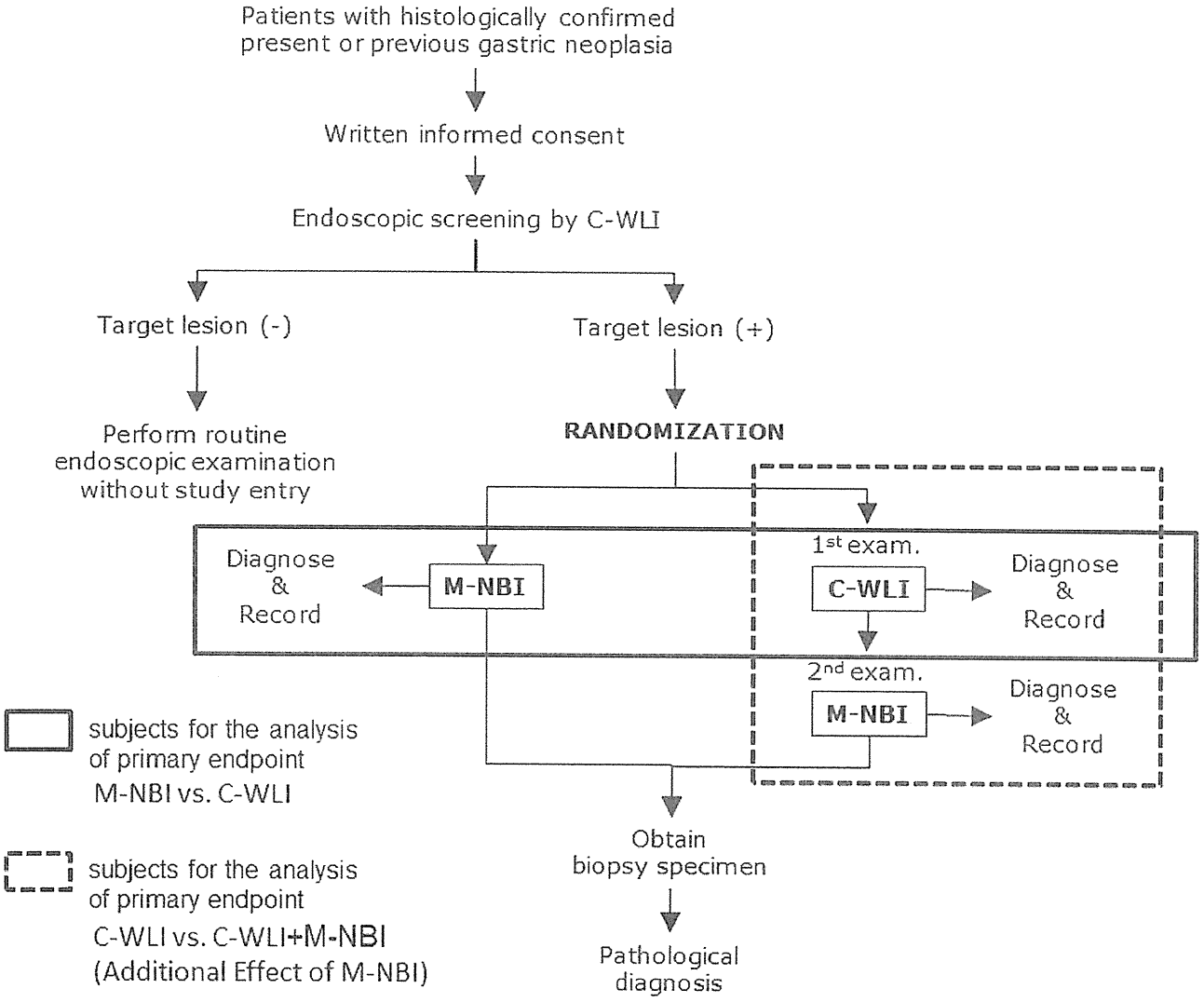

Supplementary Figure 1. Study flow.

Conventional White-light Imaging (C-WLI)

		Spiny Depressed Area		
		present	absent	indeterminate
Irregular Margin	present	cancer		
	absent		noncancerous	
	indeterminate			inconclusive

Magnifying Narrowband Imaging (M-NBI)

		Irregular Microvascular Pattern		
		present	absent	indeterminate
Demarcation Line	present	cancer		
	absent		noncancerous	
	indeterminate			inconclusive

Supplementary Figure 2. Diagnostic method based on endoscopic findings.

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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.

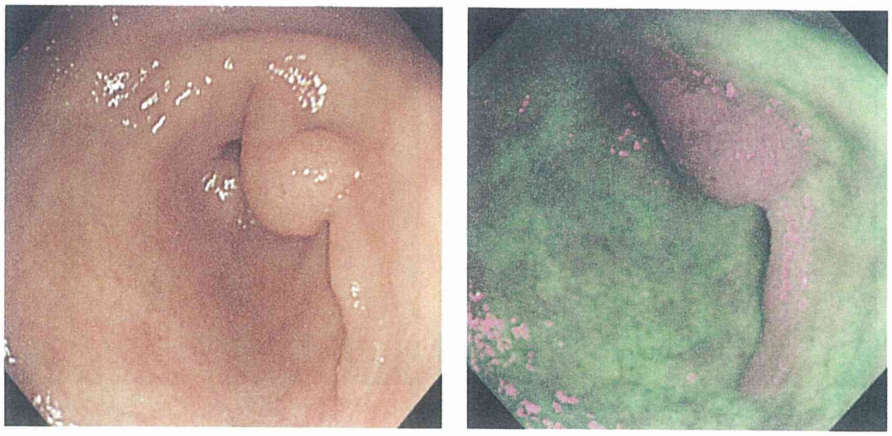
2. Methods

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 (NCCH) 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 NCCH 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



(a) (b)

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% Cl)
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 [κ = 0.42 (95% CI 0.33–0.51)] and WLE [κ = 0.52 (95% CI 0.43–0.61)]; less experienced group: AFI [κ = 0.52 (95% CI 0.43–0.61)] and WLE [κ = 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

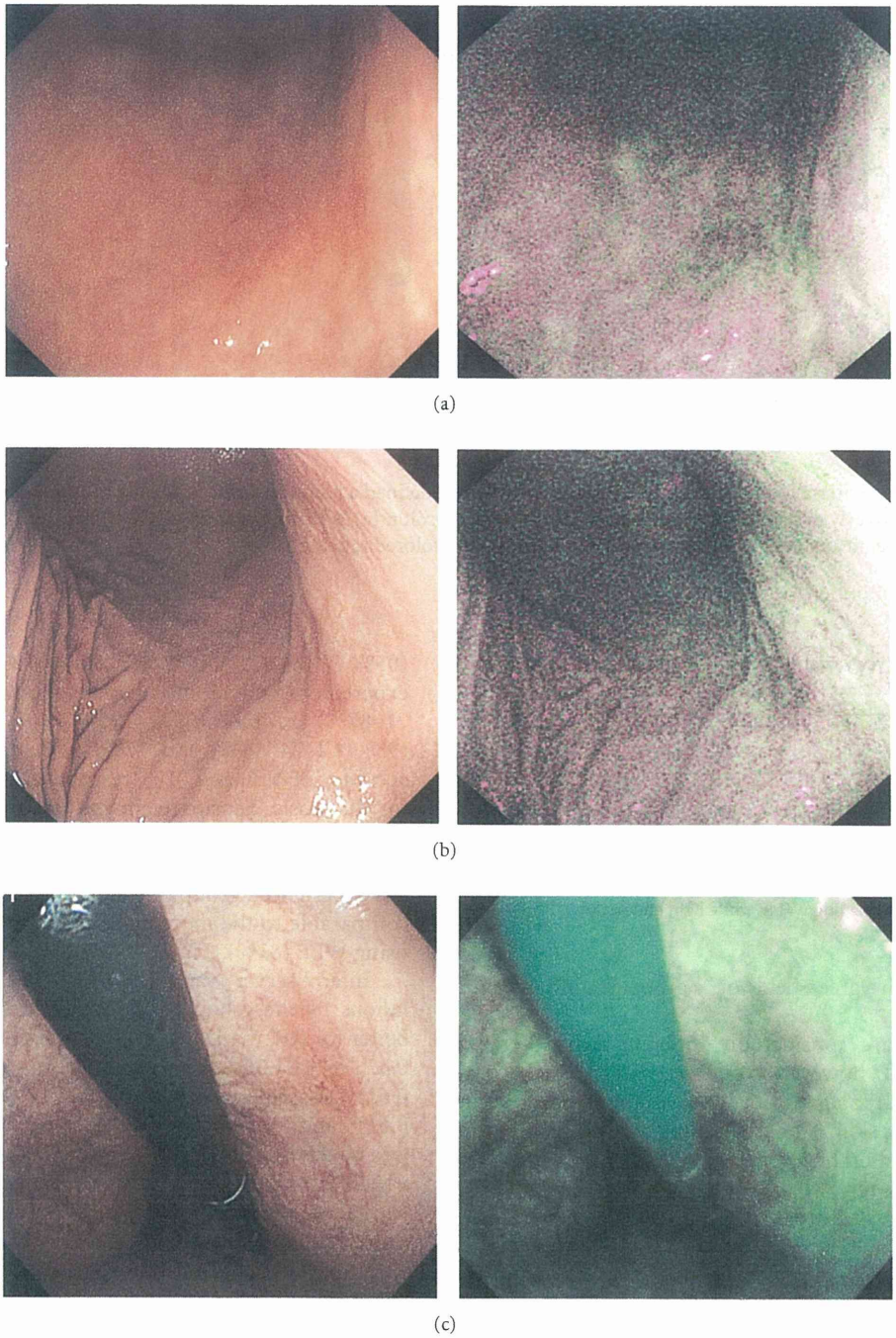


FIGURE 2: These three neoplastic lesions were diagnosed more easily using WLE. All three appeared reddish in color with a slightly depressed area.

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").

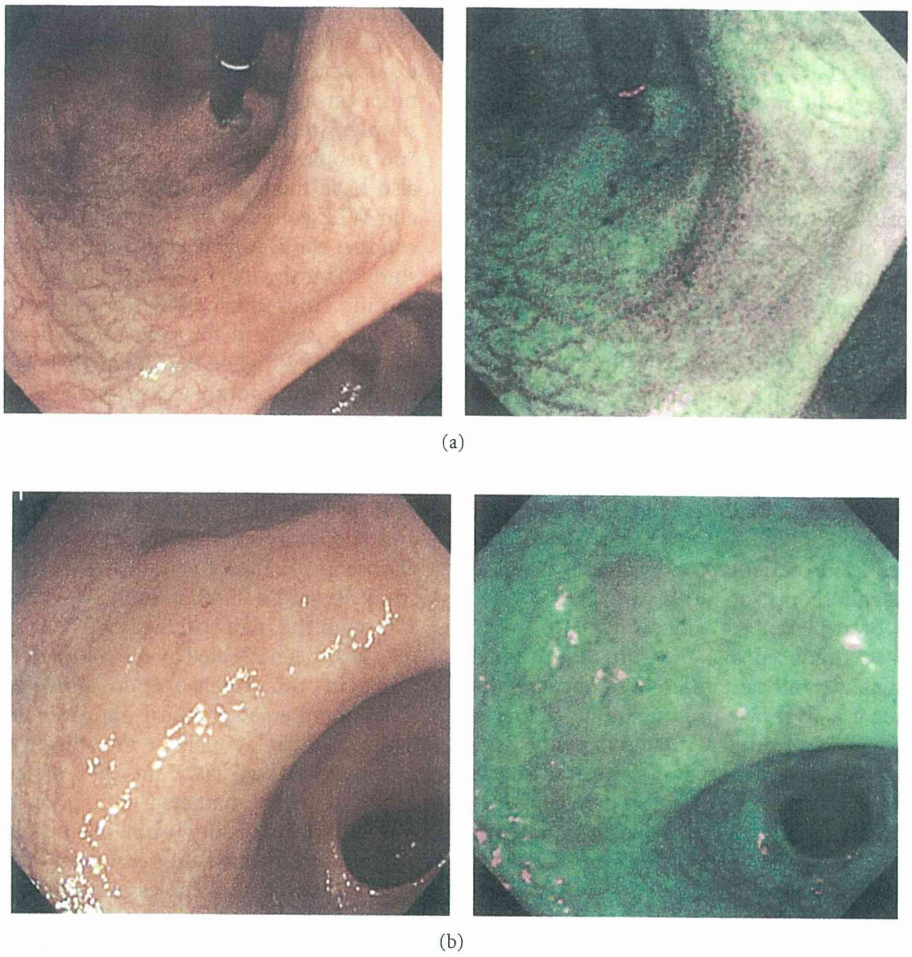


FIGURE 3: Here are two examples of neoplastic lesions diagnosed more easily using AFI. Each of them appeared as an isochromatic flat lesion using WLE.

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

AFI, autofuorescence imaging; WLE, white light endoscopy; n.s., no signifcant diference.

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 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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GASTROENTEROLOGY

Conflicting clinical environment about the management of antithrombotic agents during the periendoscopic period in Japan

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Key words
anticoagulant, antiplatelet agent, bleeding, cerebrovascular and cardiovascular disease, complication, endoscopy.

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Abstract

Background and Aims: Although there are guidelines for the management of antithrombotic agents during the periendoscopic period, gaps between various guidelines create a confusing situation in daily clinical practice. The purpose of this study was to examine the current management of antithrombotic agents during the periendoscopic period in Japan.
Methods: This is a prospective cohort study in 12 high-volume endoscopy centers in Japan. A total of 970 outpatients receiving antithrombotic agents underwent endoscopies (705 esophagogastroduodenoscopies and 265 colonoscopies) with or without invasive procedures. Main outcome measures are adverse events in these patients.
Results: Need for cessation of antithrombotics before endoscopy was mostly determined by non-gastroenterologists (51%) who are unfamiliar with the Japan Gastroenterological Endoscopy Society (JGES) guideline, although cessation periods after endoscopy for most patients were determined by endoscopists (78%). Consequently, most patients underwent endoscopy without cessation (25%) or after a cessation period of 6–7 days (33%), indicating low permeation of the JGES guideline in Japan. Among 970 patients, two patients experienced major complications that may be related to thromboembolic events or gastrointestinal bleeding (95% confidence interval [CI]: 0–0.7%). One of these patients died due to sudden onset ventricular tachycardia. Invasive procedures, including 40 biopsies and two mucosal resections, were performed in 42 patients without cessation of antithrombotics, and no patients experienced major complications (95% CI: 0–8.4%).
Conclusions: This study revealed a conflicting clinical environment due to absence of a unified guideline in Japan. Further accumulation of data is mandatory to establish a unified guideline based upon solid evidence.

Introduction

There is solid evidence supporting the prophylactic use of antithrombotic agents for cerebrovascular and cardiovascular events.[1–5] However, these agents increase the risk of gastrointestinal bleeding.[6–9] On the other hand, discontinuation of these agents during the periendoscopic period can induce thromboembolic complications.[10] Therefore, endoscopists must make difficult decisions for patients with cerebrovascular and cardiovascular comorbidities during the periendoscopic period.

Although various societies have published guidelines regarding this dilemma, the permeation of these guidelines is low in Japan.[10–12] This is partly because of gaps between guidelines of Eastern and Western countries[13] and between those of Japanese societies, as shown in Table 1.

Table 1 Management of antithrombotic agents in various guidelines

	Low-risk procedure	High-risk procedure
American Society for Gastrointestinal Endoscopy *et al.*	Continue	Continue for aspirin and NSAIDs. Discontinue 7–10 days for clopidogrel and ticlopidine. Discontinue 3–5 days for warfarin.
The British Society of Gastroenterology *et al.*	Continue	Continue for aspirin. Discontinue 7 days for clopidogrel. Discontinue 5 days for warfarin and check of INR < 1.5.
Japan Gastroenterological Endoscopy Society	Discontinue 3 days for aspirin, 5 days for ticlopidine, 7 days for combination. Discontinue 3–4 days for warfarin. Check of INR < 1.5 before high-risk procedure.	Discontinue 7 days for aspirin, 10–14 days for ticlopidine before extremely high-risk procedure.
The Japanese Circulation Society	Discontinue 3 days for aspirin, 5 days for ticlopidine, 7 days for combination. Check of INR < 1.5 for discontinuation of warfarin.	Discontinue 7 days for aspirin, 10–14 days for ticlopidine, 3 days for cilostazol.

INR, international normalized ratio; NSAIDS, non-steroidal anti-inflammatory drugs;

The guideline of the Japan Gastroenterological Endoscopy Society (JGES) recommends cessation even for minimally invasive endoscopic procedures including biopsy, although most Western guidelines do not.[13–18] This discrepancy is based upon racial differences of bleeding risks and thromboembolic risks between Asians and Caucasians. However, there is insufficient evidence to support this racial difference.

Another reason for the low permeation in Japan is the difficulty of estimating thromboembolic risk for each patient's comorbidities. Thus, cessation is determined by the prescribing physicians of non-gastroenterological specialties who may be unfamiliar with the JGES guideline.[12] Meanwhile, most endoscopists sometimes perform endoscopy without cessation of antithrombotic therapy for patients with a high thromboembolic risk state based upon the premise of second endoscopy for biopsy if necessary. A second endoscopy eventually requires cessation for biopsy and only postpones difficult decisions. However, this clinical daily practice can delay a final diagnosis that is mandatory for initiating therapy.

To cope with these dilemmas, we performed a fact-finding study in a multi-center setting to clarify the present problems concerning management of antithrombotic agents during the periendoscopic period in Japan.

Methods

This study was conducted for two consecutive months between February 2010 and July 2010 at each institution after approval by the ethics committee of each institution. The following 12 institutes participated in this study: The University of Tokyo, Tokyo; Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; National Center for Global Health and Medicine, Tokyo; National Cancer Center Hospital, Tokyo; St Luke's International Hospital, Tokyo; Niigata Prefectural Central Hospital, Niigata; Tokyo Medical University, Tokyo; Hitachi General Hospital, Hitachi; Tonan Hospital, Sapporo; Cancer Institute Hospital, Tokyo; Kobe University School of Medicine, Kobe; and Tokyo KoseiNenkin Hospital, Tokyo, Japan.

The method of investigation is approximately the same as our previous study in a single institute.[12] In brief, outpatients receiving anticoagulants or antiplatelet agents were enrolled to complete a questionnaire that was handed out before endoscopy. The patients returned the following questionnaires approximately 14 days after endoscopy.

- What anticoagulants or antiplatelet agents do you take?
- For what comorbidity were you prescribed each agent?
- What is the specialty of the physician who prescribed each agent?
- How long were you ordered to stop each agent before and after endoscopy?
- What is the specialty of the physician who determined your cessation period?
- Are you prescribed any antiulcer agents or other agents affecting the digestive organs?
- Have you experienced any additional symptoms before and during the two weeks after endoscopy?

To minimize the number of dropout patients, we called all patients who had not sent back or submitted responses by the deadline.

We defined the following as antiplatelet agents: cyclooxygenase inhibitors (e.g. aspirin), phosphodiesterase inhibitors (e.g. cilostazol), purinergic receptor antagonists (e.g. ticlopidine), serotonin receptor antagonists (e.g. sarpogrelate), eicosapentaenoic acid preparations (e.g. icosapentate), and prostaglandin preparations. We investigated esophagogastroduodenoscopy (EGD) and colonoscopy (CS) with and without invasive procedures. Invasive procedures were defined as biopsy or resection including polypectomy and endoscopic mucosal resection (EMR) because subjects were limited to outpatients. Major complications were defined as symptomatic events requiring additional medical treatment.

Endoscopy was ordered by more than 100 physicians with various specialties during the study period. All patients received explanations of the risks and benefits of these endoscopies and were provided written informed consent by the physicians in charge. Furthermore, written informed consent for this study was obtained with questionnaires. By summarizing responses to questionnaires, we analyzed the actual current practice concerning management of antithrombotic agents during the periendoscopic period and estimated safety of the current practice in a prospective manner.

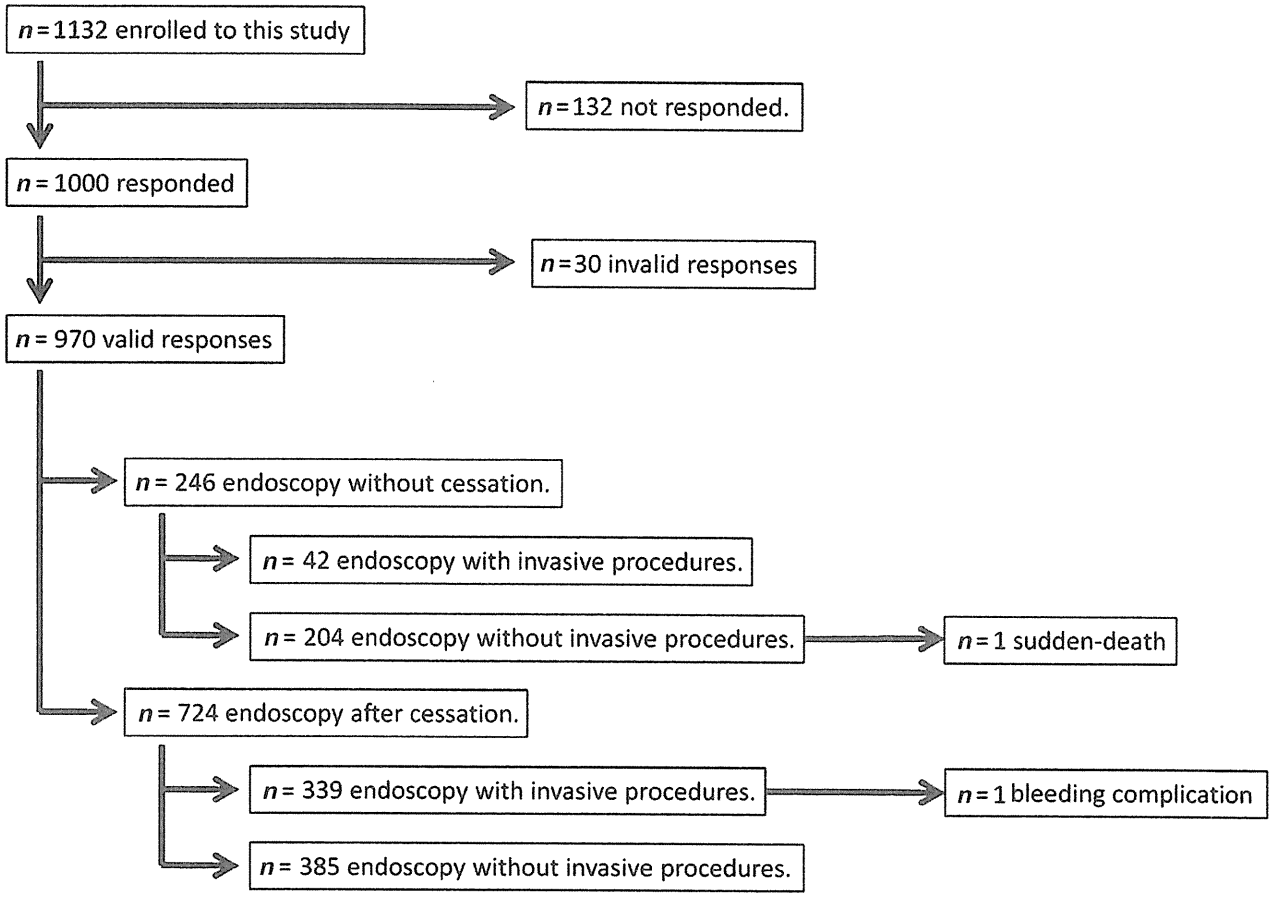

Figure 1 Flow diagram of the study (*n*, patients).

Statistical analyses were conducted using the χ^2 test with Yates' modification and Student's *t*-tests. $P < 0.05$ was considered significant.

Results

In total, 1132 patients were enrolled to this study. One thousand patients (88%) submitted responses to questionnaires. Among 1000 responses, 970 valid responses (86%) were analyzed as shown in Figure 1. Characteristics of 970 patients are summarized in Table 2. EGD and CS were performed in 705 patients (72.7%) and 265 patients (27.3%), respectively. Biopsy and resection were performed in 308 patients (31.7%) and 73 patients (7.6%), respectively. Differences of patients who underwent endoscopy with and without cessation are summarized in Table 3. The ratio of patients who underwent invasive procedures was lower in patients without cessation than in patients with cessation. Additionally, patients receiving multi-agents have a tendency to undergo no invasive procedures without cessation.

Proportion of prescribed agents

Among 970 patients, 804 patients (82.9%) were on a single agent, and 166 patients (17.1%) were on more than two agents. One

Table 2 Characteristics of 970 patients who sent back valid responses

	n	%
Age (years)	71.4 ± 8.1	
Gender (M : F)	715:255	
Number of agents		
Single-agent	804	82.9
Multi-agents	166	17.1
Two agents	141	14.5
Three agents	14	1.4
More than four agents	11	1.1
Modality		
Esophagogastroduodenoscopy	705	72.7
Colonoscopy	265	27.3
Endoscopic procedures		
Non-invasive procedures	589	60.7
Biopsy	308	31.7
Mucosal resection	73	7.6
Prophylactic antacid agent		
None	491	50.6
Proton pump inhibitor	235	24.2
H2 receptor antagonist	114	11.8
Others	130	13.4

Table 3 Difference of patients who underwent endoscopy with/without cessation

	With cessation ($n = 724$)	Without cessation ($n = 246$)	*P*-value
Age (years)	71.9 ± 7.8	70.2 ± 8.9	NS
Gender (M : F)	532:192	183:63	NS
Number of agents			< 0.05
Single-agent	620	184	
Multi-agents	104	62	
Two agents	85	56	
Three agents	11	3	
More than four agents	8	3	
Modality			< 0.05
Esophagogastroduodenoscopy	511	194	
Colonoscopy	213	52	
Endoscopic procedures			< 0.05
Non-invasive procedures	385	204	
Biopsy	268	40	
Mucosal resection	71	2	
Prophylactic antacid agent			NS
None	377	114	
Proton pump inhibitor	170	65	
H2 receptor antagonist	81	33	
Others	96	34	

NS, Not significant.

hundred and ninety-one patients (19.7%) received warfarin as anticoagulants. The most common antiplatelet agent was aspirin in 563 patients (58.0%), followed by clopidogrel, eicosapentaenoic acid preparation, and cilostazol. Four hundred and seventy-nine patients (49.4%) received agents for peptic ulcer healing including 349 patients (36.0%) on proton pump inhibitors (24.2%) or H2 receptor antagonists (11.8%).

Proportion of pre-existing comorbidities of patients

The most common comorbidity requiring anticoagulants or antiplatelet agents was ischemic heart disease in 271 patients (27.9%), followed by cerebrovascular disturbance and arrhythmia in 216 (22.3%) and 164 patients (16.9%), respectively (Fig. 2). Among 271 patients with ischemic heart disease, 141 patients (52.1%) had undergone implantation of a mechanical stent in a coronary artery.

Cessation period

The histograms of cessation periods before endoscopy are shown in Figure 3. Most patients underwent endoscopy without cessation or after a cessation period of 6–7 days (58.5%). For further analysis, histograms of the cessation period in patients receiving warfarin, aspirin, ticlopidine, and a combination of aspirin and ticlopidine are shown in Figure 4.

Among 970 patients, valid responses were obtained from 941 patients. The cessation period after endoscopy is shown in Figure 5. Among 572 patients who underwent endoscopy without invasive procedures, 505 patients (88.3%) restarted these agents within 2 days. On the other hand, among 369 patients who underwent endoscopy with invasive procedures, 316 patients (85.6%) restarted within 4 days.

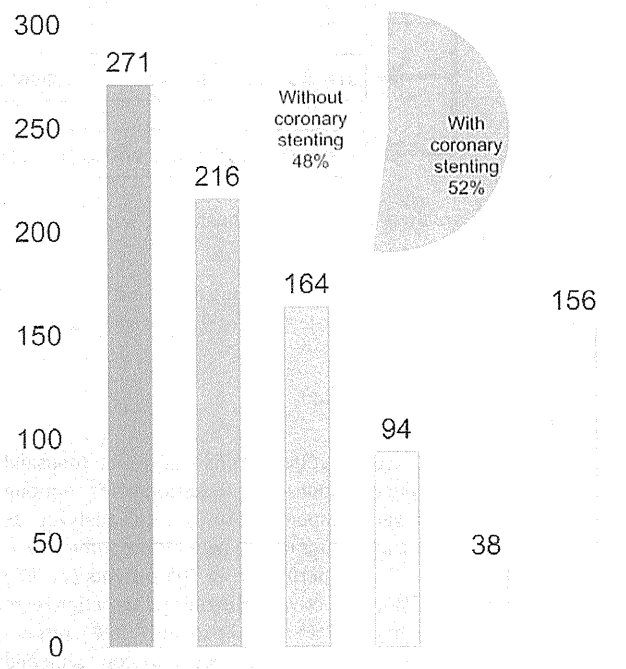

Figure 2 Comorbidities of 970 patients. ■, ischemic heart disease; ■, cerebrovascular disturbance; ■, arrhythmia; ■, peripheral vascular disturbance; ■, valvular heart disease; ■, other disease.

Specialty of physicians who determined cessation periods

Cessation periods before endoscopy were determined by non-gastroenterologists for 51% of patients. For 49% of patients, the cessation period before endoscopy was determined by gastroen-

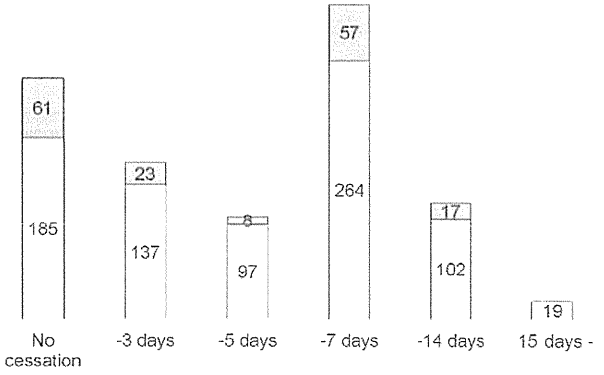

Figure 3 Cessation periods before endoscopy for 970 patients receiving single- or multi-agent therapies. ▨, multi-agent; □, single-agent.

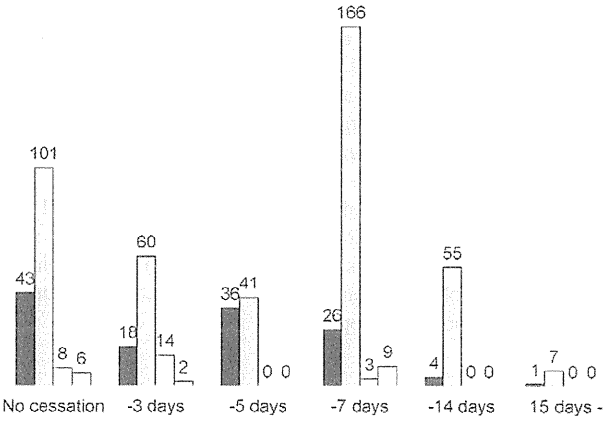

Figure 4 Cessation periods before endoscopy for patients receiving warfarin (WFR), aspirin (ASP), ticlopidine (TPD), or a combination of aspirin and ticlopidine. ■, WFR; □, ASP; □, TPD; □, ASP + TPD.

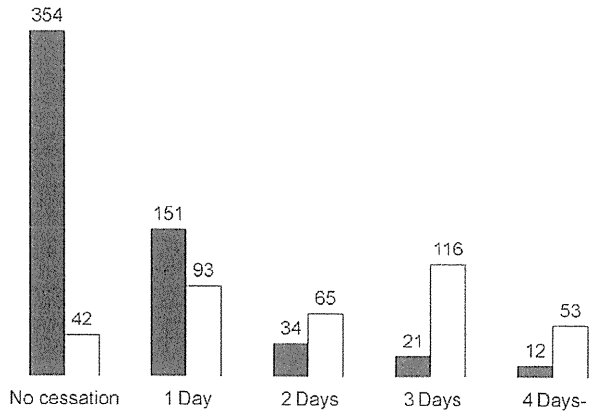

Figure 5 Cessation periods after endoscopy with or without invasive procedures for 941 patients. ■, without invasive procedure; □, with invasive procedure.

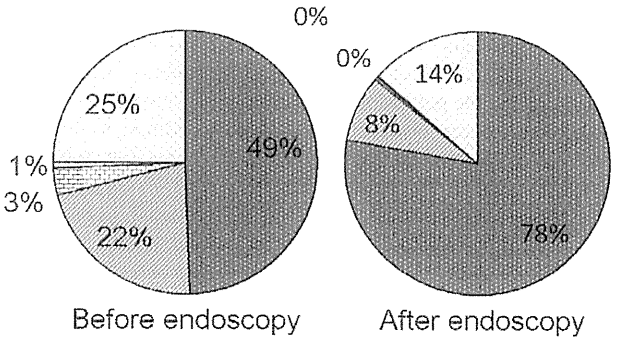

Figure 6 Specialties of doctors who determined cessation periods before and after endoscopy. ■, gastroenterology specialist; ▨, cardiology specialist; ▨, neurology specialist; ▨, orthopedic specialist; □, other specialist.

terologists (Fig. 6). By contrast, for 78% of the patients, cessation periods after endoscopy were determined by gastroenterologists, including endoscopists.

Complications

In this study, two patients experienced major complications that might be related to thromboembolic events or gastrointestinal bleeding (Table 4). One patient on warfarin for arrhythmia restarted warfarin on the third day after colonic EMR and experienced hematochezia on the fourth day. This patient underwent endoscopic clipping and recovered well. The other patient had previously undergone pacemaker implantation for arrhythmia and died due to sudden onset ventricular tachycardia on the 14th day after endoscopy without any invasive procedures. This patient continued clopidogrel during the periendoscopic period. The 95% confidence interval of the major complication rate of all patients taking these agents is estimated to be 0.0–0.7%.

Procedures without cessation

Invasive procedures were performed without cessation in 42 patients (two resections and 40 biopsies in 35 EGDs and seven CSs). Both resections were performed in CSs. Among these, no patient experienced major bleeding complications. The 95% confidence interval of the major complication rate in patients who underwent invasive procedures without cessation is estimated to be 0.0–8.4%.

Discussion

Previous studies revealed the current clinical daily practice concerning management of antithrombotics in a single but high volume endoscopy center.[11,12] Confusion in clinical daily practice might be the result of low permeation of the guideline, and the same may be true throughout Japan. Generally, absence of a unified guideline may create a confusing situation about management of antithrombotic agents during the periendoscopic period in Japan.

Table 4 Profile of patients who experienced major complications in this study

No.	Age (years)	Gender	Co-morbidity	Agents	Cessation (days)		Modality	Procedure	Complication	Treatment
					Before	After				
1	61	M	Arrythmia	WFR	5	3	CS	EMR	Hematochezia on 4th day	Clipping
2	85	M	Arrythmia	CP	0	0	EGD	No	CPA on 14th day	CPR

CP, clopidogrel; CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; CS, colonoscopy; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; WFR, warfarin.

Although the JGES guideline recommends 3 days for aspirin, 5 days for ticlopidine, and 7 days for combination therapy with both, most patients discontinued these agents for 0 or 7 days. This tendency means that most physicians order 7 days' cessation uniformly for patients with a low thromboembolic risk state. We speculate that this length of cessation was determined by considering the lifetime of the platelet. Consequently, permeation of the cessation period recommended in the JGES guideline is low. In other words, lack of evidence to support the guideline might create a low permeation because the cessation period recommended in the JGES guideline is based upon only one article.[19]

This study revealed complications in patients taking these agents during the periendoscopic period. Only one major bleeding complication was observed in this study. Although this case required endoscopic hemostasis, this case recovered well with no blood transfusion. On the other hand, the other complication was a severe and lethal cardiogenic event. Even though this case underwent endoscopy without cessation and was not finally diagnosed as a thromboembolic complication, this case demonstrates the severity of cardiogenic events that can occur in a high thromboembolic risk state. By contrast, no bleeding complications were observed among 42 patients that underwent invasive procedures without cessation even though many endoscopists might hesitate to perform invasive procedures for patients receiving antithrombotic agents as shown in Table 3.

It is difficult to conclude that thromboembolic complications can result in a more severe outcome than bleeding complications based on this study alone. However, 3 of 13 representative endoscopists at different institutions experienced thromboembolic complications during the cessation period.[10] Among them, one endoscopist experienced a lethal outcome due to thromboembolic complications although none of the 13 endoscopists experienced a lethal outcome due to bleeding complications. Furthermore, Sung JJ *et al.* recently reported that continuation of low-dose aspirin for patients with peptic ulcer bleeding may increase the risk for recurrent bleeding but reduces mortality rates.[20] Additionally, postprocedural bleeding events in the periendoscopic period are not increased in anticoagulated patients.[21] Considering the severity of thromboembolic complications during the cessation period and the absence of solid evidence for racial differences of bleeding risk and thromboembolic risk, less invasive procedures or biopsies might be feasible for Asians as the Western guidelines recommend.

This study also revealed an important clue about restart of these agents after endoscopy. In most guidelines, including the JGES guideline, restart of antithrombotic therapy is recommended shortly after endoscopy as low risks of bleeding are confirmed after endoscopy depending on procedure-specific circumstances. However, there are no solid criteria to judge restart. In this study, approximately 86% of patients who underwent invasive procedures after a cessation period restarted these agents within 4 days. Among them, 37% of patients restarted these agents on the day of or the day after endoscopy. Considering the low rate of bleeding complications in this study, restart of therapy within 4 days or sometimes within 2 days can be reasonable for outpatient procedures.

The limitation of this study is its small number of participants and low complication rate, although we conducted a multicenter study to recruit about 1000 patients. As a result, the confidence interval is too wide to evaluate safety, particularly for the complication rate in patients undergoing invasive procedures.

In summary, this multi-center study revealed a confusing clinical situation due to absence of a unified guideline in Japan. It is mandatory to establish a unified guideline based upon solid evidence in close coordination between endoscopists and non-gastroenterology physicians. Although cessation before biopsy may be dispensable for Asians or Japanese people, we need further evidence to support this proposal.

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Competing interests

This study design was discussed by participants at the 11th meeting of Tokyo Gastrology Clinical Diagnosis Conference (TGCDC), supported by Eisai Co. and the contents were partially presented at the 15th TGCDC meeting, Tokyo, Japan, on 27 August, 2010.

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Should Elderly Patients Undergo Additional Surgery After Non-Curative Endoscopic Resection for Early Gastric Cancer? Long-Term Comparative Outcomes

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OBJECTIVES: **Endoscopic resection (ER) including endoscopic submucosal dissection has been widely accepted for treatment of early gastric cancer (EGC) in Japan. Additional surgery is recommended when ER is non-curative histologically. Many elderly patients, however, do not undergo radical surgery due to comorbid disease or limited life expectancy. The aim of this study is to assess the survival outcomes of radical surgery compared with observation only in elderly patients after non-curative ER.**

METHODS: **We reviewed existing data of all elderly patients (older than 75 years) who had undergone ER for EGC at the National Cancer Center Hospital between January 1999 and December 2005. We compared the overall and disease-free survival rates between three patients groups: curative ER, non-curative ER with additional surgery, and non-curative ER without additional surgery.**

RESULTS: **In total, 428 patients underwent ER; 308 (72%) curative ER and 120 (28%) non-curative ER. Of the 120 non-curative ER patients, 38 patients (31.7%) underwent additional surgery and 82 patients (68.3%) were followed without surgery. There was no significant difference in American Society of Anesthesiologist score between three groups. Patients who did not undergo surgery tended to be older. Overall 5-year survival rates in the curative ER, non-curative ER with surgery, and non-curative ER without surgery were 85, 92, and 63%, respectively. There was no significant difference in overall and disease-free survival between patients in the curative ER and non-curative ER with surgery groups. On the contrary, a significant difference in overall and disease-free survival was evident between the curative ER and non-curative ER without surgery groups (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).**

CONCLUSIONS: **In our elderly patient cohort, additional surgery following non-curative ER improved overall and disease-free survival compared with non-surgical observation only. Thus, surgery should be considered following non-curative ER in EGC patients >75 years of age.**

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INTRODUCTION

Life expectancy in elderly patients has increased dramatically worldwide (1,2). Although surgical techniques and preoperative management have improved minimally invasive curative treatment is preferable for the elderly, particularly for early stage cancer (EGC).

Endoscopic resection (ER) has been accepted as standard treatment for EGCs that meet guideline or expanded criteria (3,4), which have a low risk of lymph node metastasis. Following ER, meticulous pathological evaluation of the resected specimen is used to stratify patient management. Patients with lesions that meet the guideline or expanded criteria are followed closely, whereas those who have had a non-curative ER are considered for additional surgery.

Gastrectomy is associated with high surgical risk for the general population. Partial or total gastrectomy is also associated with short and long-term morbidity, and mortality (5,6). Furthermore, the majority of elderly patients who are 75 years or older

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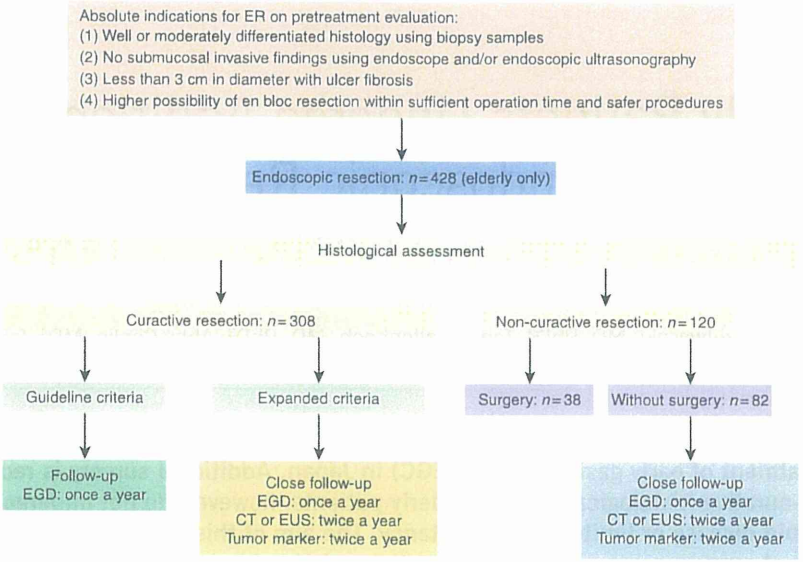

Figure 1. Flowchart of critical procedure. CT, computed tomography; EGD, endogastroduodenoscopy; ER, endoscopic resection; EUS, endoscopic ultrasonography.

have multiple diseases and functional disorders influencing daily life (7,8). In this study, we describe the long-term outcomes of ER for EGC in patients aged 75 years or older. We primarily aim to determine whether lesions beyond the guideline or expanded criteria in this elderly cohort can be treated adequately with ER alone.

METHODS

Study design

We reviewed existing data on all patients who had undergone ER for EGC at the National Cancer Center Hospital, Tokyo, between January 1999 and December 2005. Patients whose lesions did not meet criteria for ER following preoperative diagnosis were excluded. We defined elderly patients as 75 years or older (7). Elderly patients were divided into three groups: curative ER, non-curative ER with additional radical surgery, and non-curative ER without surgery. We used the American Society of Anesthesiologist (ASA) score and Charlson Index (9) as a measurement of patients overall health status, and surgical risk. All patients provided written informed consent.

Method

Starting in 1999, our institution has routinely followed a standard protocol for the ER of EGC.

Indication for ER

Indication criteria for ER—"differentiated histology," "macroscopic absence of submucosal invasive findings using endoscope and/or endoscopic ultrasonography," "lesion size- <3 cm in diameter with ulcer fibrosis," and "high probability of safe en bloc resection with short procedure duration." Patients deemed unfit for open surgery due to their general condition were also judged to be poor candidates for ER (**Figure 1**).

Historical assessment

Resection specimens were classified according to the Japanese Classification for Gastric Carcinoma (10). In this study, ER was declared curative when the specimen showed en bloc resection with margins free of cancer and if applicable, met the expanded criteria: (i) intramucosal cancer, differentiated type, no lymphatic or/and venous invasion, and no ulceration, irrespective of tumor size; (ii) intramucosal cancer, differentiated type, no angiolymphatic invasion, and tumor <3 cm in size, irrespective of ulceration findings; (iii) minimally invasive submucosal cancer (invasion depth $\leq 500\,\mu$m, sm1), differentiated type, no lymphatic or/and venous invasion, and tumor <3 cm in size.

Post ER management

All patients were followed according to our standard protocol (**Figure 1**). Surveillance upper endoscopy was performed annually. Curative cases with expanded criteria also underwent abdominal computed tomography or endoscopic ultrasonography and tumor-marker studies (carcinoembryonic antigen, CA19–9) every 6 months to exclude lymph node or distant metastasis. Patients who underwent non-curative ER and were deemed fit for surgery were referred and consented for radical resection and lymph node dissection. Patients with the non-curative ER without surgery due to physician judgment or strong patient refusal were followed up by the same protocol as patients with curative resection with expanded criteria.

Statistical analysis

Differences in patient characteristics between the three groups were examined by χ^2 test. Survival curves were calculated using the Kaplan–Meier method. To compare overall and disease-free survival among the treatment status, Cox proportional-hazards model was performed to estimate hazard ratio (HR) and 95% confidence interval (CI). The following covariates were included

in the multivariable analyses: age, sex, ASA score, past history of cancer (stratified by cancer stage), and comorbid illnesses. We also compare the overall and disease-free survival in the multivariable analyses included age, sex, and Charlson Index. All P values reported are two-sided, and significance level was set at $P<0.05$. All statistical analyses were performed with the SAS software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

A total of 2,012 cases (2,399 lesions) of EGC were treated endoscopically at the National Cancer Center Hospital between January 1999 and December 2005. Of these, 1,947 cases (2,331 lesions) met the indication for ER following preoperative diagnosis. In all, 428 (519 lesions) of the 1,947 cases were elderly (75 years or older). Of these cases in elderly patients, 26 lesions were treated by endoscopic mucosal resection and 493 lesions were treated by endoscopic submucosal dissection. A total of 308 elderly patients (72%, 308/428) had a curative ER and 120 patients (28%, 120/428) had a non-curative ER. Of the 120 patients with non-curative ER, 38 patients (31.7%, 38/120) underwent radical surgery and 82 patients (68.3%, 82/120) were followed without surgery.

Patient characteristics are summarized in **Table 1**. ASA score of all patients except nine was 2. In all, 312 patients (72.9%, 312/428) were Charlson Index 2, 65 patients (15.2%, 106/428) were 3, 41 patients (9.6%, 41/428) were 4, and 10 patients were over 5 (2.3%, 10/428). There was no significant difference in ASA score and Charlson Index between three groups (ASA score, $P=0.17$; Charlson Index; $P=0.33$). There was a significant difference in age and the prevalence of cardiovascular disease. Patients who did not undergo surgery tended to be older.

Reasons for not undergoing surgery in the remaining 82 patients included patients' choice ($n=29$), physicians' judgment ($n=45$) (including 10 very elderly (mean age 84 years), one with chronic renal dysfunction, one with ventilatory impairment and one with aneurysm of the thoracic aorta, concomitant cancer in other organs ($n=7$)) and unknown ($n=8$).

Table 1. **Patient characteristics**

	Curative resection	Non-curative resection with surgery	Non-curative resection without surgery
Number of patients (%)	308 (72.0)	38 (8.9)	82 (19.2)
Age, mean (s.d.)	78.8 (3.3)	76.9 (2.3)	80.1 (3.9)
Gender ratio, men: women	228:80	32:6	67:15
Concomitant disease (%)			
Cancer	59 (19.2)	3 (7.9)	13 (15.9)
Cardiovascular diseases	48 (15.6)	16 (42.1)	11 (13.4)
Diabetes	29 (9.4)	6 (15.8)	7 (8.5)
Respiratory diseases	6 (1.9)	1 (2.6)	3 (3.7)
Other diseases	15 (4.9)	2 (5.3)	6 (7.3)
ASA score (%)			
2	304 (100)	37 (100)	78 (98.7)
3	0	0	1
Missing information	4	1	3
Charlson Index			
2	232 (75.3)	25 (65.8)	55 (67.1)
3	43 (14.0)	8 (21.1)	14 (17.1)
4	25 (8.1)	4 (10.5)	12 (14.6)
5+	8 (2.6)	1 (2.6)	1 (1.2)

ASA, American Society of Anesthesiologist.

Survival

The median follow-up period in the curative ER, non-curative ER with surgery, and non-curative ER without surgery was 40.6, 43.1, and 38.1 months, respectively. Overall 5-year survival in each group was 84, 95, and 63%, respectively (**Table 2**). Using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases, there was no significant difference in overall and disease-free survival between the patients with curative ER ($n=308$) and non-curative ER with surgery ($n=38$). On the contrary, a significant difference in overall and disease-free survival was evident between the patients with curative ER ($n=308$) and non-curative ER without surgery ($n=82$) (HR (95% CI): 1.89 (1.08–3.28), 2.30 (1.35–3.94); **Table 2**, **Figure 2**). The multivariable analysis using Charlson Index, age, and sex shows a statistical difference in overall and disease-free survival between the patients with curative ER and non-curative ER without surgery (HR (95% CI): overall survival, 2.35 (1.36–4.05); disease-free survival, 2.76 (1.64–4.67)).

In total, 59 patients (13.8%, 54/428) died during this study period. The majority (55.9%, $n=33/59$) of deaths occurred in the curative ER group followed by the non-curative ER without surgery group (40.7%, $n=24/59$). Only two (3.4%) deaths occurred in the group who had non-curative ER with surgery. Of the 428 patients, 1.2% ($n=5$) died as a result of gastric cancer and 12.6% ($n=59/432$) died from another causes (**Table 2**). Of the five patients who died of gastric cancer, one patient died from metachronous advanced gastric cancer following curative ER of the index lesion. Four patients in the non-curative ER without surgery died from lymph node metastasis or distant metastasis. There were no deaths from cancer recurrence in the non-curative ER with surgery.

Survival according to the risk of lymph node metastasis

We divided non-curative ER groups into two groups according to the risk of lymph node metastasis: A—high risk ("positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion") and B—low risk (other reasons except high risk of lymph node metastasis such as intramucosal cancer >30 mm in size with ulcer findings and minute submucosal cancer

Table 2. **Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to curability**

	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted[a]	
			HR	95% CI	HR	95% CI
Curative ER	33 (1)	84	1.00		1.00	
Non-curative ER with surgery	2 (0)	95	0.52	0.13–2.17	0.70	0.16–2.98
Non-curative ER without surgery	24 (4)	63	2.62	1.54–4.46	1.89	1.08–3.28

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

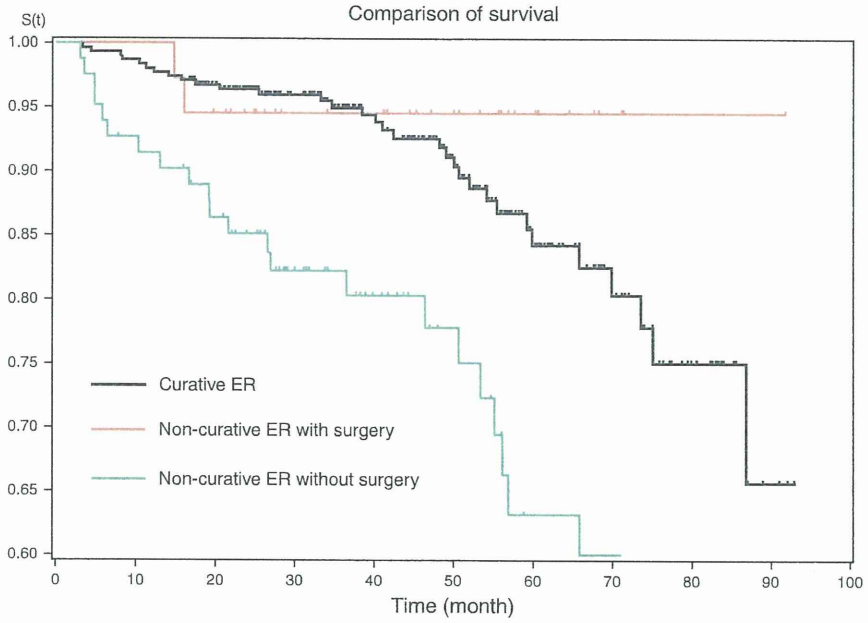

Figure 2. Survival for elderly patients (overall survival). ER, endoscopic resection.

(sm1) >30 mm in size). Among the non-curative ER patients, 29 of the 67 high-risk patients (43.3%) underwent additional surgery compared with only 9 patients of the 53 low-risk patients (17.0%). **Table 3** shows overall survival according to the risk of lymph node metastasis using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases. Overall 5-year survival rate in non-curative ER-A without surgery group was lowest (52%). There were significant difference in overall and disease-free survival between the patients with curative ER ($n=308$) and non-curative ER-A without surgery group (HR (95% CI): 3.31 (1.67–6.58), 4.26 (2.20–3.94); **Table 3**). In the multivariable analysis using Charlson Index, age, and sex, a statistical significance was evident in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery (HR (95% CI): overall survival, 4.15 (2.18–7.89); disease-free survival, 5.30 (2.85–9.84)).

DISCUSSION

Surgery continues to be the mainstay of treatment for gastric cancer—with a reported high resection rate (96%) and a low surgical complication rate (8%) even in elderly patients (11). However, 5-year survival after surgery in elderly patients varies among institutions, and is reported to be 69–74% for EGC. This is compared with 5-year survival rates of >90% in young and middle-aged patients (12). Age-related disease, in fact, is the main etiology of the relatively low survival in elderly patients. Thus, less invasive surgical treatment is desirable in the elderly, and ER is attractive in this respect.

ER targets EGC lesions that have a negligible likelihood of lymph node metastasis, estimated at <1% for intramucosal cancer and <3% for submucosal invasive cancer (4). Several recent studies have reported that endoscopic submucosal dissection can be carried out on larger lesions resulting in a high rate of cancer-free