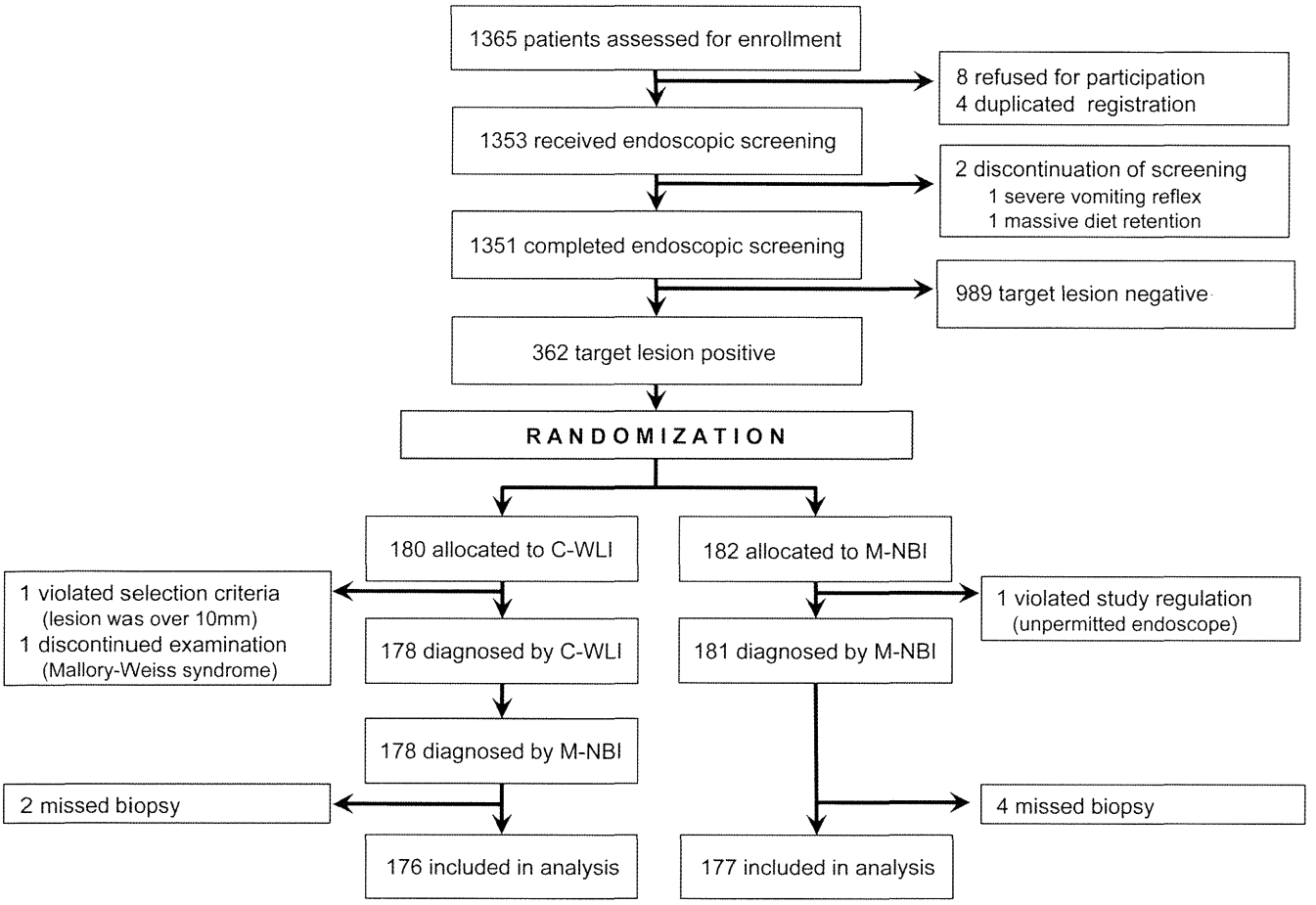

Figure 2. Patient enrollment, randomization, and examination.

C-WLI alone ($P < .001$). All patients tolerated the procedures well (Table 3).

Figure 3 shows the PPV and NPV data for each examination. M-NBI significantly improved the PPV compared with C-WLI alone to 57.1% (95% CI, 36.0%–78.3%) from 13.8% (95% CI, 2.9%–22.7%; $P = .001$). Furthermore, C-WLI followed by M-NBI dramatically improved the PPV from 13.8% (95% CI, 2.9%–22.7%) to 79.2% (95% CI, 62.9%–95.4%; $P < .001$). Similarly, the NPV of C-WLI of 89.8% (95% CI, 84.4%–95.3%) was improved by M-NBI to 94.9% (95% CI, 91.4%–98.3%; $P = .16$) and by C-WLI followed by M-NBI to 99.3% (95% CI, 98.1%–100%; $P < .001$).

Detailed C-WLI examination was discontinued during the procedure in one patient (1/362; 0.3%) because of bleeding associated with Mallory-Weiss syndrome. Although the bleeding stopped spontaneously without any endoscopic hemostatic treatment, a biopsy specimen was not obtained because the suspicious target lesion was missed. Two patients (2/362; 0.6%) were hospitalized on the day after examination because of bleeding from the biopsy site; although one patient needed a blood transfusion, both patients were discharged within a few days. None of the 3 patients experienced prolonged adverse effects. There were no serious adverse events directly related to the endoscopic observations.

Table 4 summarizes the clinical courses and pathologic diagnoses of 40 gastric cancers in 40 patients. Thirty-two patients were treated endoscopically (by endoscopic mucosal resection or endoscopic submucosal dissection). Five patients underwent surgical resection for synchronous advanced gastric cancers. The remaining 3 patients did not receive any treatment; 2 had other concomitant noncurable malignancies, and one refused treatment. Histologically, 39 lesions were of the intestinal type and one lesion was of the diffuse type. Regarding the depth of the 37 lesions that were removed, 35 were mucosal cancers, 2 of which were accompanied by submucosal invasion (0.3 mm and 0.8 mm). The depths of the 3 untreated lesions were estimated endoscopically as 2 mucosal cancers and one submucosal cancer.

Discussion

In this multicenter randomized trial, we compared the diagnostic yield of C-WLI with that of M-NBI for small gastric cancers. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities. One was the worldwide standard method of C-WLI; the other was M-NBI, which is the most advanced imaging method at present. This end point is the most impor-

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group

	C-WLI (n = 176)	M-NBI (n = 177)	*P* value
Age (*y*)			
Median (range)	69 (45–93)	69 (37–87)	.56
Sex			
Male	138	140	.79
Female	38	37	
Endoscope			
GIF-Q240Z	71	65	.83
GIF-H260Z	104	109	
GIF-FQ260Z	1	3	
Size of lesion (*mm*)			
≤5	74	71	.75
>5	102	106	
Mean	5.6	5.6	.97
Location of lesion			
Upper third			
Anterior wall	4	2	.51
Lesser curvature	9	10	
Posterior	22	12	
Greater curvature	4	3	
Middle third			
Anterior wall	7	7	
Lesser curvature	13	25	
Posterior	12	11	
Greater curvature	8	6	
Lower third			
Anterior wall	18	23	
Lesser curvature	25	33	
Posterior	26	18	
Greater curvature	28	27	
Histopathology diagnosis			
Cancer	20	20	1.00
Noncancerous	156	157	

tant aspect of this study, because if C-WLI proves superior to M-NBI, such advanced methods are not needed in practice. However, if M-NBI is indeed better than C-WLI, it should be used more in daily practice. The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI. This end point is also important, because in daily practice M-NBI is usually performed after C-WLI. Therefore, the results might reflect the practical diagnostic potential. To evaluate these aims, we used a strictly controlled randomized study. Furthermore, the endoscopic diagnosis in each method (C-WLI and M-NBI) was made on-site and independently to avoid any bias.

M-NBI, especially when used in conjunction with C-WLI, significantly enhanced real-time sensitivity, specificity, and accuracy of diagnosis; therefore, we concluded that M-NBI is an essential modality for diagnosing small gastric mucosal cancer. Although there are reports on the diagnostic yield of M-NBI for differential diagnosis of gastric lesions, some were performed at only one institute,[9,10,12,13] one was evaluated by several expert endoscopists using stored images and did not involve real-time assessment,[12] and one included gastric lesions with a definite diagnosis.[13] To overcome these limitations, our study targeted newly detected and undiagnosed gastric superficial lesions, which were evaluated on-site. For these reasons, the present results are the most reliable and could be a milestone in the field of endoscopic diagnosis of early gastric cancers.

Regarding accuracy and specificity, M-NBI alone yielded excellent results (90.4% and 94.3%, respectively), which were significantly better than those obtained with C-WLI. However, the sensitivities of M-NBI alone (60.0%) and C-WLI alone (40.0%) were lower than the estimated values: 85% for M-NBI and 60% for C-WLI. The low sensitivity of C-WLI might be acceptable considering the difficulty of diagnosing small gastric cancers in daily clinical practice. Although the reason for the low sensitivity of the M-NBI group is unknown, it might be associated with the examination protocol in this study; M-NBI observation was performed without evaluating a gross finding of lesions using C-WLI. In daily practice, magnifying examinations are usually performed after C-WLI. Actually, when performed after the C-WLI observation, M-NBI yielded excellent diagnostic performance in terms of accuracy, sensitivity, and specificity (all values were >95%). In addition, M-NBI and C-WLI followed by M-NBI significantly improved the PPV and NPV compared with C-WLI alone. This has enormous significance in clinical practice, because the examination with high PPV and high NPV might enable the clinician to make appropriate judgments as to which lesion needs pathology to confirm the diagnosis. When the lesion is suspected to be a neoplasm by C-WLI followed by M-NBI, taking a biopsy specimen is highly recommended to confirm the pathology. On the other hand, when the lesion is not suspected to be a neoplasm by M-NBI alone or by C-WLI followed by M-NBI, we could avoid a negative biopsy. These results have the potential to enable so-called "optic biopsy." Taken together, C-WLI followed by M-NBI might be the best

Table 2. Endoscopic Diagnoses for All Small Depressed Lesions

		Cancerous lesion (%)			Noncancerous lesion (%)		
Group	Method	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis
M-NBI	M-NBI	12/20 (60.0)	7/20 (35.0)	1/20 (5.0)	146/157 (93.0)	9/157 (5.7)	2/157 (1.3)
C-WLI	C-WLI	8/20 (40.0)	12/20 (60.0)	0/20 (0)	100/156 (64.1)	50/156 (32.1)	6/156 (3.8)
	C-WLI+M-NBI	19/20 (95.0)	1/20 (5.0)	0/20 (0)	149/156 (95.5)	5/156 (3.2)	2/156 (1.3)

Table 3. Diagnostic Performance of C-WLI and M-NBI for Gastric Small Depressed Lesions

Group	Method	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Examination time (s), median (interquartile range)
M-NBI	M-NBI	90.4[a] (85.1–94.3)	60.0 (36.1–80.9)	94.3[a] (89.4–97.3)	55[a] (23–97)
C-WLI	C-WLI	64.8 (57.2–71.8)	40.0 (19.1–63.9)	67.9 (60.0–75.2)	21 (12–40)
	C-WLI + M-NBI	96.6[b] (93.5–99.1)	95.0[b] (75.1–99.9)	96.8[b] (92.7–99.0)	72[b] (40–144)

[a]$P < .001$ for M-NBI vs C-WLI; [b]$P < .001$ for C-WLI vs C-WLI + M-NBI.

approach for making accurate diagnoses of small gastric cancers.

The durations of the M-NBI and C-WLI followed by M-NBI examinations were 34 seconds and 51 seconds, respectively, significantly longer than that required for C-WLI alone. However, these durations are clinically acceptable, because we managed to make accurate diagnoses without having to insert a spraying catheter or use indigo carmine. The importance of simple methods and accurate diagnoses for clinical practice is indisputable. Thus, Li et al showed that confocal laser endomicroscopy can be used to identify gastric superficial cancers with high validity and reliability.[26] However, confocal laser endomicroscopy requires the intravenous administration of a contrast agent. In contrast, M-NBI can be used by simply pushing a button on the endoscope. In addition, evaluation of demarcation lines and irregular microvascular patterns is sufficient for diagnosis with M-NBI, whereas confocal laser endomicroscopy requires knowledge of histopathology procedures for diagnosis.

Major bleeding caused by an endoscopic biopsy is rarely reported.[27] However, in our study, 2 patients experienced bleeding from the biopsy site. The best way of avoiding such bleeding is to avoid unnecessary biopsies. M-NBI, especially when used in conjunction with C-WLI, could help to reduce the number of unnecessary biopsies.

Our study has some limitations. First, the number of cancerous lesions was small, and it was less than the required sample size. This might be associated with insufficient power to evaluate sensitivity adequately. Then, further large numbers of patients for screening are needed to evaluate the sensitivity for diagnosing small gastric mucosal cancers of each modality. Second, this study was open labeled because the endoscopists knew which imaging modality was in use. Thus, a blinded study was impossible. Third, there is no arm that includes a dye-based imaging method such as indigo carmine or acetic acid. Indigo carmine and acetic acid are useful, but these dyes are only used in a few countries and institutes, and the standard worldwide endoscopic method to diagnose early gastric cancer is still C-WLI without any dye use. In addition, if we added a chromoendoscopy arm in this study, the required sample size would need to be enlarged and the study design and statistical analyses would be excessively complex. For these reasons, we did not include the dye-based imaging method.

Early detection of small gastric cancers makes it possible to effect a cure using minimally invasive treatments such as endoscopic mucosal resection and endoscopic

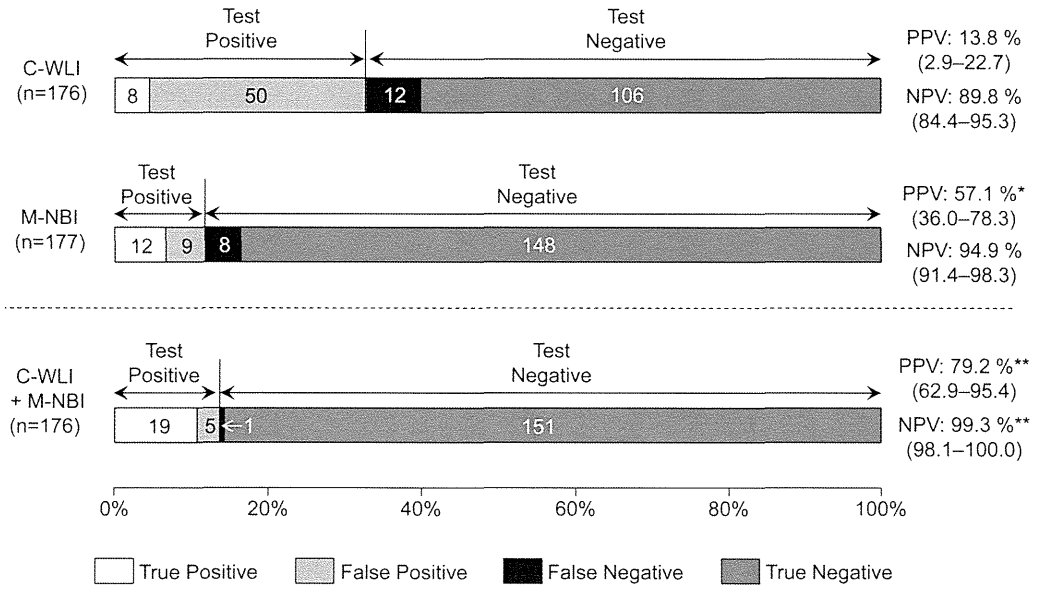

Figure 3. PPV and NPV in each examination. *The PPV for M-NBI was significantly higher than for C-WLI ($P = .001$). The NPV in M-NBI was higher than that of C-WLI; however, the difference was not significant ($P = .16$). **Both PPV and NPV were significantly enhanced by additional examination using M-NBI compared with C-WLI alone ($P < .001$).

Table 4. Clinical Course and Pathologic Diagnosis of Patients With Gastric Cancers

No. of patients	40
Treatment	
Endoscopic mucosal resection/endoscopic submucosal dissection	2/30
Surgery	5
No treatment	3
Histologic type	
Adenocarcinoma	40
Intestinal type	39
Diffuse type	1
Other diagnosis	0
Pathologic depth	
Mucosa	35
Submucosa	2
Muscularis propria	0
Unknown	3

submucosal dissection. In this study, all of the newly diagnosed small gastric cancers were good candidates for these procedures. Among the 37 cancers removed, 35 (95%) were mucosal. Early diagnosis using M-NBI and minimally invasive treatment is ideal for patients with gastric cancers, because it will improve their survival and quality of life. Although eradication of *Helicobacter pylori* is effective in reducing the incidence of gastric cancer,[17,28] endoscopic examination using M-NBI in conjunction with C-WLI should be indicated for high-incidence areas such as East Asia, South America, Eastern European countries, and Russia.[29]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.08.007.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–2917.
2. Tada M, Murakami A, Karita M, et al. Endoscopic resection of early gastric cancer. Endoscopy 1993;25:445–451.
3. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–229.
4. Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3:219–225.
5. Everett SM, Axon AT. Early gastric cancer in Europe. Gut 1997;41:142–150.
6. Hirasawa T, Gotoda T, Miyata S, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009;12:148–152.
7. Tajiri H, Ohtsu A, Boku N, et al. Routine endoscopy using electronic endoscopes for gastric cancer diagnosis: retrospective study of inconsistencies between endoscopic and biopsy diagnoses. Cancer Detect Prev 2001;25:166–173.
8. Nakayoshi T, Tajiri H, Matsuda K, et al. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). Endoscopy 2004;36:1080–1084.
9. Yao K, Iwashita A, Tanabe H, et al. Novel zoom endoscopy technique for diagnosis of small flat gastric cancer: a prospective, blind study. Clin Gastroenterol Hepatol 2007;5:869–878.
10. Ezoe Y, Muto M, Horimatsu T, et al. Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study. Gastrointest Endosc 2010;71:477–484.
11. Yao K, Iwashita A, Tanabe H, et al. White opaque substance within superficial elevated gastric neoplasia as visualized by magnification endoscopy with narrow-band imaging: a new optical sign for differentiating between adenoma and carcinoma. Gastrointest Endosc 2008;68:574–580.
12. Kaise M, Kato M, Urashima M, et al. Magnifying endoscopy combined with narrow-band imaging for differential diagnosis of superficial depressed gastric lesions. Endoscopy 2009;41:310–315.
13. Kato M, Kaise M, Yonezawa J, et al. Magnifying endoscopy with narrow-band imaging achieves superior accuracy in the differential diagnosis of superficial gastric lesions identified with white-light endoscopy: a prospective study. Gastrointest Endosc 2010;72:523–529.
14. Tamai N, Kaise M, Nakayoshi T, et al. Clinical and endoscopic characterization of depressed gastric adenoma. Endoscopy 2006;38:391–394.
15. Uedo N, Ishihara R, Iishi H, et al. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. Endoscopy 2006;38:819–824.
16. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Ann Intern Med 2003;138:W1–W12.
17. Aoi T, Marusawa H, Sato T, et al. Risk of subsequent development of gastric cancer in patients with previous gastric epithelial neoplasia. Gut 2006;55:588–589.
18. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392–397.
19. Nakajima T, Oda I, Gotoda T, et al. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? Gastric Cancer 2006;9:93–98.
20. Gono K, Yamazaki K, Doguchi N, et al. Endoscopic observation of tissue by narrow band illumination. Opt Rev 2003;10:211–215.
21. Gono K, Obi T, Yamaguchi M, et al. Appearance of enhanced tissue feature in narrow-band endoscopic imaging. J Biomed Opt 2004;9:568–577.
22. Muto M, Katada C, Sano Y, et al. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in the superficial neoplasia. Clin Gastroenterol Hepatol 2005;3(Suppl 1):S16–S20.
23. Yao K, Nagahama T, So S, et al. Morphological correlation between ordinary and magnifying endoscopic findings with regard to small depressed-type gastric cancers [in Japanese]. Stomach Intest 2006;41:781–794.
24. Yao K, Oishi T, Matsui T, et al. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. Gastrointest Endosc 2002;56:279–284.
25. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251–255.
26. Li WB, Zuo XL, Li CQ, et al. Diagnostic value of confocal laser endomicroscopy for gastric superficial cancerous lesions. Gut 2011;60:299–306.
27. Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. Prospective evaluation of complications in outpatient GI endoscopy: a survey among German gastroenterologists. Gastrointest Endosc 2001;53:620–627.

28. Chiba T, Marusawa H, Seno H, et al. Mechanism for gastric cancer development by Helicobacter pylori infection. J Gastroenterol Hepatol 2008;23:1175–1181.
29. Jemal A, Center MM, DeSantis C, et al. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893–1907.

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Conflicts of interest

The authors disclose no conflicts.

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Case Report

Epidermoid Metaplasia of the Esophagus: Endoscopic Feature and Differential Diagnosis

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ABSTRACT

Background/Aims: Despite the recent improvement of endoscopic diagnostic accuracy, there remain many undiscovered lesions in the GI tract. One such lesion is epidermoid metaplasia of the esophagus. The aim of this study is to clarify the endoscopic and pathological characteristics of epidermoid metaplasia of the esophagus.
Methodology: We reviewed all histological records of gastrointestinal endoscopic biopsy specimens obtained in our institution from September 2003 to August 2006 and identified five lesions from four patients with characteristic pathological findings of epidermoid metaplasia.
Results: All four patients were heavy drinkers and had a synchronous or metachronous squamous cell carcinoma. Three of them had multiple lugol-voiding lesions in the background esophageal mucosa. Endoscopic examination revealed common findings in these lesions: clear demarcation, slightly elevated shape, translucent white color, scaly or shaggy surface, and unstained appearance after Lugol's iodine staining. These endoscopic findings resembled those of superficial esophageal cancer. The pathological features of these lesions were uniform in hyperkeratotic and distinct granular layers of the epithelium and were very similar to those of normal epidermis of the skin.
Conclusions: Since the endoscopic features of epidermoid metaplasia resemble those of superficial esophageal cancer, we must pay enough attention to this new entity at the endoscopic examination.

KEY WORDS: Esophagus; Epidermoid metaplasia; Esophageal cancer; Differential diagnosis; GERD

ABBREVIATIONS: Multiple Lugol–Voiding Lesions (m–LVLs); Endoscopic Mucosal Resection (EMR); Gastro–Esophageal Reflux Disease (GERD); Gastrointestinal (GI)

INTRODUCTION

Despite the recent improvement of endoscopic diagnostic accuracy, it is likely that there are many undiscovered lesions in GI tract. One such lesion is epidermoid metaplasia, which we describe in this report. To our knowledge, there are only two previous reports of epidermoid metaplasia. In 1997, Nakanishi *et al.* reported similar characteristic pathological features, which they termed "epidermization" (1), detected as an irregularly shaped area that was unstained by Lugol's iodine in a surgically resected specimen of esophageal cancer; however, they did not publish an endoscopic picture of the lesion. In 2006, Fukui *et al.* briefly reported a minor lesion with the features of an epidermoid metaplasia located proximal to the gastroesophageal junction (2). This was the only previous report to describe both the endoscopic and pathological appearance of an epidermoid metaplasia. However, the specific characteristics of their endoscopic findings have not been clarified. To clarify the specific gross features of these lesions, it is important to find the common characteristics by reviewing a certain number of cases with epidermoid metaplasia.

METHODOLOGY

We reviewed all histological records of gastrointestinal endoscopic biopsy specimens obtained in our institution from September 2003 to August 2006 and identified five lesions from four patients with characteristic pathological findings diagnosed as epidermoid metaplasia. Thereafter, we reviewed all recorded endoscopic pictures and biopsy specimens obtained from these patients with epidermoid metaplasia.

RESULTS

The clinical background of each patient and the endoscopic findings of each lesion are summarized in **Table 1**. The four patients were two men and two women, whose ages ranged from 48 to 71 years. All reported high alcohol consumption but no special eating habits. All four patients had a concomitant or previous history of squamous cell carcinoma: three patients had a history of esophageal squamous cell carcinoma, and one had oropharyngeal squamous cell carcinoma. None of the patients had any other disease history or concomitant disease.

In two patients (patients 1 and 2), endoscopic examination was performed for the detailed evaluation of the esophageal cancer. Patient 3 was evaluated by routine follow-up after endoscopic mucosal resection (EMR) for superficial esophageal cancer, and patient 4 was evaluated by screening of the upper gastrointestinal tract before multimodal treatment for oropharyngeal cancer detected at another

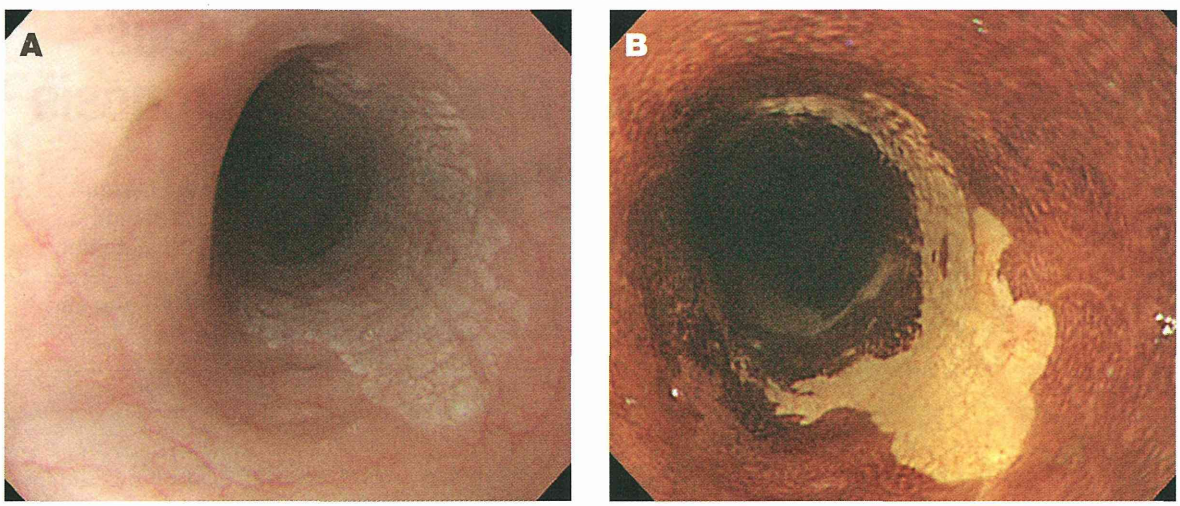

FIGURE 1
Patient 1. Endoscopic images of the large epidermoid metaplasia on the oral side of the cancerous lesion. **A**: A well–demarcated, translucent white scaly lesion that involved one half of the luminal circumference. **B**: Well–demarcated unstained area seen with Lugol's iodine staining.

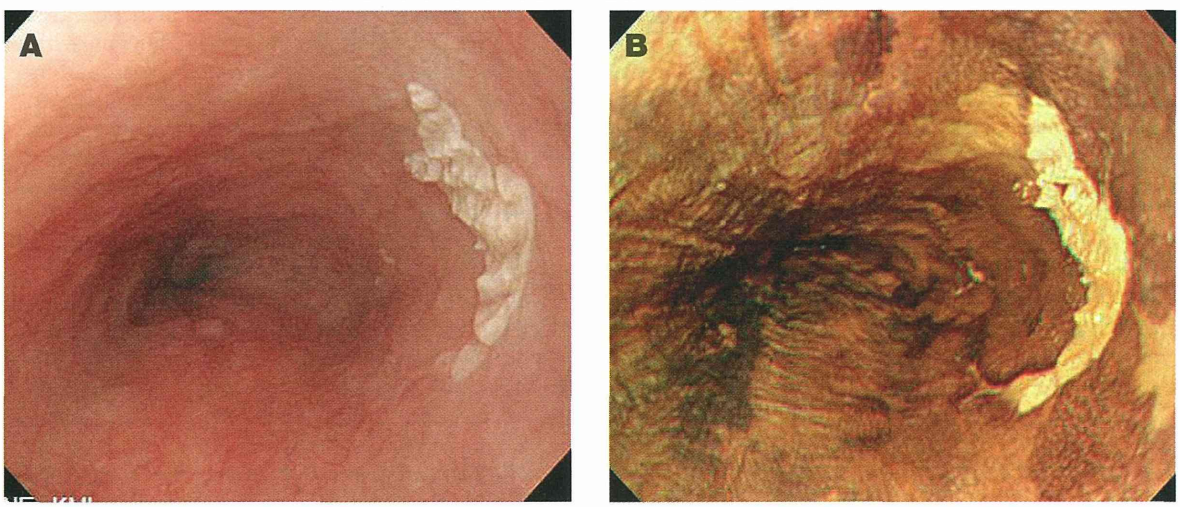

FIGURE 2
Patient 2. Endoscopic images of the small epidermoid metaplasia. **A**: A well–demarcated, white shaggy lesion that measured 15mm on its major axis. **B**: A clearly demarcated, unstained area after Lugol's iodine staining. Multiple Lugol–voiding lesions are seen all over the esophagus without any relation to the epidermoid metaplasia.

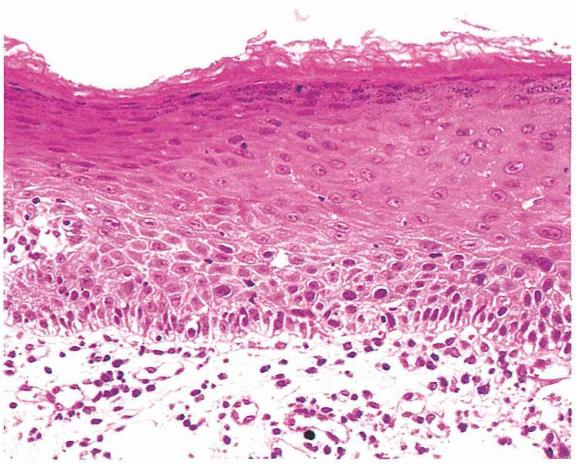

FIGURE 3
Histological features of epidermoid metaplasia (HE). There are hyperkeratotic and distinct granular layers in the epithelium and granulation tissue, with abnormal infiltration of inflammatory cells in the subepithelial layer.

hospital. The lesions were located in the middle or lower esophagus, and the size of the major axis ranged from 6 to 40mm. Patient 1 had two lesions and the others each had one lesion.

Endoscopic examination revealed common findings of the lesions: clear demarcation, slightly elevated shape, translucent white colour, scaly or shaggy surface without erosion or ulceration, and unstained appearance after Lugol's iodine staining (**Figures 1** and **2**). These endoscopic features differed from those associated with other esophageal abnormalities (**Table 2**), and these features seem to be specific to epidermoid metaplasia. In three patients, endoscopic examination had been performed previously. Therefore, we reviewed all of the recorded endoscopic pictures and biopsy specimens taken from the lesions and used this information to determine that both endoscopic and histological findings had not changed during the course of follow-up. In addition, there were multiple Lugol-voiding lesions (m-LVLs (3-5)) all through the entire esophagus in three of four patients. No patient had gastro-esophageal reflux disease (GERD). The pathological features of these lesions were uniform in both the hyperkeratotic and distinct granular layers of the epithelium (**Figure 3**). These histological findings differed considerably from other known histological findings in various esophageal abnormalities, but appeared very similar to normal epidermis of the skin and were also consistent with the microscopic findings in two previous reports of epidermoid metaplasia (1, 2). Accordingly, we regarded these findings as epidermoid metaplasia. In addition, one biopsy specimen obtained from the lesion contained granu-

TABLE 1 Patient Characteristics and Endoscopic Findings

	Background					Endoscopic findings							
No	Age	Gender	Alcohol abuse	History of SCC	Other concomitant disease	Location	size (mm)	Demarcation	Surface	Color	Lugol stain	Previous endoscopic examination	m-LVLs	GERD
1	58	M	yes	esophagus	no	Mt	30	clear	scaly	white	unstained	no	yes	no
						Lt	40	clear	scaly	white	unstained			
2	58	F	yes	esophagus	no	Lt	15	clear	shaggy	white	unstained	yes	yes	no
3	71	M	yes	esophagus	no	Mt	6	clear	shaggy	white	unstained	yes	no	no
4	48	F	yes	H&N	no	Lt	10	clear	shaggy	white	unstained	yes	yes	no

No: Number of case; SCC: Squamous Cell Carcinoma; m-LVLs: multiple Lugol-Voiding Lesions; GERD: Gastro-Esophago Reflux Disease; H&N: Head and Neck; M: Male; F: Female; Mt: Middle Thoracic esophagus; Lt: Lower Thoracic esophagus

lation tissue in the subepithelial layer (**Figure 3**).

DISCUSSION

In all patients, the epidermoid metaplasia seemed to be adherent to the esophageal mucosa and to resemble plaques. It had a translucent white color, scaly or shaggy surface without erosion or ulceration, and retained an unstained appearance after Lugol's iodine staining. They are the common endoscopic findings of the epidermoid metaplasia of the esophagus.

Differential diagnosis needs to be made based on lesions with similar appearance, such as papilloma, hyperkeratosis, glycogenic acanthosis, plaque associated with reflux esophagitis, localized esophagitis, esophageal candidiasis and superficial esophageal cancer. Epidermoid metaplasia differs from these lesions with respect to the points shown in **Table 2**. Because epidermoid metaplasia has clear borders, it can be distinguished from inflammatory lesions (*e.g.* plaque associated with reflux esophagitis, localized esophagitis and esophageal candidiasis), which generally have poorly defined borders. Lugol's iodine solution more clearly distinguishes some lesions from epidermoid metaplasia because epidermoid metaplasia is unstained by Lugol's iodine solution, whereas papilloma and hyperkeratosis stain weakly and glycogenic acanthosis stains strongly. The most important lesion to distinguish from epidermoid metaplasia is superficial esophageal cancer because the latter is also unstained by Lugol's iodine.

Elevated superficial esophageal cancer (type 0-IIa) sometimes has a white colored surface and is therefore difficult to distinguish from epidermoid metaplasia. Superficial cancer has a dim white or slightly reddish color and multiple irregular nodules because it is a solid tumor, whereas epidermoid metaplasia has a translucent white color and a shaggy or almost flat surface. These important endoscopic features may be used to distinguish between them. In addition, after staining with Lugol's iodine, superficial cancer generally tends to be tinged with a pink color as time progresses (called the "pink color sign" in Japan), whereas epidermoid metaplasia does not show this color.

In rare cases, a hyperkeratotic layer covers the surface of depressed superficial squamous cell carcinoma (type 0-IIc), and this type of lesion resembles epidermoid metaplasia, making it the most difficult to diagnose endoscopically (**Figure 4**). If the hyperkeratotic layer covers the surface of cancer completely, the endoscopic appearance is so similar to that of epidermoid metaplasia that it may become almost impossible to distinguish them. On the other hand, when the coverage is incomplete, some details may suggest the coexistence of cancer at the gap in the hyperkeratotic layer: slightly reddish color, minute irregular surface and pink color after staining with Lugol's iodine (pink color sign).

Close endoscopic examination may provide a more exact diagnosis of epidermoid metaplasia by

TABLE 2 Endoscopic Findings of Various Lesions with Plaque–like Appearance in the Esophagus

	Demarcation	Surface structure	Color	Lugol's iodine staining pattern
Epidermoid metaplasia	clear	shaggy	translucent-white	unstained
Papilloma	clear	papillary protrusion	discolored	weakly stained
Hyperkeratosis	clear	almost flat	white	weakly stained
Glycogenic acanthosis	clear	flat and smooth	white	strongly stained
Plaque associated with reflux esophagitis	unclear	flat and smooth	dim-white	strongly stained around the lesion
Localized esophagitis	unclear	flat and smooth	dim-white or reddish	weakly stained
Esophageal candidiasis	unclear	diffuse rice-grain sized granule	cream-white	slightly stained or stained
Superficial cancer	clear	Irregular granule or nodule	dim-white or reddish	unstained and tinged with pink color

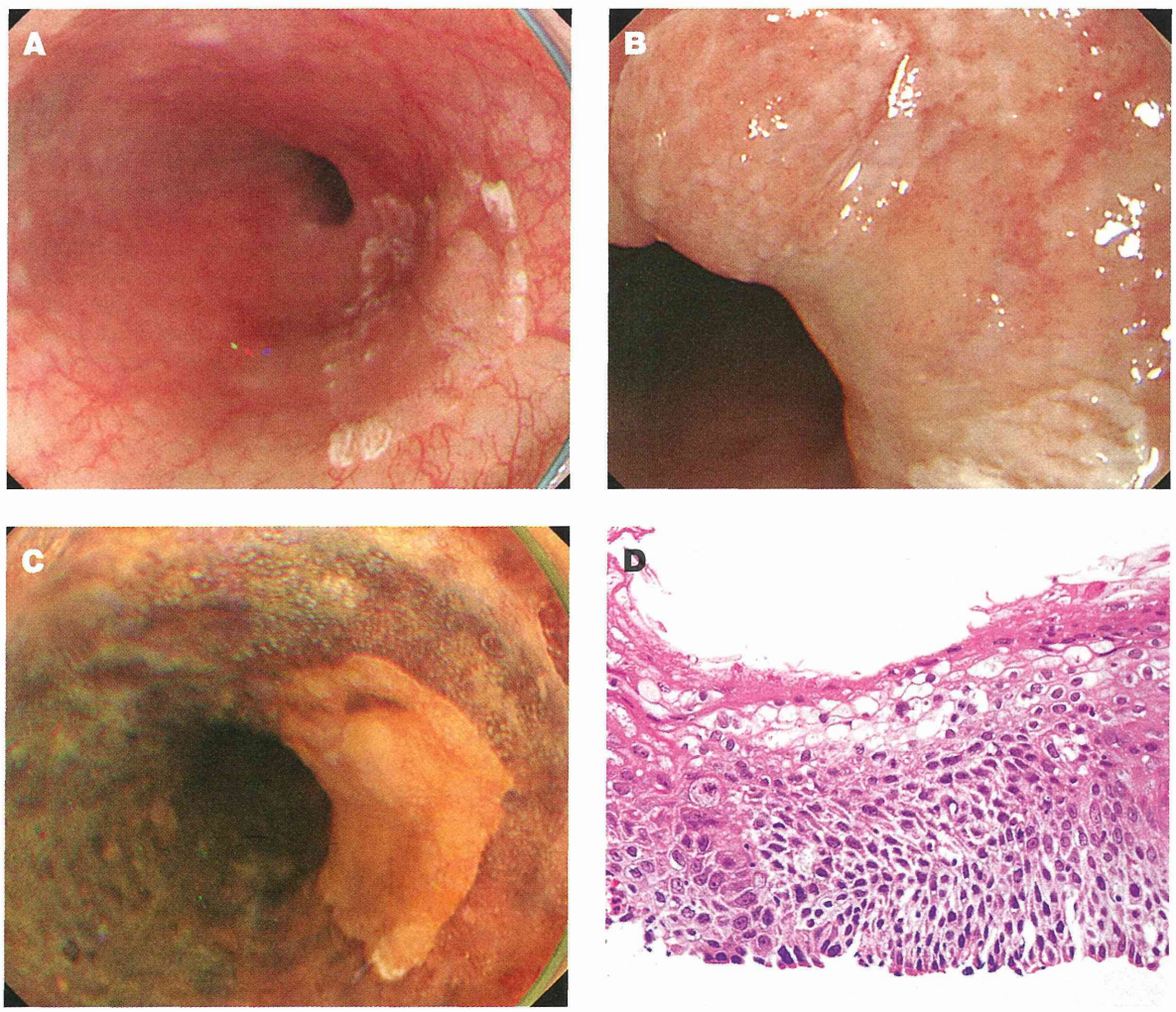

FIGURE 4 Endoscopic images of the depressed superficial carcinoma with hyperkeratosis on its surface.
A: Hyperkeratosis sometimes covers the surface of a depressed superficial carcinoma, and the endoscopic appearance of such lesions is very similar to that of epidermoid metaplasia.
B: Close endoscopic view shows several slightly reddish areas with an irregular surface. These findings are specific for the superficial carcinoma.
C: After Lugol's iodine dyeing, the superficial carcinoma tends to be tinged with a subtle pink color as time progresses. This is a specific finding for carcinoma but not for other benign lesions.
D: Histological finding of biopsy specimen obtained from superficial carcinoma with hyperkeratosis on its surface. The hyperkeratotic layer covers the surface of a superficial carcinoma.

evaluating the key findings described above. To confirm the diagnosis, it is important to collect a large biopsy specimen containing deep tissue sufficient for histological evaluation.

The etiology of epidermoid metaplasia is unknown. Fukui *et al.* speculated that epidermoid metaplasia develops as an unusual response to acid reflux, although Barrett's epithelium usually develops in response to chronic irritation (2). Dianna *et al.* reported epidermoid metaplasia in the uterine cervix and proposed that exposure of the cervix to chronic irritation was the etiology of cervical epidermoid metaplasia (3). In our series, there was no evidence of gastric acid reflux because no patient had obvious endoscopic findings or symptoms of GERD, so it did not seem likely that gastric acid was the main cause of irritation. However, biopsy specimens showed inflammatory changes microscopically, suggesting that chronic inflammation was present at the sites of epidermoid metaplasia. All four patients in this report were habitual alcohol drinkers, and chronic exposure to alcohol may be one cause of inflammation in the esophagus. The short-term natural course of epidermoid metaplasia could be assessed in three patients retrospectively (for 4-15 months), and this analysis showed no changes in the morphology or size of the lesions during the period investigated. Further long-term follow-up is needed to assess the natural course of epidermoid metaplasia and the potential for malignant transformation.

Interestingly, m-LVLs were noted in three of the four patients, suggesting the presence of multiple sites of metaplastic epithelium and parakeratosis, which are strongly associated with the development of esophageal squamous cell carcinoma (4-6). The more interesting underlying factors were a history of squamous cell carcinoma in all patients (three of the esophagus and the remaining of the oropharynx). Because of the small number of patients in the present series, we cannot compare the strength of this association between epidermoid metaplasia, m-LVLs and esophageal squamous cell carcinoma in detail. However, this may suggest that epidermoid metaplasia is a biomarker of squamous cell carcinoma, as is the case for melanosis (7).

We predict an increase in the number of case reports of epidermoid metaplasia once its endoscopic characteristics are recognized widely, and this should lead to more accurate diagnoses. Detailed investigations of a larger number of patients will help define the clinicopathological profile of esophageal epidermoid metaplasia.

REFERENCES

1. **Nakanishi Y, Ochiai A, Shimoda T, Yamaguchi H, Tachimori Y, Kato H, et al:** Epidermization in the esophageal mucosa: unusual epithelial changes clearly detected by Lugol's staining. Am J Surg Pathol 1997; 21:605-609.
2. **Fukui T, Sakurai T, Miyamoto S, Ueno S, Kido M, Kiriya K, et al:** Education and imaging. Gastrointestinal: epidermal metaplasia of the esophagus. J Gastroenterol Hepatol 2006; 21:1627-1627.
3. **Ionescu DN, Mohan D, Carter G, Dabbs DJ:** Epidermoid metaplasia of the cervix. Arch Pathol Lab Med 2004; 128:1052-1053.
4. **Muto M, Hitomi Y, Ohtsu A, Ebihara S, Yoshida S, Esumi H:** Association of aldehyde dehydrogenase 2 gene polymorphism with multiple esophageal dysplasia in head and neck cancer patients. Gut 2000; 47:256-261.
5. **Muto M, Hironaka S, Nakane M, Boku N, Ohtsu A, Yoshida S:** Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 2002; 56:517-521.
6. **Muto M, Takahashi M, Ohtsu A, Ebihara S, Yoshida S, Esumi H:** Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 2005; 26:1008-1012.
7. **Yokoyama A, Mizutani T, Omori T, Yokoyama T, Hirota T, Matsushita S, et al:** Melanosis and squamous cell neoplasms of the upper aerodigestive tract in Japanese alcoholic men. Cancer Sci 2006; 40:676-684.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Differences of image enhancement in image-enhanced endoscopy: narrow band imaging versus flexible spectral imaging color enhancement

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Abstract
Background Narrow band imaging (NBI) can emphasize images of the surface microvasculature of lesions, because the central wavelengths of the NBI filter are 415 and 540 nm and these wavelengths are well absorbed by hemoglobin. Flexible spectral imaging color enhancement (FICE) increases the contrast in depictions of mucosal lesions. However, quantitative evaluation of the image enhancement shown by NBI and FICE has not been reported. The aim of this study was to measure and compare the degrees of image enhancement in NBI and FICE.
Methods We compared the visibility of human blood diluted with distilled water between that shown by white-light imaging (WLI) and that shown by NBI or FICE. One milliliter of human blood was plated onto a 12-well transparent plastic plate to set up doubling dilutions, from 1/2 to $1/2^{23}$. High-definition endoscopes were used for each imaging method. A total of 11 endoscopists independently evaluated the visibility of the diluted blood. The median dilution was defined as the limit of visibility in each image.
Results NBI enabled clearer visualization of the presence of blood compared with conventional WLI. NBI recognized blood contamination up to a $1/2^{14}$ dilution, whereas conventional WLI recognized blood contamination up to a $1/2^{11}$ dilution. In contrast, FICE did not improve the visualization of diluted blood and recognized blood contamination up to a $1/2^{10}$ dilution.
Conclusions NBI more effectively enhanced images of diluted blood compared to conventional WLI, while FICE did not improve the visualization of the diluted blood. These data suggest the usefulness of NBI for the early detection of gastrointestinal neoplasia, which is accompanied by abundant neovascularization.

Keywords Image-enhanced endoscopy · Narrow band imaging · Flexible spectral imaging color enhancement

Introduction

Image-enhanced endoscopy (IEE) can be divided into dye-based and equipment-based approaches; the latter is a newly developed technology [1]. The diagnostic accuracy of equipment-based IEE is expected to improve in combination with magnifying endoscopy. In particular, narrow band imaging (NBI) is an equipment-based IEE approach that uses optical technology and depends on hemoglobin absorption wavelengths of 415 and 540 nm exclusively [2, 3]. The combination of NBI with magnifying endoscopy enables the clear visualization of very small mucosal structures and the microvasculature [4].

Superficial cancers in the head and neck region and in the esophagus show neovascularization and morphological changes in microvascular architecture, and novel endoscopic diagnosis by NBI has been established for such cancers [4–9]. We recently showed that NBI provided superior detection and higher diagnostic accuracy compared with conventional white-light imaging (WLI) for lesions in the head and neck region and the esophagus [10].

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Most pharyngeal and esophageal superficial cancers can be recognized as well-demarcated brownish areas which are associated with the development of irregular microvessels. Confirmation of this finding leads to a cancer diagnosis with very high accuracy. However, no reports have objectively quantified the impact of red blood cells contained in the lesions on the acquisition of the images.

Flexible spectral imaging color enhancement (FICE) is also an equipment-based IEE that employs image post-processing technology to increase the contrast of the depictions of mucosal lesions [11]. However, there are no reports documenting the superiority of FICE over conventional WLI for the detection and diagnosis of cancers in the head and neck region and in the esophagus. Additionally, images acquired using FICE require processing, but are not influenced by the amounts of red blood cells or hemoglobin. However, color enhancement in the absorption range for hemoglobin is possible in FICE images; thus, visualization of the vasculature should be facilitated with FICE. However, objective quantitative evaluation of the image enhancement shown by FICE compared with that shown by NBI has not been reported.

In the present study, we measured the degree of image enhancement in samples with different amounts of red blood cells in diluted water, comparing the results among WLI, NBI, and FICE.

Methods

To measure differences in the degree of image enhancement between IEE and conventional WLI, we compared endoscopic images of human blood diluted with distilled water. Endoscopic WLI and IEE images of diluted blood were taken under the same conditions in a dark room.

Dilution series

One milliliter of human blood (containing 5×10^7 red blood cells per μL) was plated onto a 12-well transparent plastic plate (Cellstar; Greiner Bio-one, Tokyo, Japan) to set up doubling dilutions, from 1/2 to $1/2^{23}$ (Fig. 1). The human blood was taken from one healthy volunteer (H.H.) and was divided into two experimental samples, to be used for NBI and FICE.

Endoscopic systems

High-definition endoscopes (H260Z; Olympus Medical Systems, Tokyo, Japan, and EC-590ZW; Fujifilm Medical, Tokyo, Japan) were used, with corresponding light sources (LUCERA; Olympus Medical Systems and ADVANCIA; Fujifilm), respectively. The magnifying function was not used in this study, because this study aimed to evaluate the overall visibility.

WLI and IEE conditions

WLI

Color enhancement was employed at level 0 for WLI in the Olympus system. In the Fujifilm Medical system, color enhancement was not set for WLI. While the function of the color enhancement by the Olympus system indicates hemoglobin enhancement, that of the Fujifilm system indicates enhancement of color tone. In this study, to avoid the influence of color enhancement on the results, the color enhancement function was not set in either system.

NBI

Color tone was employed at level 1 for NBI. This setting is recommended for the visualization of microvessels in the upper gastrointestinal tract in the Olympus instruction manual.

FICE

The red, green, and blue (RGB) settings for FICE were $R = 525$ nm (gain 3), $G = 495$ nm (gain 4), and $B = 495$ nm (gain 3). This setting was one of the best recommendations for the enhancement of microvascular architecture provided in the Fujifilm instruction manual.

Evaluation of the endoscopic images

The WLI endoscopic images provided by both Olympus and Fujifilm Medical; NBI; and FICE were independently reviewed by 11 endoscopists who were blinded to the information on each imaging method. The median dilution that was estimated as the limitation of the visibility of diluted blood by each endoscopist was defined as the limitation of visibility with each imaging method.

Results

In general, NBI yielded darker images than WLI in the Olympus system (Fig. 1). However, NBI enabled clear visualization of the presence of blood, which was not visible by WLI (Fig. 1). In contrast, the brightness of FICE was similar to that of WLI in the Fujifilm system (Fig. 2) and the presence of blood was also similarly observable with WLI and FICE (Fig. 2).

In the Olympus system, blood dilutions up to around $1/2^{11}$ were recognizable by WLI; however, it was difficult

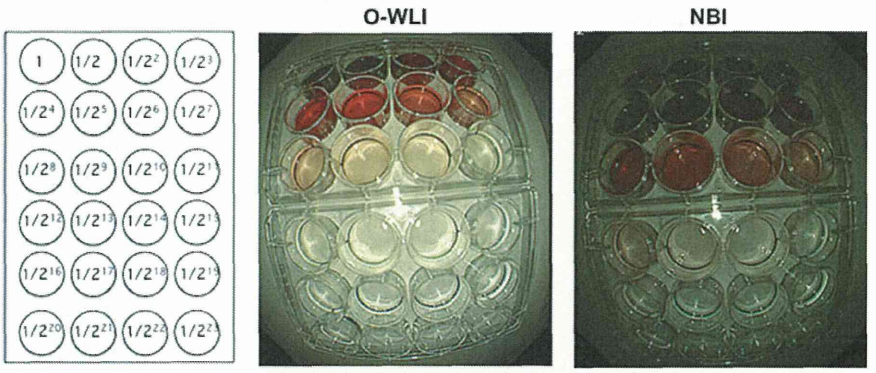

Fig. 1 Comparison of the visibility of blood diluted with distilled water using narrow band imaging (*NBI*) and conventional white light imaging (*WLI*) in the Olympus system. *O-WLI* WLI by Olympus system

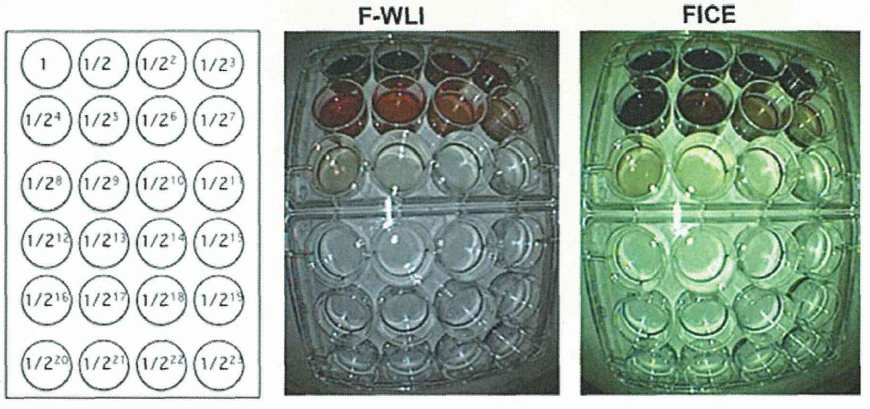

Fig. 2 Comparison of the visibility of blood diluted with distilled water using flexible spectral imaging color enhancement (*FICE*) and conventional WLI in the Fujifilm system, *F-WLI* WLI by Fujifilm system

to detect blood contamination at greater dilutions. In contrast, blood contamination up to a dilution of around $1/2^{14}$ was visualized using NBI (Fig. 1). The limit of visibility of the diluted blood in the water was $1/2^{11}$ and $1/2^{14}$ by WLI and NBI, respectively (Fig. 3). Thus, there was a 2^3-fold difference in sensitivity between these two methods.

To avoid any undesirable effect due to curved endoscopic images, we selected the demonstrable images around the limit of the visibility (Fig. 4). At a dilution of $1/2^9$, blood contamination was recognized in a relatively easy manner by WLI, but the detection was clearer using NBI. At a dilution of $1/2^{10}$, blood contamination was only marginally recognizable by WLI; in contrast, it was clearly observable using NBI. Furthermore, at a dilution of $1/2^{11}$, blood contamination was barely detectable by WLI, whereas it remained clearly visible using NBI. In addition, the presence of blood in distilled water was indicated by a brownish color in NBI images.

In the Fujifilm system, blood dilutions up to around $1/2^{10}$ were recognizable by both WLI and FICE; however, it was difficult to detect blood contamination at greater dilutions by FICE (Fig. 2). The limit of visibility of the diluted blood in the water was $1/2^{10}$ with both WLI and FICE (Fig. 3).

Similar to the Olympus system, to avoid any undesirable effect due to curved endoscopic images, we selected the

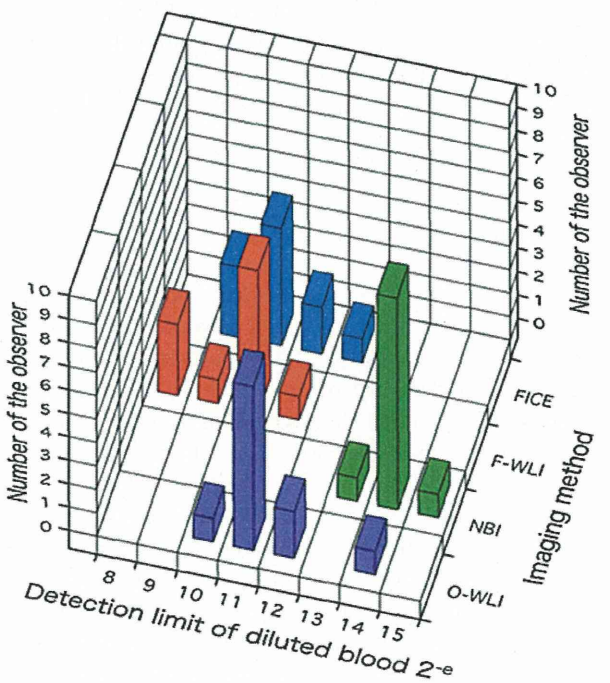

Fig. 3 Estimation of the limitation of the visibility of diluted blood by each endoscopist. *O-WLI* WLI by Olympus system, *F-WLI* WLI by Fujifilm system, $2^{-e} = 2^{-8 \sim 15}$

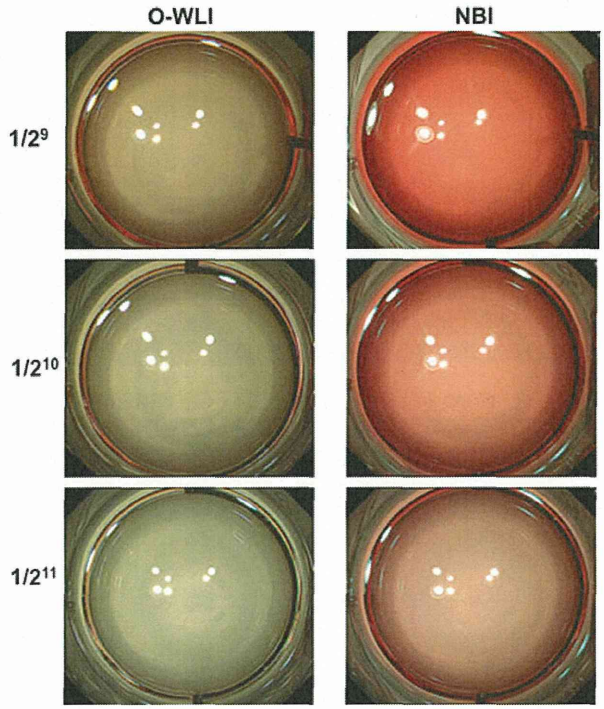

Fig. 4 Comparison of the visibility of blood dilutions from $1/2^9$ to $1/2^{11}$ using NBI and conventional WLI

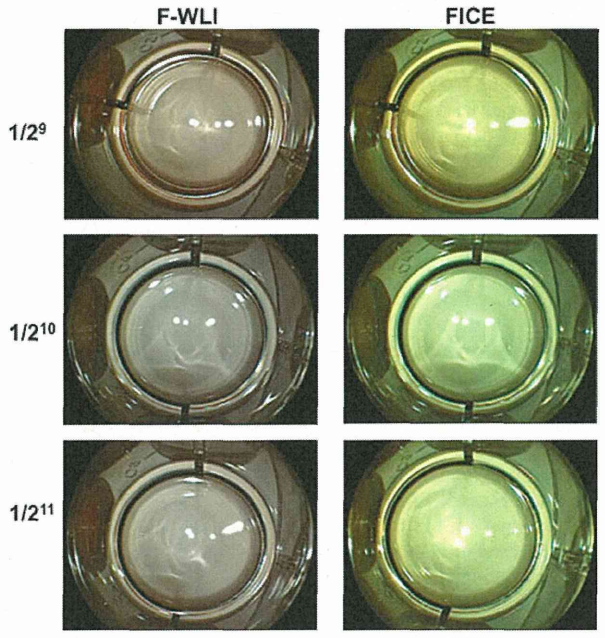

Fig. 5 Comparison of the visibility of blood dilutions from $1/2^9$ to $1/2^{11}$ using FICE and conventional WLI

demonstrable images around the limit of the visibility (Fig. 5). At a dilution of $1/2^9$, blood contamination was marginally recognized by both WLI and FICE. At a dilution of $1/2^{10}$, blood contamination was difficult to detect by both WLI and FICE. Indeed, at dilutions of $1/2^9$–$1/2^{11}$, FICE failed to provide better visualization than NBI (Figs. 4, 5).

Discussion

In this study, by using a quantitative approach, we demonstrated for the first time that the presence of blood was detectable by NBI with a high sensitivity, which was 2^3 times greater than that of conventional WLI. Since NBI light is well absorbed by hemoglobin, it follows that NBI will enhance blood detection. In addition, as blood is the content of the human microvasculature, NBI could theoretically enhance the detection of microvessels.

As cancer arising from squamous cell epithelia in the head and neck region and in the esophagus is accompanied by abundant neovascularization, the present results suggest the usefulness of NBI for the sensitive detection of these cancers [10]. Furthermore, abnormal microvessels are also observed in early cancers of the stomach and colorectum, and NBI with magnification endoscopy has been reported to be more useful for cancer diagnosis than WLI in these regions [12–14]. The present data may also confirm such clinical usefulness.

In contrast to the findings with NBI, when using FICE we did not detect blood with greater sensitivity compared with that for WLI. While the FICE preset mode in this study was one of the best recommendations for the imaging of microvessels, this result might suggest that FICE has limitations for diagnoses based on neovascularization and morphological changes in the microvascular architecture.

In general, the evaluation of visibility is subjective and varies among different individuals. Therefore, in the present study, the visibility of the diluted blood in the sterilized water was independently evaluated by a total of 11 endoscopists. While seven of them (63.6%) evaluated that the limit of visibility of the diluted blood was $1/2^{11}$ in the WLI Olympus system, nine of them (81.8%) evaluated the limit at $1/2^{14}$ with NBI. This means that visibility was objectively improved by NBI. In contrast, evaluation of the visibility of the diluted blood was similar for WLI and FICE. This means that visibility was not objectively improved by FICE.

Most superficial squamous cell carcinomas in the head and neck region and in the esophagus are recognized as brownish areas by NBI. The reason for this remains unclear. In the present study, diluted blood in distilled water was recognized as a brownish color by NBI, even at the dilution level at which the identification of blood contamination was difficult with conventional WLI. One possibility may be that most squamous cell carcinomas in

these regions exhibit marked neovascularization, and the lesions are supplied by abundant red blood cells; as a result, the lesions may be recognized as brownish areas.

The limitation of this study was that the evaluation was performed in vitro. In the human body, cancerous lesions contain not only red blood cells but also collagen tissue, inflammatory cells, and so on. Furthermore, a patient's movement and the existence of mucus will influence the image. Therefore, the possibility cannot be denied that the content of other materials in the tissue and the light condition affect the advantages of NBI. However, there are no structural components that will be absorbed by specialized light as well as NBI. And the patient's condition can be managed in the clinical setting. Thus, the presence of blood might be a strong enhancer for the visualization provided by NBI.

The disadvantage of NBI is its darkness. However, when we visualize the microvascular architecture, the magnifying function is necessary and therefore the darkness will be omitted in the conditions of close observation. Thus, the clinical implications of the present results might not be influenced for the detection but for the detailed observation by magnifying function. Also the present results could provide a plausible explanation for the better visibility of microvessels shown by NBI.

In conclusion, this study demonstrated that NBI is superior to WLI for the identification of diluted blood in an in vitro assay, whereas FICE did not have better visibility of diluted blood than WLI. These results deepen our understanding of the superiority of NBI compared to conventional WLI and also support the evidence that NBI provides better visibility of changes in the microvascular architecture of gastrointestinal neoplasia [9], which is accompanied by abundant neovascularization. Conversely, the data suggest that the visualization of a lesion lacking vascularization would not be improved by NBI.

References

1. Kaltenbach T, Sano Y, Friedland S, Soetikno R. American Gastroenterological Association (AGA) Institute technology assessment on image-enhanced endoscopy. Gastroenterology. 2009;134:327–40.
2. Gono K, Yamazaki K, Doguchi N, Nonami T, Obi T, Yamaguchi M, et al. Endoscopic observation of tissue by narrow band illumination. Opt Rev. 2003;10:211–5.
3. Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, et al. Appearance of enhanced tissue feature in narrow-band endoscopic imaging. J Biomed Opt. 2004;9:568–77.
4. Muto M, Katada C, Sano Y, Yishida S. Narrowband imaging: a new diagnostic approach to visualize angiogenesis in the superficial neoplasm. Clin Gastroenterol Hepatol. 2005;3:S16–20.
5. Muto M, Nakane M, Katada C, Sano Y, Ohtsu A, Esumi H, et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer. 2004;101:1375–81.
6. Muto M, Ugumori T, Sano Y, Ohtsu A, Yoshida S. Narrow band imaging combined with magnified endoscopy for the cancer at the head and neck region. Dig Endosc. 2005;17:S23–4.
7. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc. 2004;59:288–95.
8. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S. The value of narrow band imaging endoscope for early head and neck cancers. Otolaryngol Head Neck Surg. 2008;138:446–51.
9. Ugumori T, Muto M, Hayashi R, Hayashi T, Kishimoto S. Prospective study of early detection of pharyngeal superficial carcinoma with the narrowband imaging laryngoscope. Head Neck. 2009;31:189–94.
10. Muto M, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol. 2010;28:1566–72.
11. Pohl J, May A, Rabenstein T, Pech O, Ell C. Computed virtual chromoendoscopy: a new tool for enhancing tissue surface structures. Endoscopy. 2007;39:80–3.
12. Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology. Endoscopy. 2004;36:1080–4.
13. Sumiyama K, Kaise M, Nakayoshi T, Kato M, Mashiko T, Uchiyama Y, et al. Combined use of a magnifying endoscope with a narrow band imaging system and a multibending endoscope for en bloc EMR of early stage gastric cancer. Gastrointest Endosc. 2004;60:79–84.
14. Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, et al. Narrow-band imaging in the diagnosis of colorectal lesions: a pilot study. Endoscopy. 2004;36:1094–8.

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Macroscopic estimation of submucosal invasion in the esophagus

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KEYWORDS:
EUS;
Esophageal cancer;
Submucosal invasion

In esophageal squamous cell carcinoma, the depth of invasion into the wall is closely associated with metastasis to lymph nodes. Esophageal cancer invading the muscularis mucosae could be curably treated by endoscopic submucosal dissection but cancer with submucosal invasion necessitates surgical resection and/or chemoradiotherapy. Therefore, pretreatment diagnosis of invasion depth is crucially important for selecting appropriate treatment strategies for each individual patient. To estimate the depth of cancer invasion for early squamous cell carcinoma of the esophagus, standard endoscopy with image enhancement and endoscopic ultrasound are currently considered the best methods.

According to the staging manual published by the American Joint Committee on Cancer,[1] cancer confined to the mucosa or the muscularis mucosae is categorized as mucosal cancer (T1a). T1a esophageal cancer comprises carcinoma in situ (high-grade intraepithelial neoplasia), cancer invading the lamina propria mucosae, and cancer invading the muscularis mucosae. T1b cancer includes cancer with submucosal invasion.

In esophageal squamous cell carcinoma, the depth of invasion into the wall is closely associated with metastasis to lymph nodes (Figure 1).[2] It is important to note that the frequency of metastasis in the lymph nodes in cancer confined to the mucosa is not zero, but 3%. The risk increases to 12% in cancer invading the muscularis mucosae and markedly increases to 26%-46% in patients with submucosal invasion. Because cancers confined to the mucosal layer correlate with a low frequency of metastasis and because surgery confers a high risk of morbidity and mortality, they are considered excellent candidates for minimally invasive treatment by endoscopic mucosal resection or endoscopic submucosal dissection (ESD). Cancer invading the muscularis mucosae may still be treated by ESD, but cancer with submucosal invasion necessitates surgical resection and/or chemoradiotherapy.[3,4] Given that endoscopic resection has some risks of bleeding and perforation, pretreatment diagnosis of invasion depth is crucial for selecting appropriate treatment strategies for each individual patient.

To estimate the depth of cancer invasion for early squamous cell carcinoma of the esophagus, standard endoscopy with image enhancement and endoscopic ultrasound (EUS) are considered the best methods. Other methods such as the "barium meal," computed tomography, and positron emission tomography[5] are considered less accurate.

Indications

Conventional endoscopy with image-enhanced endoscopy is quite accurate to diagnose cancer in situ (high grade-intraepithelial neoplasia) or cancer with minimal subepithelial invasion[6,7]; in those cases, EUS is rarely indicated. In our practice, we used high-magnification endoscopy with narrow-band imaging to view the surface

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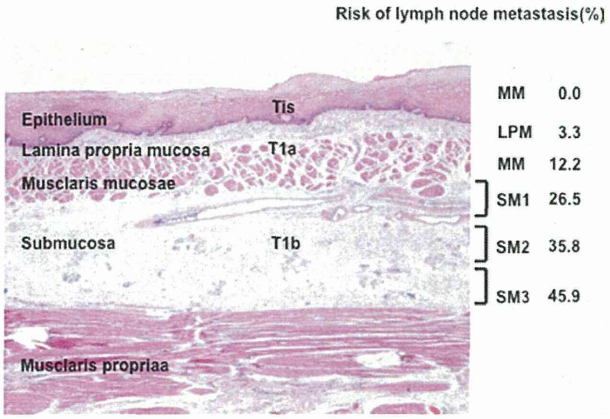

Figure 1 Risk of lymph node metastasis in the esophagus. In esophageal squamous cell carcinoma, the depth of invasion into the wall is closely associated with an increasing risk of lymph node metastasis. (Color figure is available online at www.techgiendoscopy.com.)

microvessels of early esophageal carcinoma. The patterns of these surface microvessels—called intraepithelial papillary capillary loops (IPCL)—have been shown to be predictive of the degree of mucosal and submucosal invasion.[8]

IPCL can be classified into eight different patterns; thus, the use of IPCL classification can be complex. A simpler way might be to classify the IPCL as regular and irregular. Early squamous cell carcinoma typically appears as a patch of mucosa with irregular IPCLs, which is clearly demarcated from the surrounding normal mucosa with regular IPCLs. When the carcinoma is limited to the mucosa, its surface is typically smooth and pliable. When the carcinoma has invaded the submucosa, its surface has nodular elevation, reddishness, and deeper depression. EUS can be helpful in these cases to rule out deeply submucosal invasive cancers.

Preparation

When peristalsis interferes with observation, an antispasmodic agent is required. Sedation is also necessary for stable observation.

Instruments

To visualize the distinct tissue layer of the esophageal wall, 20- or 30-MHz miniature probes should be used. This high-resolution imaging demonstrates 9-layered echo structures (Figure 2). Generally, the tumor can be seen as a low echoic mass by EUS. If the cancerous lesion invades to the submucosal layer, EUS deliver a low echoic mass in the high echo layer corresponding to the submucosal layer. A balloon can be attached to the tip of the endoscope to keep deaerated water in the esophageal lumen and prevent regurgitation to the pharynx. An endoscope with a water jet function is desirable to keep the esophageal lumen distended to obtain a clear image.

Techniques

To obtain clear images, several useful methods have been formulated. The most important issue is to keep air or air bubbles away from the scanning site.

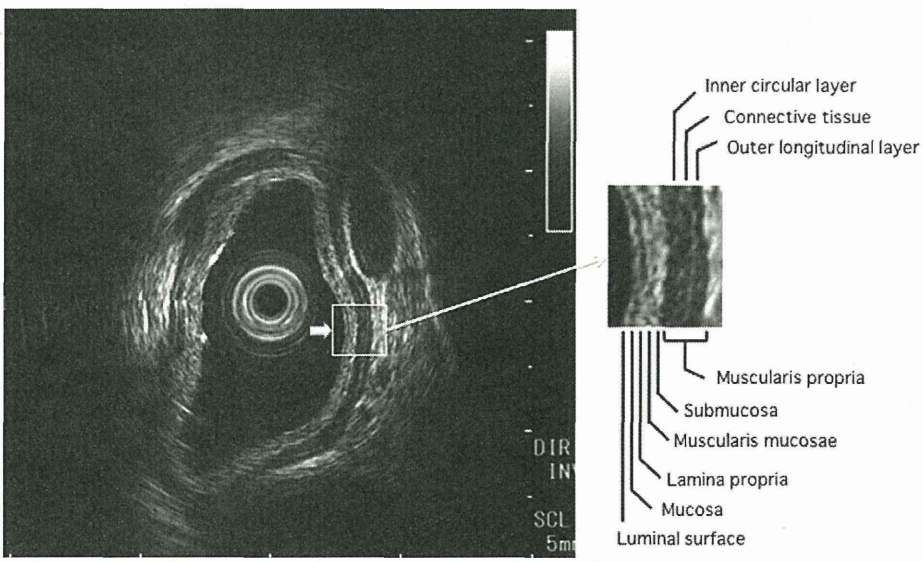

Figure 2 EUS image of the normal esophageal wall by 20-MHz miniprobe demonstrates 9-layered structures (arrow). The first 5 layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), and submucosa (high echo). Next are the inner circular (low echo) and outer longitudinal layers (low echo) of the muscularis propria. They are separated by a thin hyperechoic layer of connective tissue (high echo).

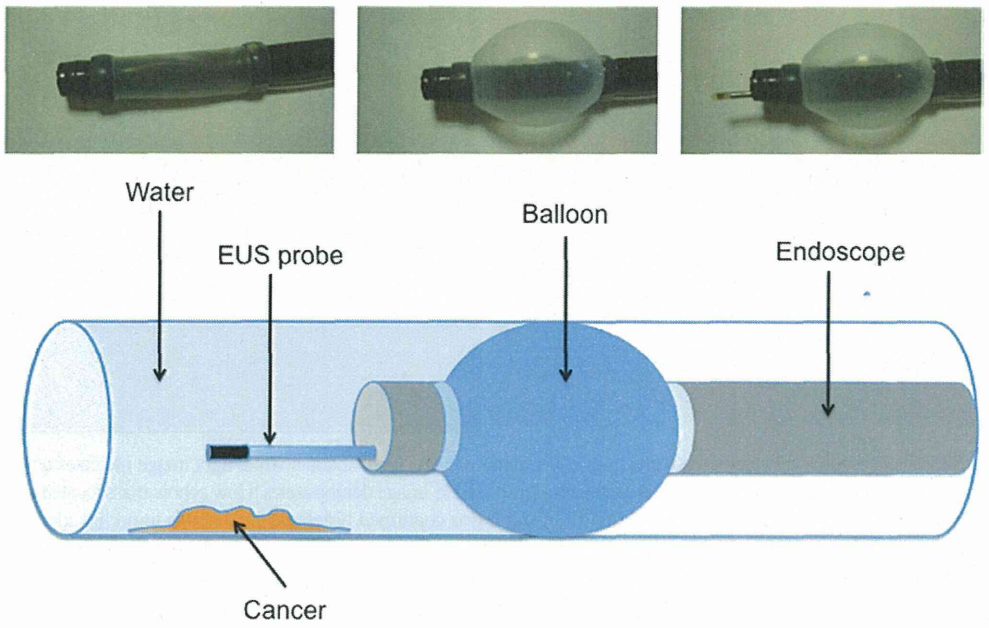

Figure 3 Photographs and scheme of EUS using the balloon method. To keep deaerated water in the esophageal lumen and prevent regurgitation to the pharynx, a balloon should be attached the endoscope itself. After insertion of the endoscope, the tip of endoscope should be directed toward the lesion. At the best position, the balloon should be dilated. With sufficient dilation of the balloon, deaerated water fills the esophageal lumen using the water jet function of the endoscope. Thereafter, scanning of the lesion will be started with a miniature probe. (Color figure is available online at www.techgiendoscopy.com.)

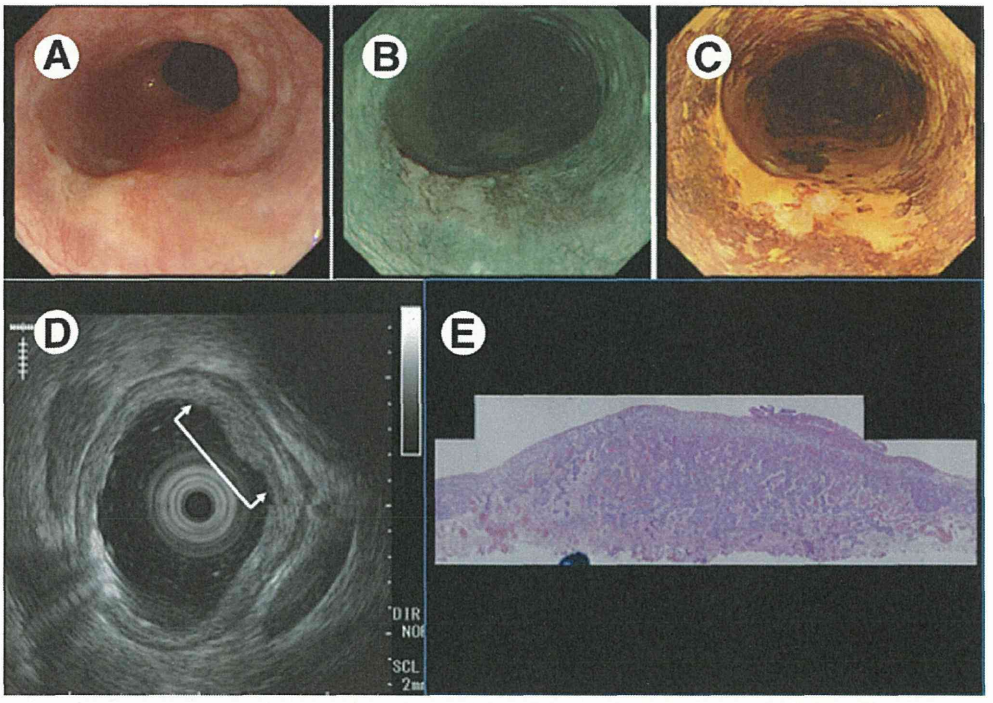

Figure 4 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image shows a reddish area. (B) Narrow-band imaging indicates a well-demarcated brownish area with a white coat. (C) Lugol's staining indicates a well-demarcated unstained area. (D) EUS image demonstrates a low echoic mass located in the submucosal layer (arrow). (E) This superficial cancer was removed by ESD and submucosal invasion of the cancer was confirmed histologically. (Color figure is available online at www.techgiendoscopy.com.)

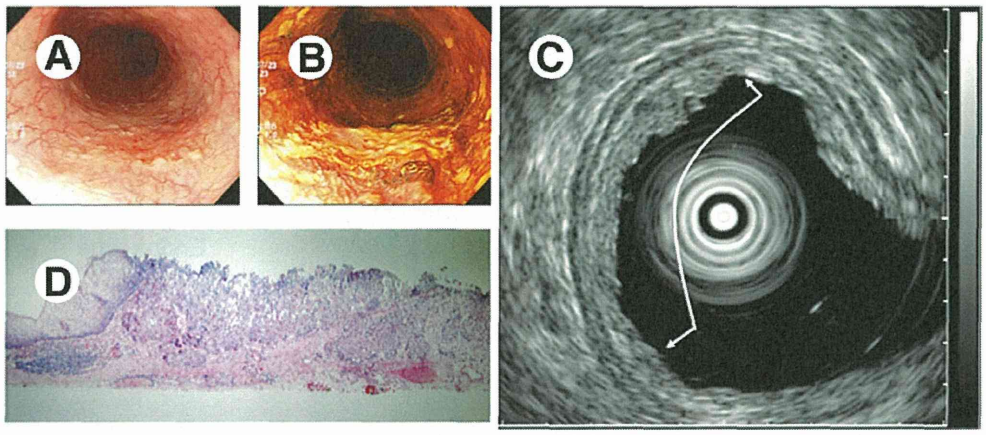

Figure 5 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image indicates a depressed reddish area. (B) Lugol's staining indicates a well-demarcated unstained area. (C) EUS image demonstrates a low echoic mass located in the submucosal layer (arrow). (D) This superficial cancer was removed by ESD and it was confirmed histologically that this tumor invaded to the muscularis mucosae but not into the submucosal layer. This case was suspected to have submucosal invasion clinically; however, the depth of invasion was histologically confirmed as mucosal cancer. (Color figure is available online at www.techgiendoscopy.com.)

Balloon method

The balloon method (Figure 3) is the generalized method. A balloon of a size that fits the endoscope should be selected.

1. To keep deaerated water in the esophageal lumen and prevent regurgitation to the pharynx, a balloon (eg, inner diameter = 10-11 mm) should be attached the endoscope itself (Figure 3A).
2. After insertion of the endoscope, we must direct the tip of the endoscope toward the lesion.
3. At the best position, the balloon should be dilated (Figure 3B).
4. With sufficient dilation of the balloon, we fill the esophageal lumen with deaerated water using the water jet function of the endoscope.
5. Thereafter, we approach the lesion and scan it with the miniature probe (Figure 3C).

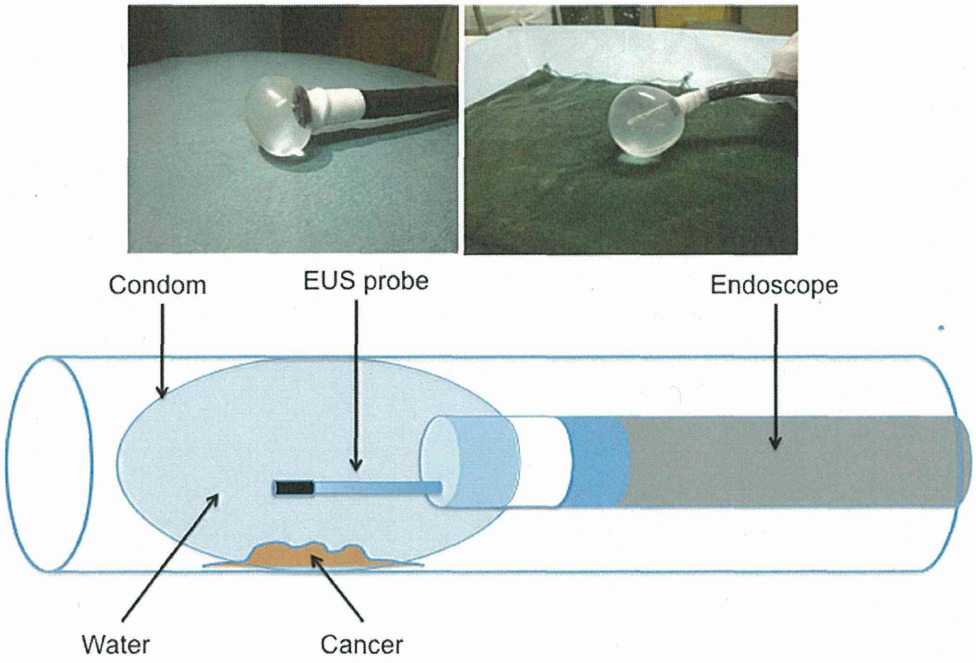

Figure 6 Photo and schema of EUS using the condom method. To keep deaerated water in the condom, a condom for gynecologic ultrasound examination should be attached to the tip of endoscope itself. (Color figure is available online at www.techgiendoscopy.com.)

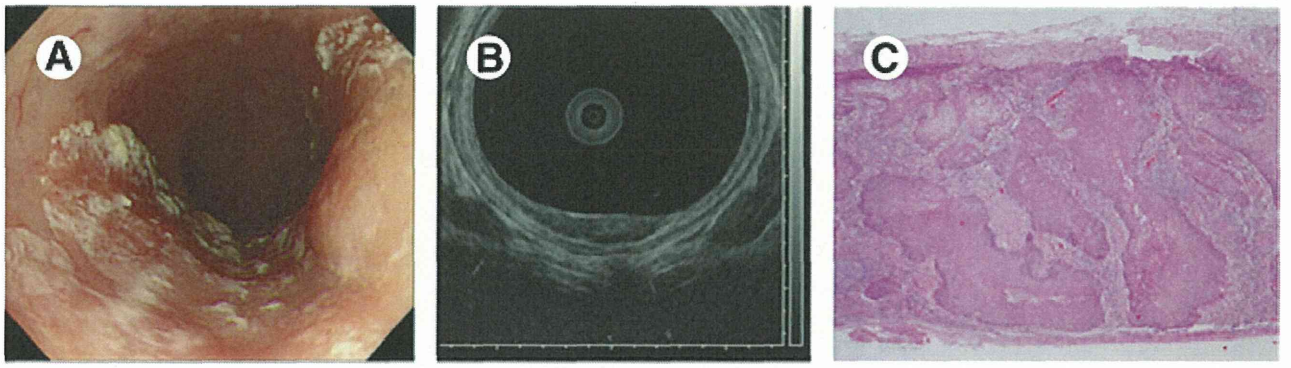

Figure 7 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image indicates a reddish area with an irregular surface. (B) EUS image indicates a low echoic mass located in the submucosal layer. (C) This superficial cancer was removed by ESD and submucosal invasion of the cancer was histologically confirmed. (Color figure is available online at www.techgiendoscopy.com.)

Sample cases are presented in Figures 4 and 5.

Condom method

Similar to the balloon method, the condom method (Figure 6) is useful to keep water in the esophageal lumen because this method can keep water in the condom itself.

A sample case is presented in Figure 7.

Echo jelly method

Echo jelly (Figure 8) is also useful to keep air away from the lesion. A sample case is presented in Figure 9.

Complications

Because the esophageal lumen is filled with deaerated water, caution must be exercised regarding aspiration caused by regurgitation. Excessive balloon expansion is a risk for esophageal injury and hemorrhage. When a patient complains of a chest pain after injection of 15-20 cc of air, the balloon is sufficiently dilated in close contact with the esophageal wall and no more pressure should be applied.

Conclusions

A completely accurate diagnosis of the depth of early esophageal carcinoma can be difficult to attain. Standard

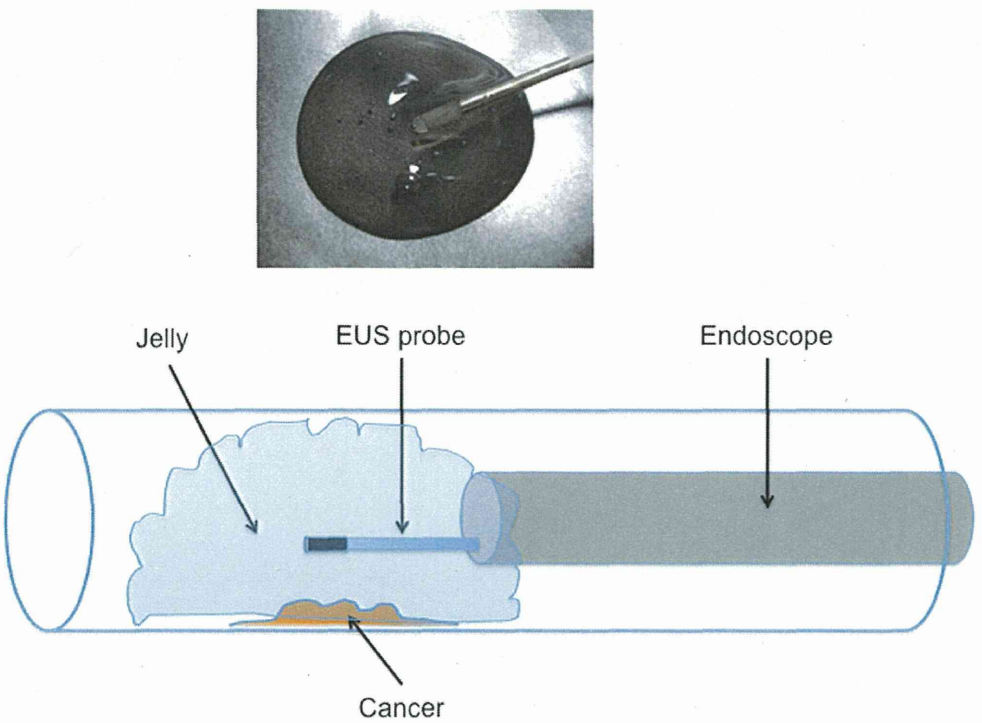

Figure 8 Schema of EUS by the jelly method. (Color figure is available online at www.techgiendoscopy.com.)