*Background:* Colonoscopy is one of the most reliable methods for detection of colorectal neoplasms, but it can overlook some lesions.

*Objective:* To evaluate the efficacy of autofluorescence imaging (AFI) with a transparent hood for detection of colorectal neoplasms.

*Design:* a 2×2 factorial designed, prospective, randomized controlled trial.

*Setting:* a tertiary cancer center.

*Patients:* Five hundred and sixty-one patients.

*Interventions:* Patients were allocated to four groups: (1) white light imaging (WLI) alone: colonoscopy using WLI without a transparent hood; (2) WLI+TH: colonoscopy using WLI with a transparent hood; (3) AFI alone: colonoscopy using AFI without a transparent hood; and (4) AFI+TH: colonoscopy using AFI with a transparent hood. Eight colonoscopists investigated using each allocated method.

*Main outcome measurements:* The difference in neoplasm detection rate (number of detected neoplasms per patient) between the WLI alone and AFI+TH groups.

*Results:* Neoplasm detection rate (95%CI) in the AFI+TH group was significantly higher than in the WLI alone group [1.96 (1.50–2.43) vs 1.19 (0.93–1.44), $P = 0.023$ (Tukey-Kramer multiple comparison test)]. Relative detection ratios (95%CI) for polypoid neoplasms based on Poisson regression model was significantly increased by mounting a transparent hood [1.69 (1.34-2.12), $P<0.001$], and relative detection ratios for flat neoplasms was significantly increased by AFI observation [1.83 (1.24-2.71), $P = 0.002$].

*Limitations:* Open trial performed in single cancer referral center.

*Conclusion:* AFI colonoscopy with a transparent hood detected significantly more colorectal neoplasms than did conventional WLI colonoscopy without a transparent

hood. (UMIN Clinical Trials Registry number, UMIN000001473)

## Introduction

Colorectal cancer is one of the most common causes of cancer death worldwide,[1] and removal of colorectal adenomas reduces the risk of subsequent colorectal cancer.[2,3] Therefore, detection of colorectal neoplasms is very important in prevention of colorectal cancer mortality.

## Background

Colonoscopy is one of the most reliable methods for detection of neoplasms, but it can overlook some lesions.[4,5] Although the reasons for overlooking are unknown, we suspect two major possibilities. One is that overlooked lesions are flat, which makes them difficult to recognize its existence using conventional colonoscopy. The other is that overlooked lesions are hidden behind colonic folds.

Autofluorescence imaging (AFI) is an endoscopic technique that uses autofluorescence emitted from the endogeneous fluorophore by exposure to short-wavelength photoexcitation.[6] AFI revealed better detection of flat lesions than white light imaging (WLI) did in previous reports, but they were not evaluated in total colonoscopy.[7,8] On the other hand, mounting a transparent hood to the tip of colonoscope can help to detect lesions behind the colonic folds by turning over the colonic folds. Therefore, we hypothesized that AFI and a transparent hood can work for detection of colorectal neoplasms, using different complementary mechanisms.[9]

We conducted a prospective, randomized controlled trial to determine whether AFI with a transparent hood achieved better detection of neoplasms than conventional WLI without a transparent hood.

## Methods

This study was designed as an open randomized trial and performed at an endoscopy unit in Osaka Medical Center for Cancer and Cardiovascular Diseases. The study protocol was approved by the Research Ethics Committee in our center. This study followed the CONSORT guidelines and was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN-CTR), UMIN000001473.

### Participants

Patients undergoing colonoscopy for investigation of a positive screening fecal occult blood testing (FOBT), or who were referred for surveillance colonoscopy after post-endoscopic resection of colorectal neoplasms, were eligible. Patients were excluded if they had: (1) a history of colorectomy or major abdominal surgery; (2) symptoms suspicious for colorectal stenosis or cancer; (3) inflammatory bowel diseases, familial polyposis and known colorectal cancer; (4) severe organ failure, non-correctable coagulopathy, or were undergoing anticoagulant therapy; or (5) if the colonoscopist judged that they cannot realize the importance of random allocation. All patients gave written informed consent to participate in this study.

### Study Design, Assignment and Masking

We adopted a 2×2 factorial design to investigate the impact of AFI and a transparent hood simultaneously. After stratification based on colonoscopists and indications for colonoscopy, the participants were assigned randomly to the following four groups: (1) WLI alone: colonoscopy using WLI without a transparent hood; (2) WLI+TH: colonoscopy using WLI with a transparent hood; (3) AFI alone: colonoscopy

using AFI without a transparent hood; and (4) AFI+TH: colonoscopy using AFI with a transparent hood. We allocated the participants by dynamic balancing using the minimization method. A randomization table was pre-ordered for each stratum by a researcher who was not involved in this trial using Excel 2008 for Mac (Microsoft Corporation, Redmond, WA, USA). The sequence was concealed to the colonoscopists until the participants were assigned. Colonoscopists were not blinded to the allocated groups in this trial.

**Procedures**

Patients were given a low-fiber diet and took preparative medication during the day before colonoscopy: 160 mg sennoside (Yodel S; Fujimoto Pharmaceutical, Osaka, Japan) after every meal, and 34 g magnesium citrate (Magcorol P; Horii Pharmaceutical, Osaka, Japan) dissolved in 180 mL of water at night. In the morning prior to colonoscopy, 68 g magnesium citrate dissolved in 1.8 L water or 137.155 g polyethylene glycol (Muben; Nihon Pharmaceutical, Tokyo, Japan, or Niflec; Ajinomoto Pharma, Tokyo, Japan) dissolved in 2 L water was used to clean the bowel. Scopolamine butylbromide (20 mg; Buscopan; Nippon Boehringer Ingelheim, Tokyo, Japan) or glucagon (1mg; Glucagon G Novo; Eisai, Tokyo, Japan) was administered just before colonoscopy. Midazolam (2.5 mg; Dormicum; Astellas Pharma, Tokyo, Japan) was used for the patient who wanted to undergo colonoscopy under sedation.

AFI colonoscopes (EVIS CF-FH260AZI; Olympus Medical Systems, Co., Ltd., Tokyo, Japan), light sources (EVIS CLV-260SL; Olympus) and video processors (EVIS LUCERA CV-260SL; Olympus) were used in this study. The AFI colonoscope was equipped with two charge-coupled devices (CCDs) for high-definition WLI and for

AFI. Each observation mode can be switched easily in a few seconds by pushing a button on the scope handle.

In the WLI+TH or AFI+TH group, a transparent hood (D-201-16403; Olympus) was attached to the tip of the AFI colonoscope. The transparent hood partially disturbed the image field, therefore, it was pushed as deep as possible in the each WLI and AFI image, before starting intubation, so that only the tip of the hood could be seen in the image field of both modes.[9]

All procedures were performed by eight colonoscopists: four "more experienced colonoscopists", who had previously done more than 1000 colonoscopies and four "trainees" (< 1000 colonoscopies). All the colonoscopists were familiar with the AFI images of colorectal neoplasms, by their experience and a lecture about AFI including five typical images of colorectal neoplasms.

In each case, the colonoscope was inserted into the cecum using the WLI mode. Insertion into the cecum was performed as quickly as possible without looking for lesions. After reaching the cecum, all colonoscopists started the study investigation. In the case of incomplete total colonoscopy, detected lesions were also recorded in the limited observed area.

The quality of bowel preparation was graded as follows: (1) excellent (almost 100% of mucosal visualization); (2) good (≥90% of mucosal visualization); or (3) poor (<90% of mucosal visualization, even after suction of residual fluid). In the patients allocated to the AFI alone and AFI+TH groups, observation was basically performed using the AFI mode, but we were allowed to use the WLI mode temporarily when the colonoscopists felt that AFI was inappropriate in the situation that the colonoscopists could not keep appropriate distance to the mucosa for AFI observation (e.g. at the

corner of the colon, in sigmoid colon with diverticulosis).

The location, size, and macroscopic type according to the Paris classification[10,11] of all detected lesions were documented. Basically, all detected lesions were biopsied, and polypectomy was not performed at the time of investigation because they were not informed about polypectomy. The fixed specimens were subjected to histological examination. The reference standard was histopathology using standard hematoxylin and eosin staining. Two histopathologists blinded to the endoscopic findings and allocated groups diagnosed all specimens according to the Vienna classification of gastrointestinal epithelial neoplasia.[12,13]

**Measured Outcomes**

The primary endpoint was the difference in colorectal neoplasm detection rate (number of detected neoplasms per patient) between the WLI alone and AFI+TH groups. Total number of patients with polyps, and patients with neoplasms, detection rate of polypoid/flat neoplasms, and adverse events were evaluated as secondary endpoints. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[14]

**Sample Size**

In previous studies, WLI without a transparent hood detected a mean 0.26–0.54 adenomas per patient.[15,16] The sample size of this trial was calculated to be sufficient to detect 30% more neoplasms in the AFI+TH group compared with the WLI alone group (assuming 0.36 neoplasms per patient, with a standard deviation of 0.3) [16,17]. Power analysis indicated that > 122 patients were needed in each group, assuming a 5%

significance level and statistical power of 80% using two-sided equivalence. We therefore estimated that a total of 550 patients would be needed, bearing in mind eligibility deviation and dropout cases.

**Statistical Analysis**

Four groups were assessed in this trial and multiple comparisons were made, therefore, we compared each groups using Tukey-Kramer multiple comparison test at first. Then, to investigate the impact of two factors that affected the neoplasm detection rate; observation mode (WLI vs AFI observation), and mounting a transparent hood or not (TH– vs TH+), relative detection ratios for overall and protruded/flat neoplasms were calculated using Poisson regression model.

We analyzed all allocated participants according to the principle of intention-to-treat, coding the participants who were considered as eligibility deviation cases and refused to enroll after randomization as patients without any lesions. We did not perform interim analysis at all. Data analysis was conducted using the statistical package *R* 2.8.1 (http://www.r-project.org/). All *P* values were two-tailed, and $P < 0.05$ was defined as statistically significant. All data were collected in our hospital and analyzed by the data center at the University of Yamanashi, Japan.

## Results

### Recruitment and Participant Flow (Figure 1)

Between November 2008 and November 2009, 923 eligible patients were scheduled to undergo colonoscopy in our endoscopy unit. A total of 362 patients were excluded from enrolment with various reasons, which left a total of 561 patients who were randomly assigned and analyzed according to the principle of intention-to-treat (the results were almost same in per-protocol analysis excluding eligibility deviation cases).

### Baseline Data

Baseline data for each group are shown in Table 1. They were analyzed between the groups and were not significantly different. Quality of bowel preparation was rated as excellent or good by the endoscopists in at least 98% of the cases in each group.

### Outcomes & estimation

A total of 1105 lesions were detected in 380 patients. Specimens were not obtained from 13 lesions because of colonoscopist's carelessness, and histological diagnosis was available for 1092 lesions. Table 2 summarizes the clinicopathological features of the detected lesions. Eight hundred and seventy-five lesions were diagnosed as neoplasms and 217 were diagnosed as non-neoplastic lesions.

The primary endpoint, neoplasm detection rate (95%CI) in the AFI+TH group was significantly higher than in the WLI alone group [1.96 (1.50–2.43) vs 1.19 (0.93–1.44), $P = 0.023$ (Tukey-Kramer multiple comparison method, Figures 2 and 3)].

AFI with a transparent hood could detect more neoplasms than conventional colonoscopy. Relative detection ratio (95% C.I.) for overall neoplasm based on Poisson regression model was 1.45 (1.18-1.77, p<0.0001) by mounting a transparent hood and 1.14 (0.96-1.36, p=0.13) by AFI observation. Although a transparent hood influenced the neoplasm detection rate more than the observation mode did, AFI observation detected neoplasms more frequently than did WLI observation, independently of mounting a transparent hood or not.

The detection rates of polypoid/flat neoplasms are shown in Table 3 (significant difference was not seen between the groups). Relative detection ratio (95% C.I.) for polypoid neoplasm based on Poisson regression model was 1.69 (1.34-2.12, p<0.0001) by mounting a transparent hood and 1.00 (0.82-1.21, p=0.98) by AFI observation. The relative detection ratio for polypoid neoplasms was significantly increased by mounting a transparent hood but not influenced by AFI observation. On the other hand, relative detection ratio (95% C.I.) for flat neoplasm was 1.83 (1.24-2.71, p=0.002) by AFI observation and 0.91 (0.59-1.41, p=0.67) by mounting a transparent hood. The relative detection ratio for flat neoplasms was significantly increased by AFI observation but not influenced by mounting a transparent hood.

**Adverse events**

Mucosal minor bleeding was seen in 4 cases (1 each in the WLI+TH and AFI alone groups and 2 in the AFI+TH group) but no hemostatic procedure was needed.

## Discussion

We demonstrated the efficacy of AFI with a transparent hood for detection of colorectal neoplasms, compared with conventional WLI without a transparent hood. In western countries, the surveillance intervals are decided according to the number of adenomas,[19,20] in addition to the detected polyp size, degree of dysplasia and presence of villous architecture. Therefore, accurate detection of colorectal adenoma is substantially important. Furthermore, in AFI image, colorectal neoplasms are easily recognizable by their color difference. We invited 4 trainees to participate in this trial and it was easy to utilize effectively AFI with a transparent hood even for trainees.

Some attempts have been made to improve the colorectal adenoma detection, and pan-colonic chromoendoscopy is one of the promising attempts.[21,22] However, pan-colonic dye spray has not been a standard method in clinical practice, because it is too complicated and time consuming. On the other hand, colonoscopists that use AFI with a transparent hood do not need spraying dye solution; all they need is to mount a transparent hood prior to examination, push the button, and wait for a few seconds during the examination.

An alternative method for dye spraying has been developed, which is classified as equipment-based image-enhanced endoscopy (IEE).[23] NBI, which is one of the equipment-based IEE methods, is expected to realize its potential as electronic chromoendoscopy.[24–26] Recently, although several investigators have been trying to show the effectiveness of NBI for detection of colorectal adenomas, most of the randomized trials, including one multicenter trial, have shown negative results.[15, 16, 27-29] Although the efficacy of NBI for detection of colorectal adenoma is controversial,[30] NBI has diagnostic accuracy for distinguishing neoplastic from non-neoplastic

lesions.[31,32] The endoscopy system used in our trial was equipped with NBI as well as AFI system, and we can resect and discard the detected lesions according to the optical diagnosis using NBI, without formal histological diagnosis.[33] AFI colonoscopy with a transparent hood can detect more neoplastic lesions than conventional WLI but it does not increase the cost of histopathological diagnosis for the detected lesions.

A transparent hood is also a promising device for better detection of colorectal neoplasms and uses a different mechanism with IEE. Although a transparent hood is expected to achieve better detection of adenomas,[17,34–36] its efficacy is under debate.[37] In the present trial, the impact of mounting a transparent hood for detection of neoplasm might have been stronger than that of AFI observation. However, AFI observation also demonstrated a better neoplasm detection rate than WLI observation, regardless of whether a transparent hood was mounted or not. In the analysis of the polypoid/flat neoplasm detected in the present trial, mounting a transparent hood helped to detect more polypoid neoplasms and AFI observation detected more number of flat neoplasms. AFI observation and a transparent hood could complement each other and the combination is effective for detection of both polypoid and flat neoplasms.

This study had several limitations. First, the study took place in a cancer referral center, which makes it difficult to apply the results to colonoscopists outside of specialist units. Second, the AFI videoendoscope is commercially available only in some Asian countries and the United Kingdom. Finally, we could not conceal the allocated group in this study because the colonoscopists were aware of the allocated equipment during the procedure. This trial therefore had to be an open trial. However, the neoplasm detection rate in the WLI alone group was comparable with previously reported data.[15,16,28,38] It shows that we did not perform negligent observation in the WLI

alone group, and the neoplasm detection rate in the AFI+TH group was significantly higher than in the WLI alone group.

In conclusion, although the results warrant a further phase III study to establish AFI with a transparent hood as a standard method for detection of colorectal neoplasms, we demonstrated the efficacy of AFI with a transparent hood for detection of colorectal neoplasms, compared with conventional WLI without a transparent hood.

**Table 1.** Baseline data of allocated groups. *FOBT; fecal occult blood testing

| | WLI alone | WLI + TH | AFI alone | AFI + TH |
|---|---|---|---|---|
| Sex (male,%) | 93/133 (70%) | 99/141 (70%) | 101/147 (69%) | 94/140 (67%) |
| Median (range) age (y) | 64 (34-84) | 63 (31-83) | 63 (35-84) | 64 (33-83) |
| Indication of colonoscopy, n (%) | | | | |
| FOBT+* | 47 (35%) | 53 (38%) | 53 (36%) | 52 (37%) |
| Surveillance | 86 (65%) | 88 (62%) | 94 (64%) | 88 (63%) |
| Bowel preparation, n (%) | | | | |
| Excellent | 113(85%) | 125(89%) | 126(86%) | 115(82%) |
| Good | 18(14%) | 13(9%) | 18(12%) | 22(16%) |
| Poor | 2(2%) | 2(1%) | 2(1%) | 3(2%) |
| Endoscopist, n | | | | |
| More experienced | 78 | 78 | 86 | 80 |
| Trainees | 55 | 63 | 61 | 60 |
| Mean (95% CI) total procedure Time (min.) | 20.7 (19.3–22.0) | 19.4 (17.8–20.9) | 24.8 (23.1–26.4) | 22.9 (21.6–24.2) |
| Cecal intubation rate , n (%) | 132/133 (99%) | 136/141 (96%) | 145/147 (99%) | 138/140 (99%) |

**Table 2.** Clinicopathological features of detected lesions and patients.

| | WLI alone | WLI + TH | AFI alone | AFI + TH | Total |
|---|---|---|---|---|---|
| Patients (n) | 133 | 141 | 147 | 140 | 561 |
| with polyps (n, %) | 83 (62%) | 98 (70%) | 95 (65%) | 104 (74%) | 383 (68%) |
| with neoplasms (n, %) | 74 (56%) | 84 (60%) | 83 (56%) | 88 (62%) | 329 (59%) |
| | | | | | |
| All detected lesions (n) | 193 | 322 | 252 | 338 | 1105 |
| Non-neoplastic polyps (n) | 40 | 66 | 49 | 62 | 217 |
| Neoplasms (n) | 152 | 248 | 200 | 275 | 875 |
| Adenoma | 146 | 242 | 197 | 269 | 854 |
| Low-grade adenoma | 144 | 237 | 189 | 257 | 827 |
| High-grade adenoma | 2 | 5 | 8 | 12 | 27 |
| Non-invasive carcinoma | 2 | 1 | 0 | 3 | 6 |
| Invasive carcinoma | 3 | 4 | 3 | 2 | 12 |
| Carcinoid | 1 | 1 | 0 | 1 | 3 |
| No histological examination (n) | 1 | 8 | 3 | 1 | 13 |
| | | | | | |
| Neoplasm detection rate (95% CI) | 1.19 (0.93–1.44) | 1.72 (1.28–2.15) | 1.36 (1.07–1.65) | 1.96 (1.50–2.43) | 1.57 (1.38,1.76) |

The *P* values for various comparisons of neoplasm detection rate; WLI alone vs. WLI + TH: 0.21, WLI alone vs. AFI alone: 0.92, WLI alone vs. AFI+TH: 0.023, WLI+TH vs. AFI alone: 0.53, WLI+TH vs. AFI+TH: 0.79, AFI alone vs. AFI+TH: 0.10.

**Table 3.** Detection rates (95% CI) of polypoid/flat neoplasms.

| | WLI alone | WLI + TH | AFI alone | AFI + TH | Total |
|---|---|---|---|---|---|
| Macroscopic type | | | | | |
| polypoid neoplasm detection rate (95% CI) | 0.86 (0.64–1.07) | 1.45 (1.03–1.87) | 0.95 (0.70–1.19) | 1.44 (1.04–1.85) | 1.17 (1.01–1.34) |
| flat neoplasm detection rate (95% CI) | 0.31 (0.16–0.45) | 0.28 (0.17–0.39) | 0.41 (0.27–0.56) | 0.51 (0.31–0.72) | 0.38 (0.30–0.46)) |

The *P* values for various comparisons of polypoid neoplasm detection rate; WLI alone vs. WLI + TH: 0.073, WLI alone vs. AFI alone: 0.98, WLI alone vs. AFI+TH: 0.075, WLI+TH vs. AFI alone: 0.15, WLI+TH vs. AFI+TH: 1.00, AFI alone vs. AFI+TH: 0.15.

The *P* values for various comparisons of flat neoplasm detection rate; WLI alone vs. WLI + TH: 1.00, WLI alone vs. AFI alone: 0.79, WLI alone vs. AFI+TH: 0.25, WLI+TH vs. AFI alone: 0.63, WLI+TH vs. AFI+TH: 0.15, AFI alone vs. AFI+TH: 0.78.

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## Figure legends

**Figure 1.** Flow diagram of participants enrollment and distribution into the allocated groups. Three cases in WLI+TH group and one case in AFI alone group were eligibility deviation cases and coded as patients without any lesions for intention-to-treat analysis (the results were almost same in per-protocol analysis excluding eligibility deviation cases).

**Figure 2.** Neoplasm detection rate in each group. A significantly higher detection rate was seen in the AFI+TH group than the WLI alone group. Although the mounting or not mounting a transparent hood influenced the neoplasm detection rate more than the observation mode did, AFI observation detected neoplasms more frequently than WLI observation, irrespective of whether a transparent hood was mounted or not.

**Figure 3.** Endoscopic images of a rectal flat neoplasm in a 69-year-old man who was allocated to the AFI+TH group (recorded after removal of a transparent hood). (A) The lesion was detected in the rectum during AFI observation. (B) Conventional WLI of the lesion.