detection rate (SDR).
Results 406 patients were involved; 204 in the LCI arm and 202 in the NBI arm. The total polyp detection rate, adenoma detection rate, and SDR were 54.2%, 38.7%, and 10.8%, respectively. The SDR was not significantly different between the LCI and NBI arms (12.3% vs. 9.4%; $P=0.36$). The differences in the detection rate and the per-patient number of polyps, adenomas, diminutive lesions, and flat

lesions between LCI and NBI also were not statistically significant. Multivariate analysis showed that LCI and NBI were not independent factors associated with SDR, whereas Boston Bowel Preparation Scale score (odds ratio [OR] 1.35, 95 %CI 1.03–1.76; $P = 0.03$), withdrawal time (OR 1.13, 95 % CI 1.00–1.26; $P = 0.04$), and operator experience (OR 3.73, 95 %CI 1.67–8.32; $P = 0.001$) were independent factors associated with SDR.

Conclusions LCI and NBI are comparable for SSL detection, as well as for the detection of polyps and adenomas.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide [1]. Colonoscopy remains the most important tool in the detection and removal of the precursor lesions of CRC; however, there is a reported adenoma miss rate of about 20 %–30 % by conventional colonoscopy using white-light imaging (WLI) [2, 3]. In particular, sessile serrated lesions (SSLs) are more difficult to detect than conventional adenomas, because they are often flat, inconspicuous, and covered with mucus [4, 5]. It has been reported that SSLs may contribute to approximately 20 %–30 % of sporadic CRCs [4], and missed SSLs during colonoscopy may play an important role in the development of interval CRC [6]. These findings have underlined the importance of improving the detection efficacy for SSLs.

The developments in image-enhanced endoscopy technologies have allowed better diagnostic capability and improved identification of gastrointestinal lesions [7]. Among them, narrow-band imaging (NBI) is the most widely used modality, which exploits blue and green wavelengths to emphasize the capillary pattern and the surface of the mucosa, while linked-color imaging (LCI) is a novel technology that relies on wavelength optimization of three colors (red, green, and blue) to make the lesions appear fuller [8]. Previous studies have investigated the effectiveness of NBI or LCI in the detection of colorectal lesions in comparison with WLI, some of which have favored NBI or LCI as being superior to WLI [9, 10]. Our previous study suggested that LCI could significantly improve colorectal SSL detection compared with WLI [11]. There has however been no direct comparison between LCI and NBI for colorectal SSL detection. Whether LCI could serve as a more appropriate modality than NBI for colorectal SSL detection remains unclear.

Herein, we report the results of our prospective, parallel, randomized controlled trial (RCT) investigating the superiority between LCI and NBI for colorectal SSL detection. We hoped to provide reliable evidence to guide clinical practice in the future.

Methods

Study design

This was a single-center, prospective RCT with parallel arms of LCI and NBI colonoscopy conducted in the Digestive Endoscopy Center of the Shanghai Tenth People's Hospital in China. The study was conducted according to the Consolidated Standards of Reporting Trials, and was approved by the ethics committees of the Shanghai Tenth People's Hospital. Written informed consent was obtained from all participants. All authors had access to the data and approved the final manuscript.

Sample size calculation and randomization

The sample size calculation was performed using PASS software (version 15.0; NCSS, USA). According to a recent study that investigated LCI versus NBI for colorectal polyp detection, the serrated lesion detection rate was 22.1 % by LCI and 34.6 % by NBI [12]. The required sample size was calculated in an inequality test for two independent proportions using a two-sided Z test (unpooled), with a significance level of 0.05 and a statistical power of 80 %. As a result, 212 patients were needed in each group, allowing for a dropout rate of 5 %.

Eligible patients were randomly allocated to the NBI or LCI groups in a 1:1 ratio. Randomization was carried out using the sealed envelope method.

Patient enrollment

The indications for colonoscopy complied with current guidelines [13–15]. Generally, the indications included screening, diagnostic, and surveillance purposes when the patients were referred to the endoscopy center. After fulfilling the inclusion and exclusion criteria, a total of 424 participants were enrolled in the present study between June and October 2021. The inclusion criteria were: age between 35 and 75 years; no prior history of colonoscopy; agreement to participate in the trial and to provide signed informed consent. The exclusion criteria were: poor condition and unable to tolerate or cooperate with the examination; known inflammatory bowel disease, colorectal cancer or familial adenomatous polyposis; refractory constipation; anticoagulation or antiplatelet medication that could not be suspended; severe anemia, uncontrolled infection, or another high risk condition; pregnancy.

Bowel preparation

A split-dose regimen of high volume polyethylene glycol solution plus simethicone was normally taken by the patients for bowel preparation prior to the colonoscopy. Remedial bowel preparation with a further 1–3 liters of polyethylene glycol solution was suggested in patients with poor bowel preparation, and colonoscopy was performed afterwards. The quality of the bowel preparation was evaluated according to the Boston Bowel Preparation Scale (BBPS). Scores of <6, 6–7, and 8–9 were defined as “inadequate”, “good,” and “excellent” bowel preparation, respectively.

Colonoscopy procedures

The colonoscopy procedures were performed with high definition colonoscopes using a LASEREO 7000 or ELUXEO 7000 system (Fujifilm) in the LCI arm and an EVIS LUCERA ELITE 290 system (Olympus) in the NBI arm. Once cecal intubation had been confirmed, the endoscope was withdrawn and endoscopists inspected the mucosa under the specified mode: LCI or NBI. The same modality, LCI or NBI, was adopted in both the insertion and withdrawal phase.

The withdrawal procedures were at the discretion of the endoscopists. Cold snare resection was immediately performed for diminutive lesions (diameter ≤ 5 mm) and a limited number of lesions (usually < 5). Patients with larger lesions (diameter > 5 mm) or more than five lesions were recommended for hospitalization for scheduled endoscopic resection. All of the colonoscopies were performed by seven endoscopists, four of whom were experienced, having performed > 500 colonoscopies, and three of whom were non-experienced, having performed < 200 colonoscopies.

Histopathology

All resected specimens were fixed in 10 % formalin and the histopathological evaluation adhered to a standardized process. The assessments were conducted by two individual pathologists who were specialists in colorectal lesion diagnosis and blinded to the patient allocation. The diagnosis of SSLs complied with the criteria of the most recent World Health Organization guidelines [16]. By definition: one unequivocal architecturally distorted crypt was sufficient for the diagnosis of an SSL. Training for SSL diagnosis was also performed before initiation of the study. If there was doubt with regards to a lesion, a multidisciplinary discussion including endoscopists and pathologists was held to determine the final diagnosis.

End points and definitions

The primary end point was the SSL detection rate (SDR), defined as the proportion of colonoscopies with at least one SSL detected. Other end points included the polyp detection rate (PDR), adenoma detection rate (ADR), the number of polyps or adenomas per patient, the detection rate of diminutive (diameter ≤ 5 mm) or flat lesions, the number of diminutive (diameter ≤ 5 mm) or flat lesions per patient, the advanced ADR, SSL with dysplasia (SSLD) detection rate, and adenoma miss rate. The adenoma miss rate was defined as the proportion of patients with an adenoma detected during the treatment colonoscopy than was not identified during the first colonoscopy. The withdrawal time was defined as the total inspection time, excluding the mucosa rinsing, diagnostic, and therapeutic time.

Statistical analysis

Continuous variables were expressed as mean (SD) and analyzed using Student's *t* test. The comparison of categorical variables was conducted using the chi-squared test. Multivariate analysis was conducted using the stepwise logistic regression model for variable selection and independent factor identification. Statistical significance was defined as a two-sided *P* value ≤ 0.05. All statistical analyses were performed using SPSS software (version 23.0; SPSS Inc.).

Results

Study population and clinical characteristics

The flow diagram for patient selection is shown in Fig. 1s, see online-only Supplementary material. After patients with bowel obstruction due to advanced CRC or in whom the cecum was not reached for other reasons had been excluded, along with those who had no histology specimens either from biopsy or resection, a total of 406 patients were finally included, with 204 in the LCI arm and 202 in the NBI arm. The detailed clinical characteristics are presented in ▶ **Table 1**. There was no significant difference between the two arms in terms of age, sex, body mass index (BMI), indication for colonoscopy, family history, or operator experience.

Colonoscopy outcomes

The detailed colonoscopy outcomes are presented in ▶ **Table 2**. There were no significant differences in the intubation time, withdrawal time, or in bowel preparation between the two arms. The total PDR, ADR, and SDR were 54.2 %, 38.7 %, and 10.8 %, respectively. ▶ **Fig. 1** shows two cases of typical SSLs that were detected by LCI and NBI, respectively.

The SDR was numerically higher in the LCI arm when compared with that in the NBI arm; however, the difference was not statistically significant (12.3 % vs. 9.4 %; $P = 0.36$). Similarly, although LCI detected higher rates of diminutive lesions and flat lesions and larger per-patient numbers of these lesions than NBI did, none of the differences between the two modalities reached statistical significance. There were also no significant differences between the two arms in terms of PDR, ADR, SSLD detection rate, advanced adenoma detection rate, or the number of polyps or adenomas per patient.

Among the 74 patients who were hospitalized for a treatment colonoscopy, 19 had other adenomas detected during the treatment colonoscopy, resulting in a total adenoma miss rate of 25.7 %. The adenoma miss rate was numerically lower in the LCI arm than that in the NBI arm, but the difference was not significant (22.0 % vs. 30.3 %; $P = 0.41$).

Factors associated with the SDR

Univariate and multivariate analysis showed that neither LCI or NBI were independent factors associated with the SDR, whereas the BBPS (odds ratio [OR] 1.35, 95 %CI 1.03–1.76; $P = 0.03$), withdrawal time (OR 1.13, 95 %CI 1.00–1.26; $P = 0.04$), and operator experience (OR 3.73, 95 %CI 1.67–8.32; $P = 0.001$) were independent factors associated with the SDR (▶ **Table 3**).

Subgroup analysis

As shown in ▶ **Fig. 2**, the SDR was numerically higher by LCI than by NBI when the colonoscopies were performed by experienced operators (17.9 % [21/117] vs. 14.0 % [15/107]; $P = 0.42$), when the withdrawal time was ≥ 9 minutes (21.7 % [13/60] vs. 18.4 % [7/38]; $P = 0.70$), and with good, but not excellent, bowel

▶ **Table 1** Comparison of the clinical characteristics of the patients in the linked-color imaging (LCI) and narrow-band imaging (NBI) groups.

Variables	Total (n = 406)	LCI group (n = 204)	NBI group (n = 202)	*P* value
Age, years, mean (SD)	53.6 (11.1)	53.8 (11.7)	53.4 (10.5)	0.73
Sex, n (%)				0.85
▪ Male	173 (42.6)	86 (42.2)	87 (43.1)	
▪ Female	233 (57.4)	118 (57.8)	115 (56.9)	
BMI, mean ± SD	23.8 (3.1)	23.6 (3.0)	24.0 (3.1)	0.13
Indication for colonoscopy, n (%)				0.92
▪ Screening[1]	210 (51.7)	105 (51.5)	105 (52.0)	
▪ Diagnostics	196 (48.3)	99 (48.5)	97 (48.0)	
Family history, n (%)				0.37
▪ No or unknown	350 (86.2)	179 (87.7)	171 (84.7)	
▪ Yes	56 (13.8)	25 (12.3)	31 (15.3)	
Operator, n (%)				0.38
▪ Experienced	224 (55.2)	117 (57.4)	107 (53.0)	
▪ Non-experienced	182 (44.8)	87 (42.6)	95 (47.0)	

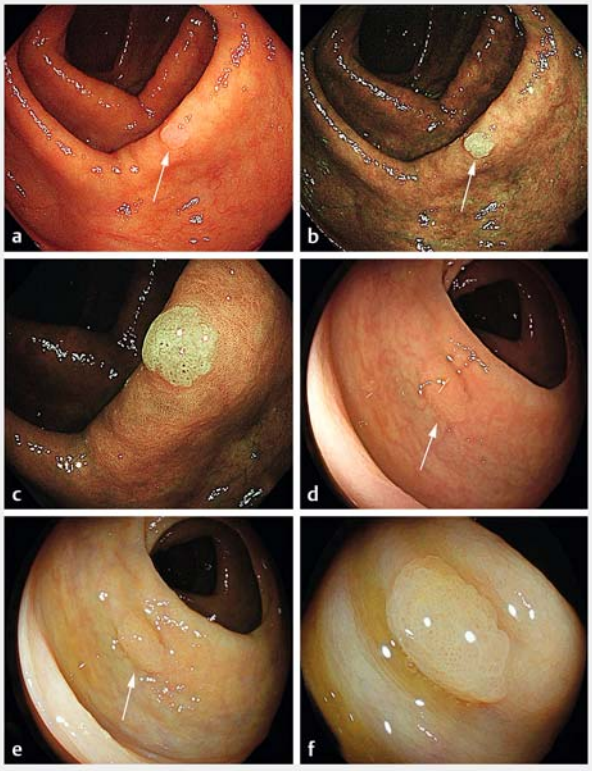
BMI, body mass index.
[1] The indication "screening" included both primary screening colonoscopy and programmed screening colonoscopy after positive fecal occult blood test or elevated serum tumor biomarkers (CEA, CA724, CA199, etc.) among patients without any symptoms.

▶ **Table 2** Comparison of colonoscopy outcomes between the linked-color imaging (LCI) and narrow-band imaging (NBI) groups.

Variables	Total	LCI group (n = 204)	NBI group (n = 202)	*P* value
Intubation time, mean (SD), minutes	4.5 (4.1)	4.6 (3.4)	4.3 (4.7)	0.53
Withdrawal time, mean (SD), minutes	7.7 (2.2)	7.9 (2.3)	7.6 (2.1)	0.18
BBPS, mean (SD)	6.5 (1.2)	6.5 (1.1)	6.5 (1.3)	0.84
Polyp detection rate	54.2 % (220/406)	53.9 % (110/204)	54.5 % (110/202)	0.91
Adenoma detection rate	38.7 % (157/406)	39.7 % (81/204)	37.6 % (76/202)	0.67
SSL detection rate	10.8 % (44/406)	12.3 % (25/204)	9.4 % (19/202)	0.36
SSL dysplasia detection rate	1.5 % (6/406)	1.5 % (3/204)	1.5 % (3/202)	> 0.99
Advanced adenoma detection rate	9.9 % (40/406)	10.3 % (21/204)	9.4 % (19/202)	0.76
Diminutive lesion detection rate	40.4 % (164/406)	43.6 % (89/204)	37.1 % (75/202)	0.18
Flat lesion detection rate	45.1 % (190/406)	46.6 % (95/204)	43.6 % (88/202)	0.54
Polyps per patient, n (SD)	1.7 (3.4)	1.8 (3.8)	1.6 (2.9)	0.52
Adenomas per patient, n (SD)	0.9 (2.1)	1.1 (2.4)	0.8 (1.7)	0.24
Diminutive lesions per patient, n (SD)	0.9 (2.0)	1.0 (2.2)	0.7 (1.8)	0.17
Flat lesions per patient, n (SD)	1.2 (2.6)	1.4 (3.0)	1.1 (2.2)	0.32
Additional adenoma detection rate during treatment colonoscopy	25.7 % (19/74)	22.0 % (9/41)	30.3 % (10/33)	0.41

BBPS, Boston bowel preparation scale; SSL, sessile serrated lesion.

preparation (12.8 % [16/125] vs. 8.3 % [10/121]; *P* = 0.25); however, none of the differences reached statistical significance. Additionally, the SDR was almost equivalent for LCI and NBI when the colonoscopies were performed by non-experienced operators (4.6 % [4/87] vs. 4.2 % [4/95]; *P* = 0.90), when the withdrawal time was < 9 minutes (8.3 % [12/144] vs. 7.3 % [12/



▶ **Fig. 1** Examples of typical sessile serrated lesions (SSLs) detected by: **a–c** narrow-band imaging (NBI); **d–f** linked-color imaging (LCI); as seen on: **a, d** white-light imaging; **b, e** image-enhanced distant view; **c, f** image-enhanced close observation.

164]; $P=0.74$), and with inadequate (5.6% [2/36] vs. 5.0% [2/40]; $P>0.99$) or excellent bowel preparation (16.3% [7/43] vs. 17.1% [7/41]; $P>0.99$). The optical visibility of the colorectal mucosa under LCI or NBI in patients with good or excellent bowel preparation is shown in ▶ **Fig. 3**.

Discussion

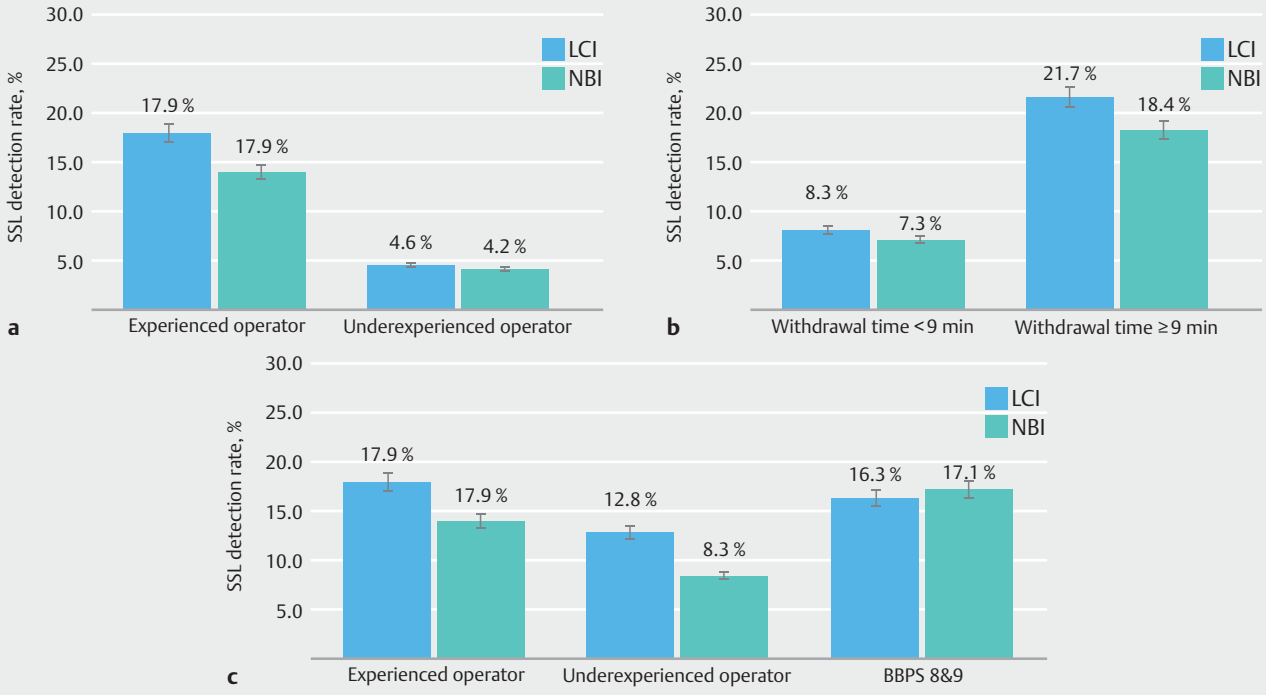
NBI has been investigated extensively for its potential in improving colorectal lesion detection; however, the results from previous studies have been contradictory. Some earlier RCTs and meta-analyses showed that NBI had no superiority over WLI in detecting colorectal neoplasms [17–20]. One major reason for these results could be the low resolution and dark images achieved with early-generation NBI systems. The new-generation NBI system has been modified to achieve high resolution images and increased brightness in the colonic lumen. Recent studies have demonstrated that new-generation NBI has improved the visibility and detection of polyps and adenomas when compared with WLI [21–24].

Furthermore, many studies have reported that NBI can significantly improve the detection of easily overlooked flat or diminutive lesions [25, 26]. In particular, several studies have added to the debate on the effectiveness of NBI in detecting colorectal serrated lesions. Rex et al. reported that new-generation NBI may increase the detection of serrated lesions in the proximal colon when compared with WLI [27]. Hazewinkel et al. reported that, in patients with serrated polyposis syndrome, the miss rates were 29% for WLI and 20% for NBI, respectively [28]. Recent meta-analyses also demonstrated that NBI detected significantly more proximal, flat, non-adenomatous (presumed serrated) lesions than WLI [21, 29]. Taken together, these studies indicated a potential advantage of new-generation NBI in detecting colorectal SSLs. Similarly, the effectiveness of LCI in

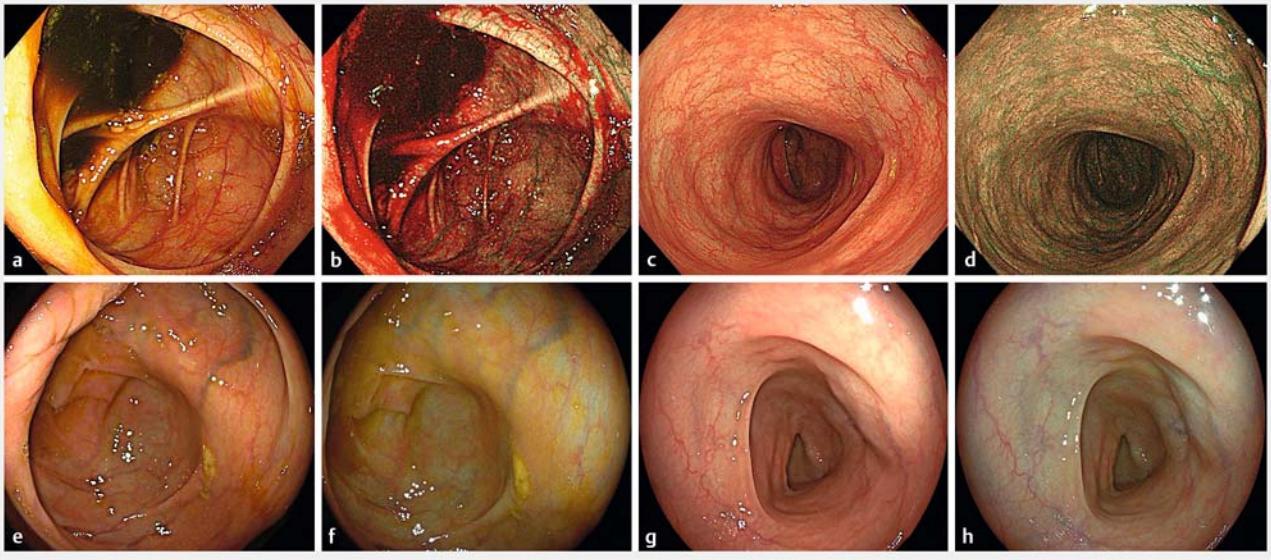
▶ **Table 3** Multivariate analysis for factors associated with the sessile serrated lesion (SSL) detection rate.

Factors	SSL detection rate			
	Univariate	Multivariate		
	P	Odds ratio	95%CI	*P*
Sex: male vs female	0.47	NA	NA	NA
Age, years	0.35	NA	NA	NA
Body mass index	0.44	NA	NA	NA
Indication: screening vs. diagnostic	0.47	NA	NA	NA
Family history: yes vs. no	0.18	NA	NA	NA
Operator: experienced vs. non-experienced	**<0.001**	3.73	1.67–8.32	**0.001**
Intubation time, minutes	0.22	NA	NA	NA
Withdrawal time, minutes	**0.02**	1.13	1.00–1.26	**0.04**
BBPS	**0.01**	1.35	1.03–1.76	**0.03**
Group: LCI vs. NBI	0.356	NA	NA	NA

BBPS, Boston bowel preparation scale; LCI, linked color imaging; NBI, narrow band imaging; NA, not applicable.



▶ **Fig. 2** Comparisons of sessile serrated lesion (SSL) detection rates between linked-color imaging (LCI) and narrow-band imaging (NBI) for: **a** experienced operators (left) and non-experienced operators (right); **b** for colonoscopies with a withdrawal time < 9 minutes (left) and ≥ 9 minutes (right); **c** colonoscopies with inadequate (left), good (middle), and excellent (right) bowel preparation according to the Boston bowel preparation scale (BBPS). Error bars show the 95 %CIs.



▶ **Fig. 3** The optical visibility of the colorectal mucosa under: **a,c,e,g** white-light imaging (WLI); **b,d** narrow-band imaging (NBI); and **f, h** linked-color imaging (LCI); in patients with: **a, b** good bowel preparation under WLI and NBI; **c, d** excellent bowel preparation under WLI and NBI; **e, f** good bowel preparation under WLI and LCI; **g, h** excellent bowel preparation under WLI and LCI.

detecting colorectal neoplasms has also been investigated extensively. Some studies, together with our previous study, have also suggested a certain superiority of LCI over WLI for SSL detection [10, 11, 30–34].

So far, only one study has reported a comparison between NBI and LCI for colorectal polyp detection [12]. The authors performed a prospective, randomized, tandem colonoscopy study and showed that NBI resulted in a higher PDR, ADR, and percentage of serrated lesions than LCI. Multivariable analysis indicated that NBI was an independent factor associated with the PDR. These results provided an early experience in LCI versus NBI for colorectal lesion detection; however, the involved study population was not equal in the two groups, with significantly more symptomatic patients in the LCI group than in the NBI group. The withdrawal time was also significantly longer in the NBI group than in the LCI group for both the first and second examination. Moreover, the tandem colonoscopies were performed using the same modality (NBI followed by NBI and LCI followed by LCI). The true benefit of tandem colonoscopies with the same modality remains unclear, while tandem colonoscopies using alternative modalities may be more beneficial. Additionally, a recent systematic analysis suggested that a tandem study is more likely to yield positive results than a parallel trial, indicating a higher likelihood of bias in tandem studies [35]. Therefore, it was suggested the results of tandem studies should be accepted only when validated by parallel trials. Finally, the serrated lesions in this study included all three classifications of serrated lesions (traditional serrated adenomas, SSLs, and hyperplastic polyps), without attention being dedicated to SSLs. Whether LCI or NBI performs better for SSL detection and is worth widespread recommendation remains unclear, pending a large-scale parallel trial in an equal average-risk patient population.

In the present study, we performed the first prospective parallel RCT to compare LCI with NBI for the detection of colorectal SSLs among an average-risk population. The LCI and NBI systems used were both the latest generation, which had high resolution images and improved brightness. The baseline clinical characteristics and colonoscopy-related variables showed no significant differences between the two arms. Our main findings indicated no significant difference in the SDR between LCI and NBI. The differences in the detection rate and the per-patient numbers of polyps, adenomas, diminutive lesions, and flat lesions between LCI and NBI were also not statistically significant. Given the fact that existing evidence has suggested the superiority of both LCI and NBI over WLI in colorectal lesion detection, our results were rational and consistent with the published literature.

It bears mentioning that, although not statistically significant, there was a slight tendency toward a higher SDR in the LCI arm than in the NBI arm, and this tendency seemed more pronounced when the colonoscopies were performed by experienced endoscopists, with prolonged withdrawal time (≥ 9 minutes), or in patients with suboptimal bowel preparation. Consistent with our previous study, the present study also revealed that endoscopists' experience and withdrawal time were independent factors associated with the SDR [11]. Familiarity with new techniques is important in performing an effective procedure. In our center, LCI and NBI have been routinely used in the evaluation of gastrointestinal lesions; the experience in LCI and NBI for individual endoscopists accumulated correspondingly with the total colonoscopy volume. The withdrawal time of at least 9 minutes has also been reported to improve the ADR and SDR in previous studies [36, 37].

Interestingly, the present study revealed that the BBPS was also an independent factor associated with the SDR, which was inconsistent with the results of our previous study. This discrepancy may likely be attributed to the involvement of NBI in the present study. The importance of high quality bowel preparation in NBI has been proposed by abundant numbers of studies. A parallel RCT on NBI versus WLI found that, in patients with "good" bowel preparation, there was a statistically significant benefit of NBI over WLI for adenoma detection, whereas there was no difference between NBI and WLI when preparation was "fair" [38]. A recent meta-analysis of RCTs also showed NBI had a higher ADR than WLI, and this effect was greater when bowel preparation was optimal [22]. The residual liquids appear dark red under NBI and can significantly impair mucosal visualization and negate its benefits. In contrast, the color of residual liquids is less influential under LCI inspection. Therefore, the application of NBI in colorectal lesion detection may require more rigorous bowel preparation than LCI does.

Taken together, these results may imply a potential superiority of LCI over NBI for SSL detection in real-world situations where the bowel preparation in the majority of patients is just "good" but hardly "best", and when the endoscopists have sufficient experience of the technique in their own hands and perform the colonoscopy examination with an adequate inspection time.

There were several limitations of the present study. First, it was conducted in a single tertiary hospital, which may impact generalization of the results. Second, it is not possible to blind the endoscopists to the modality (LCI or NBI). Third, the colonoscopies were performed for both diagnostic and screening purposes. Therefore, these results should be properly interpreted with attention paid to potential differences from studies with only screening colonoscopies. Fourth, because we have previously reported a comparison between LCI and WLI for the detection of colorectal SSLs [11], and the effectiveness of NBI vs. WLI in colorectal SSL detection has also been reported previously [21, 27–29], we did not include another WLI arm in the present study. It was more practical to conduct a direct comparison between the different modalities rather than comparing them with WLI again. Finally, although we involved a large number of participants (n = 406), the sample size seemed insufficient in subgroup analyses based on the low prevalence of colorectal SSLs.

In conclusion, the present study is the first and to date the largest parallel RCT focusing on comparing LCI with NBI for the detection of SSLs. The results demonstrated that LCI is comparable to NBI for SSL detection, as well as for polyp and adenoma detection. Future multicenter RCTs with larger sample sizes are warranted to validate our results and to further elucidate the superiority of LCI and NBI among stratified patients.

Competing interests

The authors declare that they have no conflict of interest.

Funding

Shanghai Health Commission Scientific Research Project General Program201940082
Shanghai Health Commission Promotion Project for Advanced and Proper Technology2019SY050

Clinical trial

Trial Registration: Chinese Clinical Trial Registry (http://www.chictr.org/) | Registration number (trial ID): ChiCTR2100046071 | Type of study: Prospective, Parallel, Randomized, Controlled Trial

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