

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

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1 **ABSTRACT (300 max)**

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

7 **Methods:** In this prospective international, randomised trial, 210 patients undergoing colonoscopy
8 surveillance for longstanding UC were randomised between 1 August 2013 and 10 March 2017 for
9 inspection with either AFI or CE (105:105). Randomisation was minimised for a previous history of
10 dysplasia and a previous history of primary sclerosing cholangitis. The main outcome was the relative
11 dysplasia detection rate calculated by the ratio of AFI versus CE. This relative dysplasia detection rate
12 was determined for the proportion of UC patients in which at least one dysplastic lesion was
13 detected and for the mean number of dysplastic lesions per patient. The relative dysplasia detection
14 rate needed to be above 0·67 for both outcomes to support performing a subsequent large non-
15 inferiority trial, using an 80% confidence interval. Analysis was performed per protocol. The trial is
16 registered at Netherlands Trial Register (NTR4062).

17 **Findings:** AFI detected dysplasia in 13 (12·4%) patients, compared to 20 patients (19·1%) with CE. The
18 relative dysplasia detection rate of CE versus AFI for the proportion of UC patients with at least one
19 dysplastic lesion was 0·65 (80% CI; 0·43-0·99). The mean number of detected dysplastic lesions per
20 patient was 0·13 for AFI compared to 0·37 for CE (relative dysplasia detection rate 0·36, 80% CI; 0·21-
21 0·61). Two patients experienced an adverse event (intraprocedural mild bleeding = 1, abdominal
22 pain = 1) in the AFI-arm and three patients (intraprocedural mild bleeding = 2, perforation = 1) in the
23 CE-arm.

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

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31

1 **RESEARCH IN CONTEXT**

2 Evidence before this study

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

13 Added value of this study

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

21 Implications of all the available evidence

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

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1 INTRODUCTION

2 Patients with longstanding ulcerative colitis (UC) are at increased risk of developing
3 colorectal cancer (CRC).¹ The risk of cancer is 2·4 times higher in UC patients compared to the general
4 population, rising to 4·8 times in those with extensive colitis,¹ and the risk of cancer-related death is
5 1·6 times higher.² As cancer develops from normal mucosa to low- and high-grade dysplasia, early
6 detection and intervention could halt this process. Multiple practice guidelines therefore recommend
7 that patients with longstanding extensive or left-sided colitis should undergo surveillance at set
8 intervals depending on individual risk factors.³⁻⁵ The gain of colonoscopic surveillance has recently
9 been demonstrated in both colorectal cancer development and CRC-related mortality, the latter
10 probably due to cancers being detected at an earlier stage when compared to no surveillance.⁶ It is
11 logical that these early stage cancers also have a more favorable prognosis, leading to improved
12 survival. Although colonoscopic surveillance is effective in terms of reducing morbidity and mortality,
13 a significant proportion of CRCs detected in these patients are post-colonoscopy CRCs.^{7,8} This finding
14 suggests accelerated carcinogenesis or ineffective surveillance where dysplastic lesions may be
15 missed during surveillance 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
21 method for dysplasia surveillance. As dysplasia in patients with UC tends to be flat and indistinct,^{10,11}
22 using CE for surveillance highlights subtle mucosal differences and thereby enhances dysplasia
23 detection.¹² Although CE facilitates improved dysplasia detection rates and is widely recommended
24 as surveillance strategy in current guidelines, it has not yet been completely adopted into daily
25 endoscopy practice.¹³ Explanations for this poor adoption include the long learning curve associated
26 with CE, longer procedural times and skepticism whether CE improves clinically relevant outcomes
27 such as CRC incidence and mortality in patients with longstanding UC.¹⁴ Therefore, alternative
28 surveillance methods are being investigated which might be more straightforward, in order to
29 improve detection 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

1 light emitted differs between neoplastic and normal colonic tissue.¹⁹ The endoscopic system
2 processes the autofluorescent light into a real time pseudo-colour image on the screen. With AFI,
3 neoplastic lesions are seen as purple and non-neoplastic mucosa appears green, thereby increasing
4 the contrast between neoplastic and non-neoplastic mucosa. This push-button technology does not
5 require additional dyes or catheters and is less likely to prolong procedure time than CE. It may also
6 be simpler to interpret the images generated to show dysplasia with a simple colour change;
7 however the resolution and image stability is less good than standard high definition white light and
8 endoscopists are highly reliant 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
13 controlled trial is that CE and AFI are equally effective for the detection of dysplastic lesions in
14 patients undergoing colonoscopic surveillance for UC. Performing a formal non-inferiority trial would
15 require over 1,000 participants. Therefore we decided to perform a phase II pathfinder study with
16 predefined performance thresholds. The primary outcome was dysplasia detection, and the focus of
17 this study was on investigating whether AFI could meet clinical criteria to go forward to an
18 appropriately powered study versus CE.

19

1 **METHODS**

2 *Study Design and Setting*

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

7

8 *Patients*

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

20

21 *Endoscopists, Clinical Teaching Session and Endoscopy Equipment*

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

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

1 session a standardised teaching module was delivered and a hands-on colonoscopy demonstration
2 was performed. In this standardised teaching module both lesion detection with AFI and CE were
3 discussed 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
5 (Olympus Medical Systems Co., Tokyo, Japan). High-definition monitor output was used for both
6 arms placed at 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;
10 <http://www.tenalea.com/>) by a research assistant to undergo colonoscopy with either AFI or CE (1:1
11 ratio). Patients with no inflammatory signs and acceptable bowel preparation were randomised
12 when the caecum was reached prior to start of withdrawal. Minimisation was performed for previous
13 personal history of histological proven dysplasia and personal history of concomitant primary
14 sclerosing cholangitis (PSC). Both variables are associated with an increased risk of developing future
15 dysplasia.³⁻⁵ All study centers 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
22 benzodiazepines and opiates when requested. Carbon dioxide insufflation was used for all
23 colonoscopies. The endoscope was advanced to the caecum with the endoscope set in the high-
24 definition white light endoscopy (HD-WLE) mode. Caecal intubation was confirmed by identification
25 of the appendiceal orifice and ileocaecal valve or by intubation of the ileum. Upon reaching the
26 cecum, the level of bowel preparation was determined according to the Boston Bowel Preparation
27 Score (BBPS).²³ In case the BBPS was <6 or the patient had active colitis, the endoscope was
28 withdrawn in the HD-WLE mode and the patient was excluded from the study. If the bowel
29 preparation was sufficient and there was no active inflammation, the patient underwent
30 colonoscopy according to the study protocol. At the start of withdrawal, 20 mg hyoscine

1 butylbromide (Buscopan, Bohringer Ingelheim) was given intravenously at the discretion of the
2 endoscopist to reduce colonic motility.

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

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

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

22

23 *Histopathology*

24 Histological samples were processed per participating center using standard procedures and
25 evaluated by a gastrointestinal specialist pathologist. Biopsies were graded in accordance with the
26 Vienna criteria of gastrointestinal neoplasia and dysplasia consisted of adenocarcinoma, high-
27 grade dysplasia or low-grade dysplasia. Biopsies demonstrating any grade of dysplasia were reviewed
28 by a second gastrointestinal specialist pathologist to confirm the initial diagnosis. In total, 10% of
29 representative samples were double reported as part of internal control. Both dysplastic lesions and
30 SSLs were considered neoplastic for secondary analysis. Indefinite for dysplasia was considered
31 neither dysplastic nor neoplastic. The histological diagnosis of all biopsies was used as the reference

1 standard diagnosis in each patient. Any histopathology slides or samples transferred for external
2 review had all identifiable data removed except for the unique study number.

3

4 *Study outcomes*

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

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

18

19 *Determination of valuable clinical endpoints and calculation of sample size*

20 The main outcome was the relative dysplasia detection rate calculated by the quotient of CE
21 over AFI. Although there were two co-primary outcomes, the sample size was based on the binary
22 outcome (dysplasia yes/no) as this was the outcome likely to provide less statistical power. After
23 discussion with contributing authors, we determined that AFI would be clinically non-inferior to CE if
24 its dysplasia detection rate would be within 33% of the dysplasia detection of CE. The non-inferiority
25 margin of 33% was based on expert opinion of clinicians taking part in this study who all have
26 experience of clinical trials of endoscopic techniques to increase dysplasia detection and serve on
27 national committees related to endoscopy. The margin therefore likely reflects the differences
28 clinicians would be prepared to tolerate before one technique was sufficiently inferior that the wider
29 endoscopic community would not support a large non-inferiority trial. The chosen non-inferiority
30 margin of 33% would result in a relative dysplasia detection rate of AFI against CE of at least 0.67
31 calculated for the two co-primary endpoints. If both relative dysplasia detection rates were 0.67 or

1 higher, AFI would be taken forward to an appropriately powered non-inferiority study. If AFI would
2 perform below this relative dysplasia detection rate of 0.67 for one of two co-primary endpoints, this
3 would represent a clinically important difference between groups representing a sufficiently large
4 difference. In this case, it would be decided not to proceed with a full non-inferiority study.

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

16

17 *Statistical methods*

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

1 distribution and a log link function. This was used in order to obtain the relative detection rate. For
2 number of dysplastic lesions, negative binomial regression was again used.

3 Secondary outcomes were the detection and number of neoplastic lesions, detection and
4 number of SSLs, and also similar outcomes relating to targeted biopsies. These were also analysed on
5 a per patient basis in an equivalent way to the primary and co-primary outcomes. An additional
6 outcome was the dysplasia yield for targeted biopsies (excluding obvious hyperplastic and
7 inflammatory polyps), which was analysed as polyp level variable. To account for the repeat
8 measurements from the same patients, the analysis was performed using multilevel logistic
9 regression. A two-level model was used with polyps nested within patients. A final secondary
10 outcome, withdrawal time, was analysed using the Mann-Whitney test due to skewed distribution of
11 the outcome.

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

13

14 *Ethical Approval and Role of the Funding Source*

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

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1 **RESULTS**

2

3 Between 1 August 2013 and 10 March 2017, 407 patients were assessed for eligibility and
4 251 fulfilled the inclusion criteria and gave informed consent before the trial was completed. Eleven
5 patients were excluded prior randomisation because of poor bowel preparation (BBPS <6) and 24
6 patients because of active inflammation (Mayo score ≥ 2). A total of 210 patients were randomised to
7 undergo inspection with either AFI or CE (flowchart 1). All 210 patients, 105 in each arm, completed
8 the study protocol and were available for analysis. Five participants experienced complications as
9 intraprocedural bleeding after polypectomy (N = 3), a submucosal tear due to manipulation with
10 biopsy forceps (N = 1) and post-procedural abdominal pain (N = 1) and this did not differ between AFI
11 and CE. Three of these patients were treated directly with clip placement.

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

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

22

23 *Primary study outcomes*

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

29 The results for the primary outcomes relating to dysplastic lesions suggested that AFI
30 performed less well than CE and did not meet the criteria for proceeding to a larger non-inferiority
31 study of a relative dysplasia detection rate above 0.67 for either primary outcome measure. Using
32 CE, dysplasia was detected in 20 (19.1%) patients, while 14 patients (12.4%) were diagnosed with

1 dysplasia during AFI resulting in a ratio of 0.65 (80% CI 0.43-0.99). More dysplastic lesions per patient
2 were detected in the CE group than in the AFI group, with a mean of 0.37 (SD \pm 1.02) per patient in
3 the CE group, compared to 0.13 (SD \pm 0.37) in the AFI group, relative dysplasia detection rate of 0.36
4 (80% CI 0.21-0.61), which was statistically significant ($p=0.01$) in an exploratory superiority analysis.
5 There was no significant difference between groups when it came to the proportion of patients with
6 one or more dysplastic lesions. Results from sensitivity analysis resulted in similar outcomes and are
7 shown in supplementary material 3. Figure 1 shows a low-grade dysplastic lesion photographed with
8 AFI (1a) and corresponding narrow band imaging (1b) and white light images (1c and 1d).

9

10 *Secondary study outcomes*

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

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

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

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

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

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

1 DISCUSSION

2 This randomised trial with predefined performance thresholds aimed to investigate non-
3 inferiority of AFI compared to CE for dysplasia detection in patients with longstanding UC. Based on
4 the relative detection rate of AFI versus CE for the proportion of patients with at least one dysplastic
5 lesion and the mean number of dysplastic lesions detected per patient, AFI did not meet diagnostic
6 criteria to be taken forward to an appropriately powered non-inferiority study. Exploratory analysis
7 showed that CE detected significantly more dysplastic and neoplastic lesions per patient.
8 Furthermore, using CE during extubation increased the proportion of patients with targeted biopsies
9 at the cost of prolonged procedural times. Based on our predefined thresholds, we suggest current
10 AFI technology should not be further studied as alternative to CE, and CE remains the preferred
11 method for performing dysplasia surveillance in patients with longstanding UC.

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

30 In this study, CE resulted in more targeted biopsies on average and on a per patient basis.
31 The per biopsy yield of these targeted biopsies did not differ between AFI and CE (20.0% versus
32 26.8%, $p=0.29$). Furthermore, random biopsies did not prove to be beneficial for detecting additional
33 patients with invisible dysplasia compared to targeted biopsies. In this study, only 2 random biopsies

1 contained invisible dysplasia. The per-biopsy yield was only 0.1% (95% CI, 0-0.4). A recent published
2 prospective study in 1,000 IBD patients found that over 30,000 random biopsies yielded a 0.2% per-
3 biopsy rate when performing CE during extubation.³⁵ However, random biopsies did increase the per-
4 patient dysplasia detection rate by 12.8%. Dysplasia detected by random biopsies was associated
5 with presence of PSC, previous dysplasia and a tubular shortened colon. In a randomised, multicentre
6 study, 246 patients underwent either targeted plus random biopsies or targeted biopsies alone.³⁶ The
7 targeted biopsies group was equally high in yield of dysplasia compared to random and targeted
8 biopsy group. The targeted biopsy approach appeared to be more cost-effective. In line with recent
9 guidelines^{4,5}, random biopsies may be omitted because of their low yield when performing
10 surveillance with CE, although specific risk-groups may benefit from this approach, such as those with
11 PSC.³⁵

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

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

1 Although multiple studies and practice guidelines clearly support the use of CE for dysplasia
2 surveillance in patients with longstanding UC, adoption of this technique in daily clinical practice
3 remains challenging.⁴⁴ As CE is associated with a long learning curve, training tools should be
4 developed to promote ongoing learning and improvement of dysplasia detection. Development of
5 image- and video-libraries, online quizzes and hands-on training days may facilitate learning curves.
6 Furthermore, prospective longitudinal studies with registration of post-colonoscopy CRCs, morbidity
7 and mortality are needed to defend against skepticism about using CE for dysplasia surveillance. In
8 this light, evaluation of findings at follow-up surveillance colonoscopy of FIND-UC participants and
9 their rates of dysplasia may be of further interest to underline current conclusions and potential
10 benefit of CE over AFI. Last, as CE has been shown to increase procedural times, redefining
11 reimbursement payments for performing CE may increase its adoption into clinical practice.

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

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

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

17

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31 analysis.

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1 Table 1. Patient characteristics.

| | Autofluorescence imaging (N=105) | Chromoendoscopy (N=105) |
|-------------------------------------------------------------|----------------------------------|-------------------------|
| Mean age, years (SD) | 56.3 (13.1) | 56.1 (12.3) |
| Female, n (%) | 44 (41.9%) | 44 (41.9%) |
| UC duration in years, median (IQR) | 22.5 (15.0-32.8) | 19.0 (13.0-27.3) |
| Extent of colitis, n (%) | | |
| Pancolitis (E3) | 68 (64.8%) | 74 (70.5%) |
| Left sided (E2) | 37 (35.2%) | 31 (29.5%) |
| Previous dysplasia detected during surveillance, n (%) | 16 (15.2%) | 18 (17.1%) |
| Concomitant diagnosis of PSC, n (%) | 18 (17.1%) | 20 (19.0%) |
| Surveillance interval in years, median (IQR) | 3.0 (1.5-4.0) | 3.0 (1.0-4.0) |
| Family history of CRC, n (%) | 17 (16.3%) | 17 (16.3%) |
| Previous or current use of immunomodulating* therapy, n (%) | 56 (53.3%) | 60 (57.1%) |

2 *Immunomodulating therapy is defined as methotrexate, thiopurines and biological therapy

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1 Table 2. Colonoscopy characteristics.

| | Autofluorescence imaging | Chromoendoscopy | P-value (2-sided) |
|------------------------------------------------------------------------------------------|--------------------------|------------------|-------------------|
| Mayo 1 colitis, n (%) | 25 (23·8%) | 24 (22·9%) | 0·87 |
| Post inflammatory polyps , n (%) | 23 (21·9%) | 22 (21·0%) | 0·87 |
| Tubular shortened colon, n (%) | 5 (4·8%) | 6 (5·7%) | 0·76 |
| BBPS, median (IQR) | 8 (7-9) | 8 (8-9) | 0·11 |
| Sedation, n | | | 0·69 |
| None | 15 | 9 | |
| Midazolam and/or fentanyl | 88 | 90 | |
| Propofol | 2 | 6 | |
| Hyoscine butylbromide, n (%) | 64 (61%) | 68 (65%) | 0·29 |
| Colonoscopies per center, n | | | 1·00 |
| Center 1 | 34 | 32 | |
| Center 2 | 24 | 26 | |
| Center 3 | 15 | 16 | |
| Center 4 | 18 | 18 | |
| Center 5 | 14 | 13 | |
| Caecal intubation time in min, median (IQR) | 10·0 (7·0-16·6) | 11·7 (8·0-17·0) | 0·15 |
| Withdrawal time in min, median (IQR) | 18·0 (15·0-24·9) | 25·1 (18·9-33·8) | <0·0001 |
| Inspection time in min, median (IQR) | 15·2 (12·0-19·0) | 16·0 (12·9-26·0) | 0·15 |
| Time related to dye-application, bowel cleansing and lesion removal in min, median (IQR) | 3·1 (2·0-3·1) | 7·0 (1·2-13·2) | 0·02 |

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1 Table 3. Main and secondary study outcome measures.

| | Autofluorescence imaging | Chromoendoscopy | Ratio (2-sided 80% CI) | P-value (2-sided) |
|--------------------------------|--------------------------|-----------------|----------------------------------|-------------------|
| <u>Patient level analysis</u> | | | | |
| Dysplastic – y/n | 12.4% (13/105) | 19.1% (20/105) | 0.65 (0.43,0.99) | 0.18 |
| Dysplastic – N | 0.13 ± 0.37 | 0.37 ± 1.02 | 0.36 (0.21,0.61) | 0.01 |
| | | | | |
| Neoplastic – y/n | 15.2% (16/105) | 24.8% (26/105) | 0.62 (0.43, 0.89) | 0.08 |
| Neoplastic – N | 0.17 ± 0.43 | 0.52 ± 1.20 | 0.34 (0.21, 0.54) | 0.002 |
| | | | | |
| SSL – y/n | 2.9% (3/105) | 6.7% (7/105) | 0.43 (0.18, 1.02) | 0.19 |
| SSL – N | 0.04 ± 0.24 | 0.13 ± 0.62 | 0.29 (0.10, 0.80) | 0.12 |
| | | | | |
| Targeted biopsy – y/n | 41.9% (44/105) | 63.8% (67/105) | 0.66 (0.55, 0.78) | 0.002 |
| Targeted biopsy – N | 0.69 ± 1.07 | 1.39 ± 1.69 | 0.49 (0.41, 0.59) | 0.0003 |
| | | | | |
| <u>Polyp level analysis</u> | | | | |
| Dysplasia yield ^(*) | 20.0% (13/65) | 26.8% (37/138) | 1.13 (0.47, 2.70) ^(#) | 0.86 |

2 Summary statistics are: Percentage (n/N) or mean ± standard deviation. (*) Excluding obvious hyperplastic & inflammatory
 3 polyps. (#) Relative differences reported as odds ratio (80% CI)

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1 Table 4. Characteristics of detected dysplastic lesions.

| | Autofluorescence imaging (N=14) | Chromoendoscopy (N=38) |
|----------------------------------------------------------|---------------------------------|------------------------|
| Location, n | | |
| Caecum | 5 | 2 |
| Ascending | 6 | 5 |
| Transverse | 2 | 15 |
| Descending | 0 | 5 |
| Sigmoid | 1 | 8 |
| Rectum | 0 | 3 |
| | | |
| Located in previous or current inflamed colon segment, n | 7 | 25 |
| | | |
| Size, median (IQR) | 3mm (2-4) | 3mm (2-8) |
| | | |
| Morphology, n | | |
| Sub-pedunculated (Isp) | - | 2 |
| Sessile (Is) | 5 | 10 |
| Flat or flat elevated (IIa or IIb) | 8 | 25 |
| Depressed (IIc) | - | 1 |
| | | |
| Removal, n | | |
| Biopsy | 4 | 20 |
| Cold polypectomy | 6 | 14 |
| Endoscopic mucosal resection | 3 | 4 |
| | | |
| Direct complete removal, n | 11 | 27 |
| | | |
| Dysplasia, n | | |
| Low-grade dysplasia | 14 | 36 |
| High-grade dysplasia | 0 | 1 |
| Invasive cancer | 0 | 1 |

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1 Figure 1. CONSORT patient flowchart.

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

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