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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Claudio Luchini, MD, PhD, Associate Professor of Pathology, Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona 37134, Italy. claudio.luchini@univr.it

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Efficacy of image-enhanced endoscopy for colorectal adenoma detection: A multicenter, randomized trial

Zhi-Peng Qi, En-Pan Xu, Dong-Li He, Yan Wang, Bai-Sheng Chen, Xue-Si Dong, Qiang Shi, Shi-Lun Cai, Qi Guo, Ni Li, Xing Li, Hai-Yan Huang, Bing Li, Di Sun, Jian-Guang Xu, Zhang-Han Chen, Ayimukedisi Yalikong, Jin-Yi Liu, Zhen-Tao Lv, Jian-Min Xu, Ping-Hong Zhou, Yun-Shi Zhong

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Dong-Li He, Qi Guo, Endoscopy Center, Shanghai Xuhui Central Hospital, Shanghai 200030, China

Yan Wang, Endoscopy Center, Traditional Chinese Medical Hospital, Rongcheng 264300, Shandong Province, China

Bai-Sheng Chen, Department of Endoscopy Center, Xiamen Branch of Affiliated Zhongshan Hospital of Fudan University, Xiamen 361000, Fujian Province, China

Xue-Si Dong, Ni Li, Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100000, China

Xing Li, Department of Gastroenterology, Pingxiang People's Hospital, Pingxiang 337000, Jiangxi Province, China

Hai-Yan Huang, Department of Clinical Medicine, Xiaogang Hospital, Ningbo 315000, Zhejiang Province, China

Jian-Guang Xu, Endoscopy Center, Quzhou People's Hospital, Quzhou 324000, Zhejiang Province, China

Jian-Min Xu, Department of General Surgery, Zhongshan Hospital of Fudan University, Shanghai 200030, China

Corresponding author: Yun-Shi Zhong, MD, PhD, Doctor, Surgeon, Endoscopy Center, Zhongshan Hospital of Fudan University, No. 180 Fenglin Road, Shanghai 200030, China. zhong.yunshi@zs-hospital.sh.cn

Abstract

BACKGROUND

Improved adenoma detection at colonoscopy has decreased the risk of developing

colorectal cancer. However, whether image-enhanced endoscopy (IEE) further improves the adenoma detection rate (ADR) is controversial.

AIM

To compare IEE with white-light imaging (WLI) endoscopy for the detection and identification of colorectal adenoma.

METHODS

This was a multicenter, randomized, controlled trial. Participants were enrolled between September 2019 to April 2021 from 4 hospital in China. Patients were randomly assigned to an IEE group with WLI on entry and IEE on withdrawal (n = 2113) or a WLI group with WLI on both entry and withdrawal (n = 2098). The primary outcome was the ADR. The secondary endpoints were the polyp detection rate (PDR), adenomas per colonoscopy, adenomas per positive colonoscopy, and factors related to adenoma detection.

RESULTS

A total of 4211 patients (966 adenomas) were included in the analysis (mean age, 56.7 years, 47.1% male). There were 2113 patients (508 adenomas) in the IEE group and 2098 patients (458 adenomas) in the WLI group. The ADR in two group were not significantly different [24.0% *vs* 21.8%, 1.10, 95% confidence interval (CI): 0.99-1.23, P = 0.09]. The PDR was higher with IEE group (41.7%) than with WLI group (36.1%, 1.16, 95%CI: 1.07-1.25, P = 0.01). Differences in mean withdrawal time (7.90 ± 3.42 min *vs* 7.85 ± 3.47 min, P = 0.30) and adenomas per colonoscopy (0.33 ± 0.68 *vs* 0.28 ± 0.62, P = 0.06) were not significant. Subgroup analysis found that with narrow-band imaging (NBI), between-group differences in the ADR, were not significant (23.7% *vs* 21.8%, 1.09, 95%CI: 0.97-1.22, P = 0.15), but were greater with linked color imaging (30.9% *vs* 21.8%, 1.42, 95%CI: 1.04-1.93, P = 0.04). the second-generation NBI (2G-NBI) had an advantage of ADR than both WLI and the first-generation NBI (27.0% *vs* 21.8%, P = 0.01; 27.0% *vs* 21.2.0%, P = 0.01).

CONCLUSION

This prospective study confirmed that, among Chinese, IEE didn't increase the ADR compared with WLI, but 2G-NBI increase the ADR.

Key Words: Endoscopy; Image-enhanced endoscopy; Adenoma detection rate; White-light imaging; Narrow-band imaging

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Core Tip: This study is the biggest randomized controlled trial comparing image-enhanced endoscopy (IEE) with white-light imaging (WLI) over the world, providing the solid evidence. This study provides strong evidence that IEE do not increase adenoma detection rate (ADR) compared with WLI, but second-generation-narrow-band imaging increase the ADR. IEE improved the polyp detection rate without additional withdrawal time.

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INTRODUCTION

Colorectal cancer is relatively common worldwide, with over 1 million new cases and an estimated 550000 deaths reported in 2018[1]. The 5-year survival rate of advanced colorectal cancer is less than 40%, but detection at an early stage greatly improves the prognosis. Increasing the adenoma detection rate (ADR) by 1.0% can reduce the risk of colorectal cancer by 3.0%[2]. Colonoscopy is an ideal strategy for decreasing the prevalence of colorectal cancer by early detection and endoscopic resection of precancerous lesions. The current standard practice for detecting polyps and adenomas is endoscopy with white-light imaging (WLI), and it has a reported polyp/adenoma miss rate of 26%[3,4]. Given the need

for improved detection, image-enhanced endoscopy (IEE) was developed to overcome the limitations of conventional colonoscopy.

IEE includes narrow-band imaging (NBI), flexible spectral imaging color enhancement, linked color imaging (LCI), and i-Scan, which are continually evolving. IEE improves the visualization of mucosal microstructure and microvasculature and the identification of lesions compared with WLI[5]. In a multicenter, randomized, crossover trial comparing LCI and WLI in polyp detection, Min *et al*[6] reported that the polyp detection rate (PDR) of LCI was 8% higher than that of WLI. A meta-analysis found that the ADR of NBI was significantly higher than that of WLI in patients with the best bowel preparations[7]. However, some studies have reported that NBI did not increase ADR or PDR[8-10]. As the additional benefit of IEE is still controversial, we conducted a prospective, multicenter, randomized, controlled study named the Image-Enhanced Endoscopy in Colonoscopy Screening trail in 4 hospitals in China to compare the ADR of IEE and WLI during colonoscopies. The primary objective was to determine whether IEE detected significantly more adenomas than WLI in patients with elective screening, surveillance, or diagnostic colonoscopy.

MATERIALS AND METHODS

Methods

Trail design: This prospective, multicenter, randomized, controlled trial was conducted at 4 hospitals in China in following the ethical principles of Declaration of Helsinki (B2019-131R). The study was prepared following the Consolidated Standards of Reporting Trials statement for reporting randomized controlled trials (RCTs)[11], and was registered on the Chinese Clinical Trial Registry (ChiCTR19000-26026). This was a nonprofit study, and no funding was received or solicited from endoscopy equipment manufacturers. All authors had access to the study data and have reviewed and approved the final manuscript. The full trial protocol see supplement.

Trial participants: Consecutive eligible patients who were 18-80 years of age and scheduled to undergo colonoscopy were considered eligible for this trial. Patients without bowel preparation or poor bowel preparation indicated by a Boston Bowel Preparation Scale (BBPS) score < 6, or with untreated adenoma in previous examinations, familial polyposis, severe emphysema, interstitial pneumonia, or ischemic heart disease; and those who could not tolerate anesthesia and examination, and patients or their family members who could not understand the conditions and goals of this study were excluded. Eligible patients were informed by the endoscopists about the study aims, procedures, and potential risks. Written informed consent was obtained from all patients.

Randomization: Before colonoscopy withdrawal, eligible patients were randomly assigned 1:1 to the IEE group with WLI on entry and IEE on withdrawal or the WLI group with WLI on both entry and withdrawal. Patients were stratified by age to groups < 50 and ≥ 50 years of age. The investigators used a central customized system (https://uapkd.bioknow.net/#/) to generate random numbers for the group assignments for the eligible patients at each center. Then, the investigators will allocate the patients to different groups based on the results of the customized random system and each center will compete for entry.

Endoscopists and endoscopy equipment: The participating endoscopist at each study center had at least 5 years of work experience in colonoscopy and had rigorous IEE diagnostic training. The endoscopy systems used in this study included CV-260, CV-290 (Olympus) or ELUXEO 7000 (Fujifilm) devices, and high definition colonoscopes was used for all procedures without any mucosal exposure devices.

Endoscopic procedures and histopathology: All patients performed bowel preparations following the local hospital protocol, and conscious sedation was administered according to the judgment of the anesthetist. The endoscope was advanced to the cecum under WLI. Cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve or by intubation of the ileum, and the bowel preparation was assessed by the BBPS score obtained during advancement of the endoscope to the cecum. Once cecal intubation was confirmed, the colonoscope was withdrawn to the anus by the assigned method, either IEE or WLI. Detected lesions were evaluated by the Paris morphological classification criteria and removed by the endoscopist[12]. The size and location of lesions were recorded. Withdrawal time were defined as the time from cecal intubation to extraction through the anus and were measured with a stopwatch, excluding the time used for washing of the colonic mucosa, suctioning of fluid, or performance of polypectomy, biopsy, or any other therapeutic maneuvers[13]. The data were recorded on standardized case report forms before being transferred to online electronic report forms (https://wa.zs-hospital.sh.cn/).

Histological samples were fixed in paraffin, processed by standard procedures, and examined by experienced pathologists who were blinded to the study procedures. Histological results were reported following the Vienna classification of gastrointestinal neoplasia[14]. Advanced adenoma was defined as

an adenoma ≥ 10 mm in diameter with any villous histology, high-grade dysplasia, or invasive carcinoma[15].

Outcomes: The primary endpoint was ADR, defined as the proportion of patients with at least one detected adenoma of any size[15]. The secondary endpoints were PDR, diminutive ADR, adenomas per colonoscopy, and factors related to adenoma detection. PDR was defined as the proportion of patients with at least one detected polyp. The diminutive ADR included detection of at least one adenoma that was < 5 mm. Screening colonoscopies included those for which there was no diagnostic or surveillance indication. Surveillance colonoscopies included those for which there was no diagnostic indication and were performed in a patient who had a colonoscopy within the previous 10 years or who had a history of polyps or colorectal cancer. Diagnostic colonoscopies were those performed in patients who had one or more symptoms before the procedure[16].

Sample size calculation

The sample size estimate was based on an ADR of 13.4% by WLI in Chinese populations in previous studies[16]. In our experience, the ADR was around 10% when WLI was used. An increase in the ADR of 3% with IEE was considered clinically significant. Participants were allocated to the experimental and control groups in equal numbers. The Power and Sample Size Calculation program (PASS 2008; NCSS, LLC; https://www.ncss.com), estimated a sample size of 2012 per group using chi-square or Mann-Whitney *U* tests for comparison, assuming a type I error rate of 5% with 80% power, and a single-sided $P < 0.05$ for statistical significance. We planned to include 4200 subjects. The sample size was calculated by Dr. Li and Dr. Dong.

Statistical analysis

Intention-to-treat (see Supplementary Tables 1-7) and per protocol analyses were both conducted. Differences were expressed as relative risk (RR) with 95% confidence intervals (CIs). Continuous variables were tested for normal distribution and reported as means and standard deviation. Normally distributed variables were compared with student's *t*-test and non-normally distributed variables were compared with the Mann-Whitney *U* test. Categorical variables were reported as frequencies and percentages (%), and compared with the χ^2 test or Fisher's exact test when applicable. The χ^2 test was used for the analysis of the primary outcome (ADR). RR and 95%CIs were calculated for dichotomous outcomes and for the ADR in the IEE group relative to the WLI group. Secondary dichotomous outcomes and subgroup outcomes were analyzed in the way as the primary outcome. For the safety analysis, the frequency of adverse events and adverse reactions were calculated and analyzed using χ^2 or Fisher exact tests. Details of adverse events and adverse reactions were recorded for deep analysis. The analysis was performed with SPSS v.18.0. (IBM Corp. Armonk, NY, United States). All reported *P*-values were two-sided, and those ≤ 0.05 were considered significant.

RESULTS

Study population

Figure 1 was a flow chart of the trial design and procedures. Between September 2019 and April 2021, 4372 consecutive patients were considered for inclusion, and 91 were excluded because they were < 18 or > 80 years of age or had previously unresected colorectal polyps (Figure 1). The remaining 4281 patients were randomized to the IEE (n = 2140) or WLI (n = 2141) groups. 70 patients failed cecal intubation because of poor bowel preparation, technical difficulties, or intolerance. A total of 4211 patients were included in the analysis, with 2113 in the IEE group and 2098 in the WLI group. No adverse events related to endoscopy occurred. The baseline characteristics of the patients in the two groups were similar (Table 1). The mean age, number of men, colorectal surgery history, and colonoscopy history of IEE and WLI were 56.7 ± 12.9 years and 56.8 ± 13.0 years, 1002 (47.7%) and 982 (46.8%), 149 (7.1%) and 134 (6.4%), 892 (42.2%) and 879 (41.9%), respectively. Between-group differences were not significant (all $P > 0.05$). The most common colonoscopy indication in both groups was diagnostic, 880(41.6%) patients in the IEE group and 876 (41.8%) in the WLI group ($P > 0.05$).

Primary outcome

The primary outcome results are shown in Table 2 and Figure 2. A total of 966 adenomas were detected in 4211 patients. 508 adenomas were found in 2113 IEE patients and 458 were found in 2098 WLI patients. The ADR were 24.0% in the IEE patients and 21.8% in the WLI patients (RR = 1.10, 95%CI: 0.99-1.23, $P > 0.05$). The mean withdrawal time were 7.90 ± 3.42 min in the IEE group and 7.85 ± 3.47 min in the WLI group ($P > 0.05$). Differences in advanced ADR and diminutive ADR in the two groups were not significant (all $P > 0.05$). Regardless of age (< 50 or ≥ 50 years of age), sex, and colonoscopy indication, differences in the ADR were not significant (all $P > 0.05$).

Table 1 Baseline characteristics

	IEE group (*n* = 2113)	WLI group (*n* = 2098)
Age (yr)	56.7 ± 12.9	56.8 ± 13.0
Male gender	1002 (47.7)	982 (46.8)
BMI (kg/m^2)	23.4 ± 3.2	23.5 ± 3.2
Comorbidities		
ASA1	1468 (69.5)	1510 (72.0)
ASA2	640 (30.3)	580 (27.6)
ASA3	5 (0.2)	8 (0.4)
Colorectal surgery history	149 (7.1)	134 (6.4)
Colonoscopy indication		
Diagnostic	880 (41.6)	876 (41.8)
Surveillance	613 (29.0)	601 (28.6)
Screening	620 (29.3)	621 (29.6)
Colonoscopy history	892 (42.2)	879 (41.9)

Dates are *n* or *n* (%). IEE: Image-enhanced endoscopy; WLI: White-light imaging endoscopy; BMI: Body mass index.

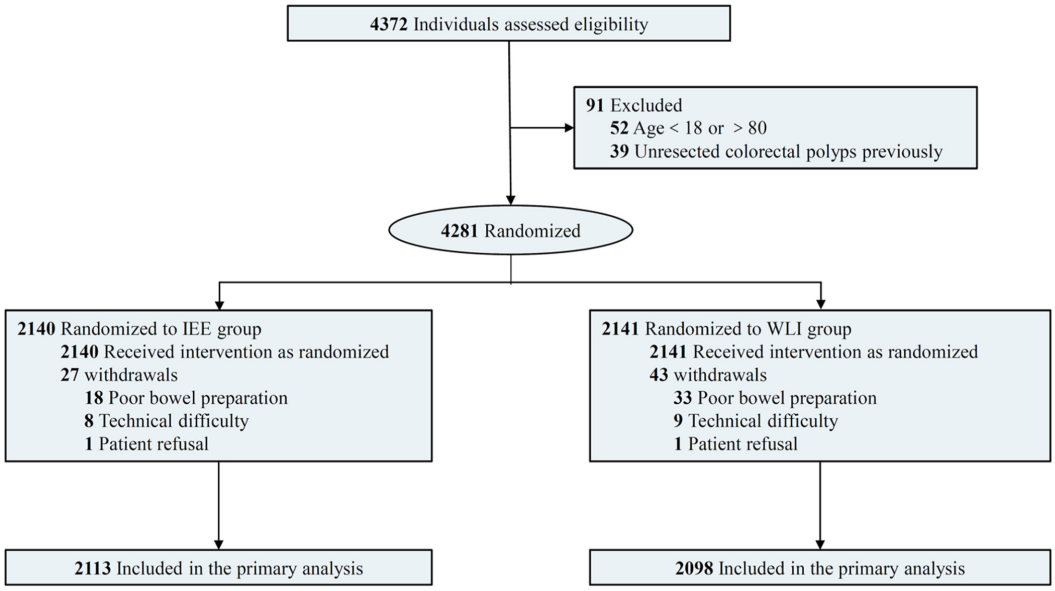

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Figure 1 Flow chart. IEE: Image-enhanced endoscopy; WLI: White-light imaging endoscopy.

Secondary outcomes

The secondary outcomes are shown in Table 3 and Figure 2. A total of 2907 polyps were detected in 4211 patients, including 1588 polyps in 2113 IEE patients and 1319 polyps in 2098 WLI patients. The PDR in the IEE group was significantly greater than that in the WLI group (41.7% *vs* 36.1%, RR = 1.16, 95%CI: 1.07-1.25, $P = 0.01$). Pathological evaluation found that adenomas were the most common polyps in both the IEE (43.5%) and WLI (44.7%) groups, and that the difference was not significant (RR = 0.97, 95%CI: 0.90-1.06, $P > 0.05$). Adenomas per colonoscopy were 0.33 ± 0.68 and 0.28 ± 0.62, respectively in the IEE and WLI groups ($P > 0.05$). There were also no significant differences in the size, morphology, pathology, or site of the adenoma polyps detected in both groups (all $P > 0.05$).

Subgroup analysis

The outcomes of the NBI and WLI groups are shown in Tables 4 and 5, Supplementary Table 8 and 9, and Figure 2. The ADR of the two groups were similar (23.7% *vs* 21.8%, RR = 1.09, 95%CI: 0.97-1.22, P =

Table 2 Overall adenoma detection rate in patients of the two group

	IEE group (*n* = 2113)	WLI group (*n* = 2098)	*P* value	Relative risk (95%CI)
ADR	508/2113 (24.0)	458/2098 (21.8)	0.09	1.10 (0.99-1.23)
Advanced ADR	127/2113 (6.0)	116/2098 (5.5)	0.50	1.09 (0.85-1.39)
Diminutive ADR	323/2113 (15.3)	286/2098 (13.6)	0.13	1.12 (0.97-1.30)
ADR in different ages				
< 50 yr	67/586 (11.4)	54/557 (9.7)	0.34	1.18 (0.84-1.66)
≥ 50 yr	441/1527 (28.9)	404/1541 (26.2)	0.10	1.10 (0.98-1.24)
ADR in different gender				
Male	288/1002 (28.7)	254/982 (25.9)	0.15	1.11 (0.96-1.28)
Female	220/1111 (19.8)	204/1116 (18.3)	0.36	1.08 (0.91-1.29)
ADR with different indications				
Diagnostic				
< 50 yr	26/270 (9.6)	23/256 (9.0)	0.80	1.07 (0.63-1.83)
≥ 50 yr	179/610 (29.3)	166/620 (26.8)	0.32	1.10 (0.92-1.31)
Surveillance				
< 50 yr	9/104 (8.7)	7/93 (7.5)	0.77	1.15 (0.45-2.97)
≥ 50 yr	138/509 (27.1)	126/508 (24.8)	0.40	1.09 (0.89-1.5)
Screening				
< 50 yr	32/212 (15.1)	24/208 (11.5)	0.28	1.31 (0.80-2.14)
≥ 50 yr	124/408 (30.4)	112/413 (27.1)	0.30	1.12 (0.90-1.39)
Withdrawal time	7.90 ± 3.42	7.85 ± 3.47	0.30	

Dates are *n* or *n* (%). ADR: Adenoma detection rate; IEE: Image-enhanced endoscopy; WLI: White light imaging; CI: Confidence interval.

0.15). The mean withdrawal time of the two groups were 7.90 ± 3.46 min and 7.85 ± 3.47 min ($P > 0.05$), and between-group differences in the values of other variables related to ADR were not significant. However, the second-generation NBI (2G-NBI) had an advantage of ADR than both WLI and first-generation NBI (1G-NBI) [27.0% *vs* 21.8%, RR = 1.24, 95%CI: 1.08-1.42, $P = 0.01$; 21.2% *vs* 27.0% (2G), RR = 0.78, 95%CI: 0.67-0.92, $P = 0.01$]. The mean withdrawal time of them was similar ($P > 0.05$). And the 2G-NBI was more suitable for small adenoma than WLI and 1G-NBI [17.1% *vs* 13.6%, RR = 1.26, 95%CI: 1.05-1.51, $P = 0.01$; 13.5% *vs* 17.1% (2G), RR = 0.79, 95%CI: 0.64-0.97, $P = 0.02$]. The PDR in the NBI group was significantly greater than that in the WLI group (41.6% *vs* 36.1%, RR = 1.15, 95%CI: 1.07-1.25, $P < 0.01$). There were no significant differences in the size, morphology, pathology, or site of the adenomas detected in the two groups (all $P > 0.05$). The PDR in the 2G-NBI group was significantly greater than that in both the WLI group (50.7% *vs* 36.1%, RR = 1.41, 95%CI: 1.29-1.53, $P = 0.01$), and the 1G-NBI group [34.7% *vs* 50.7% (2G), RR = 0.68, 95%CI: 0.62-0.76, $P = 0.01$].

As shown in Tables 4 and 5. The ADR was higher in the LCI than in the WLI group (30.9% *vs* 21.8%, RR = 1.42, 95%CI: 1.04-1.93, $P = 0.04$) and in the LCI *vs* the WLI group in screening patients < 50 years of age (47.1% *vs* 11.5%, RR = 4.08, 95%CI: 2.17-7.65, $P = 0.01$). The PDR were also not significantly different (44.3% *vs* 36.1%, RR = 1.23, 95%CI: 0.98-1.55, $P = 0.10$). In all treatment groups, the proportions of adenomas, hyperplastic polyps, and cancers was higher with LCI than with WLI (all $P < 0.05$), but the proportions of inflammatory polyps and chronic mucosal inflammation was higher in WLI group (both $P < 0.05$). The number of adenomas per colonoscopy in the LCI group was more than that of WLI (0.44 ± 0.87 *vs* 0.28 ± 0.62, $P = 0.03$) and there were no significant differences in the size, morphology, pathology, or site (all $P > 0.05$).

The outcomes of the NBI and LCI groups are shown in Tables 4 and 5. The ADR in each group were not significantly different (23.7% *vs* 30.9%, RR = 0.77, 95%CI: 0.56-1.04, $P = 0.10$), but the ADR in patient < 50 years of age was lower in the NBI group than in the LCI group (10.2% *vs* 25.0%, RR = 0.41, 95%CI: 0.24-0.71, $P = 0.01$). The PDR were also not significantly different (41.6% *vs* 44.3%, RR = 0.94, 95%CI: 0.75-1.18, $P = 0.60$). The proportions of adenomatous and hyperplastic polyps, and cancer were higher in with LCI compared with NBI (all $P < 0.05$), but differences in the proportions of inflammatory polyps and chronic mucosal inflammation were at the contrary (both $P < 0.05$). There were no significant

Table 3 All polyps analysis of both group

	IEE group (*n* = 2113)	WLI group (*n* = 2098)	*P* value	Relative risk (95%CI)
PDR	882/2113 (41.7)	757/2098 (36.1)	0.01	1.16 (1.07-1.25)
All polyps	1588	1319		
Inflammatory polyp	426 (26.8)	341 (25.9)	0.55	1.04 (0.92-1.17)
Hyperplastic polyp	179 (11.3)	150 (11.4)	0.93	0.99 (0.81-1.22)
Adenoma polyp	690 (43.5)	590 (44.7)	0.49	0.97 (0.90-1.06)
Sessile serrated adenoma	10 (0.6)	11 (0.8)	0.52	0.76 (0.32-1.77)
Chronic inflammation	262 (16.5)	211 (16.0)	0.71	1.03 (0.87-1.22)
Cancer	16 (1.0)	13 (1.0)	0.95	1.02 (0.49-2.12)
Others	5 (0.3)	3 (0.2)	0.74[1]	1.38 (0.33-5.78)
Adenoma per colonoscopy	0.33 ± 0.68	0.28 ± 0.62	0.06	
Adenoma polyp	690	590		
Size			0.44	
≤ 5 mm	338 (49.0)	294 (49.8)		0.98 (0.88-1.10)
6-9 mm	211 (30.6)	163 (27.6)		1.11 (0.93-1.32)
≥ 10 mm	141 (20.4)	133 (22.5)		0.91 (0.74-1.12)
Shape			0.39	
Pedunculated	72 (10.4)	76 (12.9)		0.81 (0.60-1.10)
Subpedunculated	186 (27.0)	154 (26.1)		1.03 (0.86-1.24)
Flat	432 (62.6)	360 (61.0)		1.03 (0.94-1.12)
Pathology			0.80	
Tubular adenoma	670 (97.1)	569 (96.4)		1.01 (0.99-1.03)
Tubulovillous adenoma	18 (2.6)	19 (3.2)		0.81 (0.43-1.53)
Villous adenoma	2 (0.3)	2 (0.3)		0.86 (0.12-6.05)
Site			0.50	
Left	258 (37.4)	236 (40.0)		0.94 (0.81-1.07)
Right	357 (51.7)	299 (50.7)		1.02 (0.92-1.14)
Rectum	75 (10.9)	55 (9.3)		1.17 (0.84-1.62)

[1]Using fisher exact test.

Others in image-enhanced endoscopy group: Dermatofibroma × 1, fibroepithelial polyp × 1, neuroendocrine tumor × 1, soft fibroma × 1, gland hyperplasia × 1. Others in white light imaging group: Neuroendocrine tumor × 1, lymphoid polyps × 1, inflammatory granulation tissue × 1. Dates are *n* or *n* (%). PDR: Polyp detection rate; IEE: Image-enhanced endoscopy; WLI: White light imaging; CI: Confidence interval.

differences in the size, morphology, pathology, or site of polyps detected by NBI and LCI (all $P > 0.05$).

DISCUSSION

IEE was developed to meet the need improve the ADR, but the superiority of IEE is controversial. This randomized trial compared the ADR achieved with IEE and WLI in a large population, which, to the best of our knowledge, largest endoscopy study in China even over the world.

In this study, IEE had a higher ADR than WLI, but the difference was not statistically significant (24.0% *vs* 21.8%, $P = 0.09$). The lack of difference may have resulted from the 54.3 percentage of adenomas detected by the 1G-NBI modality, which, in the subgroup analysis had an ADR similar to that of WLI (21.2% *vs* 21.8%, $P = 0.67$). The NBI generally required better bowel preparation, as residual debris severely impaired visualization of the colonic mucosa and dim light reduced the recognizability of adenoma, weakening its effect. It was consistent with previous literature reports. One meta-analysis

Table 4 Overall adenoma detection rate in patients of the subgroup

	NBI group (*n* = 2016)	LCI group (*n* = 97)	WLI group (*n* = 2098)	*P* value[1]	RR (95%CI)	*P* value[2]	RR (95%CI)	*P* value[3]	RR (95%CI)
ADR	478/2016 (23.7)	30/97 (30.9)	458/2098 (21.8)	0.15	1.09 (0.97-1.22)	0.04	1.42 (1.04-1.93)	0.10	0.77 (0.56-1.04)
Advanced ADR	122/2016 (6.1)	5/97 (5.2)	116/2098 (5.5)	0.47	1.10 (0.86-1.40)	0.87	0.93 (0.39-2.23)	0.72	1.17 (0.49-2.80)
Diminutive ADR	304/2016 (15.1)	19/97 (19.6)	286/2098 (13.6)	0.19	1.11 (0.95-1.28)	0.10	1.44 (0.95-2.18)	0.23	0.77 (0.51-1.17)
ADR in different ages									
< 50 yr	55/538 (10.2)	12/48 (25.0)	54/557 (9.7)	0.77	1.05 (0.74-1.51)	0.01	2.58 (1.49-4.48)	0.01	0.41 (0.24-0.71)
≥ 50 yr	423/1478 (28.6)	18/49 (36.7)	404/1541 (26.2)	0.14	1.09 (0.97-1.23)	0.10	1.40 (0.96-2.04)	0.22	0.78 (0.54-1.14)
ADR in different gender									
Male	270/953 (28.3)	18/49 (36.7)	254/982 (25.9)	0.22	1.10 (0.95-1.27)	0.09	1.42 (0.97-2.08)	0.21	0.77 (0.53-1.13)
Female	208/1063 (19.6)	12/48 (25.0)	204/1116 (18.3)	0.44	1.07 (0.90-1.27)	0.24	1.37 (0.83-2.27)	0.36	0.78 (0.47-1.30)
ADR with different indications									
Diagnostic									
< 50 yr	23/247 (9.3)	3/23 (13.0)	23/256 (9.0)	0.90	1.04 (0.60-1.80)	0.46[4]	1.45 (0.47-4.47)	0.47[4]	0.71 (0.23-2.20)
≥ 50 yr	171/590 (29.0)	8/20 (40.0)	166/620 (26.8)	0.39	1.08 (0.90-1.30)	0.19	1.49 (0.86-2.60)	0.29	0.73 (0.42-1.26)
Surveillance									
< 50 yr	8/96 (8.3)	1/8 (12.5)	7/93 (7.5)	0.84	1.11 (0.42-2.93)	0.50[4]	1.66 (0.23-11.87)	0.53[4]	0.67 (0.10-4.69)
≥ 50 yr	134/496 (27.0)	4/13 (30.8)	126/508 (24.8)	0.42	1.09 (0.88-1.34)	0.75[4]	1.24 (0.54-2.84)	0.76[4]	0.88 (0.38-2.01)
Screening									
< 50 yr	24/195 (12.3)	8/17 (47.1)	24/208 (11.5)	0.81	1.07 (0.63-1.81)	0.01	4.08 (2.17-7.65)	0.01[4]	0.26 (0.14-0.49)
≥ 50 yr	118/392 (30.1)	6/16 (37.5)	112/413 (27.1)	0.35	1.11 (0.89-1.38)	0.40	1.38 (0.72-2.65)	0.58	0.80 (0.42-1.54)
Withdrawal time	7.90 ± 3.46	7.82 ± 2.67	7.85 ± 3.47	0.47		0.02		0.05	

[1]The *P* value between narrow band imaging group and white light imaging group.
[2]The *P* value between linked color imaging group and white light imaging group.
[3]The *P* value between narrow band imaging group and linked color imaging group.
[4]Using fisher exact test.
Dates are *n* or *n* (%). ADR: Adenoma detection rate; RR: Relative risk; NBI: Narrow band imaging; WLI: White light imaging; LCI: Linked color imaging; CI: Confidence interval.

with nine RCTs and 2936 subjects comparing the ADR between 1G-NBI and WLE showed that ADR was similar on both group (36% *vs* 34%; *P* = 0.413)[17]; Another meta-analysis also show that 1G-NBI failed to express a better ADR compared with HD-WLE [odds ratio (OR) = 1.01, 95%CI: 0.74- 1.37][8]. However, 2G-NBI having been changed to obtain brighter images than 1G-NBI, even brighter than WLE, to improve ADR. In our subgroup analysis, 2G-NBI depicted a better ADR than WLE as previously reported. An RCT comparing 2G-NBI with WLE showed that the 2G-NBI could detect more adenomas per patient compared with WLE (2.0 *vs* 1.51, *P* = 0.031)[18]. One meta-analysis enrolling 11 RCTs, including 3 RCTs using 2G-NBI, showed 2G-NBI had a better ADR than WLE (OR = 1.28; 95%CI: 1.05-1.56, *P* = 0.02)[7]. The great number of 1G-NBI covered the advantage of 2G-NBI, leading to IEE failed to improve ADR. However, 2G-NBI had a better ADR showed by our subgroup analysis, and it can help improve the quality of colonoscopy.

Table 5 Subgroup analysis of all polyps

	NBI group (*n* = 2016)	LCI group (*n* = 97)	WLI group (*n* = 2098)	*P* value[1]	RR (95%CI)	*P* value[2]	RR (95%CI)	*P* value[3]	RR (95%CI)
PDR	839/2016 (41.6)	43/97 (44.3)	757/2098 (36.1)	0.01	1.15 (1.07-1.25)	0.10	1.23 (0.98-1.55)	0.60	0.94 (0.75-1.18)
All polyps	1519	69	1319						
Inflammatory polyp	421 (27.7)	5 (7.2)	341 (25.9)	0.26	1.07 (0.95-1.21)	0.01	0.28 (0.12-0.66)	0.01	3.83 (1.64-8.93)
Hyperplastic polyp	164 (10.8)	15 (21.7)	150 (11.4)	0.63	0.95 (0.77-1.17)	0.01	1.91 (1.19-3.07)	0.01	0.50 (0.31-0.80)
Adenoma polyp	647 (42.6)	43 (62.3)	590 (44.7)	0.25	0.95 (0.88-1.04)	0.01	1.39 (1.15-1.69)	0.01	0.68 (0.56-0.83)
Sessile serrated adenoma	10 (0.7)	0 (0)	11 (0.8)	0.59	0.79 (0.34-1.85)	1.00[4]		1.00[4]	
Chronic inflammation	259 (17.1)	3 (4.3)	211 (16.0)	0.45	1.07 (0.90-1.26)	0.01	0.27 (0.09-0.83)	0.01	3.92 (1.29-11.93)
Cancer	13 (0.9)	3 (4.3)	13 (1.0)	0.72	0.87 (0.40-1.87)	0.04[4]	4.41 (1.29-15.12)	0.03[4]	0.20 (0.06-0.68)
Others	5 (0.3)	0 (0)	3 (0.2)	0.73[4]	1.45 (0.35-6.04)	1.00[4]		1.00[4]	
Adenoma per colonoscopy	0.32 ± 0.67	0.44 ± 0.87	0.28 ± 0.62	0.11		0.03		0.10	
Adenoma polyp	647	43	590						
Size				0.56		0.22		0.33	
≤ 5 mm	315 (48.7)	23 (53.5)	294 (49.8)		0.98 (0.87-1.09)		1.07 (0.80-1.44)		0.91 (0.68-1.22)
6-9 mm	196 (30.3)	15 (34.9)	163 (27.6)		1.10 (0.92-1.31)		1.26 (0.82-1.94)		0.87 (0.57-1.33)
≥ 10 mm	136 (21.0)	5 (11.6)	133 (22.5)		0.93 (0.76-1.15)		0.52 (0.22-1.19)		1.81 (0.78-4.18)
Shape				0.43		0.79		1.00[4]	
Pedunculated	68 (10.5)	4 (9.3)	76 (12.9)		0.82 (0.60-1.11)		0.72 (0.28-1.88)		1.13 (0.43-2.95)
Subpedunculated	174 (26.9)	12 (27.9)	154 (26.1)		1.03 (0.86-1.24)		1.07 (0.65-1.76)		0.96 (0.59-1.58)
Flat	405 (62.6)	27 (62.8)	360 (61.0)		1.03 (0.94-1.12)		1.03 (0.81-1.31)		1.00 (0.79-1.26)
Pathology				0.90		0.68[4]		0.67	
Tubular adenoma	627 (96.9)	43 (100)	569 (96.4)		1.01 (0.98-1.03)				
Tubulovillous adenoma	18 (2.8)	0 (0)	19 (3.2)		0.86 (0.46-1.63)				
Villous adenoma	2 (0.3)	0 (0)	2 (0.3)		0.91 (0.13-6.45)				
Site				0.57		0.29[4]		0.31	
Left	246 (38.0)	12 (27.9)	236 (40.0)		0.95 (0.83-1.09)		0.70 (0.43-1.14		1.36 (0.83-2.23)
Right	330 (51.0)	27 (62.8)	299 (50.7)		1.01 (0.90-1.12)		1.24 (0.97-1.58)		0.81 (0.64-1.04)
Rectum	71 (11.0)	4 (9.3)	55 (9.3)		1.18 (0.84-1.64)		1.00 (0.38-2.62)		1.18 (0.45-3.08)

[1]The *P* value between narrow band imaging group and white light imaging group.

[2]The *P* value between linked color imaging group and white light imaging group.
[3]The *P* value between narrow band imaging group and linked color imaging group.
[4]Using fisher exact test.
Dates are *n* or *n* (%). Others in narrow band imaging group: Dermatofibroma × 1, fibroepithelial polyp × 1, neuroendocrine tumor × 1, soft fibroma × 1, gland hyperplasia × 1. Others in white light imaging group: Neuroendocrine tumor × 1, lymphoid polyps × 1, inflammatory granulation tissue × 1. PDR: Polyp detection rate; RR: Relative risk; NBI: Narrow band imaging; WLI: White light imaging; LCI: Linked color imaging; CI: Confidence interval.

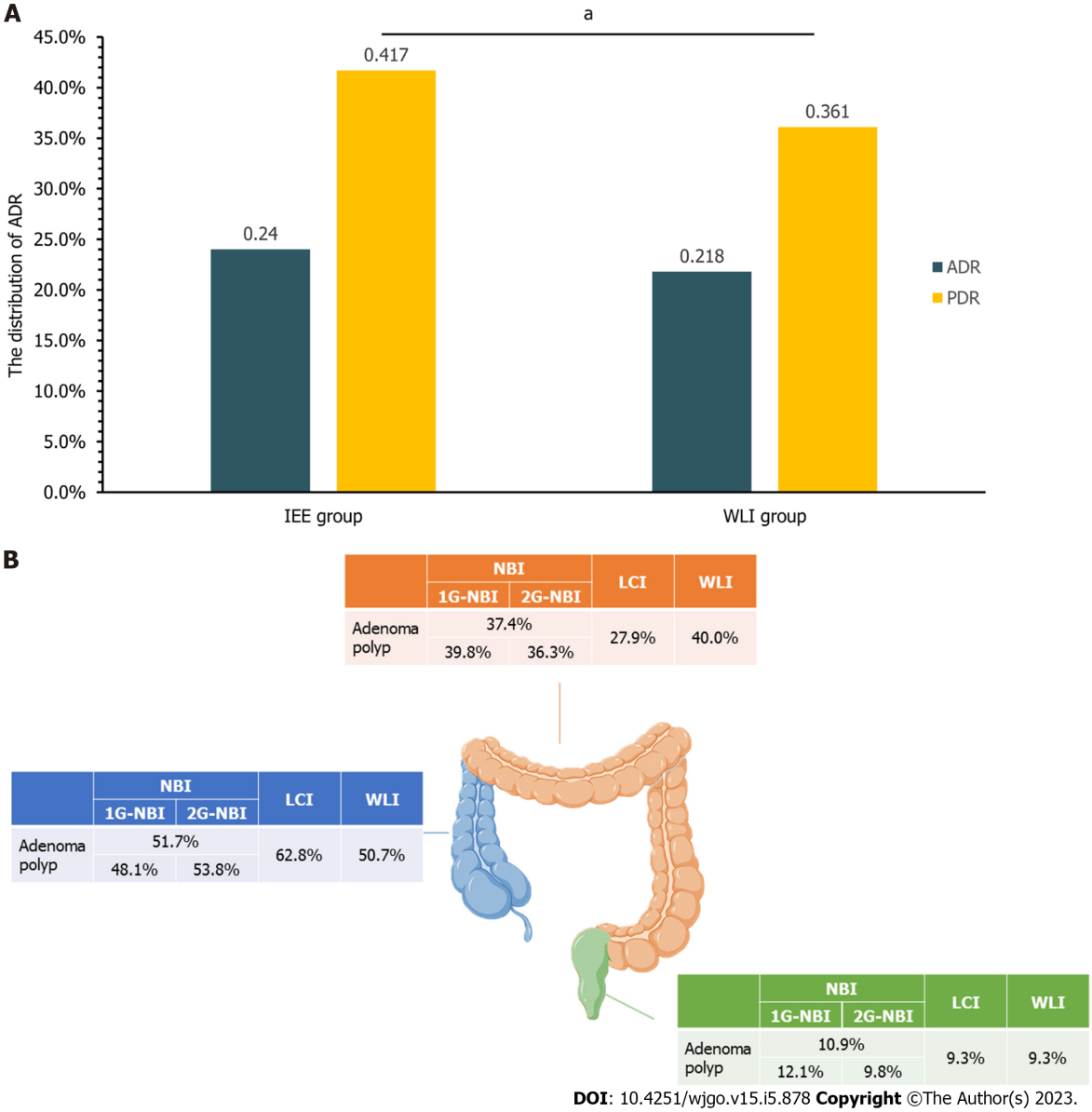

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Figure 2 The distribution of adenoma detection rate and adenoma. A: The adenoma detection rate and polyp detection rate of image-enhanced endoscopy and white-light imaging endoscopy group; B: The distribution of adenomas in the colorectum. [a]*P* < 0.05. IEE: Image-enhanced endoscopy; WLI: White-light imaging endoscopy; ADR: Adenoma detection rate; PDR: Polyp detection rate; NBI: Narrow-band imaging; LCI: Linked color imaging; 1G-NBI: First-generation narrow-band imaging.

The experience of endoscopists is known to affect the ADR[5]. Munroe *et al*[4] showed that the adenoma miss rate of trainees decreased as their experience increased and competency improved during tandem colonoscopy training. In another retrospective study involving 24943 procedures and 14 endoscopists, the number of procedures was independently associated with ADR. Endoscopists with > 1000 procedures had a higher ADR than those with < 200 procedures (OR = 1.51, 95%CI: 1.33-1.71, *P* = 0.001)[19]. All endoscopists in our study had at least 5 years of colonoscopy experience, and had a higher ADR (21.8%) than the 20% aspirational target recommended by the working group in the United Kingdom and Ireland[20], and most Asian endoscopists (ADR: 8%-20.3%)[16,21,22]. Operator experience might narrow the difference between WLI and IEE. Endoscopist performance may also be affected by the Hawthorne effect. Several studies reported that endoscopists paid more attention during

the procedure than usual when they knew they were being monitored[23,24]. The high ADR of our endoscopists might explain the smaller than expected differences between the ADR achieved with WLI and IEE.

Although the difference between the ADR observed with IEE and WLI was similar, the PDR of IEE was higher than that of WLI (41.7% *vs* 36.1%, $P = 0.01$), which meant that IEE had a higher sensitivity of polyp detection than WLI. The result is consistent with previous reports that IEE (NBI, i-SCAN, and autofluorescence) benefited polyp detection[25-27]. However, most small non-neoplastic lesions of < 5 mm diameter are benign and need not be removed. Therefore, it is important to distinguish neoplastic from non-neoplastic polyps before endoscopic biopsy to avoid additional treatment-related complications and costs. We were unable to accurately assess the specificity of IEE because of incomplete NBI and LCI classification records, but many studies have previously confirmed that IEE was better than WLI for the differentiation of neoplastic from non-neoplastic polyps[28-30]. A randomized study showed that NBI with magnification had a sensitivity of 90.5% and a specificity of 89.2% for the differentiation of neoplastic and non-neoplastic lesions, which was comparable to magnifying chromoendoscopy. Therefore, IEE detected more polyps and more accurately differentiated neoplastic from non-neoplastic polyps. We recommend that trainees use IEE to reduce messed diagnoses. Although NBI reduced brightness, it significantly improved the visual characterization of polyps. Therefore, senior, expert endoscopy experts can choose white light or IEE mode according to their preference, but for trainees, NBI or LCI mode are recommended to improve the ADR whenever it is difficult to identify lesions in the white light mode.

Subgroup analysis showed 2G-NBI not only had advantage of ADR, but detecting the small adenoma or polyp. Our result revealed that 2G-NBI depicted more small adenomas than WLI and 1G-NBI ($P < 0.05$). What's more, the proportion of inflammatory polyps, usually having a small size, was higher in 2G-NBI than others (all $P < 0.05$). Rex *et al*[31] recorded that 2G-NBI could demonstrate a better ADR with 5-10 mm than WLI ($P = 0.032$). Another RCT in 2015 also showed that 2G-NBI might have priority to adenoma with < 5 mm than WLI ($P = 0.039$)[18]. Combining our data, we recommend 2G-NBI as the major IEE modality.

Subgroup analysis also found a significant difference in the ADR achieved with LCI and WLI (30.9% *vs* 21.8%, $P = 0.04$) and the mean number of adenomas per colonoscopy (0.44 ± 0.87 *vs* 0.28 ± 0.62, $P = 0.03$). ADR and the mean number of adenomas per colonoscopy are both critical indicators reflecting the quality of colonoscopy[32], and improved performance might be clinically relevant because a highly quality colonoscopy has been associated with an increased ADR[15]. LCI, using an appropriate balance of combined narrow-band short-wavelength light and white light, achieves a bright, clear image, making up for the shortcomings of NBI[33]. Therefore, in clinical practice, when NBI or WLI is too dim to identify a polyp, LCI can be of assistance. Although our results are similar to those of previous studies[6,15], the limit of insufficient sample size in the LCI group could cause bias, which required a larger sample size to provide statistical significance for the ADR. The detection rate for sessile serrated lesions was low, reflecting a different prevalence in Chinese patients[16], and the detailed results was attached in Supplementary Table 10.

When we calculated the sample size, we assumed that the ADR was around 10% when WLI was used. That was far lower than the final result, but it does not impair the reliability of the study, and may even make it more reliable. If the ADR used to calculate the sample size was, then fewer than 4200 subjects were needed. Consequently, the result based on the protocol was reasonable and reliable.

This study strengths included its large sample (4211) which was the largest endoscopic study in China even over the word. In additional, it was the first large, multicenter endoscopic RCT in China, which provided strong evidence with Asian population for guideline development and provided reference for other populations. What's more, multi-center involved hospitals of different regions and levels in China making the data become more popularize. Furthermore, IEE and WLI procedures had similar withdrawal time, which improving the comparability of ADR between the two groups. Finally, we included two IEE modalities, NBI and LCI, providing a reference for follow-up studies.

The study limitations included a lack of double blinding because of the obvious image characteristics of IEE. Furthermore, the proficiency of different operators in different enhancement modes may have introduced selection bias[34]. Moreover, most patient re-examinations were performed after the study had ended, and the results were not included in the analysis. It was thus difficult to verify the missed diagnosis and misdiagnosis rates of IEE and WLI. In addition, there were objective differences in population distribution and medical conditions in various regions of our country, resulting in different sample sizes of groups enrolled in each center.

CONCLUSION

In summary, in this RCT performed in an expert setting, IEE did not increase the proportion of patients with at least one detected adenoma compared with WLI. However, the 2G-NBI depicted a better ADR than WLI.

ARTICLE HIGHLIGHTS

Research background

Adenoma detection rate (ADR) as main outcome quality parameter of colonoscopy is under controversial with the use of the image-enhanced endoscopy (IEE). Although there have some randomized controlled trials (RCTs) to compare different IEE with white-light imaging (WLI), the sample is limited and there is still lacking the RCT of IEE with Asian population.

Research motivation

To compare IEE with WLI for the detection and identification of colorectal adenoma and provide the solid outcomes.

Research objectives

To compare IEE with WLI endoscopy for the detection and identification of colorectal adenoma.

Research methods

We designed a prospective, multicenter, randomized, controlled trial to compere the ADR between the IEE group and WLI group.

Research results

The ADR in two group were not significantly different [24.0% *vs* 21.8%,1.10, 95% confidence interval (CI): 0.99-1.23, P = 0.09]. The polyp detection rate was higher with IEE group (41.7%) than with WLI group (36.1%, 1.16, 95%CI: 1.07-1.25, P = 0.01). Differences in mean withdrawal time (7.90 ± 3.42 min *vs* 7.85 ± 3.47 min, P = 0.30) and adenomas per colonoscopy (0.33 ± 0.68 *vs* 0.28 ± 0.62, P = 0.06) were not significant. Subgroup analysis found that with narrow-band imaging (NBI), between-group differences in the ADR, were not significant (23.7% *vs* 21.8%, 1.09, 95%CI: 0.97-1.22, P = 0.15), but were greater with linked color imaging (30.9% *vs* 21.8%, 1.42, 95%CI: 1.04-1.93, P = 0.04). The second-generation NBI (2G-NBI) had an advantage of ADR than both WLI and 1G-NBI (27.0% *vs* 21.8%, P = 0.01; 27.0% *vs* 21.2.0%, P = 0.01).

Research conclusions

This prospective study confirmed that, among Chinese, IEE didn't increase the ADR compared with WLI, but 2G-NBI increase the ADR. Colonoscopists with low ADR might consider using 2G-NBI for performance.

Research perspectives

The efficacy of various modes of IEE still needs to be verified by clinical research.

FOOTNOTES

Author contributions: Qi ZP, Xu EP and He DL contributed equally. Li N, Xu JM, Zhou PH, and Zhong YS contributed to the concept and design of the study and critical revision of the manuscript for important intellectual content; Qi ZP and Xu EP drafted the manuscript; Dong XS and Li N contributed to the statistical analysis; Zhang YS obtained funding; He DL, Xu JM, Zhou PH, and Zhong YS involved in the administrative, technical, or material support; Wang Y, Chen BS, Guo Q, and Li X contributed to the supervision of this manuscript; and all authors involved in the acquisition, analysis, or interpretation of data.

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Country/Territory of origin: China

ORCID number: Zhi-Peng Qi 0000-0003-0489-4163; En-Pan Xu 0000-0001-7341-3437; Dong-Li He 0000-0002-1825-9307; Shi-Lun Cai 0000-0002-5000-9658; Ni Li 0000-0003-1742-3803; Bing Li 0000-0002-8727-3591; Di Sun 0000-0003-1823-5759; Ayimukedisi Yalikong 0000-0002-7328-8354; Zhen-Tao Lv 0000-0003-4460-0166; Ping-Hong Zhou 0000-0002-5434-0540; Yun-Shi Zhong 0000-0001-8382-3747.

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