

An international multicenter randomised controlled trial of chromoendoscopy versus autoFluorescence Imaging for Neoplasia Detection in patients with longstanding Ulcerative Colitis (FIND-UC)

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ABSTRACT (300 max)

Background: Patients with longstanding ulcerative colitis (UC) undergo regular dysplasia surveillance because of increased colorectal cancer risk. Previous studies demonstrated that autofluorescence imaging (AFI) and chromoendoscopy (CE) increased dysplasia detection. The aim of this study was to determine whether AFI should be further studied as an alternative method for dysplasia surveillance in patients with longstanding UC.

Methods: In this prospective international, randomised trial, 210 patients undergoing colonoscopy surveillance for longstanding UC were randomised between 1 August 2013 and 10 March 2017 for inspection with either AFI or CE (105:105). Randomisation was minimised for a previous history of dysplasia and a previous history of primary sclerosing cholangitis. The main outcome was the relative dysplasia detection rate calculated by the ratio of AFI versus CE. This relative dysplasia detection rate was determined for the proportion of UC patients in which at least one dysplastic lesion was detected and for the mean number of dysplastic lesions per patient. The relative dysplasia detection rate needed to be above 0.67 for both outcomes to support performing a subsequent large non-inferiority trial, using an 80% confidence interval. Analysis was performed per protocol. The trial is registered at Netherlands Trial Register (NTR4062).

Findings: AFI detected dysplasia in 13 (12.4%) patients, compared to 20 patients (19.1%) with CE. The relative dysplasia detection rate of CE versus AFI for the proportion of UC patients with at least one dysplastic lesion was 0.65 (80% CI; 0.43-0.99). The mean number of detected dysplastic lesions per patient was 0.13 for AFI compared to 0.37 for CE (relative dysplasia detection rate 0.36, 80% CI; 0.21-0.61). Two patients experienced an adverse event (intraprocedural mild bleeding = 1, abdominal pain = 1) in the AFI-arm and three patients (intraprocedural mild bleeding = 2, perforation = 1) in the CE-arm.

Interpretation: In this randomised study comparing AFI with CE for dysplasia surveillance in patients with longstanding UC, AFI did not meet criteria for proceeding to a large non-inferiority trial. Therefore, current AFI technology should not be further investigated as an alternative dysplasia surveillance method.

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RESEARCH IN CONTEXT

Evidence before this study

Patients with longstanding ulcerative colitis are at increased risk for developing colorectal cancer. To detect cancer and dysplasia at an early stage, periodic colonoscopic surveillance is recommended. Chromoendoscopy, in which the application of topical dye is used to highlight subtle mucosal changes, is currently advised in guidelines for performing dysplasia surveillance. However, chromoendoscopy is poorly adopted because it is time-consuming and laborious. We searched PubMed using Mesh-terms “ulcerative colitis”, “autofluorescence imaging” and “dysplasia”. We found one prospective, randomised back-to-back colonoscopy trial in 50 patients with longstanding ulcerative colitis which compared miss-rates of autofluorescence imaging compared with standard white light endoscopy. This study reported a 50% miss rate of white light endoscopy and 0% miss rate of autofluorescence imaging.

Added value of this study

This is the first study to assess a direct head-to-head comparison of autofluorescence imaging versus chromoendoscopy for dysplasia detection in patients with longstanding ulcerative colitis. This study was designed to determine whether autofluorescence imaging should be further studied as a dysplasia surveillance method that is non-inferior to chromoendoscopy. Our data demonstrate that, autofluorescence imaging did not meet predefined endpoints, and should not be further studied as an alternative dysplasia surveillance method. In a post hoc analysis chromoendoscopy was superior for number of dysplastic lesions detected.

Implications of all the available evidence

This study contributes to the growing body of evidence that chromoendoscopy is the preferred method for performing dysplasia surveillance in patients with longstanding ulcerative colitis. Further efforts should be undertaken to improve adoption of chromoendoscopy in current daily practice. Additional long-term studies are needed to determine whether increased dysplasia detection results in reduced CRC incidence and mortality.

1 INTRODUCTION

2 Patients with longstanding ulcerative colitis (UC) are at increased risk of developing colorectal
3 cancer (CRC).¹ The risk of cancer is 2·4 times higher in UC patients compared to the general population,
4 rising to 4·8 times in those with extensive colitis,¹ and the risk of cancer-related death is 1·6 times
5 higher.² As cancer develops from normal mucosa to low- and high-grade dysplasia, early detection and
6 intervention could halt this process. Multiple practice guidelines therefore recommend that patients
7 with longstanding extensive or left-sided colitis should undergo surveillance at set intervals depending
8 on individual risk factors.³⁻⁵ The gain of colonoscopic surveillance has recently been demonstrated in
9 both colorectal cancer development and CRC-related mortality, the latter probably due to cancers
10 being detected at an earlier stage when compared to no surveillance.⁶ It is logical that these early stage
11 cancers also have a more favorable prognosis, leading to improved survival. Although colonoscopic
12 surveillance is effective in terms of reducing morbidity and mortality, a significant proportion of CRCs
13 detected in these patients are post-colonoscopy CRCs.^{7,8} This finding suggests accelerated
14 carcinogenesis or ineffective surveillance where dysplastic lesions may be missed during surveillance
15 colonoscopies.

16 The optimal method of surveillance has been the focus of several studies. In the recent
17 published SCENIC consensus statement, all currently available evidence regarding dysplasia
18 surveillance was summarised.⁹ This statement used rigorous methodology for meta-analyses and
19 development of recommendations. The conclusion of the available evidence was that
20 chromoendoscopy (CE) performed with high-definition endoscopic systems was the preferred method
21 for dysplasia surveillance. As dysplasia in patients with UC tends to be flat and indistinct,^{10,11} using CE
22 for surveillance highlights subtle mucosal differences and thereby enhances dysplasia detection.¹²
23 Although CE facilitates improved dysplasia detection rates and is widely recommended as surveillance
24 strategy in current guidelines, it has not yet been completely adopted into daily endoscopy practice.¹³
25 Explanations for this poor adoption include the long learning curve associated with CE, longer
26 procedural times and skepticism whether CE improves clinically relevant outcomes such as CRC
27 incidence and mortality in patients with longstanding UC.¹⁴ Therefore, alternative surveillance
28 methods are being investigated which might be more straightforward, in order to improve detection
29 rates and adherence to current surveillance guidelines.¹⁵⁻¹⁷

30 Autofluorescence imaging (AFI) is an imaging technique that has been developed to improve
31 detection of dysplastic lesions.¹⁸ AFI is an advanced imaging technique during which blue light is used
32 to illuminate the mucosa. Endogenous tissue fluorophores e.g. collagen are excited by blue light and
33 subsequently emit fluorescent light at a longer wavelength.¹⁸ The intensity of the autofluorescent light

1 emitted differs between neoplastic and normal colonic tissue.¹⁹ The endoscopic system processes the
2 autofluorescent light into a real time pseudo-colour image on the screen. With AFI, neoplastic lesions
3 are seen as purple and non-neoplastic mucosa appears green, thereby increasing the contrast between
4 neoplastic and non-neoplastic mucosa. This push-button technology does not require additional dyes
5 or catheters and is less likely to prolong procedure time than CE. It may also be simpler to interpret
6 the images generated to show dysplasia with a simple colour change; however the resolution and
7 image stability is less good than standard high definition white light and endoscopists are highly reliant
8 on the technology to red flag dysplasia.

9 Both AFI and CE have been shown to be superior to white light endoscopy in dysplasia
10 detection in patients with longstanding UC,^{12,20} but have never been investigated in a head-to-head
11 comparison. The hypothesis for the “chromoendoscopy versus autoFluorescence Imaging for
12 Neoplasia Detection in patients with longstanding Ulcerative Colitis” (FIND-UC) randomised controlled
13 trial is that CE and AFI are equally effective for the detection of dysplastic lesions in patients undergoing
14 colonoscopic surveillance for UC. Performing a formal non-inferiority trial would require over 1,000
15 participants. Therefore we decided to perform a phase II pathfinder study with predefined
16 performance thresholds. The primary outcome was dysplasia detection, and the focus of this study
17 was on investigating whether AFI could meet clinical criteria to go forward to an appropriately powered
18 study versus CE.

METHODS

Study Design and Setting

This prospective, parallel randomised international trial compared dysplasia detection rates of AFI against CE in an UC-dysplasia surveillance cohort in 5 centres in the Netherlands and the UK. The study is reported in accordance with the CONSORT statement for reporting randomised controlled trials.²¹

Patients

Consecutive eligible patients undergoing dysplasia surveillance for longstanding UC were approached for inclusion in this trial. Patients were considered eligible who were aged 18 years or older and had been diagnosed with extensive colitis (Montreal E3) at least 8 years ago or left-sided colitis (Montreal E2) at least 15 years ago. Exclusion criteria included a change in bowel habit in the preceding two months under maintenance therapy, prior colonic resection, presence of severe comorbidity, proven genetic predisposition for CRC, coagulopathy or use of an anticoagulant drug precluding taking biopsies, and those with known colonic neoplasia (referred patients or patients refusing endoscopic or surgical treatment). Discontinuation criteria after consent included active colitis (defined as partial endoscopic Mayo score ≥ 2 ²²) and poor bowel preparation (scoring < 6 points on the Boston Bowel Preparation Scale²³). All patients were prepared with osmotic laxatives according to the local hospital protocol.

Endoscopists, Clinical Teaching Session and Endoscopy Equipment

At each participating center, 2 endoscopists performed colonoscopies for inclusion in this study. These endoscopists had extensive experience (> 500 colonoscopies) as well as experience in performing dysplasia surveillance colonoscopies in patients with longstanding UC using CE. At the start of the study, participating endoscopists were required to have performed at least 20 procedures with the AFI study equipment in patients with longstanding UC. We presumed that this resulted in comparable scope-handling abilities and interpretation of the endoscopic images between endoscopists when using AFI.

Prior to the start of the study, all participating endoscopists were invited for a one-day clinical teaching session at the Academic Medical Center, Amsterdam, the Netherlands. During this session a

1 standardised teaching module was delivered and a hands-on colonoscopy demonstration was
2 performed. In this standardised teaching module both lesion detection with AFI and CE were discussed
3 in detail. The teaching included 40 still images of AFI and corresponding HD-WLE images.

4 Both arms used CFH240AZL/I colonoscopes and Lucera Elite video processor system (Olympus
5 Medical Systems Co., Tokyo, Japan). High-definition monitor output was used for both arms placed at
6 appropriate viewing distances at the discretion of the endoscopist.

7 8 *Randomisation and allocation concealment*

9 Patients were allocated by an online randomisation program (ALEA; <http://www.tenalea.com/>)
10 by a research assistant to undergo colonoscopy with either AFI or CE (1:1 ratio). Patients with no
11 inflammatory signs and acceptable bowel preparation were randomised when the caecum was
12 reached prior to start of withdrawal. Minimisation was performed for previous personal history of
13 histological proven dysplasia and personal history of concomitant primary sclerosing cholangitis (PSC).
14 Both variables are associated with an increased risk of developing future dysplasia.³⁻⁵ All study centers
15 had access to this randomisation program.

16 The executing endoscopists could not be blinded for the endoscopic strategy used (AFI or CE)
17 as the two strategies are highly different in the images generated. As colonic tissue from patients in
18 the CE arm contained blue dye in the specimen, the pathologists might also not be blinded.

19 20 *Procedure*

21 The procedures were performed under conscious sedation using intravenous benzodiazepines
22 and opiates when requested. Carbon dioxide insufflation was used for all colonoscopies. The
23 endoscope was advanced to the caecum with the endoscope set in the high-definition white light
24 endoscopy (HD-WLE) mode. Caecal intubation was confirmed by identification of the appendiceal
25 orifice and ileocaecal valve or by intubation of the ileum. Upon reaching the cecum, the level of bowel
26 preparation was determined according to the Boston Bowel Preparation Score (BBPS).²³ In case the
27 BBPS was <6 or the patient had active colitis, the endoscope was withdrawn in the HD-WLE mode and
28 the patient was excluded from the study. If the bowel preparation was sufficient and there was no
29 active inflammation, the patient underwent colonoscopy according to the study protocol. At the start
30 of withdrawal, 20 mg hyoscine butylbromide (Buscopan, Bohringer Ingelheim) was given intravenously
31 at the discretion of the endoscopist to reduce colonic motility.

1 When the patient was allocated to AFI on entering the cecum, the imaging mode was directly
2 switched to AFI for scrutinizing the entire colon for the presence of suspicious areas, mucosal
3 irregularities, unusual ulcers and strictures during inspection on withdrawal. In the CE arm, each
4 segmental part of the colon was sprayed with 0.1% methylene blue solution or 0.2% indigocarmine
5 solution using a dye-spray catheter in a segmental manner on withdrawal of the endoscope, excess of
6 dye was suctioned and each colonic segment was scrutinised in the HD-WLE mode.

7 All suspicious areas were classified according to the Paris classification.²⁴ The size in millimetres
8 and segment of the colon was recorded. For all detected lesions, their location with respect to the
9 extent of colitis (proximal to or within the inflammatory changed colon on endoscopy) was noted.
10 Digital still images of all detected lesions and their adjacent mucosa were taken. Subsequently, all
11 detected lesions and their adjacent 'normal' mucosa were sampled for histopathological evaluation.
12 In case of obvious hyperplastic or inflammatory lesions, histopathology was performed for a maximum
13 of three of these lesions. Two random biopsy specimens were taken from every bowel segment to
14 document the presence of histologic inflammation or invisible dysplasia.

15 Research personnel attending the endoscopy recorded all procedural findings on a
16 predesigned case record form and used a stopwatch to time the total colonoscopy and withdrawal
17 times. The stopwatch was paused for bowel cleansing, lesion removal, and dye-spray application and
18 this time was calculated as the difference between the withdrawal time and the inspection time.

20 *Histopathology*

21 Histological samples were processed per participating center using standard procedures and
22 evaluated by a gastrointestinal specialist pathologist. Biopsies were graded in accordance with the
23 Vienna criteria of gastrointestinal neoplasia and dysplasia consisted of adenomacarcinoma, high-grade
24 dysplasia or low-grade dysplasia. Biopsies demonstrating any grade of dysplasia were reviewed by a
25 second gastrointestinal specialist pathologist to confirm the initial diagnosis. In total, 10% of
26 representative samples were double reported as part of internal control. Both dysplastic lesions and
27 SSLs were considered neoplastic for secondary analysis. Indefinite for dysplasia was considered neither
28 dysplastic nor neoplastic. The histological diagnosis of all biopsies was used as the reference standard
29 diagnosis in each patient. Any histopathology slides or samples transferred for external review had all
30 identifiable data removed except for the unique study number.

Study outcomes

The primary study outcome was the relative dysplasia detection rate of dysplasia by AFI versus CE. This relative dysplasia detection rate was calculated for two co-primary outcome measure; (1) the proportion of UC patients in which at least one histological proven dysplastic lesion was detected and (2) the mean number of histological proven dysplastic lesions per patient. If AFI did not achieve a relative dysplasia detection rate above 0.67 for either co-primary outcome measure, criteria for proceeding to a larger non-inferiority study were not fulfilled.

Secondary end points included the proportion of patients with at least one neoplastic lesion and sessile serrated lesion (SSL), the mean number of neoplastic lesions and SSLs, total procedure and colonoscopy withdrawal times, the yield of dysplasia on targeted tissue acquisition versus random non-targeted biopsies, description of detected lesions and procedure-related complications. The diagnostic test accuracies of endoscopic prediction of dysplasia of AFI and CE, and analysis of endoscopic features predicting dysplasia were not reported as these were beyond the scope of the current manuscript.

Determination of valuable clinical endpoints and calculation of sample size

The main outcome was the relative dysplasia detection rate calculated by the quotient of CE over AFI. Although there were two co-primary outcomes, the sample size was based on the binary outcome (dysplasia yes/no) as this was the outcome likely to provide less statistical power. After discussion with contributing authors, we determined that AFI would be clinically non-inferior to CE if its dysplasia detection rate would be within 33% of the dysplasia detection of CE. The non-inferiority margin of 33% was based on expert opinion of clinicians taking part in this study who all have experience of clinical trials of endoscopic techniques to increase dysplasia detection and serve on national committees related to endoscopy. The margin therefore likely reflects the differences clinicians would be prepared to tolerate before one technique was sufficiently inferior that the wider endoscopic community would not support a large non-inferiority trial. The chosen non-inferiority margin of 33% would result in a relative dysplasia detection rate of AFI against CE of at least 0.67 calculated for the two co-primary endpoints. If both relative dysplasia detection rates were 0.67 or higher, AFI would be taken forward to an appropriately powered non-inferiority study. If AFI would perform below this relative dysplasia detection rate of 0.67 for one of two co-primary endpoints, this would represent a clinically important difference between groups representing a sufficiently large difference. In this case, it would be decided not to proceed with a full non-inferiority study.

The relative detection rate was used to determine the sample size analysis and was based on the proportion of patients with longstanding UC in which at least one dysplastic lesion was detected. Previous studies have found a per patient dysplasia detection rate of 20% when CE was used.²⁵ If AFI would detect 33% less patients with at least one dysplastic lesion than CE, this would correspond to a dysplasia detection rate of AFI of 13.3%. The sample size was based on calculating a confidence interval that would not cross the point of no difference (i.e. a relative difference of 1), if the relative difference was exactly as hypothesized (e.g. relative detection rate of 0.67) with an 80% confidence level. It is calculated that 105 patients per arm were required for the study. With this sample size, if the relative dysplasia detection rate was 0.67, an 80% two-sided confidence interval would range from 0.44 and 1.00. Calculation of sample size was performed using nQuery Advisor version 7.0 (Statistical Solutions, Cork, Ireland)."

Statistical methods

The primary outcome was the relative detection rate related to dysplasia detection. The relative dysplasia detection rate was expressed as a ratio of AFI against CE, along with corresponding two-sided 80% confidence intervals (CIs). The first co-primary outcome for calculation of the relative detection rate was any dysplastic lesion per patient (yes/no), whilst the second, related, co-primary outcome was the number of dysplastic lesions per patient. The analysis of the co-primary outcomes were performed on a superiority basis, examining the difference between AFI and CE. The Chi-square test was used for the analysis of dysplasia detection, with confidence intervals for the relative difference based on the standard error of the log relative risk. For the number of dysplastic lesions, the data was assumed to follow the negative binomial distribution, as it did not fit the Poisson distribution well due to overdispersion (i.e. the variance was much greater than the mean), and negative binomial regression was used to compare between groups. This approach was a change from that described in the protocol, as it was felt to be a more appropriate method of analysis (supplementary material 1). For both co-primary outcomes, a 20% significance level was assumed due to the specific nature of the study. Sensitivity analyses for the primary outcomes were performed to adjust for the two factors used in the minimisation; previous dysplasia and PSC. For dysplasia detection this was performed using a generalised linear model assuming a binomial distribution and a log link function. This was used in order to obtain the relative detection rate. For number of dysplastic lesions, negative binomial regression was again used.

Secondary outcomes were the detection and number of neoplastic lesions, detection and number of SSLs, and also similar outcomes relating to targeted biopsies. These were also analysed on

a per patient basis in an equivalent way to the primary and co-primary outcomes. An additional outcome was the dysplasia yield for targeted biopsies (excluding obvious hyperplastic and inflammatory polyps), which was analysed as polyp level variable. To account for the repeat measurements from the same patients, the analysis was performed using multilevel logistic regression. A two-level model was used with polyps nested within patients. A final secondary outcome, withdrawal time, was analysed using the Mann-Whitney test due to skewed distribution of the outcome.

Analyses were performed with Stata version 13.1 (StataCorp LP., College Station, Texas, USA).

Ethical Approval and Role of the Funding Source

All sites received ethical approval from local institutional review boards (AMC2012_366, UK Research Ethic Committee Reference 13/SC/0369) and all patients gave written informed consent. Olympus Europe, Hamburg, Germany provided an unrestricted research grant that partially supported a research fellow to help executing the study. Olympus Keymed UK provided an unrestricted research grant to support study coordinators at each of the UK study sites. The sponsor had no role in the trial design, execution, data analysis, interpretation, decision to submit the paper, or manuscript preparation. JLV, JEE and ED had access to all the study data and all authors reviewed and approved the final manuscript.

RESULTS

Between 1 August 2013 and 10 March 2017, 407 patients were assessed for eligibility and 251 fulfilled the inclusion criteria and gave informed consent before the trial was completed. Eleven patients were excluded prior randomisation because of poor bowel preparation (BBPS <6) and 24

patients because of active inflammation (Mayo score ≥ 2). A total of 210 patients were randomised to undergo inspection with either AFI or CE (flowchart 1). All 210 patients, 105 in each arm, completed the study protocol and were available for analysis. Five participants experienced complications as intraprocedural bleeding after polypectomy ($N = 3$), a submucosal tear due to manipulation with biopsy forceps ($N = 1$) and post-procedural abdominal pain ($N = 1$) and this did not differ between AFI and CE. Three of these patients were treated directly with clip placement.

The baseline characteristics for patients who completed the trial were similar (table 1). The mean age of all participants was 56.1 years (SD 12.7), 41.9% were female and the median UC disease duration was 21.0 years (IQR 14.5-30.0). The median time since previous surveillance colonoscopy was 3 years (IQR 1-4). Characteristics of the study procedures are shown in table 2.

In total, 52 dysplastic lesions were identified in 34 patients. The overall dysplasia detection rate was 16.2% (95% CI, 11.8-21.8). Using CE, an 8mm flat depressed submucosal adenocarcinoma was detected (Paris classification IIa + IIc, supplemental material 2) and this patient was referred for subtotal colectomy. Two dysplastic lesions were detected by random biopsies. All other patients with dysplastic lesions were successfully treated endoscopically except for the patient with 2 invisible dysplastic lesions found on random biopsies.

Primary study outcomes

The per-protocol analysis for the main outcomes are summarised in table 3. Binary variables are summarised by the percentage occurrence in each group, along with the figures on which these were based. Continuous outcomes are summarised by the mean and standard deviation. For all outcomes the ratio of values in the AFI group relative to the CE group are presented, along with a two-sided 80% confidence interval. P-values from the exploratory analyses are also presented.

The results for the primary outcomes relating to dysplastic lesions suggested that AFI performed less well than CE and did not meet the criteria for proceeding to a larger non-inferiority study of a relative dysplasia detection rate above 0.67 for either primary outcome measure. Using CE, dysplasia was detected in 20 (19.1%) patients, while 14 patients (12.4%) were diagnosed with dysplasia during AFI resulting in a ratio of 0.65 (80% CI 0.43-0.99). More dysplastic lesions per patient were detected in the CE group than in the AFI group, with a mean of 0.37 (SD \pm 1.02) per patient in the CE group, compared to 0.13 (SD \pm 0.37) in the AFI group, relative dysplasia detection rate of 0.36 (80% CI 0.21-0.61), which was statistically significant ($p=0.01$) in an exploratory superiority analysis. There was no significant difference between groups when it came to the proportion of patients with one or more

dysplastic lesions. Results from sensitivity analysis resulted in similar outcomes and are shown in supplementary material 3. Figure 1 shows a low-grade dysplastic lesion photographed with AFI (1a) and corresponding narrow band imaging (1b) and white light images (1c and 1d).

Secondary study outcomes

The analysis of the secondary outcomes suggested that AFI was not non-inferior to CE for all outcomes; neoplastic lesions, SSLs, targeted biopsies and dysplasia yield. Additionally, the exploratory analyses suggested significantly better outcomes for CE for the number of neoplastic lesions, number of targeted biopsies and patient with one or more targeted biopsies. Furthermore, there was a suggestion that CE was superior for patients with one or more neoplastic lesion and for presence and number of SSLs, although these results did not quite reach statistical significance.

An additional secondary outcome, withdrawal time, was examined on a superiority basis. Total withdrawal times were significantly shorter with AFI (18.0 min, IQR 15.0-24.9) compared to withdrawal with CE (25.1 min, IQR 18.9-33.8, $p<0.0001$). This was mainly because of prolonged procedural time associated with spraying of dye, suctioning of excess dye and taking targeted biopsies (table 2).

In total, 138 targeted biopsies were taken during extubation with CE and 65 during extubation with AFI when not taking obvious hyperplastic and inflammatory polyps into account. During CE, the proportion of patients in whom targeted biopsies were taken was significantly higher than when extubation was performed with AFI (63.8% vs. 41.9%, $p=0.002$). The dysplasia yield of targeted biopsies, excluding obvious hyperplastic and inflammatory polyps did not differ between AFI and CE (20.0% vs. 26.8%, $p=0.29$).

The additional per-biopsy yield of 2,016 collected random biopsies was 0.1% (95% CI, 0-0.4) and both of these were detected in one patient who already had a visible dysplastic lesion on AFI. Calculated per patient, there was no additional yield for random biopsies in detecting patients with dysplasia.

Characteristics of detected lesions

Extubation with AFI detected 14 dysplastic lesions while inspection with CE resulted in 38 detected dysplastic lesions. Most dysplastic lesions were located proximal to the descending colon (table 4). In two (2.6%) of 78 lesions where the surrounding mucosa was biopsied, dysplasia was

1 detected. In addition to these dysplastic lesions, 151 non-dysplastic lesions were detected by targeted
2 biopsies in both arms. Three lesions were histologically diagnosed as indefinite for dysplasia and 1
3 neuro-endocrine tumour grade 1 was detected.

4 Furthermore, 18 SSLs were diagnosed at histopathology. Of these, 13 (72%) were located
5 proximal to the splenic flexure, and their median size was 8mm (range 2-30). Fifteen (83%) of 18 SSLs
6 were located in a (previously) inflamed segment. The majority of SSLs (67%) had flat (Paris IIa)
7 morphology. Eleven SSLs were removed completely, while the others were biopsied only. None of
8 these SSLs contained dysplasia at histological analysis. In 1 (10%) of 10 patients diagnosed with SSL, a
9 synchronous dysplastic lesion was detected.

10 11 12 13 14 15 16 17 18 19 20 21 22 23 **DISCUSSION**

24 This randomised trial with predefined performance thresholds aimed to investigate non-
25 inferiority of AFI compared to CE for dysplasia detection in patients with longstanding UC. Based on
26 the relative detection rate of AFI versus CE for the proportion of patients with at least one dysplastic
27 lesion and the mean number of dysplastic lesions detected per patient, AFI did not meet diagnostic

criteria to be taken forward to an appropriately powered non-inferiority study. Exploratory analysis showed that CE detected significantly more dysplastic and neoplastic lesions per patient. Furthermore, using CE during extubation increased the proportion of patients with targeted biopsies at the cost of prolonged procedural times. Based on our predefined thresholds, we suggest current AFI technology should not be further studied as alternative to CE, and CE remains the preferred method for performing dysplasia surveillance in patients with longstanding UC.

Although a previous study showed a decrease in miss rates using AFI compared to WLE, results could not be corroborated in this head-to-head comparison to CE.²⁰ Using AFI, dysplastic tissue is visible as purple against a green background of normal colonic tissue. However, two previous retrospective studies showed that a purple lesion was observed in 38-86% of dysplastic lesions, possibly indicating that purple AFI color may not lead to detection of all dysplastic lesions in patients with longstanding UC.^{26,27} Possibly, those dysplastic lesions that were green on AFI were missed. Other push-button image-enhanced endoscopy technologies such as narrow band imaging (NBI) have been formally studied in dysplasia surveillance in IBD patients, without documenting a benefit of NBI over WLE or CE.^{9,20,25,28,29} In a recently published trial performed by Bisschops et al. NBI and CE were similar in dysplasia detection.³⁰ However, this study was powered to detect a threefold detection capacity of either technique relative to the other technique thereby precluding any conclusions on non-inferiority of NBI compared to CE. A recent study comparing I-SCAN to CE and HD-WLE in colitis did not show a difference in detection between the techniques.³¹ We are not aware of any other data available for I-SCAN or Flexible spectral Imaging Color Enhancement (FICE) in colitis. Future studies proving non-inferiority of new-generation image-enhanced endoscopy techniques may be of interest. A study primarily looking at implementation suggested a benefit of high definition CE over HD-WLE.³² As HD-WLE remains an attractive alternative to high-definition CE several randomized trials are currently comparing these modalities and the results are awaited.^{33,34}

In this study, CE resulted in more targeted biopsies on average and on a per patient basis. The per biopsy yield of these targeted biopsies did not differ between AFI and CE (20.0% versus 26.8%, $p=0.29$). Furthermore, random biopsies did not prove to be beneficial for detecting additional patients with invisible dysplasia compared to targeted biopsies. In this study, only 2 random biopsies contained invisible dysplasia. The per-biopsy yield was only 0.1% (95% CI, 0-0.4). A recent published prospective study in 1,000 IBD patients found that over 30,000 random biopsies yielded a 0.2% per-biopsy rate when performing CE during extubation.³⁵ However, random biopsies did increase the per-patient dysplasia detection rate by 12.8%. Dysplasia detected by random biopsies was associated with presence of PSC, previous dysplasia and a tubular shortened colon. In a randomised, multicentre study, 246 patients underwent either targeted plus random biopsies or targeted biopsies alone.³⁶ The

1 targeted biopsies group was equally high in yield of dysplasia compared to random and targeted biopsy
2 group. The targeted biopsy approach appeared to be more cost-effective. In line with recent
3 guidelines^{4,5}, random biopsies may be omitted because of their low yield when performing surveillance
4 with CE, although specific risk-groups may benefit from this approach, such as those with PSC.³⁵

5 In this study, a non-significant trend was observed favoring CE for SSL detection. The majority
6 of colitis associated cancers may develop from an inflammation-related cancer pathway and the
7 traditional adenoma-carcinoma pathway.³⁷ Very little is known on the role of the serrated neoplasia
8 pathway in patients with longstanding UC. Studies on SSL incidence in colitis patients are scarce, and
9 may be unreliable due to underreporting of serrated lesions as these were considered having no
10 malignant potential in colitis. In addition, these may have been hard to identify during colonoscopy
11 due to background inflammation, and their similar endoscopic appearance to post-inflammatory
12 changes. Previous translational work has shown that a minority of cancers in colitis are related to the
13 serrated neoplasia pathway.^{38,39} Whether SSLs are sporadic bystanders or related to ongoing
14 inflammation is unknown. Interestingly, the majority of SSLs (83%) detected in this study were located
15 in a (previously) inflamed segment. Previous work also suggests that the synchronous and
16 metachronous dysplasia risk in patients with SSLs or serrated epithelial changes may be higher.⁴⁰⁻⁴² As
17 published results are scarce, limited by small samples and outcomes are heterogeneous, we advise to
18 completely remove SSLs in colitis patients whenever possible.

19 This trial was designed as a phase II pathfinder trial with 210 patients, but proved to be a
20 challenging trial in terms of recruitment as 407 patients were assessed for eligibility. This was in part
21 due to our very strict in- and exclusion criteria and the nature of the underlying disease as a
22 considerable fraction of patients was excluded at the time of colonoscopy because of active Mayo 2
23 inflammation (N=24) in a bowel segment or poor preparation (N=11). It has been shown previously
24 that patients undergoing dysplasia surveillance in IBD have less good adherence to bowel
25 preparation.⁴³ Conducting the very large studies that would be needed to show a benefit of CE in terms
26 of colorectal cancer prevention are likely to represent a formidable logistical challenge.

27 Although multiple studies and practice guidelines clearly support the use of CE for dysplasia
28 surveillance in patients with longstanding UC, adoption of this technique in daily clinical practice
29 remains challenging.⁴⁴ As CE is associated with a long learning curve, training tools should be developed
30 to promote ongoing learning and improvement of dysplasia detection. Development of image- and
31 video-libraries, online quizzes and hands-on training days may facilitate learning curves. Furthermore,
32 prospective longitudinal studies with registration of post-colonoscopy CRCs, morbidity and mortality
33 are needed to defend against skepticism about using CE for dysplasia surveillance. In this light,

1 evaluation of findings at follow-up surveillance colonoscopy of FIND-UC participants and their rates of
2 dysplasia may be of further interest to underline current conclusions and potential benefit of CE over
3 AFI. Last, as CE has been shown to increase procedural times, redefining reimbursement payments for
4 performing CE may increase its adoption into clinical practice.

5 This study has a number of limitations. Three of the five centres were tertiary academic
6 centres, so the patient populations may not be completely representative of the wider IBD surveillance
7 population. This is indicated by the high rates of patients with previous dysplasia and PSC, and the high
8 overall dysplasia detection rate compared to recently published large population based cohorts of
9 chromoendoscopy in IBD.^{35,45,46} Most endoscopists were also sub-specialists with extensive experience
10 in performing CE, and were not blinded which may have led to unconscious bias and may have favored
11 CE. In common with most trials of CE we did not control for the “washing” effect of dye-spray which
12 may have improved mucosal visualization, although overall inspection times were similar.
13 Furthermore, AFI did not meet the predefined clinical acceptability thresholds, and CE was superior to
14 AFI for the mean number of detected dysplastic lesions per patient. The dysplasia detection rate per
15 patient of AFI (12.4%) in the FIND-UC trial was at least similar compared to that of recently published
16 WLE dysplasia detection rates in academic centers.^{28,35,46} Moreover, detected dysplastic lesions were
17 predominantly diminutive in size and whether the size of dysplastic lesions is of clinical importance
18 remains to be addressed. Therefore, we do not think that patients that were allocated to undergo
19 dysplasia surveillance with AFI encountered any disadvantage by participating in this study. Last, some
20 endoscopists performed more study colonoscopies than other possibly introducing a learning curve
21 for AFI during the study. To minimise this learning curve during the study, participating endoscopists
22 were required to have performed at least 20 procedures with the AFI study equipment in patients with
23 longstanding UC prior to the start of the study. All study endoscopists also participated in a one-day
24 teaching session and therefore we presume that this resulted in comparable scope-handling abilities
25 and interpretation of the endoscopic images between endoscopists when using AFI.

26 This study can be regarded as an exemplar for the introduction of new endoscopic technology
27 into daily clinical practice. Prior research showed AFI to be superior to WLE in dysplasia detection in a
28 randomised order back-to-back colonoscopy study. In order to be a reasonable alternative to CE, which
29 is currently advised in prevailing guidelines, AFI should be at least non-inferior to CE. Performing such
30 a formal non-inferiority trial would have required over 1,300 participants. Therefore we decided to
31 perform a phase II pathfinder study with predefined performance thresholds which should be reached
32 before AFI should be further investigated in a larger non-inferiority trial. Our approach avoided the
33 very considerable extra efforts that would have been needed to undertake such a large trial.

1 In conclusion, in this randomised controlled trial AFI could not demonstrate predefined
2 performance thresholds compared to CE for dysplasia detection in patients with longstanding UC. CE
3 was superior in an exploratory post-hoc evaluation and therefore remains the preferred surveillance
4 technique. Future work should focus on comparing CE with high-definition white light endoscopy or
5 high-definition image-enhanced endoscopy techniques as NBI, FICE and iScan. In the meantime,
6 strenuous efforts should be undertaken to increase the adoption of CE as preferred dysplasia
7 surveillance method in daily clinical practice.

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22 analysis.

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24 Figure 1. CONSORT patient flowchart.

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Figure 2. Image of 10mm flat-elevated lesion detected with AFI (1a) with corresponding narrow band imaging (1b) and white light images (1c). The lesion was lifted with submucosal methylene blue prior to endoscopic mucosal resection (1d).

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REFERENCES

1. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2012; **10**(6): 639-45.

2. Jess T, Frisch M, Simonsen J. Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2013; **11**(1): 43-8.

3. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010; **59**(5): 666-89.

4. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. *Journal of Crohn's & colitis* 2013; **7**(12): 982-1018.

5. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010; **138**(2): 738-45.
6. Bye WA, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colon cancer in patients with inflammatory bowel disease. *The Cochrane database of systematic reviews* 2017; **9**: CD000279.
7. Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, et al. Incidence of Interval Colorectal Cancer Among Inflammatory Bowel Disease Patients Undergoing Regular Colonoscopic Surveillance. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(9): 1656-61.
8. Wang YR, Cangemi JR, Loftus EV, Jr., Picco MF. Rate of early/missed colorectal cancers after colonoscopy in older patients with or without inflammatory bowel disease in the United States. *The American journal of gastroenterology* 2013; **108**(3): 444-9.
9. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointestinal endoscopy* 2015; **81**(3): 489-501.e26.
10. Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? *Gastrointestinal endoscopy* 2007; **65**(7): 998-1004.
11. Sugimoto S, Naganuma M, Iwao Y, et al. Endoscopic morphologic features of ulcerative colitis-associated dysplasia classified according to the SCENIC consensus statement. *Gastrointestinal endoscopy* 2017; **85**(3): 639-46.e2.
12. Wu L, Li P, Wu J, Cao Y, Gao F. The diagnostic accuracy of chromoendoscopy for dysplasia in ulcerative colitis: meta-analysis of six randomized controlled trials. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2012; **14**(4): 416-20.
13. Shinozaki M, Kobayashi K, Kunisaki R, et al. Surveillance for dysplasia in patients with ulcerative colitis: Discrepancy between guidelines and practice. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society* 2017.
14. Sanduleanu S, Kaltenbach T, Barkun A, et al. A roadmap to the implementation of chromoendoscopy in inflammatory bowel disease colonoscopy surveillance practice. *Gastrointestinal endoscopy* 2016; **83**(1): 213-22.
15. Dekker E, van den Broek FJ, Reitsma JB, et al. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. *Endoscopy* 2007; **39**(3): 216-21.
16. Ortner MA, Fusco V, Ebert B, et al. Time-gated fluorescence spectroscopy improves endoscopic detection of low-grade dysplasia in ulcerative colitis. *Gastrointestinal endoscopy* 2010; **71**(2): 312-8.
17. Leifeld L, Rogler G, Stallmach A, et al. White-Light or Narrow-Band Imaging Colonoscopy in Surveillance of Ulcerative Colitis: A Prospective Multicenter Study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015; **13**(10): 1776-81.e1.
18. DaCosta RS, Wilson BC, Marcon NE. Optical techniques for the endoscopic detection of dysplastic colonic lesions. *Current opinion in gastroenterology* 2005; **21**(1): 70-9.
19. DaCosta RS, Andersson H, Wilson BC. Molecular fluorescence excitation-emission matrices relevant to tissue spectroscopy. *Photochemistry and photobiology* 2003; **78**(4): 384-92.
20. van den Broek FJ, Fockens P, van Eeden S, et al. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. *Gut* 2008; **57**(8): 1083-9.
21. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of internal medicine* 2010; **152**(11): 726-32.

22. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *The New England journal of medicine* 1987; **317**(26): 1625-9.
23. Calderwood AH, Jacobson BC. Comprehensive validation of the Boston Bowel Preparation Scale. *Gastrointestinal endoscopy* 2010; **72**(4): 686-92.
24. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointestinal endoscopy* 2003; **58**(6 Suppl): S3-43.
25. Pellise M, Lopez-Ceron M, Rodriguez de Miguel C, et al. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. *Gastrointestinal endoscopy* 2011; **74**(4): 840-8.
26. Yoshioka S, Mitsuyama K, Takedatsu H, et al. Advanced endoscopic features of ulcerative colitis-associated neoplasias: Quantification of autofluorescence imaging. *International journal of oncology* 2016; **48**(2): 551-8.
27. Matsumoto T, Nakamura S, Moriyama T, Hirahashi M, Iida M. Autofluorescence imaging colonoscopy for the detection of dysplastic lesions in ulcerative colitis: a pilot study. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2010; **12**(10 Online): e291-7.
28. Ignjatovic A, East JE, Subramanian V, et al. Narrow band imaging for detection of dysplasia in colitis: a randomized controlled trial. *The American journal of gastroenterology* 2012; **107**(6): 885-90.
29. Efthymiou M, Allen PB, Taylor AC, et al. Chromoendoscopy versus narrow band imaging for colonic surveillance in inflammatory bowel disease. *Inflammatory bowel diseases* 2013; **19**(10): 2132-8.
30. Bisschops R, Bessissow T, Joseph JA, et al. Chromoendoscopy versus narrow band imaging in UC: a prospective randomised controlled trial. *Gut* 2017.
31. Iacucci M, Kaplan GG, Panaccione R, et al. 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. *The American journal of gastroenterology* 2017.
32. Picco MF, Pasha S, Leighton JA, et al. Procedure time and the determination of polypoid abnormalities with experience: implementation of a chromoendoscopy program for surveillance colonoscopy for ulcerative colitis. *Inflammatory bowel diseases* 2013; **19**(9): 1913-20.
33. Mohammed N, Kant P, Abid F, et al. High definition white light endoscopy (HDWLE) versus high definition with chromoendoscopy (HDCE) in the detection of dysplasia in long standing ulcerative colitis: A randomised controlled trial. *Gut* 2015; **64**: A14-A5.
34. Park SJ, Kim HS, Yang DH, et al. High definition chromoendoscopy with water-jet versus high definition white light endoscopy in the detection of dysplasia in long standing ulcerative colitis: A multicenter prospective randomized controlled study. *Gastroenterology* 2016; **1**: S1270.
35. Moussata D, Allez M, Cazals-Hatem D, et al. Are random biopsies still useful for the detection of neoplasia in patients with IBD undergoing surveillance colonoscopy with chromoendoscopy? *Gut* 2017.
36. Watanabe T, Ajioka Y, Mitsuyama K, et al. Comparison of Targeted vs Random Biopsies for Surveillance of Ulcerative Colitis-Associated Colorectal Cancer. *Gastroenterology* 2016; **151**(6): 1122-30.
37. Triantafillidis JK, Nasioulas G, Kosmidis PA. Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. *Anticancer research* 2009; **29**(7): 2727-37.
38. Odze RD, Brien T, Brown CA, Hartman CJ, Wellman A, Fogt F. Molecular alterations in chronic ulcerative colitis-associated and sporadic hyperplastic polyps: a comparative analysis. *The American journal of gastroenterology* 2002; **97**(5): 1235-42.
39. Aust DE, Haase M, Dobryden L, et al. Mutations of the BRAF gene in ulcerative colitis-related colorectal carcinoma. *International journal of cancer Journal international du cancer* 2005; **115**(5): 673-7.

- 1 40. Jackson WE, Achkar JP, Macaron C, et al. The Significance of Sessile Serrated Polyps in
2 Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2016; **22**(9): 2213-20.
- 3 41. Johnson D, Khanna S, Smyrk T, et al. Prevalence and outcomes of colonic serrated epithelial
4 changes in patients with ulcerative colitis and crohn's colitis. *American Journal of Gastroenterology*
5 2013; **108**: S541.
- 6 42. Parian A, Koh J, Limketkai BN, et al. Association between serrated epithelial changes and
7 colorectal dysplasia in inflammatory bowel disease. *Gastrointestinal endoscopy* 2016; **84**(1): 87-95
8 e1.
- 9 43. Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on
10 quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of
11 Gastrointestinal Endoscopy European multicenter study. *Gastrointestinal endoscopy* 2005; **61**(3):
12 378-84.
- 13 44. Gallinger ZR, Rumman A, Murthy SK, Nguyen GC. Perspectives on endoscopic surveillance of
14 dysplasia in inflammatory bowel disease: a survey of academic gastroenterologists. *Endoscopy*
15 *international open* 2017; **5**(10): E974-E9.
- 16 45. Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, et al. Chromoendoscopy for
17 Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With
18 Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study. *The*
19 *American journal of gastroenterology* 2015; **110**(7): 1014-21.
- 20 46. Carballal S, Maisterra S, Lopez-Serrano A, et al. Real-life chromoendoscopy for neoplasia
21 detection and characterisation in long-standing IBD. *Gut* 2016.

22