A Randomized Trial Comparing High Definition Colonoscopy Alone With High Definition Dye Spraying and Electronic Virtual Chromoendoscopy for Detection of Colonic Neoplastic Lesions During IBD Surveillance Colonoscopy

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OBJECTIVES: **Dye spraying chromoendoscopy (DCE) is recommended for the detection of colonic neoplastic lesions in inflammatory bowel disease (IBD). The majority of neoplastic lesions are visible endoscopically and therefore targeted biopsies are appropriate for surveillance colonoscopy. To compare three different techniques for surveillance colonoscopy to detect colonic neoplastic lesions in IBD patients: high definition (HD), (DCE), or virtual chromoendoscopy (VCE) using iSCAN image enhanced colonoscopy.**

METHODS: **A randomized non-inferiority trial was conducted to determine the detection rates of neoplastic lesions in IBD patients with longstanding colitis. Patients with inactive disease were enrolled into three arms of the study. Endoscopic neoplastic lesions were classified by the Paris classification and Kudo pit pattern, then histologically classified by the Vienna classification.**

RESULTS: **A total of 270 patients (55% men; age range 20–77 years, median age 49 years) were assessed by HD (*n*=90), VCE (*n*=90), or DCE (*n*=90). Neoplastic lesion detection rates in the VCE arm was non-inferior to the DCE arm. HD was non-inferior to either DCE or VCE for detection of all neoplastic lesions. In the lesions detected, location at right colon and the Kudo pit pattern were predictive of neoplastic lesions (OR 6.52 (1.98–22.5 and OR 21.50 (8.65–60.10), respectively).**

CONCLUSIONS: **In this randomized trial, VCE or HD-WLE is not inferior to dye spraying colonoscopy for detection of colonic neoplastic lesions during surveillance colonoscopy. In fact, in this study HD-WLE alone was sufficient for detection of dysplasia, adenocarcinoma or all neoplastic lesions.**

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INTRODUCTION

Patients with longstanding inflammatory bowel disease (IBD) have an increased risk of developing colorectal cancer, initially estimated to be 18% at 30 years after diagnosis (1). Recent studies reported a decline in incidence of colorectal cancer, which could potentially relate to improved control of inflammation and implementation of dysplasia surveillance programs (2).

Surveillance colonoscopy techniques for detection of dysplasia are variable in clinical practice. Standard definition white light endoscopy (SD-WLE) with random mucosal biopsies has

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historically been the most common method of IBD surveillance colonoscopy, but it is time consuming, expensive, and often poorly adopted in clinical practice (3–6). To increase the detection of neoplastic lesions in patients with IBD, targeted biopsies may be the preferred surveillance method compared with random biopsies (7). Studies have shown that dye spraying chromoendoscopy (DCE) with targeted biopsies increases the detection rate of neoplastic lesions (8–10). The new and advanced endoscopic technologies have markedly improved the resolution of images compared with previous SD-WLE colonoscopies, so dysplasia has become easier to see from the greater image detail.

The recent SCENIC consensus considered DCE the most sensitive modality for dysplasia detection in IBD (6). For example, data to support DCE was provided by Marion *et al.* (11) who reported a follow-up evaluation of 68 patients from 2006 to 2011 with longstanding IBD. However, results from a large, retrospective study have shown that DCE did not increase dysplasia detection compared with WLE with targeted or random biopsies (12). A prior study using narrow-banding imaging also did not find a difference in detection of dysplasia in DCE compared with HD -WLE (13–15).

New chip technologies have markedly improved the resolution of image compared with previous standard definition colonoscopies. The HD iSCAN (Pentax, Tokyo, Japan) technique is a digital electronic chromoendoscopy method (16–18). We conducted a randomized study comparing three different techniques for surveillance colonoscopy to detect colonic neoplastic lesions in IBD patients: HD alone, DCE (with HD scopes), and VCE using iSCAN digital image enhanced HD colonoscopy. The study was powered for noninferiority to ascertain if the emerging standard of practice, which is DCE (6), can be replaced by other techniques such as VCE. We also used HD-WLE as a comparator to determine whether with improving technology chromoendoscopy is still required. We also aimed to identify the specific clinical and endoscopic features of colonic lesions that were predictors of dysplasia in IBD.

METHODS

This was a randomized prospective trial conducted at a single large tertiary referral center at the University of Calgary.

The Calgary Conjoint Health Services Research Ethics Board of the University of Calgary approved the study. The study was registered at ClinicalTrials.gov with identification number: NCT02098798.

IBD patients referred for surveillance colonoscopy were enrolled after they provided informed consent between March 2014 and March 2016.

The primary outcome of the study was to compare the detection rates of colonic neoplastic lesions in longstanding ulcerative colitis or Crohn's disease with HD+DCE versus HD+VCE. Secondary outcomes included comparison of detection rates of neoplastic lesions in longstanding ulcerative colitis or Crohn's disease with HD alone versus HD +DCE and HD alone versus HD+VCE.

A further study goal included characterisation of endoscopic features of neoplastic colonic lesions detected for prediction of dysplasia. These inclusion criteria were extensive or left sided ulcerative colitis, colonic Crohn's disease, or unclassified colitis involving at least one third of the colonic mucosa (i.e., ileocecal disease alone were not included and these patients did not undergo surveillance in our center), duration of the disease >8 years, or any duration in patients with concomitant diagnosis of primary sclerosing cholangitis, who could enter surveillance irrespective of disease duration. Clinical and endoscopic remission with Mayo total score <3, and a Mayo endoscopic subscore of 1 or 0 (overall Mayo endoscopic score and no segment of colon had Mayo endoscopic score >1), or Harvey–Bradshaw Index <5 and Simple Endoscopic Score of Crohn's disease of ≤4 (19,20).

Patients were excluded if they were pregnant, had active inflammatory disease, did not have optimal bowel preparation, had coagulopathy, had a known allergy to dye spray, or were unable to provide informed consent.

All patients enrolled were randomly allocated in blocks of four and assigned at a 1:1:1 ratio to undergo colonoscopy with high definition WLE (HD-WLE, group A), high definition DCE (HD-DCE, group B), or high definition VCE (HD-VCE, group C) using a computer generated allocation. The randomization was assigned before the colonoscopy by an independent coordinator blinded to the patients' history. The patients were randomized consecutively without stratification by presence or absence of primary sclerosing cholangitis, family history, or by gender. The different groups of surveillance patients according to surveillance methods are shown in **Table 1**. A flow diagram of the study is shown in **Figure 1**.

Endoscopic assessment

The colonoscopies were performed by a single operator (MI) experienced in dye, optical, and digital electronic virtual chromoendoscopy (VCE) and colonic lesions characterisation. This ensured uniform application of technique and uniform cognitive skills. The histology was assessed by XG, SU, and PM, who were blinded to the endoscopic reports. All the endoscopic procedures were performed using HD+ iSCAN Pentax EC-3490Fi with EPKi 7000 (Pentax) video processor. The system consists of three types of algorithms: Surface Enhancement iSCAN 1 (SE) for detection of abnormalities and lesions in the gastrointestinal tract, and Tone Enhancement and Contrast Enhancement iSCAN 2 and 3, for pattern and vascular characterisation. Each of these algorithm sets could be selected by pressing a pre-assigned button on the hand-piece of the scope (17,18).

Quality of bowel preparation was graded using the Ottawa bowel preparation scale defined as excellent, good, fair, poor, and inadequate (21). Only patients with excellent or good bowel preparation were included in the study. Endoscopic activity of the disease was assessed using the Mayo endoscopic subscore for ulcerative colitis (19) and Simple Endoscopic Score for Crohn's disease activity (22). The colonoscope was advanced to the cecum and the colonic mucosa was meticulously washed with the water jet pump. On withdrawal, each segment (cecum, ascending colon, transverse colon, descending-sigmoid, and rectum) was sequentially examined for lesions using HD endoscopic technique for group A, DCE using 0.04% methylene blue or 0.03% of indigo carmine for group

Table 1. Characteristics by surveillance group

Characteristic	HD (*n*=90)	DCE (*n*=90)	VCE (*n*=90)	*P* value
Male gender, *n* (%)	45 (50)	46 (51.1)	57 (63.3)	0.13
Age, years, mean±s.d.	48.14±13.73	49.92±11.96	48.03±14.6	0.21
Family history of colorectal cancer, *n* (%)	7 (7.8)	16 (17.8)	6 (6.7)	0.04
Personal history of colorectal dysplastic lesions, *n* (%)	20 (22.2)	20 (22.2)	20 (22.2)	1
Primary sclerosing cholangitis, *n* (%)	17 (18.9)	9 (10)	9 (10)	0.15
Ulcerative colitis/Crohn's disease/indeterminate colitis, *n* (%)	42/44/4	43/47/0	44/45/1	0.98/0.92/0.13
Pancolitis, *n* (%)	25 (61)	24 (54.5)	30 (70)	0.59
Left-sided colitis, *n* (%)	16 (39)	20 (45.5)	13 (30)	0.42
Colonic Crohn's disease, *n* (%)	21 (46.7)	26 (56.5)	29 (64.4)	0.42
Ileocolonic Crohn's disease, *n* (%)	24 (53.3)	20 (43.5)	16 (35.6)	0.37
Duration of IBD, years, mean±standard deviation	16.51±9.66	17.92±9.07	18.81±10.28	0.27
Treatment: mesalamine, *n* (%)	29 (32.2)	34 (37.8)	26 (28.9)	0.47
Treatment: immunosuppressants, *n* (%)	12 (13.3)	11 (12.2)	11 (12.2)	1
Treatment: biologics, *n* (%)	18 (20)	23 (25.6)	20 (22.2)	0.69
Treatment: combination treatment, *n* (%)	14 (15.6)	7 (7.8)	16 (17.8)	0.11
Treatment: no treatment, *n* (%)	16 (17.8)	14 (15.6)	14 (15.6)	0.93
Treatment: steroids, *n* (%)	2 (2.2)	2 (2.2)	1 (1.1)	1

DCE, dye spraying chromoendoscopy; HD, high definition; IBD, inflammatory bowel disease; VCE, virtual chromoendoscopy.

B, and VCE in the iSCAN 2 and 3 mode for group C. We detected and characterised lesions on withdrawal after dye spraying or after turning on iSCAN or with HD-WLE. We did not focus on detection at insertion of the colonoscope, a protocol similar to the Kiesslich *et al.* (8) study.

The time to withdraw from the cecum to the rectum was measured in each patient in all the different groups.

Biopsy protocol

Mucosal abnormalities were recorded in each group with regard to location (distance from the anus in centimetres), morphology (polypoid or non-polypoid), and size using the Paris classification (23). For each lesion, the mucosal pit pattern was characterised using the Kudo pit pattern (24). On withdrawal of the colonoscope, targeted biopsy specimens or endoscopic resection specimen from targeted suspicious areas of dysplasia (circumscribed lesions with irregular surface) were obtained. When the colonic lesion was endoscopically resectable, cautery snare polypectomy or endoscopic mucosal resection was performed, and a few histological samples were taken from the perilesional surrounding mucosa to rule out any multifocal dysplasia. Biopsies were taken to assess inflammatory activity.

Endoscopic characterisation of the colonic lesions

Endoscopic colonic lesions were classified by the Kudo pit pattern and the Paris classification (23,24), and histology was characterised by the Vienna classification (consensus amongst pathologists). Lesions were classified as polypoid and non-polypoid dysplastic lesions, adenocarcinoma, sessile serrated adenomas/, and tubular adenoma in non-colitic areas.

Histopathologic evaluation

Inflammatory activity in samples of each specimen container was classified into the following categories based on pathology: no inflammation, mild to moderate inflammation, or severe inflammation (25). Neoplastic changes were classified with the new modified Vienna classification into hyperplasia, low-grade dysplasia, high-grade dysplasia, or adenocarcinoma in the colitic areas (**Table 2**). Areas that were suspicious for neoplasia were sent to a second or third experienced pathologist for further review (26).

Statistical analysis

The study was powered for non-inferiority with a one-way threshold difference of rates of 10% in detection of all neoplastic lesions between DCE and VCE arms and assuming a detection rate of 20% for all neoplastic lesions (10% for dysplastic lesions and adenocarcinoma), requiring a sample size of 90 patients in each group for one-tail $P<0.025$ with 80% power. The assumption rates for detection of all neoplastic lesions was based on previous publications (6–8,11,27,28).

Quantitative variables were expressed as means±s.d.s. Categorical variables were expressed as total number and frequencies (%). Quantitative variables were analyzed using Fisher's Exact test. The data were analyzed for the most significant lesions (dysplasia polypoid or non-polypoid or adenocarcinoma) or for all neoplastic lesions (sessile serrated adenoma, tubular adenoma in non-colitic

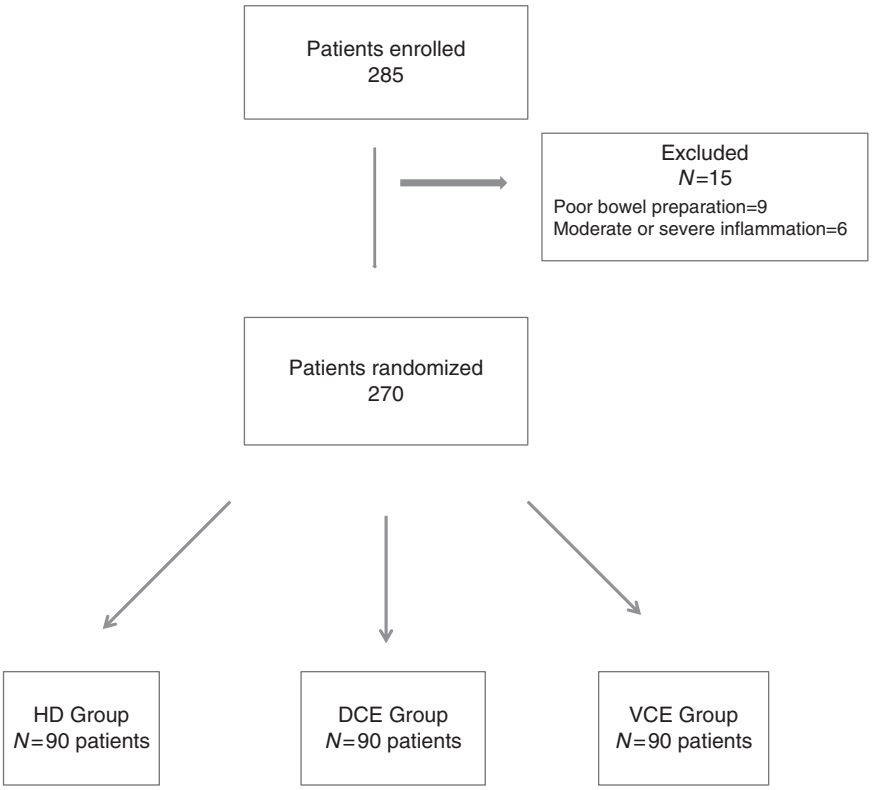

Figure 1. Patients recruited in the study.

Table 2. Colonic lesions found in each surveillance group: histological evaluation as modified by the Vienna classification

Lesion	HD (*n*=90)	DCE (*n*=90)	VCE (*n*=90)
Serrated adenoma	14(33.3%)	8(29.6%)	11(47.8%)
Tubular adenoma (non colitic areas)	6(14.3%)	3(11.1%)	1(4.3%)
Dysplasia non-polypoid: low grade	4(9.5%)	2(7.4%)	2(8.7%)
Dysplasia non-polypoid: high grade	0	0	0
Dysplasia polypoid: low grade	18(42.9%)	13(48.1%)	9(39.1%)
Dysplasia polypoid: high grade	0	0	0
Adenocarcinoma	0	1(3.7%)	0
Total lesions	42 (100%)	27 (100%)	23 (100%)

DCE, dye spraying chromoendoscopy; HD, high definition; VCE, virtual chromoendoscopy.

areas, dysplasia, or adenocarcinoma): *P* values <0.05 were considered statistically significant.

Exploratory univariate logistic regression analysis was performed for selecting endoscopic variables associated with the presence of dysplasia or cancer. Those features that were significant at the univariate stage were included in a multivariate logistic regression. We included ORs with 95% CIs to quantify the association of the endoscopic findings with dysplasia/cancer

Finally, estimates of predictive accuracy were attained using a bootstrapping technique. Training data were derived by randomly sampling from the observations with replacement. The test data were the observations not used for training. This process was done 500 times, to get estimates of standard error about the validity measures. The multivariate model was fit for each iteration of the bootstrap and predictions were made for the test data. This allows for the estimates of accuracy, sensitivity, specificity, PPV, and NPV and accuracy for characterisation of colonic lesions were calculated for patients in each arm of the surveillance groups, with histology as the gold standard.

The analysis was "per protocol" and statistical analysis was performed using the statistical software package SPSS 23.0 (IBM, NY, USA).

RESULTS

Demographics characteristics of the patients

A total of 285 consecutive patients with longstanding IBD who consented to study participation underwent surveillance colonoscopy between March 2014 and March 2016. Fifteen patients were excluded because they did not meet the inclusion criteria owing to insufficient bowel preparation or active inflammation (**Figure 1**). The demographic details of the patients are summarized in **Table 1**.

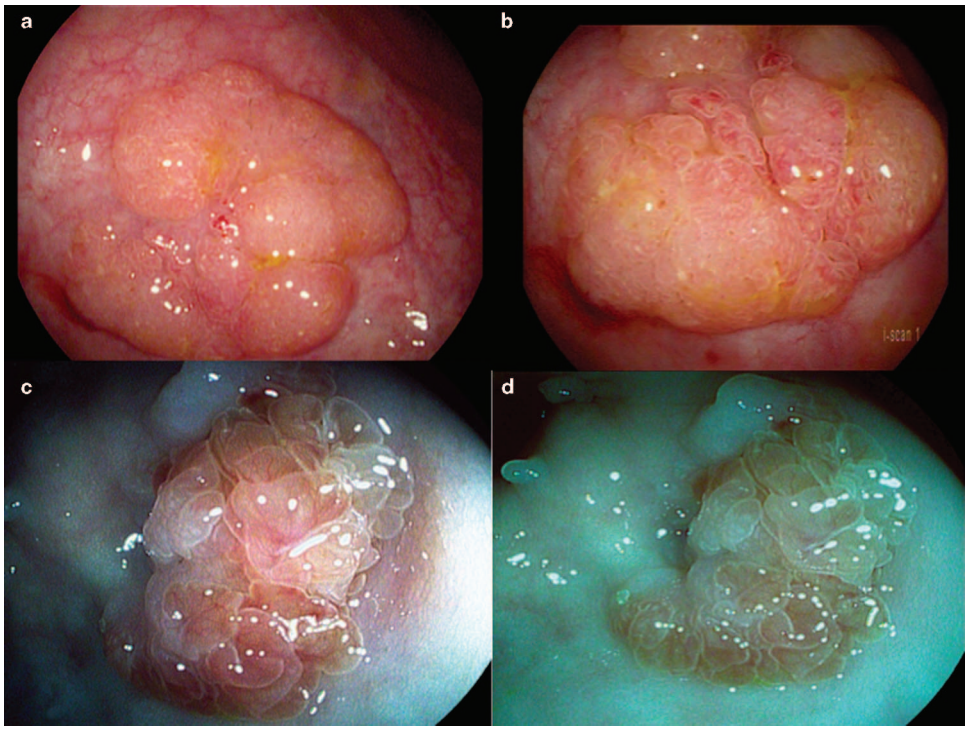

Figure 2. Polypoid lesion with low grade dysplasia: (**a**–**b**) High definition showed sessile lesion, Paris classification Is with areas of Kudo pit pattern II–IV and definite margins; (**c–d**) polypoid lesion with low grade dysplasia assessed by virtual electronic chromoendoscopy and Kudo pit pattern IIIL–IV.

A total of 270 patients (55% men; age range 20–77 years, median age 49 years) fulfilled the inclusion criteria and were enrolled in the trial (48% ulcerative colitis, 50.3% Crohn's disease, 1.8% unclassified colitis). The disease duration ranged from 2 to 46 years (median disease duration 14.5 years).Twenty-nine (10.7%) patients had a family history of colon cancer and 60 (22.2%) had a personal history of colonic lesions diagnosed at previous colonoscopies (**Table 1**). No patients in the study had adverse events such as bleeding, perforation, or death.

Colonic neoplasia detection rates among the different endoscopic procedures group

Out of the 270 patients, 90 patients were enrolled in the HD arm, 90 patients in the DCE arm, and 90 patients in the VCE arm. In the study, 33 sessile serrated adenomas were found in 21 patients (7.7% of patients), 9 tubular adenoma were found in 5 patients in non-colitic areas (1.9% of patients), 49 dysplastic lesions (41 were polypoid and 8 were non-polypoid) were found in 39 patients (14.4% of patients), and adenocarcinoma was found in one patient (0.3% of patients). The colonic neoplastic lesions found in each surveillance arm and in each patient cohort are detailed in **Tables 2 and 3**.

The primary outcome of VCE was non-inferior to DCE for detection of dysplasia and adenocarcinoma and for all lesions (Fisher's Exact P=1 and 0.64); 95% confidence limits of the rate difference for all lesions was −0.17–0.08 establishing non-inferiority of VCE compared with DCE (one-way difference not crossing the pre-specified non-inferiority threshold of 0.1, i.e., 10%). HD was non-inferior to DCE for detection of dysplasia and adenocarcinoma and for all lesions (Fisher's Exact P=0.65 and 0.71); 95% confidence limits of the rate difference for all lesions was −0.29–0.02 establishing non-inferiority of HD compared with DCE (one-way difference not crossing the non-inferiority threshold of 0.1, i.e.,10%). HD was non-inferior to VCE for detection of dysplasia and adenocarcinoma and for all lesions (Fisher Exact P=1 and 0.58); 95% confidence limits of the rate difference for all lesions was −0.34– 0.07 establishing non-inferiority of HD compared with VCE (one-way difference not crossing the non-inferiority threshold of 0.1, i.e., 10%). Dysplasia (polypoid and non-polypoid) and adenocarcinoma detection rates were similar among the three arms of the study (P=0.84) (**Table 2**). Non-polypoid dysplasia detection rates were similar in all three groups, but the numbers were small. All lesions, including sessile serrated adenoma, tubular adenoma in non-colitic areas, dysplasia, and adenocarcinoma detection rates were similar among the three arms of the study (P=0.74).

When analyzed by number of patients with dysplasia (polypoid and non-polypoid) and adenocarcinoma (**Table 3**), the three arms were similar (P=0.91). When analyzed by number of patients with all lesions, including sessile serrated adenoma, tubular adenoma in non-colitic areas, dysplasia, and adenocarcinoma, the three arms were similar (P=0.99). VCE was not inferior to DCE in the number of lesions detected (**Table 3**).

In the DCE group, the first 18 consecutive patients enrolled underwent colonoscopy with 0.04% indigo carmine and the remaining 72 patients with 0.03% methylene blue because the indigo carmine ampules stopped being available in North America.

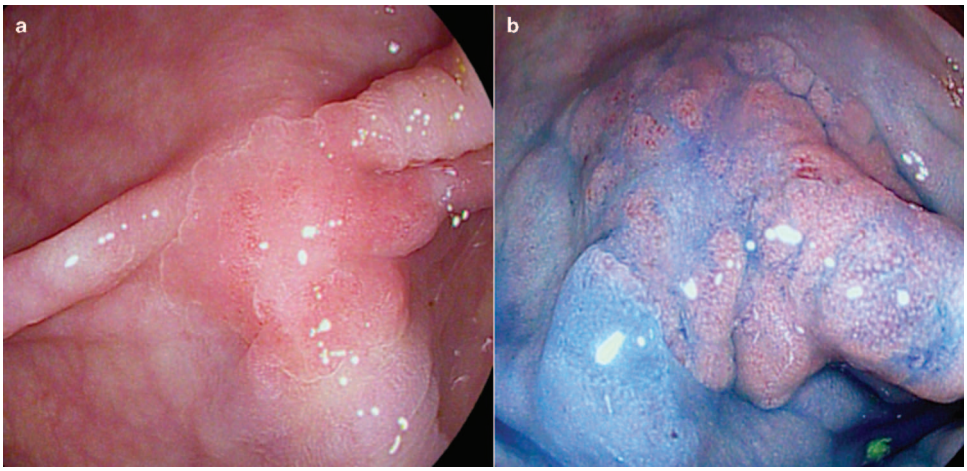

Figure 3. Non polypoid lesion: (**a**) high definition showed a flat lesions, Paris classification IIb with definite margins; (**b**) dye spraying chromoendoscopy with methylene blue 0.03%.

Regarding characterisation of lesions, the three techniques had similar sensitivity and specificity to predict histology of colonic lesions (neoplastic versus non-neoplastic; neoplastic included dysplasia, carcinoma, adenoma, and sessile serrated adenoma and non-neoplastic included pseudopolyps and hyperplastic) (**Figures 2 and 3**). The sensitivity, specificity, PPV, NPV and accuracy of each technique to predict histological determination of neoplastic lesions were determined. HD had a sensitivity of 91.3%, specificity of 78.1%, PPV 88.2%, NPV 88.2%, and accuracy 86%. DCE had a sensitivity of 84.6%, specificity of 79.5%, PPV 70.9%, NPV 88.2%, accuracy 81.4%, and VCE had a sensitivity of 92.3%, specificity of 62.5%, PPV 73%, NPV 88.2%, and accuracy 78%.

Procedure duration in the different arms of the study

The duration of the withdrawal time of colonoscopy in minutes for patients in the HD group was median 15.4 (range 10–22 min), in the DCE was median 16.2 (range 12–35 min), and in the VCE was median 15.3 (range 9–26 min). The three-way Kruskal–Wallis rank sum non-parametric test was used to compare the three groups (*P*=NS). Random biopsies were not used (apart from inflammation assessment), which reduced withdrawal time.

Clinical and endoscopic predictors of dysplasia

The endoscopic morphologic characteristics and distribution of the lesions are shown in Appendix 1. Among 270 patients, 91 colonic dysplastic lesions and 1 adenocarcinoma were found. Sixty-two were polypoid and 29 were non-polypoid. Most of these lesions (92.3%) had the Kudo pit pattern III–V types.

Results of univariate and multivariate logistic regression analysis

In the univariate analysis, the following were all associated with correct prediction of colonic neoplasia for all the lesions detected: age in years had an odds ratio (OR) of 1.05 (95% CI 1.02–1.08), localization of the lesions in the right colon had an OR of 6.15 (95% CI 3.12–12.12), Kudo pit pattern types IIO, III–IV, and V had an OR of 20.91 (95% CI 9.34–46.7), and Paris Is/Ip classification had an OR of 3.29 (95% CI 1.69–6.38) (**Table 4**). Proportional multivariate logistic regression model for the prediction of colonic neoplasia was performed for all detected lesions. Endoscopic Kudo pit pattern (OR 21.50; 95% CI 86.5–60.1) and localization of the lesions in the right colon (OR 6.52; 95% CI 1.98–22.5) were strong predictors of colonic neoplasia (**Table 5**). When we combined these independent variables of predictors of neoplastic histological changes in detected lesions, the overall accuracy was 78% (95% CI 68–88%), sensitivity 82% (95% CI 68–97%), specificity 68% (95% CI 47–89%), PPV 85% (95% CI 76–95%), and

Table 3. Number of patients with neoplastic lesions and types of neoplastic lesions found in each surveillance group

Patients with lesions	HD (*n*=23) patients with lesions	DCE (*n*=22) patients with lesions	VCE (*n*=14) patients with lesions
Serrated adenoma	9(39%)	7(31.8%)	5(3.5%)
Tubular adenoma (non colitic areas)	2(8.6%)	2(9%)	1(7.1%)
Dysplasia non-polypoid: low grade	13(56.5%)	13(59%)	8(57.1%)
Dysplasia non-polypoid: high grade	0	0	0
Dysplasia polypoid: low grade	4(17.3%)	2(9%)	2(14.2%)
Dysplasia polypoid: high grade	0	0	0
Adenocarcinoma	0	1(4.5%)	0

DCE, dye spraying chromoendoscopy; HD, high definition; VCE, virtual chromo-endoscopy.
A patient might have more than one type of neoplastic lesion.
Number of patients with neoplastic lesions: HD group 23 patients; DCE group 22 patients; VCE group 14 patients.

Table 4. Univariate analysis: endoscopic findings predictive of dysplasia

Characteristic	Odds ratio (95% CI)
Gender	1.81 (0.97–3.37)
Age	1.05 (1.02–1.08)
Duration	0.99 (0.96–1.02)
Extraintestinal manifestation (primary sclerosing cholangitis)	1.73 (0.69–4.31)
Family history of colorectal cancer	1.13(0.37–3.41)
Prior personal history of polyps (colorectal cancer)	1.70 (0.91–3.18)
Smoker	10.4 (1.36–80.2)
Size	1.49 (0.72–3.08)
Paris class	3.29 (1.69–6.38)
Kudo pit pattern (II0, III–V)	20.9 (9.34–46.7)
Localization: left colon	0.23 (0.11–0.45)
Localization: right colon	6.15 (3.12–12.1)
Extension: colonic	6.9 (1.57–30.3)
Extension: ulcerative colitis or Crohn's disease	0.54 (0.22–1.30)
Extension: pancolitis	0.71 (0.37–1.34)

Table 5. Multivariate analysis: endoscopic findings predictive of dysplasia

Characteristic	Odds ratio (95% confidence interval)
Age	1.03 (0.99–1.08)
Paris class	3.30 (1.26–8.96)
Kudo pit pattern (II0, III–V)	21.50 (8.65–60.10)
Localization: left colon	1.14 (0.33–3.88)
Localization: right colon	6.52 (1.98–22.5)

NPV 64% (95% CI 42–86%) when referenced against the histology of these detected lesions (the gold standard).

DISCUSSION

In our randomized trial we did not demonstrate a statistical difference between HD, VCE, and DCE in the detection rate of colonic dysplastic lesions in IBD patients. We have demonstrated that the neoplasia detection rate of targeted biopsies was similar among the three arms of the study: HD, DCE, and VCE. Our detection rates of neoplastic lesions were similar to other studies conducted for detection rates during surveillance in IBD (6). The results were similar when sessile serrated adenoma lesions were not considered. Therefore in this study, the finding support use of HD-WLE for IBD surveillance but multicener, multi-observer studies are required to confirm these findings.

In a retrospective observational study, Subramanian *et al.* (27) also found that dysplasia was discovered in approximately twice the number of patients undergoing HD colonoscopy compared with SD-WLE colonoscopy: the adjusted prevalence ratio was 2.2 (95% CI 1.1–4.5).

DCE is considered the standard of the care to increase detection rate of neoplasia in IBD patients. A recent meta-analysis of eight studies, which used the previous generation of SD-WLE endoscopes, revealed that DCE compared with SD-WLE significantly increased the number of dysplastic lesions detected by almost two-fold (RR=1.9; 95% CI 1.4–2.7) (6).

Mooiweer *et al.* (12) demonstrated that implementation of DCE for IBD surveillance in clinical practice did not increase dysplasia detection compared with WLE with targeted and random biopsies in a large "real-life" cohort. It is possible that with improvement in resolution of images in endoscopy and expertize in optical diagnosis, the advantage of DCE becomes less apparent, at least for expert operators.

There is still confusion and debate regarding whether DCE should be adopted by every endoscopist doing surveillance in IBD (29). There are also many unanswered questions despite SCENIC guidelines (29). Unfortunately, there are limited prospective studies comparing DCE with currently used advanced technologies such as HD-WLE and VCE. The latest generation of colonoscopes have markedly improved the brightness and sharpness of the quality of images, which has increased detection and characterisation of dysplasia more apparent. This has enabled greater prediction of the histological nature of the dysplasia, improving the definition of margins, and feasibility of local endoscopic resection versus colectomy. These developments have the potential to increase local resection based on characterisation rather than on pan-proctocolectomy (16–18).

Previous randomized studies comparing narrow band imaging to HD-WLE colonoscopy have not suggested a benefit for narrow band imaging to detect more dysplasia in IBD patients (6,13–15). The new generation of electronic chromoendoscopes are however getting better in brightness and contrast. To our knowledge, this is the first study utilizing the new generation of iSCAN VCE in surveillance IBD patients. We also need to clarify whether DCE can be performed in the community setting or only in IBD centres with expert, dedicated IBD endoscopists. The study by Pelise *et al.*suggested that DCE could be adopted widely for IBD surveillance (28,30). Similarly, we need to determine via multi-operator multicentre studies whether this is also true for HD-WLE (and VCE).

We have used targeted biopsies based on the evidence of previous literature and European Society of Gastrointestinal Endoscopy guidelines (31–33). Studies have demonstrated that only one in a thousand random biopsies revealed dysplasia and only ~1–1.5% of all patients undergoing surveillance would not have dysplasia detected if random biopsies were not performed. Spanish centres have reported similar findings following targeted biopsies in the setting of real life practice (28). Our previous report of a cohort of 450 IBD patients undergoing surveillance colonoscopy supports the view that targeted biopsy is the preferred surveillance method compared with random biopsies to increase the detection of neoplastic lesions in patients with IBD (34). This study had suggested that targeted biopsies alone may be sufficient for HD-WLE, DCE, and VCE but not for SD-WLE (34). Also in SCENIC's recent statement of replacing random by targeted biopsies, 85% of the

panelists had agreed (6). Note that SD-WLE may still require random biopsies, even if targeted biopsies alone may be sufficient for HD-WLE, DCE, and VCE, apart from a few biopsies to assess inflammatory status. In our study, patients with active inflammation in any colonic segment were not included in the study. Therefore, in our clinical practice we preferred to perform surveillance colonoscopy in IBD patients using targeted biopsies.

In our study, exploratory univariate and multivariate statistical model analysis of the colonic lesions detected and characterised by the three technologies were performed to predict clinical or endoscopic features predictive of colonic neoplasia in IBD patients (histology gold standard). The endoscopic Kudo pit pattern and localization of the lesions in the right colon were predictors of colonic neoplasia in IBD (**Tables 4 and 5**). Sensitivity analysis by excluding sessile serrated adenoma lesions did not change the conclusions. Family history of colorectal cancer was not a predictor of the colorectal neoplasia.

The value of Kudo pit patterns to predict histology in IBD patients remains controversial especially when these lesions are assessed by using standard scopes without magnification. The colonic mucosa of IBD patients might be distorted due to long-standing chronic inflammation; furthermore, dye spraying may also obscure the Kudo pit pattern. The Kudo pit pattern can be assessed with the new generation HD with or without VCE and without magnification, as in this study (32,34,35). Though not the primary objective of this study, we do present our data in the context of this study on lesion characterisation, including the Kudo pit pattern. This is the first support for using the Kudo pit pattern in neoplastic lesions characterisation in IBD surveillance. Further studies are required on lesion characterisation including usefulness of the Kudo pit pattern in the context of IBD.

In our study, there were a disproportionate number of primary sclerosing cholangitis patients in the HD group, as recruitment was not stratified. However, only one low-grade dysplastic lesion was detected in a patient with ulcerative colitis-associated primary sclerosing cholangitis who underwent surveillance in the VCE group. Analyzing the results by excluding primary sclerosing cholangitis patients did not change the conclusions, with the limitation that it reduced the sample size in each arm. As only one low-grade dysplastic lesion was detected in a patient with ulcerative colitis-associated primary sclerosing cholangitis who underwent surveillance in the VCE group, the PSC-IBD group did not impact the results of this study but we had included these PSC patients as this is an important surveillance group.

A strength of our study is that it has been prospectively performed in a randomized fashion by an expert endoscopist trained on advanced technologies and IBD, as in procedural randomization, standardizing skills, learning curve, and experience may be confounding factors with multiple endoscopists. Having one expert endoscopist harmonized the cognitive elements of lesion detection and characterisation. Performing a three arm randomized study with back to back colonoscopies in a multi-operator, multicenter format is challenging and we hope our study will help plan further studies by choosing two rather than three techniques. We hope both single observer and multi observer studies will inform the debate as this is the second randomized study comparing different techniques for surveillance colonoscopy in IBD. The operator (MI) had considerable experience with all three techniques, and the analysis of the data over quartiles of procedures did not show any increase in detection rates. Other studies such as recent study of mucosal healing endoscopic Mayo score 0 Vs 1 also involved a single experienced operator, Barreiro-de Acosta, who did all the endoscopies (36), to minimized the risk of inter-observer variability in assessment. More importantly, the pivotal paper on dye chromoendoscopy was done by a single operator, Dr M Rutter (37), However, we also acknowledge that this is also a limitation (e.g., would other operators see similar results?) and therefore multiple operators are recommended for future randomized trials. In addition, in future multicentre studies, skills, and learning curve with the three techniques should be harmonized by training modules to achieve acceptable inter-observer agreement or by central readout. This should also involve different endoscopy platforms such as iSCAN (Pentax), NBI (Olympus, Tokyo, Japan), and BLI (Fujinon, Tokyo, Japan), but because of rapid advances in technology needs harmonized skills and latest generation scopes and processors. The three-arm single-operator study should be followed up by a two arm multicentre study with multiple operators and from the results of our study it would be rational to use HD-WLE and DCE.

Kiesslich *et al.* (8) in the pivotal randomized trial establishing the use of methylene blue DCE used 1:1 randomization and not tandem colonoscopies; we followed a similar protocol in a 1:1:1 randomization as it is difficult to do tandem studies with a three-arm design and patient acceptance of tandem colonoscopy may be limited. Similar to our study, the randomized dye Chromoendoscopy vs. white light Chromoendoscopy trial by Kiesslich *et al.* (8) the lesions were only detected on withdrawal.

Stratification by primary sclerosing cholangitis or family history may also be relevant in future studies, although sensitivity analysis without these patients did not change the conclusion. Neither primary sclerosing cholangitis nor family history predicted neoplasia in multivariate analysis. There was no apparent difference between ulcerative colitis and Crohn's colitis in detection rates, although the study was not powered to answer this question.

In conclusion, our randomized trial demonstrated that for experienced operators, virtual electronic chromoendoscopy or HD colonoscopy is not inferior to dye spraying colonoscopy for detection of colonic neoplastic lesions during surveillance colonoscopy. In fact, in this study HD colonoscopy alone was sufficient for detection of dysplasia, adenocarcinoma or all neoplastic lesions. However, multicentre, multiple operator studies are required verify our conclusions.

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CONFLICT OF INTEREST

Guarantor of the article: Marietta Iacucci, MD, PhD.

Specific author contributions: Study design and idea: MI, SG. Data Acquisition: MI, AO, SG, SU, PM, XS, GGK, RP, SG, KN, CHS, YL. Analysis of data: MI, AO, SG, BCL, MLL, GGK. Writing of manuscript: MI, SG.GGK. Revision of manuscript: MI, SG, RP, AO, XG, SU, PM, GGK, KN, YL, CHS, BCL, MLL.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Dye spraying chromoendoscopy (DCE) is the recommended method for detection of neoplastic lesions in longstanding colonic inflammatory bowel disease (IBD).
- ✓ The majority of neoplastic lesions are visible endoscopically and therefore targeted biopsies are appropriate for surveillance colonoscopy.

WHAT IS NEW HERE

- ✓ In a randomized trial, we could not demonstrate that virtual electronic chromoendoscopy or high definition white light colonoscopy was inferior to dye spraying colonoscopy.
- ✓ Kudo pit pattern and location of lesion in the right colon were predictive of neoplastic lesions in surveillance colonoscopy.
- ✓ For experienced operators, virtual electronic chromoendoscopy or high definition colonoscopy is not inferior to dye spraying colonoscopy for detection of colonic neoplastic lesions during surveillance colonoscopy in inflammatory bowel disease. However, multicentre, multiple operator studies are required for further confirmation.

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APPENDIX 1

Baseline characteristics and endoscopic features of colonic neoplastic lesions

Lesions	Male	Age, mean	Ulcerative colitis/ Crohn's disease/ indeterminate colitis	Localization			Size		Paris classification			Kudo Pit pattern		
				Right	Transverse	Left	<5 mm	≥5 mm	Is/p	IIb	IIa	I/II	IIO	III-V
Serrated adenoma *n*=33	8	60.6	22/11/0	22	6	5	16	17	16	17		1	28	4
Tubular adenoma *n*=9	9	65.4	9/0/0	8	1	0	9	0	5	2	2	0	5	4
Dysplasia polypoid *n*=41	23	53.7	14/27/0	13	9	19	31	10	41	0	0	5	7	29
Dysplasia non-polypoid *n*=8	5	49.3	1/6/1	4	2	2	3	5	0	5	3	1	2	5