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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ABBREVIATIONS: ulcerative colitis (UC), colorectal cancer (CRC), chromoendoscopy (CE), Autofluorescence imaging (AFI), primary sclerosing cholangitis (PSC), high-definition white light endoscopy (HD-WLE), Boston Bowel Preparation Score (BBPS), sessile serrated lesion (SSL), confidence intervals (CIs), Flexible spectral Imaging Color Enhancement (FICE).

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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.

INTRODUCTION

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

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

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

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

Both AFI and CE have been shown to be superior to white light endoscopy in dysplasia detection in patients with longstanding UC,[12,20] but have never been investigated in a head-to-head comparison. The hypothesis for the "chromoendoscopy versus autoFluorescence Imaging for Neoplasia Detection in patients with longstanding Ulcerative Colitis" (FIND-UC) randomised controlled trial is that CE and AFI are equally effective for the detection of dysplastic lesions in patients undergoing colonoscopic surveillance for UC. Performing a formal non-inferiority trial would require over 1,000 participants. Therefore we decided to perform a phase II pathfinder study with predefined performance thresholds. The primary outcome was dysplasia detection, and the focus of this study was on investigating whether AFI could meet clinical criteria to go forward to an appropriately powered 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 Scale[23]). 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 standardised teaching module was delivered and a hands-on colonoscopy demonstration was performed. In this standardised teaching module both lesion detection with AFI and CE were discussed in detail. The teaching included 40 still images of AFI and corresponding HD-WLE images.

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

Randomisation and allocation concealment

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

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

Procedure

The procedures were performed under conscious sedation using intravenous benzodiazepines and opiates when requested. Carbon dioxide insufflation was used for all colonoscopies. The endoscope was advanced to the caecum with the endoscope set in the high-definition white light endoscopy (HD-WLE) mode. Caecal intubation was confirmed by identification of the appendiceal orifice and ileocaecal valve or by intubation of the ileum. Upon reaching the cecum, the level of bowel preparation was determined according to the Boston Bowel Preparation Score (BBPS).[23] In case the BBPS was <6 or the patient had active colitis, the endoscope was withdrawn in the HD-WLE mode and the patient was excluded from the study. If the bowel preparation was sufficient and there was no active inflammation, the patient underwent colonoscopy according to the study protocol. At the start of withdrawal, 20 mg hyoscine

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

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

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

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

Histopathology

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

standard diagnosis in each patient. Any histopathology slides or samples transferred for external review had all 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 colonoscope 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 ± 1·02) per patient in the CE group, compared to 0·13 (SD ± 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 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.

DISCUSSION

This randomised trial with predefined performance thresholds aimed to investigate non-inferiority of AFI compared to CE for dysplasia detection in patients with longstanding UC. Based on the relative detection rate of AFI versus CE for the proportion of patients with at least one dysplastic 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 targeted biopsies group was equally high in yield of dysplasia compared to random and targeted biopsy group. The targeted biopsy approach appeared to be more cost-effective. In line with recent guidelines[4,5], random biopsies may be omitted because of their low yield when performing surveillance with CE, although specific risk-groups may benefit from this approach, such as those with PSC.[35]

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

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

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

This study has a number of limitations. Three of the five centres were tertiary academic centres, so the patient populations may not be completely representative of the wider IBD surveillance population. This is indicated by the high rates of patients with previous dysplasia and PSC, and the high overall dysplasia detection rate compared to recently published large population based cohorts of chromoendoscopy in IBD.[35,45,46] Most endoscopists were also sub-specialists with extensive experience in performing CE, and were not blinded which may have led to unconscious bias and may have favored CE. In common with most trials of CE we did not control for the “washing” effect of dye-spray which may have improved mucosal visualization, although overall inspection times were similar. Furthermore, AFI did not meet the predefined clinical acceptability thresholds, and CE was superior to AFI for the mean number of detected dysplastic lesions per patient. The dysplasia detection rate per patient of AFI (12·4%) in the FIND-UC trial was at least similar compared to that of recently published WLE dysplasia detection rates in academic centers.[28,35,46] Moreover, detected dysplastic lesions were predominantly diminutive in size and whether the size of dysplastic lesions is of clinical importance remains to be addressed. Therefore, we do not think that patients that were allocated to undergo dysplasia surveillance with AFI encountered any disadvantage by participating in this study. Last, some endoscopists performed more study colonoscopies than other possibly introducing a learning curve for AFI during the study. To minimise this learning curve during the study, participating endoscopists were required to have performed at least 20 procedures with the AFI study equipment in patients with longstanding UC prior to the start of the study. All study endoscopists also participated in a one-day teaching session and therefore we presume that this resulted in comparable scope-handling abilities and interpretation of the endoscopic images between endoscopists when using AFI.

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

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

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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%)

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

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

Table 3. Main and secondary study outcome measures.

	Autofluorescence imaging	Chromoendoscopy	Ratio (2-sided 80% CI)	P-value (2-sided)
Patient level analysis				
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
Polyp level analysis				
Dysplasia yield (*)	20·0% (13/65)	26·8% (37/138)	1·13 (0·47, 2·70) (#)	0·86

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

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

Figure 1. CONSORT patient flowchart.

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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