




ORIGINAL ARTICLE

# Chromoendoscopy with targeted biopsies is superior to white-light endoscopy for the long-term follow-up detection of dysplasia in ulcerative colitis patients: a multicenter randomized–controlled trial

Jian Wan <sup>1,†</sup>, Qin Zhang<sup>1,†</sup>, Shu-Hui Liang<sup>1</sup>, Jie Zhong<sup>2</sup>, Jing-Nan Li<sup>3</sup>, Zhi-Hua Ran<sup>4</sup>, Fa-Chao Zhi<sup>5</sup>, Xiao-Di Wang<sup>6</sup>, Xiao-Lan Zhang<sup>7</sup>, Zhong-Hui Wen<sup>8</sup>, Jian-Qiu Sheng<sup>9</sup>, Hua-Xiu Shi<sup>10</sup>, Qiao Mei<sup>11</sup> and Kai-Chun Wu<sup>1,\*</sup>

<sup>1</sup>State Key Laboratory of Cancer Biology, National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, Shaanxi, P. R. China; <sup>2</sup>Department of Gastroenterology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, P. R. China; <sup>3</sup>Department of Gastroenterology, Peking Union Medical College Hospital, Beijing, P. R. China; <sup>4</sup>Division of Gastroenterology and Hepatology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, P. R. China; <sup>5</sup>Department of Gastroenterology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, P. R. China; <sup>6</sup>Department of Gastroenterology, China-Japan Friendship Hospital, Beijing, P. R. China; <sup>7</sup>Department of Gastroenterology, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, P. R. China; <sup>8</sup>Department of Gastroenterology, West China Hospital, Sichuan University, Chengdu, Sichuan, P. R. China; <sup>9</sup>Department of Gastroenterology, PLA Army General Hospital, Beijing, P. R. China; <sup>10</sup>Department of Gastroenterology, Zhongshan Hospital Affiliated to Xiamen University, Xiamen University Institute of Digestive Disease, Xiamen, Fujian, P. R. China; <sup>11</sup>Department of Gastroenterology; the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, P. R. China

\*Corresponding author. Xijing Hospital of Digestive Diseases, 127 Changle West Road, Xi'an, Shaanxi, P. R. China, Tel: +86-29-8477-1502; Fax: +86-29-8253-9041; Email: kaicwu@fmmu.edu.cn

<sup>†</sup>These authors contributed equally to this work.

## Abstract

**Background:** Data from single-center experience or small sample-sized studies have shown that chromoendoscopy (CE) might be superior to white-light endoscopy (WLE) for dysplasia surveillance in ulcerative colitis (UC) patients. We performed a prospective randomized trial with a long-term follow-up to compare the detection rate of dysplasia among WLE with targeted biopsies (WLT), WLE with random biopsies (WLR), and dye-based CE with targeted biopsies (CET) in UC patients.

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**Methods:** Patients with long-standing UC were enrolled from 11 medical centers from March 2012 to December 2013 and randomized into three arms (WLT, WLR, and CET). Only high-definition endoscopy was used in all three groups. The patients were followed up by annual endoscopy with biopsies through December 2017.

**Results:** With a median follow-up time of 55 months, a total of 122 patients with 447 colonoscopies were finally analysed in the per-protocol set: WLT ( $n = 43$ ), WLR ( $n = 40$ ), and CET ( $n = 39$ ). A total of 34 dysplastic lesions were found in 29 colonoscopies of 21 patients. WLR and CET could identify more colonoscopies that diagnosed dysplasia than WLT (8.1% and 9.7% vs 1.9%;  $P = 0.014$  and  $0.004$ , respectively). WLR obtained more biopsied samples than WLT and CET ( $16.4 \pm 5.1$  vs  $4.3 \pm 1.4$  and  $4.3 \pm 1.4$ ; both  $P < 0.001$ ). During the second half of the follow-up (37 – 69 months), CET could identify more colonoscopies that diagnosed dysplasia than WLT (13.3% vs 1.6%,  $P = 0.015$ ) and showed a trend for increasing the detection rate compared with WLR (13.3% vs 4.9%,  $P = 0.107$ ).

**Conclusions:** For a better outcome of cancer/dysplasia surveillance in patients with long-standing UC, CET appeared to be more effective than WLT and less tedious than WLR. CET was found to be particularly useful when a long-term (>3 years) follow-up was conducted for dysplasia surveillance. The trial was registered on [www.chictr.org.cn](http://www.chictr.org.cn) (ChiCTR1900023689).

**Key words:** ulcerative colitis; dysplasia; chromoendoscopy; white-light endoscopy

## Introduction

Patients with long-standing ulcerative colitis (UC) are at an increased risk of developing colorectal cancer (CRC). The dysplastic epithelium is considered to be a precancerous lesion of UC-associated colorectal cancer (UC-CRC) [1]. The cumulative incidence of UC-CRC was 1% at 10 years, 3% at 20 years, and 7% at 30 years [2]. For UC patients, the risk factors for developing CRC are long-term disease duration, extensive colitis, presence of primary sclerosing cholangitis (PSC), and family history of CRC [3]. These results emphasized the importance of early detection of CRC in UC patients.

Several international guidelines have recommended the use of white-light endoscopy (WLE) with sequential four-quadrant random biopsies at every 10-cm interval in the colon for the surveillance of UC-related dysplasia and CRC [4–7]. However, this method has long been debated and is time-consuming and costly. Based on all available evidence, the recent Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) recommended chromoendoscopy (CE) as a preferred method for CRC surveillance in UC patients [8]. Although many guidelines and recommendations were presented, a notable proportion of physicians did not follow these recommendations in their daily clinical practice and obtained biopsies only from targeted lesions [9].

In China, the most common surveillance method in clinical practice was WLE with targeted biopsies (WLT) from visible lesions. Although the prevalence of UC-CRC was lower in China compared with that in Western countries, it has increased gradually in recent years [10–12]. Thus, it has become essential to identify the best monitoring methods for the Chinese population. To date, there have been no prospective studies comparing the dysplasia- and cancer-detection rates between WLE and CE in Chinese UC patients, although much research has been performed around the world [13–18]. Furthermore, almost none of the research was designed as long-term follow-up studies to compare CE with WLE in detecting dysplasia in UC patients. Therefore, we designed this prospective, multicenter, long-term follow-up randomized trial to compare the detection rates of dysplasia and CRC among high-definition WLE (HD-WLE) with targeted biopsies, HD-WLE with random biopsies, and high-definition CE (HD-CE) with targeted biopsies in Chinese UC patients.

## Patients and methods

### Study design

This prospective, multicenter randomized-controlled trial was designed by the IBD Cancer Project Team of the 12th Five-Year Plan in China in 2011. UC patients were prospectively recruited from March 2012 to December 2013 from 11 Class A tertiary comprehensive hospitals in China.

Randomization was performed before the colonoscopy by an independent coordinator who was blinded to the patients' disease. Using a computer-aided system, all patients enrolled were randomized by using random numbers in a 1:1:1 ratio to conventional targeted biopsies using HD-WLE (conventional method, WLT group), random biopsies using HD-WLE (WLR group), or targeted biopsies using HD-CE (CET group). The randomization list was stratified according to the individual centers.

The study was approved by the ethical committee of Xijing Hospital Affiliated to the Fourth Military Medical University in Xi'an, China (No. 20111208–5) on 8 December 2011 and the trial protocol was approved by the ethics committee of each hospital. All of the patients or their legal representatives signed the informed-consent form. The trial was registered on [www.chictr.org.cn](http://www.chictr.org.cn) (ChiCTR1900023689).

### Study subjects

The inclusion criteria of patients were age 18 years or above, a confirmed diagnosis of left-sided or extensive UC, and duration of the disease  $\geq 6$  years [5, 19]. Patients were excluded if they were pregnant or breastfeeding; diagnosed with severe UC; had an allergy to methylene blue dye; had a personal history of dysplasia or CRC; had concomitant diagnosis of toxic megacolon, gastrointestinal perforation, renal insufficiency, coagulation disorder, and serious heart and liver diseases; could not tolerate colonoscopy; or had inadequate bowel preparation (defined as >10% of the mucosal surface being obscured). Patients lost to follow-up after the initial endoscopy were also excluded from per-protocol set in the study but included in the full-analysis set.

### Colonoscopy procedures

All patients received standard bowel preparation (polyethylene glycol). All colonoscopies were performed by experienced

endoscopists who had extensive experience in cancer surveillance among UC patients and using HD-CE. The colonoscope was advanced into the ileocecal valve. On withdrawal, the colon was carefully examined from the cecum to the rectum and random or targeted biopsies were obtained. In the WLT group, targeted biopsies were obtained from visible lesions when using HD-WLE. In the WLR group, using HD-WLE, sequential four-quadrant random biopsies were obtained at 10-cm intervals of the colon from the disease segments defined by the endoscopist in addition to targeted biopsies from all visible lesions. In the CET group, each segmental part of the colon was sprayed with 0.1% methylene blue solution using a dye spray catheter on withdrawal of the endoscope. The excess dye was removed by suction and then targeted biopsies were obtained from visible lesions. The abnormal-appearing colonic mucosa was recorded according to the location (segment of the colon and distance from the anus in centimeters) and morphology. The Paris classification was used to divide the lesions into polypoid or non-polypoid. High-definition endoscopies (without any other image-enhancing techniques, such as Narrow-band imaging, i-SCAN, and Fujinon intelligent color enhancement) were used for all three groups. The endoscopists were blinded to the previous results. All endoscopic examinations were performed using Olympus CFH260AZI, Olympus CFH290I, or Fujinon EC-590WM.

Biopsy samples were processed using standard histology methods and evaluated by an experienced gastrointestinal pathologist who was blinded to the study in each hospital. According to the Vienna criteria for gastrointestinal epithelial neoplasia, biopsies were graded into the following categories: negative for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), or adenocarcinoma [20]. Indefinite for dysplasia was considered as negative for dysplasia. Biopsies showing any grade of dysplasia or biopsies suspicious for dysplasia were reviewed by a second or third experienced gastrointestinal pathologist to confirm the diagnosis.

### Surveillance of dysplasia

The surveillance interval for patients without dysplasia is 1–2 years according to the American Gastroenterological Association (AGA) guidelines [7]. When a patient is diagnosed with LGD, the optimal surveillance interval is recommended as 6 months. For a patient diagnosed with resectable HGD, the surveillance interval is 6 months after all HGD lesions are completely removed. Colectomy is recommended for patients with CRC or HGD that could not be removed completely.

### Outcomes

The primary endpoint of our study was the number of colonoscopies that diagnosed dysplasia/CRC in each group. The secondary endpoints were the number of patients with dysplasia/CRC, number of dysplasia/CRC lesions, number of biopsies, and endoscopic and histological characteristics of dysplasia/CRC lesions.

### Statistical analysis

The data were analysed using the SPSS 19.0 (IBM, Armonk, NY, USA) computer software for Windows. Quantitative variables were summarized as mean values and standard deviation or median and interquartile range (IQR), and the Student's *t*-test or Kruskal–Wallis *H* test was used to compare the variables in the three groups, as appropriate. Categorical variables were expressed as frequency and percentage (%) and the  $\chi^2$  test or

Fisher's exact test was used to compare the variables when appropriate. Partitions of the  $\chi^2$  test were used for pairwise comparisons in the three groups, as a *P*-value <0.0167 was considered as statistically significant. All *P*-values were two-sided and *P* < 0.05 was considered statistically significant.

Previous studies have shown that the detection rate of colonoscopies that diagnosed dysplasia in WLT was about 10% [8, 15, 21]. In this study, we assumed that the detection rate of CE was 2.5 times higher than that of WLT and that the average number of endoscopic examinations per patient was three. The calculated sample size for this study was 141 patients (47 per group) for two-sided *P* < 0.025 with 80% power.

## Results

From March 2012 to December 2013, a total of 154 consecutive patients with long-standing UC who gave their consent for study participation in 11 centers were recruited in this study. After screening, nine patients were excluded. The remaining 145 patients were randomly assigned in a 1:1:1 ratio to the WLT group (*n* = 50), WLR group (*n* = 47), and CET group (*n* = 48). Twelve patients had to be excluded from the full-analysis set (FAS) because of their refusal for biopsy. A total of 133 patients (WLT, *n* = 47; WLR, *n* = 42; CET, *n* = 44) with 458 colonoscopies were included in the FAS. Eleven patients were excluded from the per-protocol set (PPS) and the reasons for exclusion were as follows: loss to follow-up (*n* = 7), total colectomy (*n* = 3), and accidental death not related to the colonoscopy procedure (*n* = 1). The remaining 122 patients with 447 colonoscopies completed the study protocol (WLT, *n* = 43; WLR, *n* = 40; CET, *n* = 39) and were included in the PPS (Figure 1). The baseline characteristics of the three groups were similar (Table 1).

### Number of dysplastic lesions detected by colonoscopy

During a median follow-up of 55 months (IQR, 44 – 65 months), a total of 34 dysplastic lesions were found in 29 colonoscopies of 21 patients. No case of CRC was found in the three groups. Both in the FAS group and in the PPS group, WLR and CET could detect more dysplastic lesions than WLT, while there were no significant differences between the WLR and CET groups (Table 2). There was no significant difference in the use of colonoscopy equipment (Fujinon EC-590WM, Olympus CFH290I, and Olympus CFH260AZI) among the three groups (*P* = 0.316; Supplementary Table 1). None of the patients developed any adverse events requiring special treatments.

### Number of colonoscopies with a diagnosis of dysplasia

In the FAS, WLR and CET could identify more colonoscopies that diagnosed dysplasia than WLT (8.0% vs 1.9%, *P* = 0.013; 9.3% vs 1.9%, *P* = 0.004), while there was no significant difference between the WLR and CET groups (Figure 2A). In the subgroup analysis, there was no significant difference among the three groups in the number of colonoscopies that diagnosed dysplasia during the first 3 years (2.1% vs 10.1% vs 6.7%, *P* = 0.075). In the last 33 months (37 – 69 months), the detection rate of colonoscopies that diagnosed dysplasia in the CET group was higher than that in the WLT group (13.3% vs 1.6%, *P* = 0.015) and showed a trend for an increasing detection rate compared with WLR (13.3% vs 4.9%, *P* = 0.107; Figure 3). In the PPS, WLR and CET could identify more colonoscopies that diagnosed dysplasia than WLT (8.1% vs 1.9%, *P* = 0.014; 9.7% vs 1.9%, *P* = 0.004), while

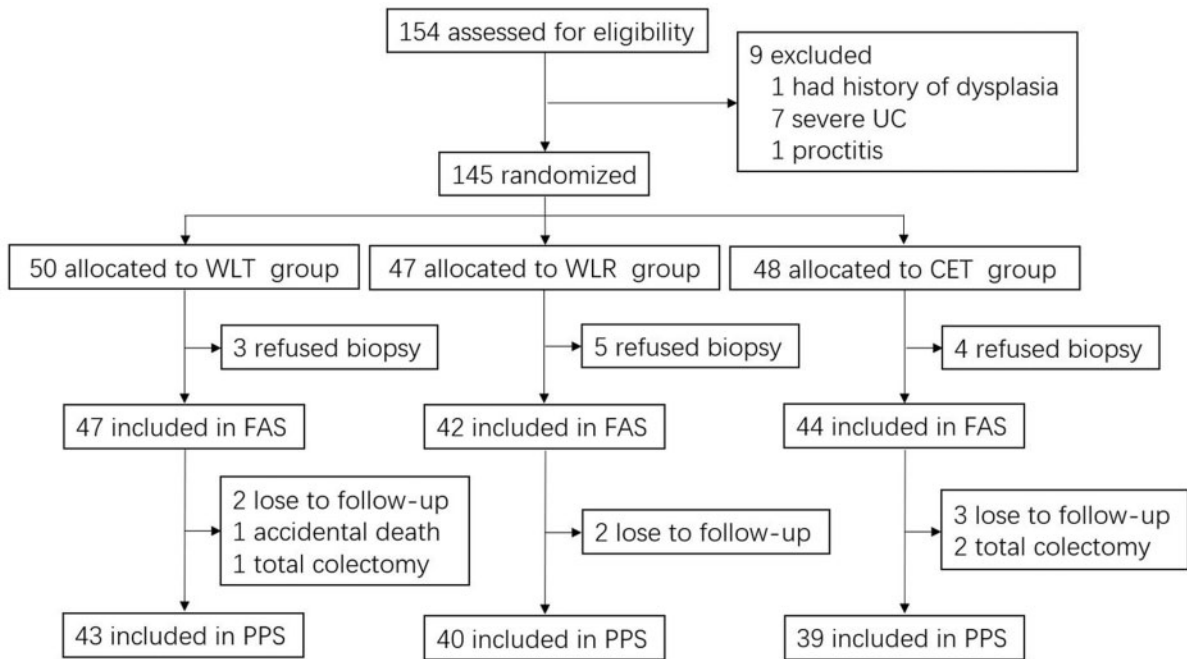


Figure 1. Flow diagram of patients recruited in the study.

UC, ulcerative colitis; WLT, white-light endoscopy with targeted biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies.

Table 1. Baseline characteristics of patients with ulcerative colitis (UC)

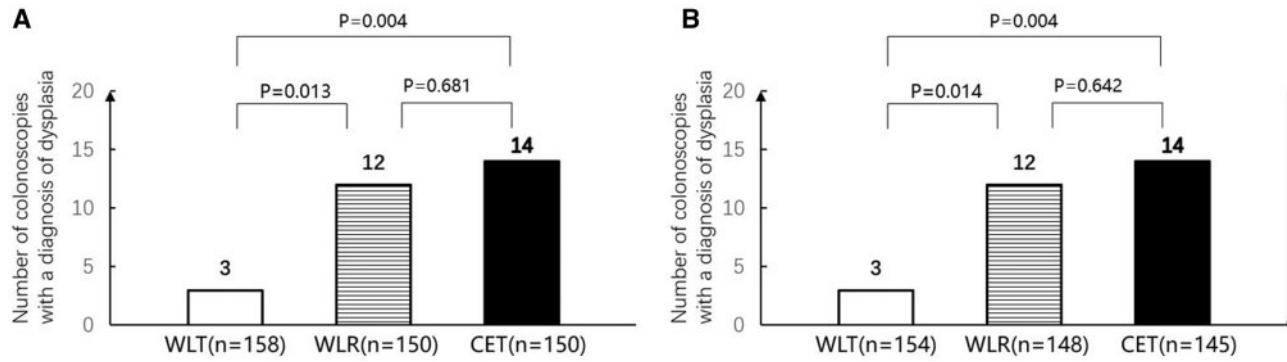
Characteristic	WLT (n=47)	WLR (n=42)	CET (n=44)	P-value
Age, years, mean $\pm$ SD	46.4 $\pm$ 12.0	44.6 $\pm$ 13.3	47.5 $\pm$ 10.8	0.547
Sex, n (%)				0.156
Male	22 (46.8)	28 (66.7)	23 (52.3)	
Female	25 (53.2)	14 (33.3)	21 (47.7)	
Age at UC onset, years, mean $\pm$ SD	36.7 $\pm$ 11.6	33.5 $\pm$ 11.1	37.1 $\pm$ 11.5	0.279
Duration of UC, n (%)				0.737
<10 years	27 (57.4)	27 (64.3)	25 (56.8)	
$\geq$ 10 years	20 (42.6)	15 (35.7)	19 (43.2)	
Extent of disease, n (%)				0.397
Left-side	27 (57.4)	26 (61.9)	21 (47.7)	
Extensive	20 (42.6)	16 (38.1)	23 (52.3)	
Primary sclerosing cholangitis, n (%)	1 (2.1)	0 (0.0)	0 (0.0)	1.000
Family history of CRC, n (%)	4 (8.5)	2 (4.8)	3 (6.8)	0.909

WLT, white-light endoscopy with targeted biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies; SD, standard deviation; CRC, colorectal cancer.

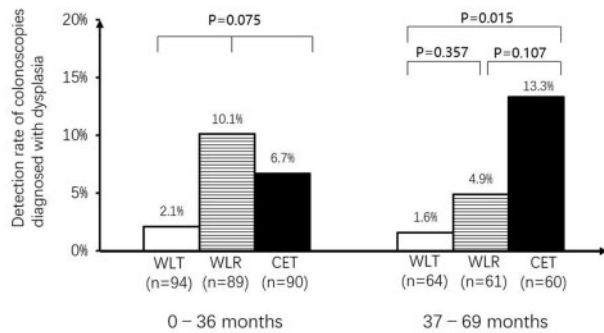
Table 2. Colonic dysplasia detected by colonoscopy among three groups

Characteristic	Full-analysis set				Per-protocol set			
	WLT	WLR	CET	P-value	WLT	WLR	CET	P-value
No. of patients	47	42	44	–	43	40	39	–
No. of colonoscopies	158	150	150	–	154	148	145	–
Follow-up time, months, median (IQR)	56 (41 – 65)	51 (40 – 64)	50 (39 – 65)	0.939	58 (47 – 66)	51 (43 – 64)	55 (44 – 66)	0.871
No. of dysplasia lesions detected by colonoscopy (%)	4 (2.5)	14 (9.3)	16 (10.7)	0.014	4 (2.6)	14 (9.5)	16 (11.0)	0.013
No. of colonoscopies with a diagnosis of dysplasia (%)	3 (1.9)	12 (8.0)	14 (9.3)	0.016	3 (1.9)	12 (8.1)	14 (9.7)	0.016
No. of patients with dysplasia (%)	2 (4.3)	10 (23.8)	9 (20.5)	0.024	2 (4.7)	10 (25.0)	9 (23.1)	0.025
No. of biopsied samples, mean $\pm$ SD	4.4 $\pm$ 1.4	16.5 $\pm$ 5.0	4.4 $\pm$ 3.5	< 0.001	4.4 $\pm$ 1.4	16.4 $\pm$ 5.1	4.3 $\pm$ 3.5	< 0.001

WLT, white-light endoscopy with targeted biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies; IQR, interquartile range; SD, standard deviation.



**Figure 2.** The number of colonoscopies diagnosed with dysplasia in the full-analysis set (A) and in the per-protocol set (B). WLT, white-light endoscopy with random biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies.



**Figure 3.** Detection rate of colonoscopies that diagnosed dysplasia in each group when the follow-up time was cut off by 36 months. WLT, white-light endoscopy with targeted biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies.

there were no significant differences between the WLR and CET groups (Figure 2B).

### Number of patients with dysplasia

In the FAS, WLR could detect more patients with dysplasia than WLT (23.8% vs 4.3%,  $P = 0.007$ ) and CET showed a trend for an increasing detection rate compared with WLT (20.5% vs 4.3%,  $P = 0.018$ ), while there were no significant differences between the WLR and CET groups (Figure 4A). In the PPS, WLR and CET could detect more patients with dysplasia than WLT (25.0% vs

4.7%,  $P = 0.008$ ; 23.1% vs 4.7%,  $P = 0.014$ ), while there was no significant difference between the WLR and CET groups (Figure 4B).

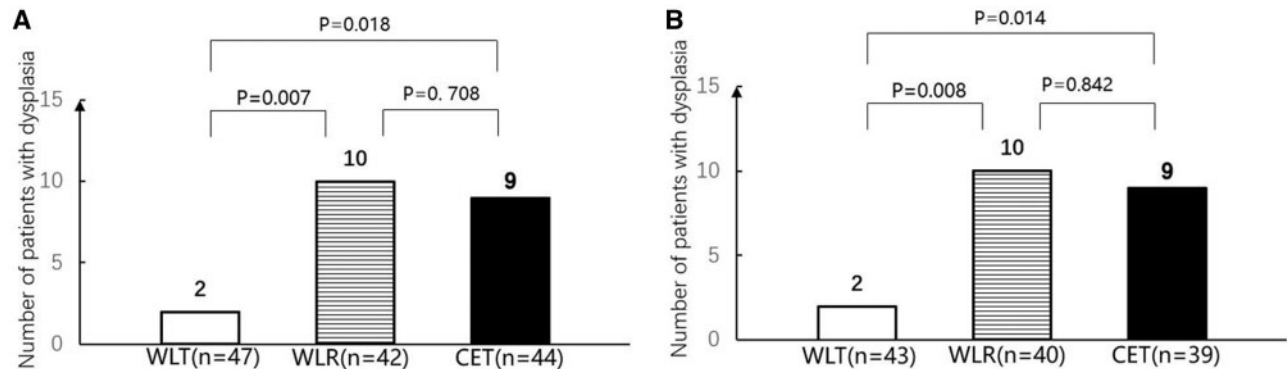
### Number of biopsied samples

Both in the FAS and in the PPS, the WLR group had more biopsied samples than the WLT and the CET groups, while there were no significant differences between the WLT and CET groups (Table 2).

### Characteristics of dysplastic lesions

The number of dysplastic lesions in the ascending colon or cecum, transverse colon, descending colon, sigmoid colon, and rectum was 4, 3, 3, 11, and 13, respectively. Among the 34 dysplastic lesions, 79.4% ( $n = 27$ ) showed LGD and 20.6% ( $n = 7$ ) showed HGD, and 52.9% ( $n = 18$ ) were non-polypoid and 47.1% ( $n = 16$ ) were polypoid (Table 3). All LGD lesions and were completely removed endoscopically. Among the seven HGD lesions, five were completely removed endoscopically and two were resected by a colectomy.

In the subgroup analysis of FAS, there was no significant difference in the detection of non-polypoid dysplastic lesions among the three groups during the first 3 years ( $P = 0.068$ ). In the last 33 months (37 – 69 months), more non-polypoid dysplastic lesions were detected in the CET group than in the WLT (9 vs 1,  $P = 0.007$ ) and WLR groups (9 vs 0,  $P = 0.001$ ) (Supplementary Table 2).



**Figure 4.** The number of patients with dysplasia in the full-analysis set (A) and in the per-protocol set (B). WLT, white-light endoscopy with targeted biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies.

**Table 3.** Endoscopic and histological characteristics of dysplastic lesions

Lesion	Total (n = 34)	WLT (n = 4)	WLR (n = 14)	CET (n = 16)
<b>Location</b>				
Ascending/cecum	4	0	0	4
Transverse	3	0	0	3
Descending	3	0	2	1
Sigmoid	11	2	5	4
Rectum	13	2	7	4
<b>Low-grade dysplasia</b>				
Polypoid	11	0	6	5
Non-polypoid	16	4	5	7
<b>High-grade dysplasia</b>				
Polypoid	7	0	3	4
Non-polypoid	5	0	3	2
Non-polypoid	2	0	0	2

WLT, white-light endoscopy with targeted biopsies; WLR, white-light endoscopy with random biopsies; CET, chromoendoscopy with targeted biopsies.

## Discussion

In our multicenter randomized trial, we demonstrated that CET and WLR had a similar dysplasia-detection rate and were superior to WLT. Despite the similar dysplasia-detection rate, more biopsies were obtained in the WLR group than in the CET group. In the second half of the follow-up period, CET could detect more non-polypoid dysplastic lesions than WLT and WLR.

The SCENIC meta-analysis revealed that significantly more patients with dysplasia were detected by using CE than HD-WLE [8]. Bessissow et al. [22] published a meta-analysis showing that CE could detect more patients with dysplasia than HD-WLE based on just one study, which Mohammed et al. [23] published in 2015 as an abstract. Carballal et al. [24] published a study which showed that the CE-incremental detection yield for dysplasia was 52.3% when compared with HD-WLE in real life. On the contrary, several studies found that CE did not increase the dysplasia-detection rate [25, 26]. Based on three studies [23, 25, 26], two meta-analyses showed that CE was not superior to HD-WLE [27, 28]. So, it still remains controversial whether CE can replace HD-WLE on the basis of these results. Moreover, almost all the patients in the above studies only underwent colonoscopy once without a long-term follow-up. Our study did not show an increased yield of CET when compared with WLR, but did find that, when obtaining targeted biopsies only, CE could detect more cases of dysplasia than HD-WLE. This highlights the importance of abandoning the real-life way of WLT because of its exceedingly low detection rate.

In our study, the detection rate of patients with dysplasia was slightly higher than that in previous studies (15.8% vs 11.4%), but the detection rate of colonoscopies that diagnosed dysplasia was extremely lower than that in previous studies (6.5% vs 11.5%) [8, 13]. The detection rate of dysplastic lesions in the WLT group in our study was much lower than that in the targeted group in Watanabe et al.'s study [18]. One possible reason may be that, in Watanabe et al.'s study, for lesions suspicious for neoplasia, they performed WLE and CE. If possible, they also performed magnifying endoscopy and determined the pit-pattern diagnosis of the lesions [29]. Another reason may be that most patients had disease duration of <10 years and had left-side colitis in our study and few patients had a concomitant diagnosis of PSC and a family history of CRC. Another more possible reason is that there were some studies that had already confirmed a lower incidence rate of UC-CRC in China when

compared with Western countries [10–12]. In our study, we still had a higher detection rate of patients with dysplasia. This may be due to the fact that all patients in our study had undergone colonoscopy more than once.

During the last 33 months of our study, we found that CET could detect more cases of dysplasia than WLT, and it seemed that CET had a trend for an increasing detection rate of dysplasia than WLR. With extension of the follow-up time, CET shows an advantage in detecting dysplasia. As already known, non-polypoid dysplasia is more likely to progress to CRC when compared with polypoid dysplasia [30]. During the second half of our study, CET detected 90% (9/10) of the non-polypoid lesions. The most important point that we wanted to emphasize was that all non-polypoid HGD lesions were detected by CET in our study. The two non-polypoid HGD lesions were detected in different intestinal segments of the same patient during two consecutive endoscopic examinations, which reminded us that patients with HGD should be switched to a more intensive surveillance scheme even when the lesions have been completely removed. In the meantime, CET is the best method to conduct surveillance.

No UC-CRC patient was identified in our long-term follow-up study. Even the patients who were diagnosed with dysplasia in the first few years of the follow-up period did not progress into UC-CRC. This may promote us to consider whether it is necessary to prolong the surveillance interval and reduce the frequency of colonoscopy in patients with long-standing UC.

The strengths of our study were that our clinical trial comparing HD-WLE and CE for dysplasia surveillance in China used a multicenter, randomized design and it was a long-term follow-up study. The study was designed as three arms to compare the real-life dysplastic surveillance method in China—the method that was suggested in the old and new guidelines. However, there are some limitations. First, the sample size was small. A larger sample-sized study is required to confirm our conclusion in the future. Second, we did not assess the withdrawal time from the cecum to the rectum, which may be a factor for the dysplasia-detection rate in UC patients. Third, 12 patients refused to undergo biopsy after they were randomized to a certain group. These patients withdrew their consent before the colonoscopy and did not undergo biopsy during the first colonoscopy. Additionally, random biopsies were obtained from the disease segments and not from the whole colon.

In conclusion, CET and WLR improved the detection rate of dysplasia when compared with WLT. More non-polypoid dysplastic lesions could be detected by obtaining fewer biopsy samples using CET; therefore, CET is the best method to conduct dysplasia surveillance in patients with long-standing UC.

## Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

## Authors' contributions

Guarantor of the article: K.C.W., K.C.W., J.Z., J.N.L., Z.H.R., F.C.Z., X.D.W., X.L.Z, Z.H.W., J.Q.S., H.X.S., and Q.M. designed the study; J.W., Q.Z., and S.H.L. acquired the data; J.W. and Q.Z. analysed the data; J.W. drafted the manuscript; K.C.W. revised the manuscript. All authors approved the final version of the manuscript.

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## Conflicts of interest

None declared.

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