

Figure 5. Colonoscopic clip closure of a perforation after endoscopic submucosal dissection (ESD). **A, B,** An unintended cut was made too deeply into the muscularis propria, resulting in a small linear perforation during ESD of a sessile lesion. **C-H,** The perforation as seen through a small-caliber tip transparent hood (ST hood). The perforation has been successfully closed by using 2 clips by approximating the lower edge to the upper edge of the perforation. (Reproduced with permission from the ASGE)

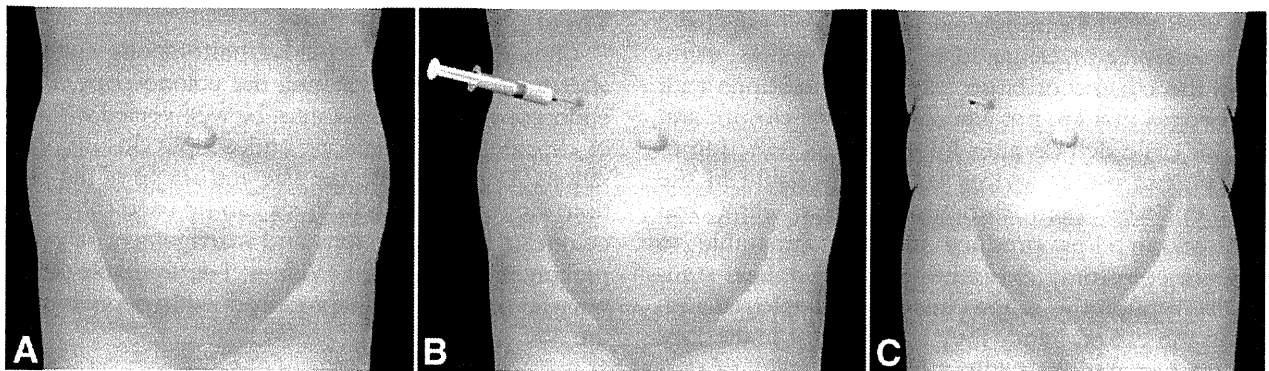


Figure 6. Needle decompression of tension pneumoperitoneum. (Reproduced with permission from the ASGE)

after satisfactory application of the first clip, which is the most critical component of closure. It is important to confirm satisfactory approximation of the edges before deployment of the clip. Perforations that are difficult to close with clips can potentially be closed with a loop-snare.⁵¹

Closure of small perforations during ESD

Instead of immediate closure of the perforation, it is important to continue ESD in order to make enough space to apply endoscopic clips. If endoscopic clips are hastily applied immediately after the recognition of the perforation, the clips may interfere with further ESD. After successful clip closure of the perforation, ESD can

be continued at the earliest opportunity and the lesion removed during the same session. Finally, the resection bed after en bloc resection should be checked carefully, and additional clips should be applied accordingly.

What should be avoided during clipping

Panic. Be calm and steady once you recognize a perforation. Be patient while applying a clip because a clip misplaced to one edge of the perforation could lead to difficulty in applying additional clips for satisfactory closure.

Long shots. Keep the endoscope close to the site of perforation and avoid deploying clips from a distance

away, because long shots will interfere with precise delivery of the clips.

Stretching of the colon. Too much pushing of the clip against the wall limits grasping of the tissue and approximation of the edges of the perforation. Once the blades of the clip are placed across the perforation, gentle suction, instead of pushing the clip, allows the tissue to come into the blades to allow better closure. Avoid air insufflation, because it can worsen pneumoperitoneum.

Over-the-scope clips

Recently, the over-the-scope clip was introduced into the market, and preliminary reports are encouraging. Conceptually, the technique is similar to using a band ligation device, which has been reported as successful.¹¹⁰ For this procedure, suction the perforation margins with or without the aid of a device to pull the edges into the cap, then deploy the clip, which creates a leak-proof seal.^{97,111}

Management after endoscopic closure

A team approach involving surgeons in the management of the patients immediately after endoscopic closure of perforations is critical. The patient should have nothing by mouth and begin therapy with broad-spectrum intravenous antibiotics and hydration. Closely monitor all patients for signs of peritoneal irritation. Resume oral intake as soon as pain and fever resolve, appetite and bowel function return, and laboratory test signs of inflammation such as leukocytosis and elevated C-reactive peptide levels return to normal. If there is any deterioration, surgery should be undertaken.

SUMMARY

Colonoscopic perforation is a serious complication of colonoscopy. Its prevention is the best treatment strategy, although when it occurs and is immediately recognized, endoscopic clip closure can be very useful to manage select cases. It is emphasized that endoscopists need to have the necessary knowledge, ability, equipment, and team required to close the perforations safely.

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Learning Curve Associated With Colorectal Endoscopic Submucosal Dissection for Endoscopists Experienced in Gastric Endoscopic Submucosal Dissection

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BACKGROUND: Colorectal endoscopic submucosal dissection requires a high level of skill and experience in therapeutic endoscopy because of the high risk of complications such as perforation and bleeding. Greater understanding of the procedural learning curve is required to standardize training and to achieve wider acceptance of this procedure.

OBJECTIVE: The aims of this study were to evaluate the clinical outcomes of colorectal endoscopic submucosal dissection and to clarify its learning curve for endoscopists.

DESIGN: We retrospectively reviewed the clinical outcomes for consecutive patients with colorectal neoplasms who underwent endoscopic submucosal dissection by 2 trainees under the guidance of experienced specialists.

SETTING: The study was performed at the National Cancer Center Hospital, Tokyo, Japan.

PATIENTS: Colorectal endoscopic submucosal dissections were performed for 101 consecutive patients with 102 colorectal neoplasms between April 2008 and December 2010.

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MAIN OUTCOME MEASURES: Procedure time, en bloc resection rate, completion rate, and complications were retrospectively compared between 4 training periods in which each trainee performed 10 endoscopic submucosal dissections per period and a final training period in which the trainees performed 10 to 12 endoscopic submucosal dissections to analyze the skill improvement with time.

RESULTS: The procedure time and en bloc resection rate were not significantly different among the training periods. However, the completion rates in the fourth (100%) and fifth (95.5%) training periods (≥ 31 cases/trainee) were significantly higher ($P < .001$) than those in the first (45%), second (70%), and third (80%) training periods (1–30 cases/trainee). Two cases of perforation occurred during the study.

LIMITATIONS: Limitations include the single-center design. Training programs and instruments vary with institution, which could affect the learning curve.

CONCLUSIONS: Trainee endoscopists are able to perform colorectal endoscopic submucosal dissection without serious complications under the guidance of experienced specialists. They can perform it safely and independently after preparatory training and experience with ≥ 30 cases.

KEY WORDS: Endoscopic gastrointestinal surgery; Colorectal cancer; Experiential learning; Treatment outcome; Intraoperative complications.

One of the most important aims of colonoscopy is prevention of the development of advanced colorectal cancer by finding and removing its precursors, adenomatous polyps.^{1–6} A flat or depressed neoplasm typified as a laterally spreading tumor (LST) is considered

a risk factor for the development of advanced cancer.⁷⁻¹⁰ Endoscopic mucosal resection (EMR) is the standard endoscopic procedure for removing such lesions; however, one indication for this procedure is the lesion size, and endoscopic piecemeal EMR is often applied for lesions larger than 20 mm.¹¹ Although this procedure is simple and time-saving, issues such as the high incidence of persistent or recurrent tumors and a low rate of histologically curative resections have been reported.^{12,13}

Endoscopic submucosal dissection (ESD) facilitates en bloc resection of large colorectal neoplasms that are difficult to resect by EMR, allows the precise histologic evaluation of resected specimens, and reduces the risk of recurrence in comparison with piecemeal EMR.¹⁴⁻¹⁶ This procedure, however, requires a high level of endoscopic skill and experience in therapeutic endoscopy because of the high risk of complications arising from the anatomical characteristics of the colon. Therefore, greater understanding of the learning curve for ESD is required to standardize training and to achieve wider acceptance of this technique. The aims of this study were to evaluate the clinical outcomes of ESD when conducted by trainees and to clarify the learning curve for this procedure.

PATIENTS AND METHODS

Patients

We retrospectively reviewed clinical outcomes for 101 consecutive patients with 102 colorectal neoplasms who underwent ESD by 2 trainees (S.F. and T.S.) under the guidance of experienced specialists at the National Cancer Center, Tokyo, Japan, between April 2008 and December 2010. T.S. performed 50 procedures, and S.F. performed 52 procedures. We conducted this study in accordance with the guidelines of our institutional review board, which approved this retrospective study without the need for informed consent. All of the patients provided written informed consent for the colonoscopy and ESD.

Prerequisites for Performing Colorectal ESD

At our institution, trainees must meet the following prerequisites to perform colorectal ESD: a high level of skill in the nonloop insertion colonoscopy technique (more than 10 cases of total colonoscopy completed within 5 min without any abdominal discomfort), skill in conventional EMR or piecemeal EMR techniques, experience with >20 gastric ESD cases, and assistance during >20 colorectal ESDs conducted by experienced endoscopists.

Indications for Colorectal ESD

All lesions to be treated endoscopically were required to have a noninvasive pattern on magnifying chromoendoscopy. An invasive pattern is characterized by irregular and distorted pits in a demarcated area, suggesting deep sub-

mucosal invasion ($\geq 1000 \mu\text{m}$), which has a high risk of lymph node metastasis; a noninvasive pattern does not have these characteristics, suggesting intramucosal neoplasia or superficial submucosal invasion ($< 1000 \mu\text{m}$).^{17,18} We defined the indications for ESD as (1) an LST non-granular (LST-NG) type lesion of >20 mm or (2) an LST granular (LST-G) nodular mixed-type lesion of >30 mm. These lesions have a high submucosal invasion rate and require accurate histologic evaluation by en bloc resection. Large villous tumors, recurrent lesions, and residual intramucosal lesions showing the nonlifting sign after EMR were also considered potential candidates for ESD.

ESD Procedure

The trainees performed the procedure using a ball-tip-type bipolar needle knife (B-B knife), in which the electrical current localizes to the needle tip with carbon dioxide insufflation rather than air insufflation.¹⁹ Bipolar coagulation forceps were also routinely applied to stop active bleeding and to decrease the risk of perforation. The lesion margins were clearly delineated before circumferential incision by the use of 0.4% indigo carmine dye spray. After injecting 10% glycerol and 5% fructose in a normal saline solution (Glyceol; Chugai Pharmaceutical Co., Tokyo, Japan) and sodium hyaluronate into the submucosal layer under the tumor, the trainees incised the mucosa with the B-B knife approximately 2 to 3 mm outside the lesion edge, on the elevation caused by the submucosal injection. An additional submucosal injection of the same solution was then applied before ESD to prevent perforation. An insulated-tip (IT) knife or B-B knife was used to dissect the submucosal layer. The electric current used for the circumferential incision and submucosal dissection was set to endocut mode (ERBE ICC-200, effect 3, output 50 W; ERBE Elektromedizin GmbH, Tübingen, Germany).

ESD was performed under conscious sedation in an endoscopy room with continued monitoring of electrocardiography and oxygen saturation. Conscious sedation allows a change in a patient's position in any direction, making it possible to apply countertraction to the lesions with the use of gravity. Moreover, under conscious sedation, we can accurately evaluate abdominal discomfort when perforation is suspected. Intravenous midazolam (2-3 mg) and intravenous pentazocine (15 mg) were administered to all patients to initiate sedation; an additional midazolam injection (2 mg) was administered if deemed necessary by the endoscopist.

Histopathological Assessment

All resected specimens were fixed in 10% buffered formalin. En bloc specimens and, where possible, larger piecemeal specimens were cut into 2-mm-thick slices. The fragments or slices were embedded in paraffin, cut into 3- μm

TABLE 1. Endoscopic characteristics of the lesions by treatment period and number of cases

Characteristic	Treatment period/cases per trainee					P
	First 1–10 (n = 20)	Second 11–20 (n = 20)	Third 21–30 (n = 20)	Fourth 31–40 (n = 20)	Fifth ≥41 (n = 22)	
Size (mm), median (IQR)	26 (20–31.5)	31 (25.3–36.5)	31 (25–40)	30 (24.3–41.5)	31 (25–44)	.343
Location, n (%)						.667
Rectum	7 (35.0)	8 (40.0)	3 (15.0)	5 (25.0)	6 (27)	
Colon	13 (65.0)	12 (60.0)	17 (85.0)	15 (75.0)	16 (73)	
Macroscopic, n (%)						.970
Protruded (0-I, LST-G) or SMT	12 (60.0)	12 (60.0)	11 (55.0)	10 (50.0)	12 (55)	
LST-NG or recurrent	8 (40.0)	8 (40.0)	9 (45.0)	10 (50.0)	10 (45)	

IQR = interquartile range; LST-G = laterally spreading tumor granular type; LST-NG = laterally spreading tumor nongranular type; SMT = submucosal tumor.

sections, stained with hematoxylin and eosin, and microscopically examined for histopathological type by pathologists specializing in gastrointestinal pathology.

Resections were evaluated according to the presence of tumor cells at the margins of the resected specimen, independent of its histopathological features, as follows: R0 resection, all margins were negative for tumor cells; R1 resection, tumor cells extended to the lateral or basal margins; and Rx resection, the margins could not be evaluated. Curative resection was achieved when an R0 resection was performed and submucosal invasion >1000 μ m from the muscularis mucosae, lymphatic invasion, vascular involvement, budding, and poorly differentiated components were absent. Clinical curative resection was considered achieved when the lateral margins of a resected specimen could not be evaluated histopathologically because of artifacts caused by coagulation necrosis during the ESD procedure or a lesion resected in a piecemeal manner had any of the factors absent in a curative resection. Curative resection of an adenoma with an unclear lateral margin was considered achieved if the adenoma met all of the other criteria. The histopathological diagnoses were based on the Japanese classification criteria for cancer of the colon and rectum and the Vienna classification system.^{20,21}

Statistical Analysis

The endoscopic characteristics of the lesions, procedure time, en bloc resection rate, completion rate, and complications were compared between 4 training periods in which each trainee performed 10 ESDs per period, as well

as a final training period in which the trainees performed 10 to 12 ESDs to allow analysis of skill improvement with time. A complete case was considered to be one in which the procedure was completely performed by the trainee without any technical assistance. The endoscopic characteristics of the lesions and clinical outcomes of ESD were analyzed by the use of the Kruskal-Wallis test for data showing nonnormality and the χ^2 test for nominal scale data. All statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX). All tests were 2-sided, and $P < .05$ was considered statistically significant by the Fisher exact probability test.

RESULTS

Endoscopic Characteristics and Clinical Outcomes

There were no significant differences in the lesion size, macroscopic type, or location between the 5 training periods (Table 1). Further, there were no significant differences in any of the clinical outcomes except for the completion rates (Table 2): the completion rates in the fourth (100%) and fifth (95.5%) training periods (≥ 31 cases/trainee) were significantly higher ($P < .001$) than those in the preceding periods (1–30 cases/trainee). When the numbers of complete and incomplete cases were compared according to their endoscopic characteristics (Table 3), the completion rate for the LST-NG type and recurrent lesions (16.3%) was significantly lower than that for the other macroscopic types (83.8%; $P < .001$).

TABLE 2. Clinical outcomes by treatment period and number of cases

Outcome	Treatment period/cases per trainee					P
	First 1–10 (n = 20)	Second 11–20 (n = 20)	Third 21–30 (n = 20)	Fourth 31–40 (n = 20)	Fifth ≥41 (n = 22)	
Procedure time (min), median (IQR)	95 (70–120)	70 (52.5–120)	67.5 (40–117.5)	70 (47.5–100)	70 (48–112.5)	.636
Perforation, n (%)	1 (5.0)	0 (0)	0 (0)	1 (5.0)	0 (0)	.658
Completion, n (%)	9 (45.0)	14 (70.0)	16 (80.0)	20 (100)	21 (95.5)	<.001
En bloc resection, n (%)	19 (95.0)	19 (95.0)	17 (85.0)	19 (95.0)	22 (100)	.151

IQR = interquartile range.

TABLE 3. Comparison of complete and incomplete cases by endoscopic characteristics

Characteristic	Complete (n = 80)	Incomplete (n = 22)	P
Size (mm), median (IQR)	28 (25–40)	30 (25–37)	.760
Location, n (%)			.192
Rectum	26 (32.5)	4 (18.2)	
Colon	54 (67.5)	18 (81.8)	
Macroscopic type, n (%)			<.001
Protruded (0-I, LST-G) or SMT	67 (83.8)	9 (40.9)	
LST-NG or recurrent	13 (16.3)	13 (59.1)	

IQR = interquartile range; LST-G = laterally spreading tumor granular type; LST-NG = laterally spreading tumor nongranular type; SMT = submucosal tumor.

Complications

Two cases of perforations occurred during the study (in the first and fourth periods); the first one occurred because of mechanical contact when the upper part of the scope was reversed after complete resection, resulting in a tiny tear in the muscular layer. The tear and ESD defect were easily repaired by using endoclips and were managed conservatively. The second case of perforation occurred during the initial submucosal dissection after circumferential incision. However, the aperture was very small (1 mm); the patient's vital signs (blood pressure, pulse rate, and arterial oxygen concentration) were stable, and the patient did not experience abdominal symptoms. We then continued submucosal dissection up to the point at which the endoclip would not obstruct the subsequent procedure after closure by endoclip.

These 2 patients did not exhibit any clinical symptoms such as abdominal pain, fever, or late bleeding, and resumption of the patients' normal diet and discharge were delayed by only 1 day. Delayed bleeding requiring emergency colonoscopy or prolonged hospitalization did not occur in any of the patients.

Histopathological Findings

Table 4 summarizes the histopathological findings for the resected lesions. Histologically, there were 23 (22.5%) cases of tubular or tubulovillous adenoma, 70 (68.6%) cases of intramucosal or superficial submucosal adenocarcinoma, 8 (7.8%) cases of deep submucosal cancer, and one (1.0%) case of carcinoid tumor. R0 and Rx resections were achieved in 29.4% and 69.7% of the cases. Although 7.8% of the resections were noncurative, 4 of these 8 cases were histopathologically considered R0 or Rx.

DISCUSSION

Clinical outcomes of colorectal ESD have not been reported for trainees. In this study, we evaluated the clinical outcomes of colorectal ESD performed by trainees and clarified the learning curve for this procedure.

TABLE 4. Histopathological findings for the lesions

Finding	No. of lesions (%)
Histopathological type	
Tubular or tubulovillous adenoma	23 (22.5)
Well-differentiated adenocarcinoma	78 (76.5)
Carcinoid tumor	1 (1.0)
Depth of invasion	
Intramucosa	84 (82.4)
Submucosa	
Shallow (<1000 μ m)	10 (9.8)
Deep (\geq 1000 μ m)	8 (7.8)
Resection type	
Curative	
R0	30 (29.4)
Rx	64 (62.7)
Noncurative	
R0	3 (2.9)
R1	4 (3.9)
Rx	1 (1.0)

R0 = all margins of the resected specimen were negative for tumor cells; R1 = tumor cells extended to the lateral or basal margins of the resected specimen; Rx = the margins could not be evaluated.

Because colorectal ESD requires a high level of skill, we defined the prerequisites for this procedure to ensure that the operator had a certain degree of skill. The nonloop insertion technique for colonoscopy is essential for ESD for colonic lesions because inadequate control during the resection increases the risk of perforation from paradoxical scope movement. In learning the ESD technique, experience with gastric lesions should be obtained before working with colorectal lesions. ESD for gastric lesions located in the antrum is relatively easy to perform because there is sufficient working space to control the endoscope and a good visual field; moreover, the gastric wall of the antrum is thicker than the colonic wall, lowering the risk of perforation. However, in Western countries, gastric cancer is less common than colorectal cancer, and it may be difficult to introduce trainees to the resection of this lesion as the first step of ESD. If required, trainees should begin clinical training for colorectal ESD with lower rectal lesions, which have a lower risk of perforation and have a setting similar to that of gastric lesions.

Given the differences between the complete and incomplete cases in our study, we believe that the macroscopic type of lesion, rather than its location, is more important in the first stage of training for ESD. The commonly held view is that endoscopic treatment is difficult for submucosal fibrosis. LST-NG type and recurrent lesions have a higher likelihood of fibrosis in the submucosal layer. In particular, the former lesion type is more likely to be affected by a prior biopsy because of its thinness, which increases its susceptibility to submucosal fibrosis because of mechanical stimulation during biopsy.²² On the other hand, LST-G-type lesions are relatively easy to resect by ESD, because most of them show

good elevation after adequate submucosal injection. Naturally, the risk of perforation of such lesions is lower than that of other lesions such as the LST-NG type or recurrent lesions.²²

The lesion size is also an important factor in determining the difficulty of colorectal ESD. Saito et al²³ reported that a tumor size of >50 mm increases the risk of complications. Given this result and the indications for colorectal ESD, we recommend that 30- to 40-mm LST-G-type lesions are the most suitable for the early stage of ESD training.

We consider the clinical outcomes of ESD in this study to be satisfactory, given the low incidence of complications and short procedure time. An ESD should be completed within 2 hours to reduce the burden on the patient, because this procedure is commonly performed under conscious sedation. In this study, most procedures were completed within 2 hours without serious complications, and the clinical outcomes were acceptable. There was no correlation between procedure time and experience with the ESD procedure. If trainees began by operating on only rectal lesions of a certain size, the procedure time might decrease with an increase in the number of ESD procedures. However, the lesion size, location, and configuration had nearly the same distributions between the training periods. Nearly all the lesions with similar clinical characteristics were treated within a certain time frame without serious incident. This result is sufficient to evaluate the learning curve for colorectal ESD at our institution.

Based on the results for completion rates, we believe that trainees require experience with >30 cases to perform colorectal ESD without guidance from an experienced specialist. The completion rates in the first to third training periods may seem insufficient; however, most trainees subsequently acquire troubleshooting skills such as endoscopic closure of perforations by using endoclips and understanding their technical limitations.

The R0 resection rate was lower than that previously reported.²² This clinical outcome mainly depends on the circumferential incision during the ESD procedure; we place the circumferential incisions very close to the lesion margin at our institution. Colorectal neoplasms commonly develop via the adenoma–carcinoma sequence, and most lesions arise from the epithelium without chronic inflammation, as in ulcerative colitis. Thus, in contrast to early gastric cancer, the margins of colorectal cancer can be recognized clearly after indigo carmine dye spraying, and marking during the endoscopic procedure is not required. Moreover, Saito et al¹³ reported that the local recurrence rate after ESD is only 2.1% in piecemeal resection cases. Therefore, we believe that Rx is not a determinant of curability. In fact, of the 72 patients in this study who underwent 1-year follow-up colonoscopy after curative en bloc resection, none showed recurrence or residual tumor. Of the 6 patients with fractional resection who

underwent follow-up colonoscopy, one showed a local residual tumor. However, it was a small intramucosal neoplasm; additional endoscopic coagulation treatment resulted in complete remission.

The main limitation of our study is its single-center design. Recently, new instruments for ESD have been developed and applied, and their availability depends on the institution. For the ESDs in this study, the trainees mainly used B-B and IT knives. The former instrument is particularly safe because of its bipolar system. A B-B knife is designed to reduce the high-frequency current sent to the muscular layer, enabling better control and greater safety for the endoscopist; the returning current toward the sheath tip ensures greater patient safety. Furthermore, the small tip at the end of the needle enables hooking of the mucosal or submucosal tissue, similar to that achieved with an IT knife. In addition, the colorectal ESD procedure is not yet covered by insurance and can be performed at only a few institutions that fulfill certain conditions. Such institutions are high-volume centers, and trainees may gain more experience in a shorter time than at other institutions. This intensive experience may also affect the overall learning curve. Another limitation is the variation in training systems for colorectal ESD among institutions; further evaluation of these differences is warranted.

CONCLUSION

Colorectal ESD can be performed without serious complications by trainee endoscopists under the guidance of experienced specialists. Trainees in colorectal ESD can perform this procedure safely and independently after a certain degree of preparatory training and experience with >30 cases.

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Clinical Study

Pilot Study on Clinical Effectiveness of Autofluorescence Imaging for Early Gastric Cancer Diagnosis by Less Experienced Endoscopists

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This study aimed to assess and compare effectiveness of Autofluorescence imaging (AFI) in diagnosis of early gastric cancer (EGC) between experienced and less experienced endoscopists. Fifty selected images (20 neoplastic lesions and 30 benign lesions/areas) of both white light endoscopy (WLE) and AFI were blindly reviewed by two groups; first consisted of five experienced endoscopists and second included five less experienced endoscopists. Sensitivity, specificity, and accuracy were 70%, 78%, and 75%, respectively, for AFI and 81%, 76%, and 78%, respectively, for WLE in the experienced group. In the less experienced group, sensitivity, specificity and accuracy were 80%, 81% and 80%, respectively, for AFI and 65%, 77%, and 72%, respectively, for WLE. Interobserver variability for the less experienced group was better with AFI than WLE. AFI improved sensitivity of endoscopic diagnosis of neoplastic lesions by less experienced endoscopists, and its use could beneficially enhance the clinical effectiveness of EGC screening.

1. Introduction

Gastric cancer incidence and mortality have declined dramatically over the past 70 years [1]. Despite these declines, gastric cancer is still the fourth most common cancer and the second leading cause of cancer-related deaths worldwide [2]. Development of esophagogastroduodenoscopy (EGD), a screening tool for early gastric cancer (EGC), in place of radiology [3] has allowed widespread availability of screening in high-risk countries such as Japan and Korea resulting in decreased mortality. In contrast, relatively few gastric cancers are discovered at an early stage in most Western countries [4].

We have witnessed firsthand significant advances in endoscopic treatment for early gastric cancer in recent years including development of endoscopic submucosal dissection (ESD) [5–7]. In order to fully benefit from the advantages

of endoscopic treatment, however, it is important to detect gastric cancers at the earliest possible stage [8]. Most cases of EGC are slightly depressed or elevated lesions and red or pale in color, but some EGC are quite flat and almost isochromatic so there is very little contrast with the surrounding mucosa. Such subtle changes of EGC can make for a challenging endoscopic diagnosis. The difficulties involved in making an accurate diagnosis can be compounded by the inexperience of some endoscopists particularly in countries where the incidence of gastric cancer is low.

Following development of a fluorescence detection method for neoplastic lesions in 1957, autofluorescence imaging (AFI) has attracted considerable attention in the diagnosis of early cancerous lesions [9, 10]. AFI is a novel imaging method that produces computerized real-time pseudocolor images by detecting faint fluorescence

TABLE 1: Neoplastic lesion characteristics and AFI colors.

		Number of lesions	AFI color	
			Magenta	Green
Pathological type	Carcinoma (differentiated)	13	9	4
	Carcinoma (undifferentiated)	3	0	3
	Adenoma	4	4	0
Location	Upper third of stomach	2	1	1
	Middle third of stomach	9	6	3
	Lower Third of Stomach	9	6	3
Macroscopic type	Elevated	9	9	0
	Flat	2	2	0
	Depressed	9	2	7
WLE color	Reddish	9	4	5
	Isochromatic	8	8	0
	Pale	3	1	2

AFI: autofluorescence imaging; WLE: white light endoscopy.

emitted from endogenous fluorophores exposed to excitation light. Neoplastic lesions with an altered fluorescence can be distinguished from the enhanced surrounding normal pattern by variations in color.

Several published reports have examined the advantages of AFI for detection of colorectal cancer [11–14]. It may also be easier for less experienced endoscopists to detect gastric neoplastic lesions using AFI even when such lesions cannot be detected by conventional white light endoscopy (WLE) [15]. The aim of this pilot study was to assess and then compare the effectiveness of AFI in the diagnosis of gastric neoplastic lesions between experienced and less experienced endoscopists.

2. Methods

2.1. Study Design. During endoscopy using a prototype AFI system that included both WLE and AFI functions performed by one experienced endoscopist (C. Yokoi), pictures of neoplastic lesions and benign lesions/areas were taken from 44 patients with EGC after obtaining their informed consent who were referred to our hospital for treatment from August 2005 to March 2006. Pictures of 45 EGCs were collected along with 172 pictures of benign lesions/areas from these 44 patients. All neoplastic and benign lesions were assessed histopathologically from biopsy specimens. Pictures of poor quality were excluded, and 50 pictures were then selected at random by the study coordinator (K. Tada) for this pilot study including 20 pictures of neoplastic lesions (four adenomas and 16 EGCs) and 30 pictures of benign lesions/areas (four polyps, six ulcer scars, four atrophic changes, and 16 normal mucosal areas). The clinicopathological characteristics of the neoplastic lesions were classified based on the Japanese Classification of Gastric Carcinoma [16] while the descriptions of WLE and AFI colors were determined by the study coordinator (Table 1). All slightly elevated and flat lesions appeared magenta in a green field, and 7 of 9 slightly depressed lesions displayed green in a magenta field. The mean lesion size was 20 mm.

We prepared 50 sets of AFI and WLE images for the same selected lesions and normal mucosa. Each image was assigned a random sequence number with the 50 AFI images displayed first followed by the 50 WLE images. A review of the images was performed individually by 10 endoscopists excluding the endoscopist who took the images and the study coordinator who were divided into two separate groups: five endoscopists with extensive experience in EGC from the National Cancer Center Hospital (NCCCH) and five less experienced endoscopists working in a general hospital. Each of the endoscopists in the first group of reviewers had over 10 years of medical experience including more than three years at NCCCH and had evaluated in excess of 700 EGCs annually. The endoscopists in the second group of reviewers each had less than five years of medical experience and had evaluated fewer than 30 cases of EGC per year. No information regarding any of the lesions was available to the reviewers. An answer sheet was given to each endoscopist with two options regarding each image: “neoplasm exists” or “no neoplasm.”

2.2. Autofluorescence Imaging System. The prototype AFI system used in this study (XGIF-Q240FZ; Olympus Medical Systems Corp., Tokyo, Japan) was equipped with two charge-coupled devices (CCDs) at the tip of the endoscope that could easily be switched by pushing a single button on the scope handle: one for high-resolution white-light observation and the other for autofluorescence observation. The AFI system digitally creates real-time pseudocolor images from autofluorescence (excitation at 390–470 nm and detection at 500–630 nm) and green reflection (G') at 540–560 nm. The system relies on a sequential method in order to provide clear image profiles and distinguish autofluorescence reduction of neoplastic lesions caused by hemoglobin absorption.

2.3. AFI Diagnostic Criteria for Neoplastic Lesions. A neoplastic lesion was defined for AFI purposes as an area that contrasts in color with the surrounding background such as

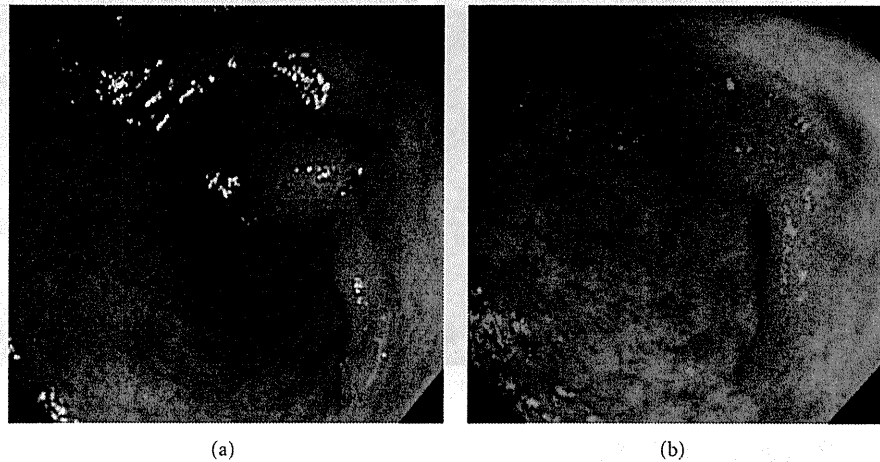


FIGURE 1: Diagnostic criteria for autofluorescence imaging (AFI). We defined a lesion suspected of being neoplasia using AFI (AFI-positive) as an area that was clearly different from the surrounding mucosa in color. (a) WLE image of an EGC. (b) AFI-positive image displayed the same EGC as a magenta area with defined margins within the green-colored mucosa.

TABLE 2: Interobserver variability for detection of neoplastic lesions with AFI and WL.

κ	AFI (95% CI)	WLE (95% CI)
Experienced endoscopists	0.42 (0.33–0.51)	0.52 (0.43–0.61)
Less experienced endoscopists	0.52 (0.43–0.61)	0.29 (0.20–0.38)

AFI: autofluorescence imaging; WLE: white light endoscopy.

“a magenta area in a green field” or “a green area in a magenta field” (Figure 1).

AFI images are considerably different from those of conventional WLE, however, so endoscopists have to become familiar with such images in order to attain an appropriate level of diagnostic skill. All participating endoscopists in this study were briefed on how to evaluate AFI images and given an opportunity to review 10 sample pictures beforehand at a 30-minute training lecture.

2.4. Statistical Analysis. We compiled the answers for the five endoscopists in each group and then calculated sensitivity, specificity, and accuracy for both groups. Data were analyzed using the chi-square test, and value differences of $P < 0.05$ were considered statistically significant. Interobserver variability was determined for each group using Kappa (κ) statistics. All statistical analyses were performed using STATA version 10.0 (StataCorp, College Station, Tex, USA).

3. Results

Detection of neoplastic lesions by the experienced endoscopists using AFI and WLE, respectively, resulted in a sensitivity of 70% (95% CI 60–78%) and 81% (95% CI 72–88%), a specificity of 78% (95% CI 71–84%) and 76%

(95% CI 69–82%), and an accuracy of 75% and 78%. Less experienced endoscopists had a sensitivity of 80% (95% CI 71–87%) and 65% (95% CI 55–74%), a specificity of 81% (95% CI 74–86%) and 77% (95% CI 70–83%), and an accuracy of 80% and 72%, respectively, using AFI and WLE for diagnosis. Sensitivity in the less experienced group of endoscopists using AFI (80%) was significantly higher than when using WLE (65%) ($P < 0.05$). And sensitivity in the less experienced group of endoscopists using AFI (80%) was comparable to the more experienced group of endoscopists using WLE (81%) (Figure 4).

Interobserver variability for detection of neoplastic lesions by the group of less experienced endoscopists was better for AFI than with WLE (experienced group: AFI [$\kappa = 0.42$ (95% CI 0.33–0.51)] and WLE [$\kappa = 0.52$ (95% CI 0.43–0.61)]; less experienced group: AFI [$\kappa = 0.52$ (95% CI 0.43–0.61)] and WLE [$\kappa = 0.29$ (95% CI 0.20–0.38)]). There was no statistically significant difference in the interobserver variability using AFI between the experienced and less experienced endoscopist groups. In contrast, there was a significant difference using WLE between the two groups with the experienced endoscopist group having significantly better interobserver variability (Table 2).

With regard to lesions diagnosed by the group of less experienced endoscopists, three of the 20 (15%) neoplastic lesions were diagnosed more often by WLE, and 11 (55%) were diagnosed more often by AFI. All three (100%) neoplasias diagnosed more often by WLE were slightly depressed lesions. (Figures 2(a), 2(b), and 2(c)). In contrast, eight of the 11 (73%) neoplasias diagnosed more often by AFI were flat lesions (Figures 3(a) and 3(b)).

4. Discussion

The effectiveness of AFI for diagnosing EGC by highly experienced endoscopists has been assessed in several studies, but

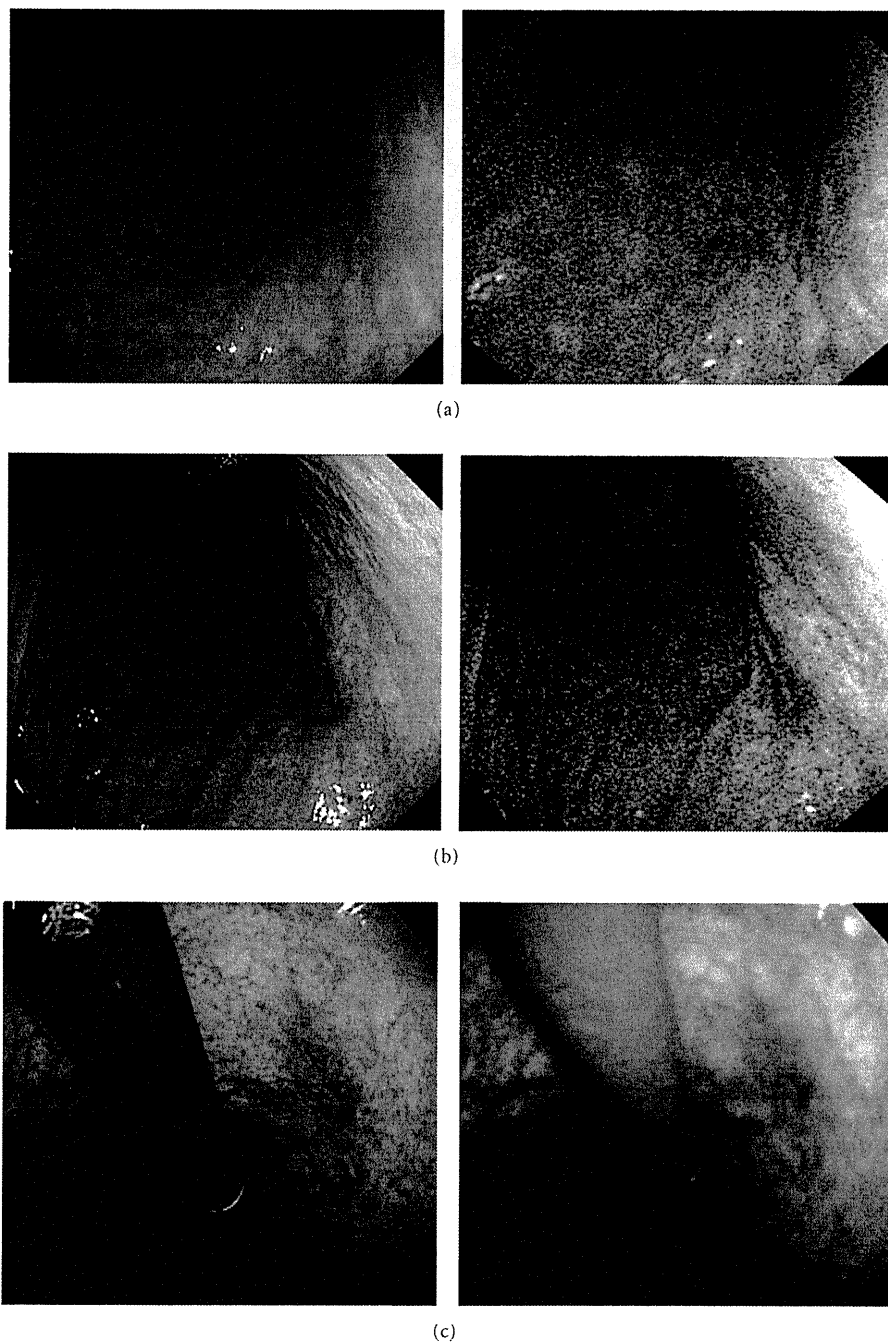


FIGURE 2: These three neoplastic lesions were diagnosed more easily using WLE. All three appeared reddish in color with a slightly depressed area.

there are no published reports evaluating less experienced endoscopists [15, 17].

AFI can differentiate tissue types based on variations in their fluorescence emissions. When tissue is exposed to short wavelength (390–470 nm) light, endogenous biological substances such as collagen, nicotinamide adenine dinucleotide, flavin, and porphyrins are excited leading to the emission of longer wavelength (500–630 nm) fluorescent

light (autofluorescence) [18]. Neoplastic and nonneoplastic tissues have different autofluorescence characteristics including nuclear-cytoplasmic ratio, mucosal layer thickness, and volume of blood flow [19]. These characteristics may facilitate differentiating between the two. During endoscopy using the AFI mode, neoplastic lesions contrast with normal mucosal tissue (i.e., “a magenta area in a green field” or “a green area in a magenta field”).

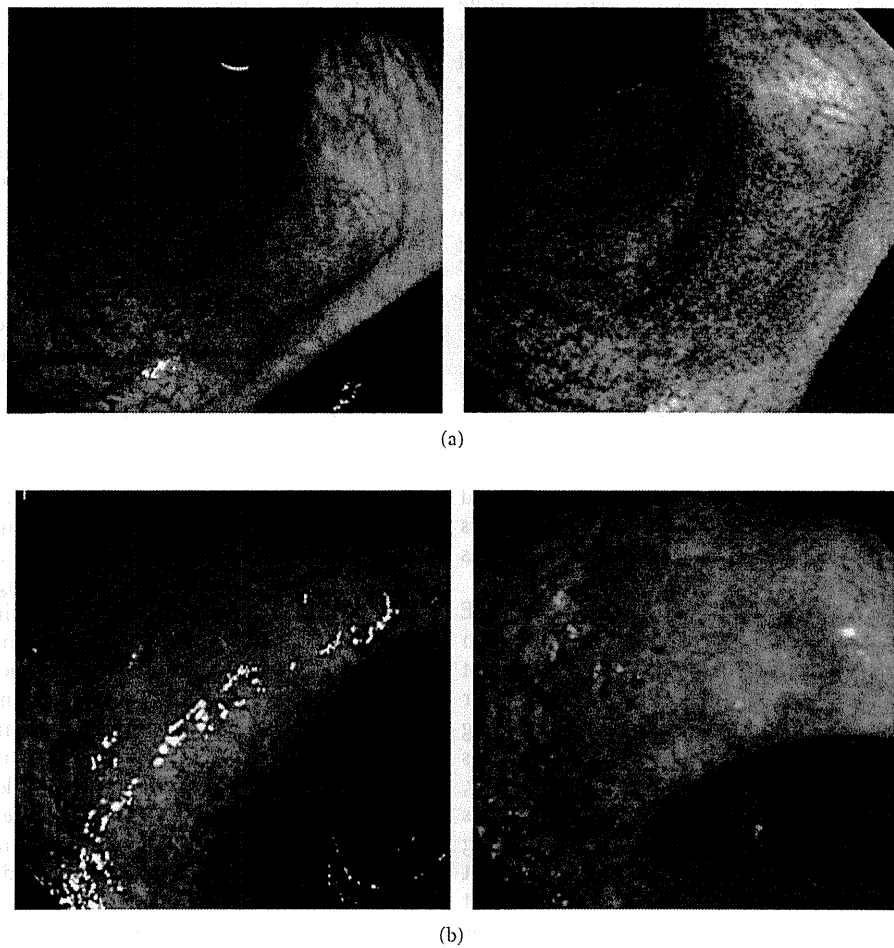


FIGURE 3: Here are two examples of neoplastic lesions diagnosed more easily using AFI. Each of them appeared as an isochromatic flat lesion using WLE.

		Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Accuracy (%)
Experienced endoscopists	AFI	70 (60–78)	78 (71–84)	75
	WLE	81 (72–88)	76 (69–82)	
		n.s.		
Less experienced endoscopists	AFI	80 (71–87)	81 (74–86)	80
	WLE	65 (55–74)	77 (70–83)	
		P < 0.05		
		n.s.		

AFI, autofluorescence imaging; WLE, white light endoscopy; n.s., no significant difference.

FIGURE 4: AFI and WLE image review results.

A number of studies have reported that AFI is effective for colorectal cancer screening, but this is still debatable while its suitability for gastric cancer screening remains somewhat more controversial [11–14, 20, 21]. Inflammatory and hyperplastic changes in the stomach can alter mucosal layer thickness and blood flow volume causing autofluorescence contrast variations with similar appearance to neoplastic lesions. Such difficulties are also reported in Barrett's esophagus [22]. False-positive results and low specificity, therefore, are more common in the stomach and Barrett's esophagus. Currently, AFI cannot distinguish precisely between gastric neoplastic lesions and inflammatory or hyperplastic changes. It is already known, however, that EGC is not easily detected by less experienced endoscopists. No detection, of course, means there is no treatment, so our primary objective in EGC screening should be higher sensitivity rather than diagnostic accuracy. False-positive lesion findings should be a secondary consideration to the actual sensitivity rate. AFI provides a simple dichromatic difference that may help less experienced endoscopists diagnose neoplastic lesions more easily. For this reason, we included less experienced endoscopists as well as highly experienced endoscopists in our study.

In the group of experienced endoscopists, the WLE sensitivity of 81% was reduced to 70% with AFI although there was no statistically significant difference indicating that AFI did not provide an advantage in terms of detection for that particular group. We postulate that sensitivity using WLE was already high in the experienced endoscopists group as variables such as surface irregularity, elasticity, thickness, hardness, converging folds, and background status were examined. The ability to interpret those changes using WLE improves with endoscopic experience. We believe that experienced endoscopists in this study attempted to interpret all characteristics of a lesion using AFI rather than just color contrast. Reliance on such variables, in fact, can mislead experienced endoscopists given AFI's low vision quality.

In contrast, AFI raised detection sensitivity from 65% to 80% and interobserver variability from 0.29 to 0.52 for less experienced endoscopists. Although the subtle mucosal changes of EGC make endoscopic diagnosis a challenge for less experienced endoscopists using WLE, our findings indicated that AFI might facilitate easier diagnosis of neoplastic lesions by such endoscopists. This was likely due to objective evidence of a definite difference in coloration between neoplastic lesions and the surrounding mucosa. AFI was particularly effective in the diagnosis of flat lesions. The overall sensitivity and interobserver agreement were unsatisfactory, however, for the differential diagnosis between neoplastic and benign lesions so we still need to perform a biopsy.

There are, however, a number of limitations to this pilot study. Firstly, we used still images taken by experienced endoscopists, and some of those lesions may not have been detected at all by less experienced endoscopists during real-time endoscopy. Quality of the AFI view depends on technical skill so less experienced endoscopists might not be able to reproduce the images used in this study. Our results, therefore, may not be reflected in actual examination, but the results of less experienced endoscopists were in fact

better than experienced endoscopists using the same AFI pictures. In the future, effectiveness of AFI for screening of EGC should be assessed in a prospective study including experienced and less experienced endoscopists with diagnosis on a real-time basis. Secondly, in order to make it simpler, we included only two options "neoplasm exists" or "no neoplasm" for reviewers. It would have been better to also have them evaluate lesion characteristics such as AFI and WLE colors as well as macroscopic type. So we plan to conduct the real-time evaluations lesion features in the next study. Thirdly, there was no yardstick used in choosing the specific kinds and relative percentages of images presented in this study, and the percentage of neoplastic lesions was considerably higher than that which would normally be the case in routine gastric screening. The actual choice of images could have had an effect on the results. For example, Kato et al. carried out a prospective study on the effectiveness of AFI for detecting EGC [17]. They reported sensitivity of 74% and specificity of 83% for WLE and sensitivity of 64% and specificity of 40% for AFI performed by experienced endoscopists. Data for the experienced endoscopists in our study showed a similar results regarding sensitivity of AFI. Although the high specificity of 78% with AFI in our study may have been affected by the choice of images, the sensitivity results in both groups of endoscopists were quite promising.

A number of practical improvements need to be made before AFI can actually be introduced into a clinical gastric screening setting (i.e., the AFI system video endoscope is too large in diameter with poor flexibility and lower overall image quality), but we believe that AFI has the potential to increase the sensitivity of endoscopic diagnosis of neoplastic lesions by less experienced endoscopists. This would be important not only in Japan but especially in those countries with a low incidence of gastric cancer. The AFI system is only being used on a limited basis in Japan and a few other countries at the present time, and greater availability and increased usage worldwide of this system should demonstrate its effectiveness and lead to wider acceptance.

The primary advantage of AFI is that it identifies suspicious lesions as areas evidencing color contrast almost instantaneously throughout the entire endoscopic field. Even if the false-positive rate using AFI is high, the examining endoscopists can use other modalities such as chromoendoscopy or NBI with magnification in addition to obtaining biopsies to verify their initial suspicion of EGC [23, 24]. This is provided, of course, that lesions are detected in the first place. AFI could then become an important technique for EGC screening by all endoscopists to diagnose suspected lesions.

This is the first study on the effectiveness of AFI by less experienced endoscopists. Although the results are encouraging, it should be noted that this was an uncontrolled pilot trial involving a relatively small number of lesions. Prospective randomized controlled trials involving a large number of subjects would be beneficial in the future to more fully evaluate the effectiveness of AFI in the diagnosis of EGC.

In conclusion, the use of AFI in this study increased sensitivity in the endoscopic diagnosis of gastric neoplastic

lesions by less experienced endoscopists. Such use may beneficially enhance the clinical impact of EGC screening by less experienced endoscopists, but this will need to be confirmed in a prospective study with diagnosis on a real-time basis.

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Clinical Study

Prospective Case Study on Characterization of Colorectal Adenomas Comparing AFI with NBI

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Aim. Compare the characterization ability of AFI and NBI for colorectal adenomas. *Methods.* We prospectively enrolled 58 patients with 89 colorectal adenomas detected by white light colonoscopy. Such lesions were subsequently observed with both AFI and NBI and then treated by endoscopic resection. With respect to the 89 lesions, 3 experienced endoscopists retrospectively evaluated the visualization quality of the AFI and NBI images in a blind manner using a three-tier scale based on excellent, fair, and poor criteria. *Results.* There were 54, 31, and 4 lesions considered as excellent, fair, and poor visualization, respectively, using AFI in comparison to 53, 19, and 17 lesions, respectively, with NBI. The percentage of excellent and fair visualization lesions was 95.5% with AFI and 80.9% with NBI ($P < .01$). *Conclusion.* This study indicated that AFI may be more effective for the characterization of colorectal adenomas because of better visualization of such lesions compared to NBI.

1. Introduction

Colorectal cancer is the fourth most common form of cancer and the second leading cause of cancer-related deaths in the United States [1]. Current trends suggest that colorectal cancer will soon become a major cause of morbidity and mortality in Japan as well [2] so detection and removal of colorectal adenomas by colonoscopy is becoming an increasingly important means of preventing such cancer [3].

Small or flat adenomas may be missed, however, during conventional colonoscopy examinations [4, 5]. In particular, depressed type colorectal tumors and nongranular type laterally spreading tumors (LST-NGs) have a high potential for malignancy [6, 7] even those smaller in size, but such lesions can be difficult to detect using standard white light colonoscopy (WLC). Although chromoendoscopy provides advantages over conventional colonoscopy in the detection of small lesions, the procedure is more complicated and takes longer [8]. In order to detect colorectal adenomas without the necessity of using chromoendoscopy, therefore, a need exists for the development of a new effective endoscopic method for that specific purpose.

The autofluorescence imaging (AFI) [9–12] and narrow-band imaging (NBI) [13–16] videoendoscope systems are recently developed noninvasive optical-digital imaging processes. It has been reported that both systems have an advantage over standard WLC in terms of providing better visualization and, therefore, may be able to improve the endoscopic characterization of colorectal adenomas. There have been no published reports, however, that have actually compared the characterization ability of AFI and NBI for colorectal adenomas based on the visualization of such lesions so we decided to conduct such a study.

2. Materials and Methods

2.1. Endoscopic Imaging Systems: AFI Videoendoscope System and NBI Videoendoscope System. The AFI videoendoscope system (Olympus Medical Systems Corp., Tokyo, Japan) is a new illumination method that allows for real-time white light endoscopy [9–12]. Neoplastic areas involve a thickening of the mucosal layer and increased hemoglobin so such areas emit weaker autofluorescence compared to nonneoplastic

areas. Recently, the AFI system has been used to enhance detection of early lesions in the esophagus, stomach, and colon.

The NBI system (Olympus Medical Systems Corp.) is another novel optical-digital imaging process that uses special narrow-band filters in the endoscopic system to provide a more detailed visualization of the mucosal architecture and capillary pattern [13–16]. As a result of the improved mucosal contrast provided by NBI, this technique also has the potential for improving the detection of colorectal lesions compared to standard WLC.

The prototype colonoscope used for AFI and NBI examinations in this study had a sequential green and blue light source (XCLV-260HP) and a high-resolution videoendo-scope (XCF-H240FZI) and video system (XCV-260HP). This endoscope also had two sets of charge-coupled devices; one for conventional white light imaging and NBI and the other for AFI. The endoscope's light source consisted of three types: conventional white light; AFI light comprised of a blue light for emitting and a green light for hemoglobin absorption; NBI light of two wavelengths for hemoglobin absorption. During the endoscopy procedures, the colonoscopist could switch from conventional imaging to AFI or NBI merely by pushing a button on the control handle of the endoscope. In addition, the videoendoscope was equipped with an accessory channel having an internal diameter of 3.2 mm. The outer diameter of the distal tip of the videoendoscope was 14.8 mm and the videoendoscope included functions for variable stiffness and magnification up to 75x with the white light image.

2.2. Patients. From June 2006 to October 2006, a total of 58 consecutive patients (males/females, 40/18; mean age, 63.7 ± 7.7 years, range 44–75 years) underwent colonoscopies during which a total of 89 colorectal adenomas were detected by high-resolution WLC and subsequently examined using both AFI and NBI. All lesions were treated by endoscopic resection and included in this prospective study at the National Cancer Center Hospital in Tokyo. The 89 colorectal adenomas were classified according to histology: low-grade dysplasia/high-grade dysplasia, 79/10; macroscopic type: IIa/Is, 68/21; tumor size: ≤ 5 mm/ >5 mm, 66/23 (Table 1). Eligible patients were adults with no history of surgical resection of the colon or rectum and without inflammatory bowel disease or familial adenomatous polyposis (FAP). Written informed consent was obtained from all patients before their examinations.

2.3. Endoscopic Examinations. Patients prepared for their colonoscopy examinations by ingesting 2–3 liters of polyethylene glycol-electrolyte solution in the morning. Every procedure was performed by one highly experienced colonoscopist (TM) in our endoscopy division.

First, routine endoscopic examinations were performed using the white light mode of the AFI videoendoscope system to identify lesions suspected of being colorectal adenomas.

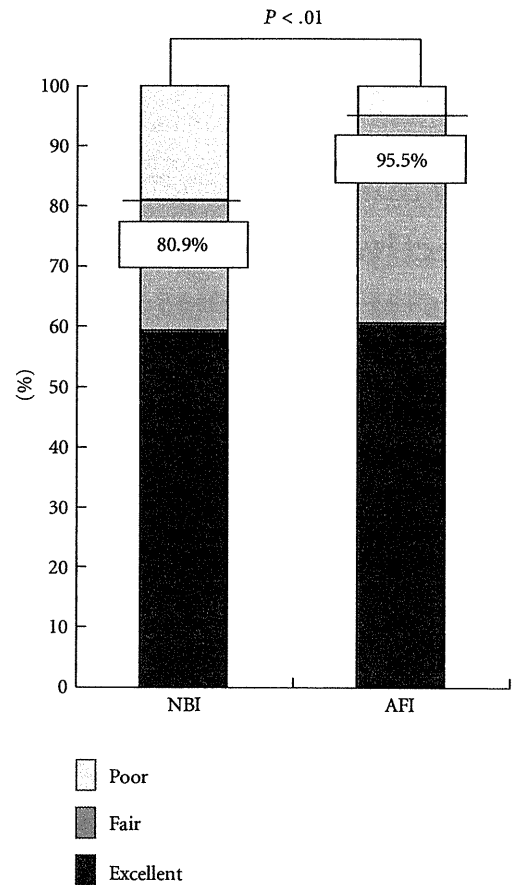


FIGURE 1: Visualization of colorectal adenomas by AFI and NBI. The percentage of lesions visualized as being excellent and fair was 95.5% with AFI and 80.9% with NBI ($P < .01$). The P -value was calculated using McNemar's Test.

TABLE 1: Clinicopathological features of 89 colorectal adenomas.

Clinicopathological features	Number of lesions
Histology	
Low-grade dysplasia	79
High-grade dysplasia	10
Macroscopic type	
IIa	68
Is	21
Lesion size	
≤ 5 mm	66
>5 mm	23
Total	89

If such a colorectal lesion was detected, the colonoscopist conducted AFI and NBI examinations by switching first to the AFI mode followed by the NBI mode. Photographs depicting the colorectal lesion in the center of the endoscopic monitor were then taken of the AFI and NBI views. In

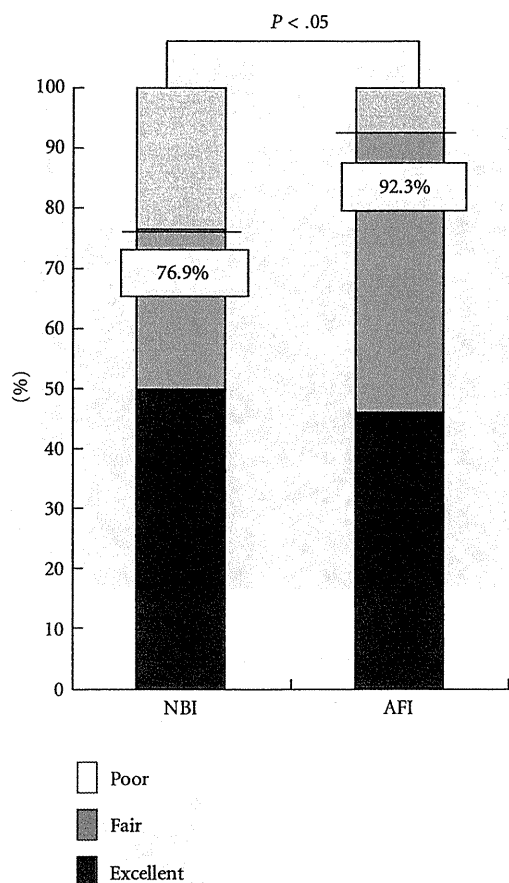


FIGURE 2: Visualization of colorectal adenoma flat lesions ≤ 5 mm in size by AFI and NBI. The percentage of lesions visualized as being excellent and fair was 92.3% with AFI and 76.9% with NBI ($P < .05$). The P -value was calculated using McNemar's Test.

addition, chromoendoscopy was performed to diagnose the detected lesion more precisely.

2.4. Endoscopic Images of Colorectal Adenomas. A lesion suspected of being a colorectal adenoma using AFI was defined as a purple or magenta demarcated area on a green background while a lesion suspected of being a colorectal adenoma using NBI was defined as a demarcated area brownish in color.

2.5. Histological Assessment. We subsequently performed endoscopic resections for all visualized lesions diagnosed as being colorectal adenomas and histological examinations were conducted on all resected specimens according to World Health Organization criteria [17].

2.6. Evaluation of Colorectal Adenoma Visualization. During the endoscopic examinations referred to above, the endoscopist took pictures of abnormal mucosal areas and a representative collection was then assembled of both AFI and NBI images of each colorectal adenoma. After

the endoscopic examinations, three other endoscopists with extensive experience in the diagnosis of colorectal adenomas (HS, TK, and YS) evaluated those lesions histologically diagnosed as being colorectal adenomas in terms of the visualization quality of the AFI and NBI images that were randomly displayed without reference to any information concerning the nature of the lesions.

The visualizations were evaluated on a three-tier scale: excellent, fair, and poor. An "excellent visualization" was defined as a lesion that could be clearly described by AFI or NBI and definitely diagnosed endoscopically as a colorectal adenoma. A "fair visualization" was defined as a lesion that could be reasonably described by AFI or NBI and diagnosed endoscopically as a colorectal adenoma although a part of the lesion's margin appeared dim. A "poor visualization" was defined as a lesion that could not be clearly described by AFI or NBI and could barely be diagnosed endoscopically as a colorectal adenoma.

Next, we confirmed the visualization scales of each lesion that had been agreed on by at least two endoscopists. In addition, we calculated the percentage of excellent and fair visualized lesions using AFI and NBI, respectively, and then compared the visualization results for the AFI and NBI images. Interobserver agreement was also assessed in relation to the visualization of colorectal adenomas.

2.7. Statistical Analysis. McNemar's Test was used for statistical analysis with the standard computer software statistical package SPSS for Windows (SPSS, Release 6.0; SPSS Inc., Chicago, Ill, USA, 1993) with a P -value $< .05$ considered significant. Interobserver agreement was calculated using kappa (κ) statistics.

3. Results

A total of 54, 31, and four such lesions were evaluated as having excellent, fair, and poor visualization, respectively, using AFI in comparison to 53, 19, and 17 such lesions, respectively, with NBI (Table 2). Significantly more colorectal adenomas could be described by AFI compared to NBI as the percentage of excellent and fair visualized lesions was 95.5% with AFI and 80.9% with NBI ($P < .01$) (Figure 1). As for Interobserver agreement in the visualization of colorectal adenomas, there was better agreement with AFI ($\kappa = 0.41$) than with NBI ($\kappa = 0.32$).

With respect to 52 flat lesions (IIa) ≤ 5 mm in size, there were 24, 24, and four such lesions evaluated as having excellent, fair, and poor visualization, respectively, with AFI compared to 26, 14, and 12 such lesions, respectively, with NBI (Table 3). Significantly more colorectal adenomas consisting of flat lesions ≤ 5 mm in size could also be described by AFI compared to NBI as the percentage of excellent and fair visualized lesions was 92.3% with AFI and 76.9% with NBI ($P < .05$) (Figure 2).

AFI and corresponding NBI images of two representative adenomas both located in the transverse colon are shown in Figures 3(a) and 3(b) and Figures 4(a) and 4(b), respectively.