Surveillance in inflammatory bowel disease: white light endoscopy with segmental re-inspection versus dye-based chromoendoscopy - a multi-arm randomised controlled trial (HELIOS)

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Original research

Surveillance in inflammatory bowel disease: white light endoscopy with segmental re-inspection versus dye-based chromoendoscopy – a multi-arm randomised controlled trial (HELIOS)

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ABSTRACT

Background It remains unclear if the increased colorectal neoplasia detection rate in inflammatory bowel disease (IBD) by high-definition (HD) dye-based chromoendoscopy compared with HD white-light endoscopy is due to enhanced contrast or increased inspection times. Longer withdrawal times may yield similar neoplasia detection rates as found by HD chromoendoscopy.

Objective To compare colorectal neoplasia detection rates for HD white-light endoscopy with segmental re-inspection and HD chromoendoscopy, using single-pass HD white-light endoscopy as an additional control group.

Design In a multicentre, randomised controlled trial, IBD patients aged ≥18 years without active disease and scheduled for endoscopic surveillance were included. Patients were 2:2:1 randomised to HD white-light endoscopy with segmental re-inspection of each colonic segment (double pass), HD chromoendoscopy or single-pass HD white-light endoscopy. The primary outcome was colorectal neoplasia detection rate. Assuming equal colorectal neoplasia rates (non-inferiority margin of 10%) between segmental re-inspection and chromoendoscopy and superiority of segmental re-inspection vs single-pass HD white-light endoscopy, a sample size of 566 patients was required.

Results In total, 563 patients were analysed per-protocol. Colorectal neoplasia detection rates were 10.3% (n=24/234) for HD white-light endoscopy with segmental re-inspection and 13.1% (n=28/214) for HD chromoendoscopy. This confirmed non-inferiority to HD chromoendoscopy (Δ−2.8%, lower limit 95% CI −7.8, p<0.01). In addition, the number of detected colorectal neoplasia per 10 min of withdrawal time was similar between HD white-light endoscopy with segmental re-inspection and HD chromoendoscopy (0.062 vs 0.058, p=0.83). Single-pass HD white-light endoscopy yielded a lower colorectal neoplasia rate (6.1%; n=7/115) than segmental re-inspection but this was not statistically significant (Δ4.1%, 95% CI −2.2:9.6%, p=0.19).

Conclusions HD white-light endoscopy with segmental re-inspection was non-inferior to HD chromoendoscopy for colorectal neoplasia detection in IBD patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with colonic inflammatory bowel disease are at increased risk of developing colorectal cancer. Most guidelines recommend endoscopic surveillance with high-definition dye-based chromoendoscopy to allow for increased colorectal neoplasia detection, which is still limited in acceptance.

⇒ It remains unclear if reported increased colorectal neoplasia detection rates of high-definition (HD) chromoendoscopy vs HD white-light endoscopy are due to enhanced contrast or increased inspection time.

WHAT THIS STUDY ADDS

⇒ HD white-light endoscopy with segmental re-inspection was non-inferior to HD chromoendoscopy in detecting colorectal neoplasia.

⇒ The similar colorectal neoplasia detection rates per 10 min of withdrawal time between both approaches suggest that the benefit of chromoendoscopy might be explained by the longer withdrawal time.

⇒ HD white-light endoscopy with segmental re-inspection (double pass) was not significantly superior to single-pass endoscopy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ HD white-light endoscopy with segmental re-inspection might be a feasible alternative to HD chromoendoscopy in clinical practice.

It can therefore be assumed that the benefit of HD chromoendoscopy may be explained by the longer withdrawal time and not necessarily the enhanced contrast. However, re-inspection per se did not lead to a significantly higher colorectal neoplasia rate than single-pass HD white-light endoscopy alone.

INTRODUCTION

Patients with colonic inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer.[1] International guidelines recommend endoscopic surveillance to detect and remove colorectal neoplasia in order to reduce colorectal cancer-related morbidity and mortality.[2–6] Thus far, the optimal endoscopic technique for surveillance in IBD with high-definition (HD) equipment has not been well established.

Most guidelines recommend HD dye-based chromoendoscopy with methylene blue or indigo carmine for improved detection of colorectal neoplasia and lesion delineation,[3–5] while some guidelines consider HD white-light endoscopy with targeted biopsies to be sufficient.[7] Both a recent randomised controlled trial (RCT) and meta-analysis reported improved colorectal neoplasia detection rates in HD chromoendoscopy vs HD white-light endoscopy, while another meta-analysis did not detect superiority of HD chromoendoscopy.[8–10] These conflicting results, in addition to issues of required training, resources and reduced visibility in case of active inflammation, may explain the low uptake of HD chromoendoscopy in clinical practice.[11 12] Importantly, the reported differences in colorectal neoplasia yield might be the result of longer withdrawal and re-inspection times in HD chromoendoscopy as observed in previous non-IBD studies.[13–15] Consequently, we hypothesised that HD white-light endoscopy with segmental re-inspection may yield similar neoplasia detection rates as HD chromoendoscopy while offering superior neoplasia detection rates compared with single-pass HD white-light endoscopy.

In order to evaluate the impact of re-inspection of colonic segments on the colorectal neoplasia detection rate in IBD, we performed a multicentre, open-label RCT, testing non-inferiority of HD white-light endoscopy with segmental re-inspection compared with HD chromoendoscopy, and superiority compared with single-pass HD white-light endoscopy.

METHODS

We conducted a three-arm, open-label, parallel group, RCT in four academic hospitals in The Netherlands with both a non-inferiority and superiority analysis (NCT04291976). Patients were not involved in the design and conduct of this research. This study was reported following the Consolidation Standards for Reporting Trials (CONSORT) guidelines (online supplemental file 1).[16 17]

Participants

We recruited patients with IBD, scheduled for endoscopic colorectal cancer surveillance following the Dutch IBD guideline.[18] This guideline closely resembles the British Society of Gastroenterology and European Crohn's and Colitis Organisation guidelines.[2 4] We included patients aged ≥18 years with colonic IBD (ulcerative colitis (UC), Crohn's disease (CD) or IBD-undetermined (IBD-U)) with an estimated colonic involvement of ≥30% and a disease duration of ≥8 years (or any disease duration in case of concomitant primary sclerosing cholangitis). The last surveillance colonoscopy had to be performed >1 year ago. Patients were excluded if >50% of the colon was resected, in case of pregnancy, or with an allergy/intolerance for methylene blue or indigo carmine. In addition, patients were excluded in case of inadequate bowel preparation (Boston Bowel Preparation Scale (BBPS) <6),[19] presence of active inflammation (defined as >20 cm of colonic involvement and/or colon not amendable to surveillance according to the endoscopist) or if patients did not undergo the study colonoscopy due to logistical or technical issues.

Interventions

All study procedures were performed by 18 gastroenterologists with expertise in endoscopic surveillance in IBD and HD chromoendoscopy (defined as having performed ≥50 of these procedures). HD endoscopes and monitors were used for all procedures (Olympus CF-HQ190L and CF-EZ1500DL series, Pentax EC38-i10 series, and Fuji EC760 series). The selection of bowel preparation regimens, sedation methods (no sedation, midazolam/(al)fentanyl, or propofol), and use of random biopsies was based on the endoscopists' discretion.

In single-pass HD white-light endoscopy, the entire colon was examined once during withdrawal after the cecum was reached. For HD white-light endoscopy with segmental re-inspection, each colonic segment was inspected on withdrawal followed by segmental re-introduction for a second inspection. Biopsy markings indicated the extent of the colonic segment for repeat inspection. HD chromoendoscopy was performed spraying dye per colonic segment during withdrawal, followed by segmental re-introduction and inspection. The applied dye was methylene blue (0.04%–0.1%) in three centres and indigo carmine (0.4%) in one centre as recommended in the SCENIC statement.[20]

If surveillance was not possible due to insufficient bowel preparation and/or active inflammation, patients were rescheduled. We included the rescheduled procedure if performed by another endoscopist from the study team. The original allocation and thus the intervention remained the same for these patients.

Data collection

Endoscopists recorded colonoscopy insertion time (time between start of procedure and cecal intubation), withdrawal time (time between start of inspection of the cecum and end of procedure, for HD chromoendoscopy, this includes dye-spraying time) and patient comfort (measured with the Modified Gloucester Comfort Scale, ranging from no discomfort (1) to severe discomfort (5)). Endoscopic inflammation was scored using the Simple Endoscopic Score for CD (SES-CD) or the UC Endoscopic Index of Severity (UCEIS) score for UC/IBD-U patients. The percentage of inflamed mucosal surface was documented separately for UC/IBD-U patients, as this feature is not captured in the UCEIS score. For HD white-light endoscopy with segmental re-inspection, we documented whether lesions were detected during the first or second round of inspection. Lesions were endoscopically classified using the Paris and Kudo classification and treated according to guideline recommendations when possible.[7] All collected tissue specimens were assessed by pathologists, specialised in gastro-intestinal diseases as part of standard care. Lesions with colorectal neoplasia were classified according to the Riddell classification as indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia or colorectal cancer. Advanced colorectal neoplasia was defined as high-grade dysplasia or colorectal cancer.

Patient and disease characteristics were collected from electronic health records, including age, IBD type, disease duration, maximal disease extent, presence of primary sclerosing cholangitis, history of colorectal neoplasia, family history of colorectal cancer, smoking status, surveillance risk category, current and prior medication use. Maximal endoscopic disease extent was defined as extensive (Montreal E3 for UC/IBD-U or >50% of colonic involvement for CD) or limited (Montreal E2 for UC/IBD-U or <50% of colonic involvement for CD).[21] Current and

prior medication use for IBD was defined as usage for more than 3 months. Colorectal cancer risk categories at inclusion were determined based on the Dutch IBD surveillance guidelines which categorise patients in low, intermediate or high colorectal cancer risk groups.[18]

Objectives

The study objective was to compare colorectal neoplasia detection rates for HD white-light endoscopy with segmental re-inspection vs HD chromoendoscopy and single-pass HD white-light endoscopy. In a non-inferiority analysis, HD white-light endoscopy with segmental re-inspection was compared with HD chromoendoscopy and a superiority analysis was performed to compare HD white-light endoscopy with segmental re-inspection with single-pass HD white-light endoscopy.

Outcomes

The primary outcome was colorectal neoplasia detection rate, defined as the proportion of patients with detected macroscopic colorectal neoplasia (indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, colorectal cancer, or sessile serrated adenoma with dysplasia). Colorectal neoplasia was defined as a colonic lesion characterised by histology as dysplastic or colorectal cancer.

Secondary outcomes included total number of resected or biopsied macroscopic lesions send to the pathologist (including lesions without dysplasia/carcinoma) per colonoscopy, total number of colorectal neoplasia per colonoscopy, procedural and withdrawal times, the impact of withdrawal time on the colorectal neoplasia detection rate (including number of detected colorectal neoplasia per 10 min of withdrawal time), and, for HD white-light endoscopy with segmental re-inspection, the number of macroscopic lesions (including non-dysplastic) detected during the first vs second inspection round.

Sample size

Sample size calculations were performed for the primary outcome only, based on the approach described by Chow *et al*.[22] Based on prior studies, colorectal neoplasia detection rates were estimated at 12% for single-pass HD white-light endoscopy and 24% for HD white-light endoscopy with segmental re-inspection and HD chromoendoscopy.[23] To show non-inferiority of HD white-light endoscopy with segmental re-inspection compared with HD chromoendoscopy, assuming a true difference of 0 percent-point with a non-inferiority margin of 10 percent-point (power 80% and one-sided alpha 5%), a total of 226 patients per group were required. To demonstrate superiority of HD white-light endoscopy with segmental re-inspection compared with single-pass HD white-light endoscopy, with a 2:1 allocation ratio, 226 and 113 patients per group were sufficient to show an estimated effect size of 12 percent-point with at least 80% power and two-sided alpha 5%. We allowed for a maximum drop-out rate of 15% (n=85) in addition to the required n=565 to reach 80% power.

Randomization

Patients were randomly assigned to HD white-light endoscopy with segmental re-inspection, HD chromoendoscopy and single-pass HD white-light endoscopy in a 2:2:1 ratio using variable block randomisation (block sizes 5, 10 or 15) after stratification by study centre. Randomisation was non-blinded and performed digitally after inclusion and pre-procedural by M.G. and A.W. for all four sites (Castor EDC, Amsterdam, the Netherlands).

Statistical methods

Patient and disease characteristics were summarised using descriptive statistics (frequencies for categorical variables and for continuous variables, a mean (SD) or median (interquartile interval)). Continuous data was compared using a two-sample t-test (or Wilcoxon rank-sum test if appropriate) and categorical data using the χ^2 test.

Colorectal neoplasia detection rates were compared between arms using the Cochran-Mantel-Haenszel CI for the risk difference described by Klingenberg *et al*, taking the stratification variable into account (ie, study centre).[24] Non-inferiority of HD white-light endoscopy with segmental re-inspection to HD chromoendoscopy was established if the lower boundary of the one-sided 95% CI was greater than the non-inferiority margin of −10 percent-point. We assessed the interaction between withdrawal time and endoscopic technique on colorectal neoplasia detection rate with a multivariable logistic regression model and calculated the average marginal effects of each group relative to HD white-light endoscopy with segmental re-inspection from this model. The presence of technique × withdrawal time interaction was assessed by a likelihood ratio test of the model with vs without interaction terms. We performed a post hoc analysis to calculate the number of colorectal neoplasia per 10 min of withdrawal time as follows: (total number of detected colorectal neoplasia per group/total withdrawal time per group)*10. For the superiority analysis and secondary outcomes, a two-sided p value <0.05 was considered statistically significant. We did not adjust for multiple testing as we compared different interventions.[25] For the secondary outcomes, we did not stratify by study centre.

The primary and secondary outcomes were analysed in both a per-protocol and modified intention-to-treat analysis. In the per-protocol analysis, all patients meeting the study selection criteria and receiving the allocated intervention according to study protocol were included. Randomised patients who did not undergo the study colonoscopy were excluded from both analyses (for example due to logistical reasons or being rescheduled to an endoscopist not participating in this study). These exclusion reasons were not impacted by randomisation arm. Therefore, we performed a modified intention-to-treat analysis in all patients meeting the study selection criteria, including those not compliant with the study protocol due to various reasons (eg, patients with incomplete HD chromoendoscopy, switch to single-pass HD white-light endoscopy due to technical reasons or patient discomfort, or an incomplete colonoscopy). The per-protocol analysis was considered the primary analysis since colonoscopies not compliant with quality indicators (including inspection of the entire colon) may result in missed lesions, resulting in ineffective surveillance.[26] Data was complete for the primary outcome. For the secondary outcomes, missing data was noted for withdrawal time (1.6% missingness). Due to this low missingness rate, analysis was only performed on complete cases without prior imputation of data. All analyses were performed using R statistical software (version 4.0.3 for Windows).

Protocol changes

Initially, we specified a fixed concentration of methylene blue in the study protocol (0.1%). An amendment was made to allow for varying concentrations (0.04%–0.1%) based on clinical practice and SCENIC recommendations.[7 20] In order to achieve the pre-specified number of patients in per-protocol analysis, the maximum number of patients to be additionally included was

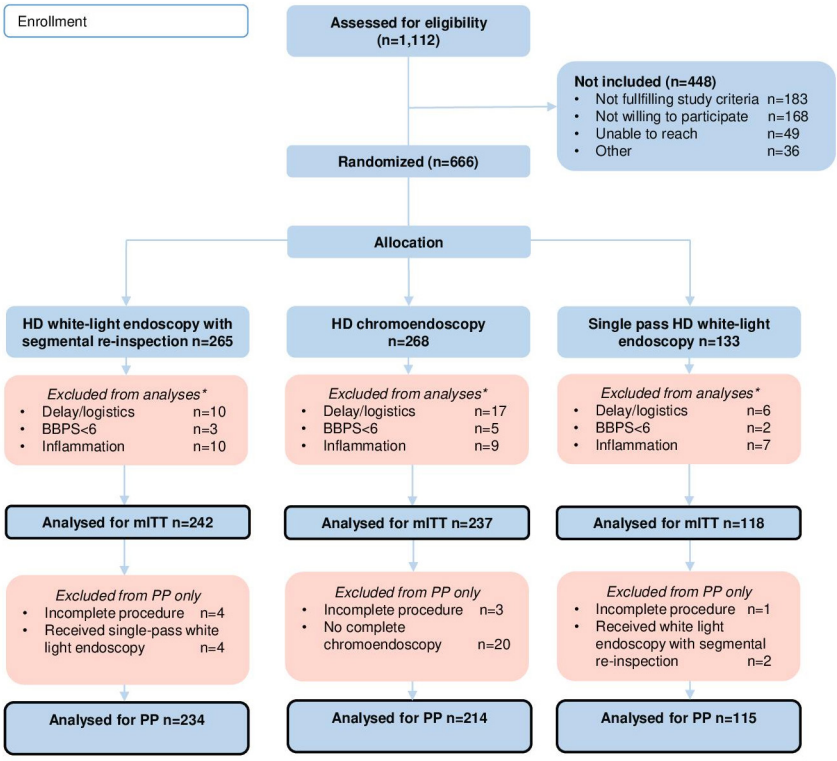

Figure 1 Flowchart of patients included in the HELIOS study (CONSORT). If surveillance was not possible due to insufficient bowel preparation and/or active inflammation, patients were rescheduled (see methods section). The number of successfully rescheduled procedures was n=10 (HD white-light endoscopy with segmental re-inspection n=5; HD chromoendoscopy n=4; and single-pass HD white-light endoscopy n=1). Nine out of 10 patients were included in per-protocol analysis and 1 only in modified intention-to-treat analysis. *: Randomised patients who did not undergo the study colonoscopy were excluded from both (categorised as 'delay/logistics', for example due to logistical reasons or being rescheduled to an endoscopist not participating in this study). BBPS, Boston Bowel Preparation Scale; HD, high-definition; mITT, modified intention-to-treat analysis; n, number; PP, per-protocol analysis.

raised from 5% (n=29) to 15% (n=85) since we experienced more drop-outs due to logistical reasons (figure 1).

RESULTS

Recruitment and participants

Patients were recruited between March 2020 and May 2023. We screened 1112 and enrolled 666 patients (figure 1). Of these, 265 were randomised to HD white-light endoscopy with segmental re-inspection, 268 to HD chromoendoscopy and 133 to single-pass HD white-light endoscopy. Table 1 provides patient and disease characteristics and table 2 procedural information. Additional information on smoking and IBD medication is provided in online supplemental file 2. Online supplemental files 3 and 4 contain this information for the modified intention-to-treat analysis. In total, 597 and 563 patients were included in the modified intention-to-treat and per-protocol analyses, respectively. There was no significant difference in exclusions per arm (HD white-light endoscopy with segmental re-inspection n=23 vs HD chromoendoscopy n=31 vs single-pass HD white-light endoscopy n=15, p=0.51).

Outcomes

The proportion of patients with colorectal neoplasia was 10.3% for HD white-light endoscopy with segmental re-inspection, 13.1% for HD chromoendoscopy and 6.1% for single-pass HD white-light endoscopy (table 3). HD white-light endoscopy with segmental re-inspection was non-inferior to HD chromoendoscopy (difference −2.8%, lower boundary of the one sided 95% CI −7.8 not exceeding the pre-defined non-inferiority margin of −10 percent-point, p<0.01, figure 2). HD white-light endoscopy with segmental re-inspection was not superior compared with single-pass HD white-light endoscopy (difference 4.1%, 95% CI −2.2:9.6%, p=0.19).

The total number of detected colorectal neoplasia was comparable between HD white-light endoscopy with segmental re-inspection and HD chromoendoscopy (n=30 vs n=36, p=0.23), and HD white-light endoscopy with segmental re-inspection vs single-pass HD white-light endoscopy (n=8, p=0.10, table 4). Only one advanced colorectal neoplasia lesion was detected (high-grade dysplasia in the HD chromoendoscopy arm), no colorectal cancer was detected. Colorectal neoplasia grade, location and morphology details are presented in table 3.

The total number of resected/biopsied macroscopic lesions (including non-dysplastic lesions) was lower for HD white-light endoscopy with segmental re-inspection compared with HD chromoendoscopy (n=123 vs n=175, p<0.01); and comparable to single-pass HD white-light endoscopy (n=54, p=0.32). For HD white-light endoscopy with segmental re-inspection, 97/120 (81%) lesions were detected during first inspection.

Withdrawal times were shorter for HD white-light endoscopy with segmental re-inspection vs HD chromoendoscopy (−8.0 min, 95% CI −9.0:−6.0, p<0.01), while HD white-light endoscopy with segmental re-inspection had a significantly longer withdrawal time compared with single-pass HD white-light endoscopy (4.0 min, 95% CI 2.0:6.0, p<0.01). Adjusted for withdrawal time, the colorectal neoplasia detection rate

Table 1 Baseline characteristics of 563 IBD patients included in HELIOS study (per-protocol analysis)

Variable	HD white-light endoscopy with segmental re-inspection	HD chromoendoscopy	Single-pass HD white-light endoscopy	Missing (%)
n	234	214	115	
Male sex, n (%)	125 (53.4)	104 (48.6)	63 (54.8)	0.0
Age (years) (median, IQR)	51.61 (36.02, 62.18)	50.74 (37.37, 63.07)	48.36 (32.80, 62.87)	0.0
IBD type, n (%)				0.0
Ulcerative colitis (UC)	128 (54.7)	113 (52.8)	72 (62.6)	
Crohn's disease (CD)	95 (40.6)	97 (45.3)	41 (35.7)	
IBD-undetermined (IBD-U)	11 (4.7)	4 (1.9)	2 (1.7)	
IBD disease duration (years) (median, IQR)	19.25 (11.42, 28.66)	17.73 (10.96, 25.80)	15.52 (8.68, 25.11)	0.0
Maximal disease extent,* n (%)				1.6
E2 (UC/IBD-U)	49 (20.9)	43 (20.1)	26 (22.6)	
E3 (UC/IBD-U)	29 (12.4)	16 (7.5)	13 (11.3)	
Pancolitis (UC/IBD-U/CD)	72 (30.8)	68 (31.8)	40 (34.8)	
<50% (CD)	31 (13.2)	34 (15.9)	13 (11.3)	
>50% (CD)	48 (20.5)	50 (23.4)	22 (19.1)	
Missing†	5 (2.1)	3 (1.4)	1 (0.9)	
Primary sclerosing cholangitis, n (%)				0.0
No	212 (90.6)	194 (90.7)	96 (83.5)	
Yes	22 (9.4)	19 (8.9)	19 (16.5)	
Unknown	0 (0.0)	1 (0.5)	0 (0.0)	
History of colorectal neoplasia, n (%)				0.0
Indefinite for dysplasia	1 (0.4)	2 (0.9)	1 (0.9)	
Low-grade dysplasia	46 (19.7)	41 (19.2)	12 (10.4)	
High-grade dysplasia	5 (2.1)	0 (0.0)	0 (0.0)	
Colorectal cancer	0 (0.0)	1 (0.5)	0 (0.0)	
Sessile serrated lesion	2 (0.9)	6 (2.8)	0 (0.0)	
None	180 (76.9)	164 (76.6)	102 (88.7)	
Family history of colorectal cancer, n (%)				33.7
No	119 (50.9)	100 (46.7)	61 (53.0)	
Yes	38 (16.2)	34 (15.9)	21 (18.3)	
Missing	77 (32.9)	80 (37.4)	33 (28.7)	
Surveillance risk category,‡ n (%)				0.9
Low	60 (25.6)	59 (27.6)	28 (24.3)	
Intermediate	113 (48.3)	106 (49.5)	60 (52.2)	
High	58 (24.8)	47 (22.0)	27 (23.5)	
Missing	3 (1.3)	2 (0.9)	0 (0.0)	

*Extensive disease based on endoscopic information and classified according to the Montreal classification for UC/IBD-U or expressed in percentages for CD.
†Data on maximal disease extent is missing as it was not possible to determine the historic maximal extent based on data in electronic health records.
‡Risk categories were based on the Dutch surveillance guidelines.
IBD, inflammatory bowel disease; n, number.

was comparable between HD white-light endoscopy with segmental re-inspection and HD chromoendoscopy (OR 0.97, 95% CI 0.92:1.03, p=0.34) and HD white-light endoscopy with segmental re-inspection vs single-pass HD white-light endoscopy (OR 1.03, 95% CI 0.93:1.14, p=0.56). No interaction between withdrawal time and endoscopic techniques could be shown (likelihood ratio test: p=0.11), that is, the yield per unit of time was not different between techniques. A post hoc analysis showed the number of colorectal neoplasia per 10 min withdrawal time was similar between HD white-light endoscopy with segmental re-inspection and HD chromoendoscopy (median 0.0616 vs 0.0584, p=0.83). In line, there was no significant difference between HD white-light endoscopy with segmental re-inspection and single-pass HD white-light endoscopy (median 0.0437, p=0.39, table 4).

For the modified intention-to-treat analysis, both primary and secondary outcomes were concordant with the per-protocol analysis (figure 2 and online supplemental files 5 and 6).

Adverse events

One patient in the HD chromoendoscopy arm experienced a post-polypectomy bleeding, which resulted in a 1-day hospitalisation with a second colonoscopy for clip placement achieving haemostasis (no blood transfusion needed, only outpatient intravenous iron suppletion).

DISCUSSION

In this large multicentre RCT, HD white-light endoscopy with segmental re-inspection was non-inferior to HD chromoendoscopy for colorectal neoplasia detection in patients with colonic IBD, with a similar number of detected colorectal neoplasia per 10 min of withdrawal time. HD white-light endoscopy with segmental re-inspection was not superior to single-pass HD white-light endoscopy, although these outcomes may have resulted from a lower-than-expected difference in neoplasia yield, resulting in reduced power.

Table 2 Details on 563 surveillance colonoscopies performed in HELIOS study (per-protocol analysis)

Variable	HD white-light endoscopy with segmental re-inspection	HD chromoendoscopy	Single-pass HD white-light endoscopy	Missing (%)
n	234	214	115	
Sedation method, n (%)				0.2
No sedation	20 (8.5)	12 (5.6)	8 (7.0)	
Midazolam/(al)fentanyl	173 (73.9)	159 (74.3)	86 (74.8)	
Propofol	40 (17.1)	43 (20.1)	21 (18.3)	
Missing	1 (0.4)	0 (0.0)	0 (0.0)	
Gloucester Comfort Scale, n (%)				2.3
No discomfort	86 (36.8)	91 (42.5)	54 (47.0)	
Minimal discomfort	87 (37.2)	85 (39.7)	42 (36.5)	
Mild discomfort	44 (18.8)	30 (14.0)	12 (10.4)	
Moderate discomfort	8 (3.4)	4 (1.9)	5 (4.3)	
Severe discomfort	2 (0.9)	0 (0.0)	0 (0.0)	
Missing	7 (3.0)	4 (1.9)	2 (1.7)	
Total Boston Bowel Preparation Scale, n (%)				0.0
Calculation not possible*	1 (0.4)	0 (0.0)	0 (0.0)	
6	8 (3.4)	17 (7.9)	15 (13.0)	
7	19 (8.1)	24 (11.2)	9 (7.8)	
8	17 (7.3)	25 (11.7)	9 (7.8)	
9	189 (80.8)	148 (69.2)	82 (71.3)	
Tubular colon and/or stenosis, n (%)				0.0
No	221 (94.4)	204 (95.3)	108 (93.9)	
Stenosis	9 (3.8)	2 (0.9)	1 (0.9)	
Tubular colon	4 (1.7)	7 (3.3)	5 (4.3)	
Both	0 (0.0)	1 (0.5)	1 (0.9)	
Total procedure time (min) (median, IQR)	30.00 (24.00, 38.00)	37.00 (30.00, 44.00)	24.00 (20.00, 32.50)	2.1
Missing	3 (1.3)	5 (2.3)	4 (3.5)	
Insertion time (min) (median, IQR)	10.00 (6.00, 15.00)	9.00 (6.00, 13.00)	9.00 (6.00, 13.00)	1.8
Missing	2 (0.9)	5 (2.3)	3 (2.6)	
Withdrawal time (min) (median, IQR)	19.00 (14.75, 26.00)	26.00 (22.00, 33.00)	15.00 (11.00, 21.00)	1.6
Missing	2 (0.9)	4 (1.9)	3 (2.6)	
UCEIS total (UC/IBD-U) (median, IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.3†
Missing	0 (0.0)	1 (0.5)	0 (0.0)	
Affected surface with colonic inflammation (UC/IBD-U), percentage (median, IQR)	0.00 (0.00, 5.00)	0.00 (0.00, 4.50)	0.00 (0.00, 2.50)	25.2†
Missing	33 (14.1)	27 (12.6)	23 (20.0)	
SES-CD excluding ileum (CD) (median, IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 3.00)	4.7†
Missing	2 (0.9)	8 (3.7)	1 (0.9)	
Endoscopic disease status, n (%)				2.1
Active disease (any degree)	29 (12.4)	25 (11.7)	21 (18.3)	
Remission/inactive disease	203 (86.8)	180 (84.1)	93 (80.9)	
Missing	2 (0.9)	9 (4.2)	1 (0.9)	

*Total Boston Bowel Preparation Scale calculation not possible due to prior colonic segment resection.
†Missing data (%) is percentage of missing data within IBD type.
CD, Crohn's disease; IBD-U, IBD-undetermined; min, minutes; n, number; SES-CD, Simple endoscopic score for Crohn Disease; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

Colitis-associated colorectal neoplasia is more difficult to visualise than sporadic colorectal neoplasia, with frequent non-polypoid morphology and surrounding (post-) inflammatory changes.[7] Although HD chromoendoscopy has previously been shown to be superior to standard-definition white-light endoscopy for colorectal neoplasia detection in IBD,[10 27] the evidence regarding the superiority of HD chromoendoscopy vs HD white-light endoscopy is conflicting.[9 10] These differences might be attributed to varying levels of surveillance expertise of participating endoscopists in studies,[8 28] and differences in withdrawal time between HD chromoendoscopy and HD white-light endoscopy.[10] Indeed, in our study, HD white-light endoscopy with segmental re-inspection was non-inferior to HD chromoendoscopy, with a similar number of detected colorectal neoplasia lesions per 10 min withdrawal time. This finding is substantiated by multiple non-IBD studies, showing a correlation between longer withdrawal times and increased colorectal neoplasia detection rates.[13 14] The shorter withdrawal time of HD white-light endoscopy with segmental re-inspection vs HD chromoendoscopy (median 19 vs 26 min) can be explained by the absence of time-consuming dye application and more resections/biopsies of macroscopic lesions in the HD chromoendoscopy arm (175 in

Table 3 Colorectal neoplasia detection rates and characteristics (proportion and total number), per-protocol analysis

Variable	HD white-light endoscopy with segmental re-inspection	HD chromoendoscopy	Single-pass HD white-light endoscopy	Missing (%)
Proportion of patients with colorectal neoplasia				
n	234	214	115	
Colorectal neoplasia (indefinite for dysplasia, low-grade or high-grade dysplasia, colorectal cancer or sessile serrated adenoma with dysplasia),* n (%)	24 (10.3)	28 (13.1)	7 (6.1)	0.0
Number of colorectal neoplasia, n (%)				0.0
0	210 (89.7)	186 (86.9)	108 (93.9)	
1	19 (8.1)	20 (9.3)	6 (5.2)	
2	4 (1.7)	8 (3.7)	1 (0.9)	
3	1 (0.4)	0 (0.0)	0 (0.0)	
Highest grade,* n (%)				
Indefinite for dysplasia	0 (0.0)	1 (0.5)	0 (0.0)	
Low-grade dysplasia	23 (9.8)	26 (12.1)	7 (6.1)	
High-grade dysplasia	0 (0.0)	1 (0.5)	0 (0.0)	
Sessile serrated adenoma with dysplasia	1 (0.4)	0 (0.0)	0 (0.0)	
Colorectal cancer	0 (0.0)	0 (0.0)	0 (0.0)	
Number of colorectal neoplasia per 10 min withdrawal time	0.0616	0.0584	0.0437	1.6
Missing	2 (0.9)	4 (1.9)	3 (2.6)	
Random biopsies taken,† n (%)	172 (73.5)	158 (73.8)	83 (72.2)	0.0
Random biopsies pathology (if positive), n (%)				0
Hyperplastic polyp	1 (0.4)	0 (0.0)	2 (1.7)	
Colorectal neoplasia characteristics (total number)				
n*	30	36	8	
Endoscopic size (mm) (median, IQR)	4.00 (3.00, 5.00)	3.50 (2.75, 5.25)	3.00 (3.00, 4.25)	6.8
Missing	1 (3.3)	4 (11.1)	0 (0.0)	
Location colon, n (%)				4.1
Right-sided	10 (33.3)	12 (33.3)	2 (25.0)	
Transverse	3 (10.0)	10 (27.8)	3 (37.5)	
Left-sided	15 (50.0)	11 (30.6)	2 (25.0)	
Rectum	1 (3.3)	2 (5.6)	0 (0.0)	
Missing	1 (3.3)	1 (2.8)	1 (12.5)	
Histological type, n (%)				0.0
Indefinite for dysplasia	0 (0.0)	1 (2.8)	0 (0.0)	
Low-grade dysplasia	29 (96.7)	34 (94.4)	8 (100.0)	
High-grade dysplasia	0 (0.0)	1 (2.8)	0 (0.0)	
Sessile serrated adenoma with dysplasia	1 (3.3)	0 (0.0)	0 (0.0)	
Paris classification, n (%)				23.0
Ip	1 (3.3)	3 (8.3)	0 (0.0)	
Is	15 (50.0)	22 (61.1)	7 (87.5)	
IIa	5 (16.7)	3 (8.3)	1 (12.5)	
Missing	9 (30.0)	8 (22.2)	0 (0.0)	
Kudo classification, n (%)				25.7
I	0 (0.0)	2 (5.6)	0 (0.0)	
II	5 (16.7)	8 (22.2)	3 (37.5)	
IIIs	2 (6.7)	2 (5.6)	0 (0.0)	
IIII	13 (43.3)	13 (36.1)	3 (37.5)	
IV	0 (0.0)	3 (8.3)	0 (0.0)	
VI	0 (0.0)	1 (2.8)	0 (0.0)	
Missing	10 (33.3)	7 (19.4)	2 (25.0)	
Endoscopic treatment, n (%)				1.4
Resection	28 (93.3)	33 (91.7)	8 (100.0)	
Biopsies only	1 (3.3)	3 (8.3)	0 (0.0)	
Missing	1 (3.3)	0 (0.0)	0 (0.0)	

*Sessile serrated adenomas without dysplasia were not included in this table.
†Number of random biopsies (if taken) was equal to two per colonic segment (eight in total) and in one study site, biopsies were taken from only two segments (so four in total).
n, number.

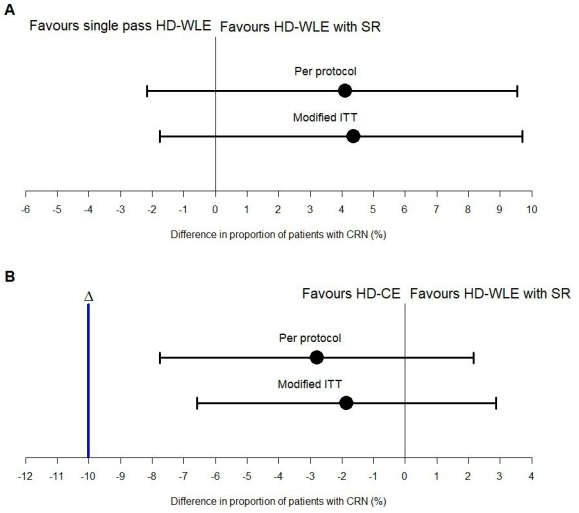

Figure 2 (A, B): Results from primary analysis (HD white-light endoscopy with segmental re-inspection vs single-pass HD white-light endoscopy [superiority analysis, panel A] and HD white-light endoscopy with segmental re-inspection vs HD chromoendoscopy [non-inferiority analysis, panel B] (per-protocol and modified intention-to-treat analysis). Results from superiority analysis (panel A): per-protocol 4.10% (95% CI −2.16:9.55, p 0.189) and modified intention-to-treat analysis 4.37% (95% CI −1.76:9.70, p 0.154). Interpretation panel B: blue line (delta −10) represents the predefined non-inferiority margin. The analysis shows non-inferiority of HD white-light endoscopy with segmental re-inspection to HD chromoendoscopy with regard to neoplasia detection rates (ie, lower boundary of the one-sided 95% CI does not exceed the pre-defined non-inferiority margin (delta)) in both per-protocol and modified intention-to-treat analysis. Results: per-protocol −2.80% (lower boundary of one-sided 95% CI −7.76, p 0.009) and modified intention-to-treat analysis −1.86% (lower boundary of one-sided 95% CI −6.58, p 0.002). CE, chromoendoscopy; CRN, colorectal neoplasia; HD, high-definition; ITT, intention-to-treat analysis; n, number; SR, segmental re-inspection; WLE, white light endoscopy.

HD chromoendoscopy vs 123 in HD white-light endoscopy with segmental re-inspection), while only 6 out of these 52 resected/biopsied macroscopic lesions in the HD chromoendoscopy group categorised as colorectal neoplasia.

HD white-light endoscopy with segmental re-inspection was not superior to single-pass HD white-light endoscopy (colorectal neoplasia detection rate 10.3% vs 6.1%), possibly due to lower than expected colorectal neoplasia yield resulting in a loss of power. Our sample size calculation and non-inferiority margin were based on expected colorectal neoplasia detection rates of 12% to 24%, based on a previous meta-analysis.[23] The difference between the colorectal neoplasia rates observed in our study (6%–13%) and previously reported rates may reflect more strictly applied surveillance guidelines and improved disease control in recent years. Considering the total number of detected/biopsied colorectal neoplasia, there was a numerical but non-significant difference between HD white-light endoscopy with segmental re-inspection and single-pass HD white-light endoscopy (30/234 procedures vs 8/115 procedures, 12.8% vs 7.0%, p=0.10). By contrast, HD white-light endoscopy with segmental re-inspection did not result in significantly more detected/biopsied non-dysplastic lesions compared with single-pass HD white-light endoscopy. 19% of all lesions (including non-dysplastic) were detected during the second inspection in HD white-light endoscopy with segmental re-inspection. This number is in a similar range as the yield of second examination in non-IBD patients (24%),[29] with studies assessing only right-sided second examination reporting detection rates that increase by approximately 5–10 percent-point.[30 31]

The uptake of HD chromoendoscopy remains low in clinical practice, with approximately 50% of endoscopists using HD chromoendoscopy in less than half of all surveillance colonoscopies.[12] Barriers include limited access to dye, reduced visualisation in case of active inflammation or suboptimal bowel preparation, inadequate training, longer procedural time, and costs.[7 12] HD white-light endoscopy with segmental re-inspection might overcome these barriers by increasing withdrawal times, inspection quality and colorectal neoplasia detection rates, without impacting biopsy/resection efficiency. In line, we found significantly less biopsied or resected non-dysplastic lesions in the HD white-light endoscopy with segmental re-inspection compared with the HD chromoendoscopy group. This may reduce the burden on both endoscopy and pathology departments, and, on a larger scale, polypectomy-related adverse events. The 8 min reduction in withdrawal time observed in HD white-light endoscopy with segmental re-inspection compared with HD chromoendoscopy may lead to cost savings. Furthermore, HD white-light endoscopy with segmental re-inspection requires no additional training and uses readily available HD equipment, further contributing to an increased uptake and efficiency compared with HD chromoendoscopy.

Most recent guideline updates recommend HD virtual chromoendoscopy as alternative to HD dye-based chromoendoscopy and HD white-light endoscopy, in contrast to guidelines available at the start of our study in 2020.[2 32] However, the supporting evidence for HD virtual chromoendoscopy remains inconclusive, with no non-inferiority trials conducted to date.[33–35] A large RCT reported comparable colorectal neoplasia detection rates between HD virtual chromoendoscopy and HD dye-based chromoendoscopy, along with a 7 min reduction in procedural time, similar as observed in HD white-light endoscopy with segmental re-inspection in our study.[34] In both a prior meta-analysis and a more recent RCT, no difference was found in performance between HD virtual chromoendoscopy and HD white-light endoscopy, while virtual chromoendoscopy was inferior to HD white-light endoscopy in a per-dysplasia analysis.[33 35] Nevertheless, HD virtual chromoendoscopy, which is recommended in non-IBD surveillance guidelines, is frequently used in the surveillance of IBD patients as well, due to its availability and ease of use.[36] Therefore, future non-inferiority trials that correct for procedural time and include an HD virtual chromoendoscopy arm are needed to definitively establish the role of HD white-light endoscopy with segmental re-inspection in clinical practice.

This study has multiple strengths. This is the largest randomised trial investigating endoscopic surveillance techniques in IBD to date. The procedures were performed by highly experienced endoscopists, with excellent cecal intubation rates (98.3%–99.2% in modified intention-to-treat analysis). We employed a three-arm study design including HD white-light endoscopy with segmental re-inspection, enabling the evaluation of the impact of the second inspection during HD chromoendoscopy without the need for post hoc analysis. Both per-protocol and modified intention-to-treat results were similar, underlining robust methodology.

There are also limitations. First, we observed lower than expected colorectal neoplasia rates with smaller than expected differences between groups, affecting both the superiority analysis and pre-specified non-inferiority margin. As a result, clinically relevant differences cannot be fully excluded, based on the

Table 4 Results from secondary analyses (HD white-light endoscopy with segmental re-inspection versus single-pass HD white-light endoscopy and HD white-light endoscopy with segmental re-inspection versus HD chromoendoscopy), per-protocol analysis. No interaction between withdrawal time and endoscopic techniques could be shown (likelihood ratio test: p=0.11), that is, the colorectal neoplasia yield per unit of time was not different between techniques

	HD white-light endoscopy with segmental re-inspection (n=234)	HD chromoendoscopy (n=214)	Single-pass HD white-light endoscopy (n=115)	Result difference (estimate, 95% CI)‡	Missing data (%)
HD white-light endoscopy with segmental re-inspection vs single-pass HD white-light endoscopy					
Colorectal neoplasia per 10 min withdrawal time	0.0616		0.0437	0.0179 (−0.0195:0.0552, p 0.39)	1.4
Total number of resected/biopsied macroscopic lesions*	123		54	5.6% (−5.5:16.7, p 0.32)	
Total number of colorectal neoplasia†	30		8	5.9% (−0.46:12.2, p 0.10)	–
Total procedure time (min) (median, IQR)	30.00 (24.00, 38.00]		24.00 (20.00, 32.50]	5.00 (3.00; 7.00, p<0.01)	2.0
Withdrawal time (min) (median, IQR)	19.00 (14.75, 26.00]		15.00 (11.00, 21.00)	4.00 (2.00; 6.00, p<0.01)	1.4
HD white-light endoscopy with segmental re-inspection vs HD chromoendoscopy					
Colorectal neoplasia per 10 min withdrawal time	0.0616	0.0584		0.0032 (−0.026:0.0324, p 0.83)	1.3
Total number of resected/biopsied macroscopic lesions*	123	175		−29.2% (−37.4:−21.0, p<0.01)	
Total number of colorectal neoplasia†	30	36		−4.0% (−10.6:2.6, p 0.23)	–
Total procedure time (min) (median, IQR)	30.00 (24.00, 38.00]	37.00 (30.00, 44.00)		−7.00 (−9.00; −5.00, p<0.01)	1.8
Withdrawal time (min) (median, IQR)	19.00 (14.75, 26.00)	26.00 (22.00, 33.00)		−8.00 (−9.00; −6.00, p<0.01)	1.3

*This number includes all resected or biopsied lesions send to the pathologist, thus also including non-dysplastic lesions.
†Colorectal neoplasia includes: indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, colorectal cancer, or sessile serrated adenoma with dysplasia.
‡Results from Wilcoxon rank sum test with continuity correction. Of note: power calculation was *not* corrected for multiple testing and all secondary analyses were analysed *not* taking into account the stratification variable for randomisation.

pre-applied non-inferiority margin. In retrospect, this margin may have been set lower to correspond with the observed colorectal neoplasia rates. However, we believe that the comparable rates of colorectal neoplasia detection in HD chromoendoscopy and HD white-light endoscopy with segmental re-inspection underscore the robustness of our findings. Second, at the start of the RCT, we expected a maximum drop-out rate of 5%, which was exceeded by approximately 10%, mostly due to logistical issues (including the COVID-19 pandemic). Since these drop-outs did not affect randomisation outcomes, we believe that this did not significantly impact our results. Finally, HD chromoendoscopy procedures were performed with methylene blue 0.04%–0.1% or indigo carmine 0.4% depending on local preferences and in line with the SCENIC statement.[7] This could have impacted outcomes due to increased heterogeneity in procedures, although there is no literature that supports a difference in performance between the two dye solutions or used concentrations.

In conclusion, HD white-light endoscopy with segmental re-inspection was non-inferior to HD chromoendoscopy while not superior to single-pass HD white-light endoscopy for colorectal neoplasia detection in IBD patients undergoing endoscopic surveillance. These outcomes may potentially be due to lower than expected colorectal neoplasia detection rates and reduced power. HD white-light endoscopy with segmental re-inspection demonstrated increased biopsy and resection efficiency compared with HD chromoendoscopy. The colorectal neoplasia detection rate per 10 min of withdrawal time was comparable between the three groups. These results suggest that the benefit of HD chromoendoscopy may be explained by the longer withdrawal time and not necessarily the dye-based contrast enhancement. Therefore, HD white-light endoscopy with segmental re-inspection may provide a feasible alternative for endoscopic surveillance in IBD.

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