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

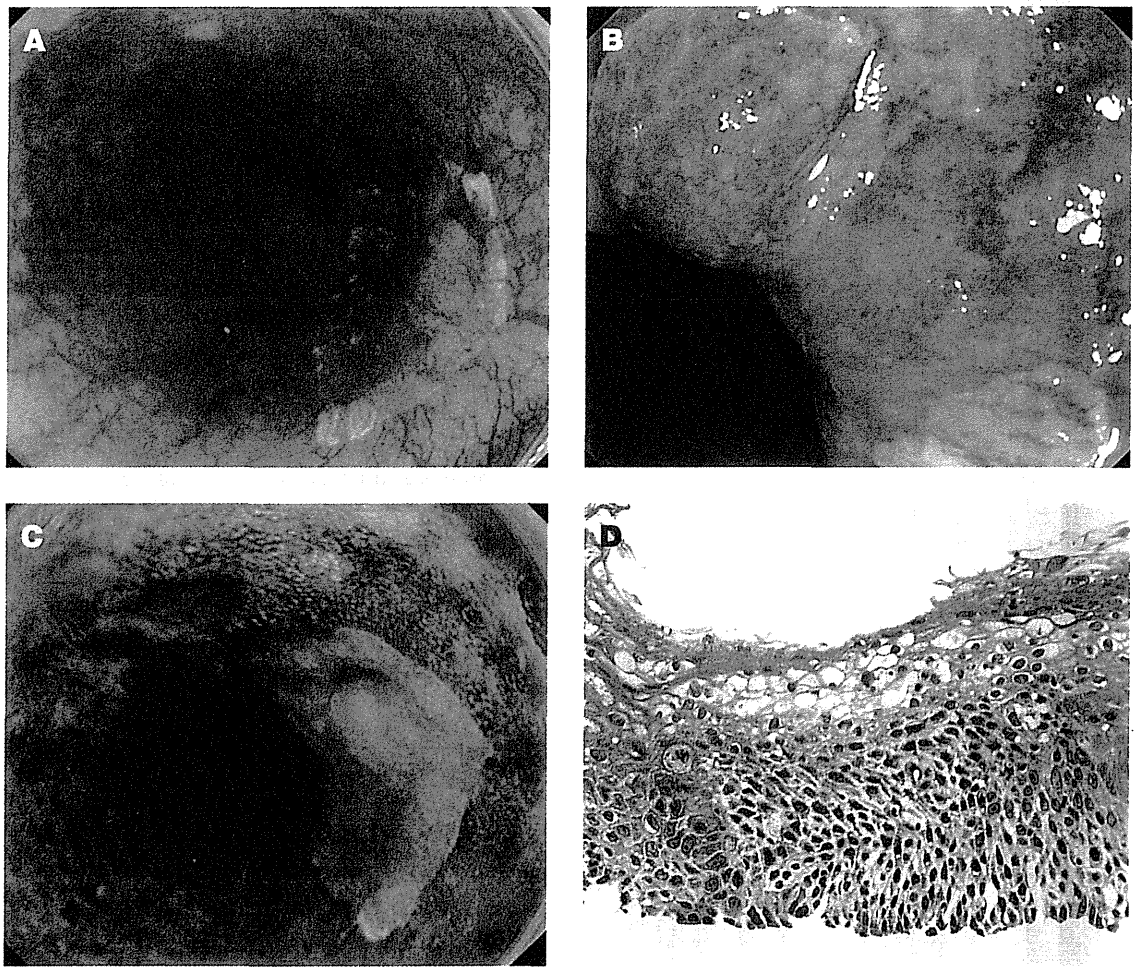

FIGURE 4 Endoscopic images of the depressed superficial carcinoma with hyperkeratosis on its surface.
A: Hyperkeratosis sometimes covers the surface of a depressed superficial carcinoma, and the endoscopic appearance of such lesions is very similar to that of epidermoid metaplasia.
B: Close endoscopic 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.

Efficacy of Preventive Endoscopic Balloon Dilation for Esophageal Stricture After Endoscopic Resection

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Background and Aim: We earlier reported that mucosal defect involving over three-fourths of the circumference of the esophagus after endoscopic mucosal resection (EMR) is a risk factor for the development of the stricture. Although endoscopic balloon dilation (EBD) is a useful procedure to relieve the stricture, there is no standard strategy for preventing development of the stricture. The aim of this study was to evaluate the efficacy and the safety of preventive EBD.

Methods: From 1993 to 2008, 41 consecutive patients with extensive mucosal defect involving over three-fourths of the esophageal circumference after EMR or endoscopic submucosal dissection (ESD) were investigated. Preventive EBD was carried out for 29 cases within 1 week just after EMR/ESD and was repeated once a week until the mucosal defect was completely healed. The remaining 12 cases were not underwent preventive EBD and used as a historic control. If postEMR/ESD stricture developed regardless of preventive EBD, conventional EBD was given repeatedly until the stricture was completely relieved.

Results: Preventive EBD decreased the incidence of stricture (59% vs. 92%, $P = 0.04$), reduced the severity of stricture [(≤ 2 mm; > 2 mm and ≤ 5 mm; > 5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] and shortened the duration required for resolving the stricture (29 d vs. 78 d, $P = 0.04$) even when stricture developed. There was no complication associated with preventive EBD procedure.

Conclusions: Preventive EBD is an effective procedure to prevent postEMR/ESD stricture. Preventive EBD should be considered when EMR/ESD results in a mucosal defect with a circumference greater than three-fourths of the esophageal lumen.

Key Words: endoscopic mucosal resection, endoscopic submucosal dissection, esophageal stricture, endoscopic balloon dilation, prevention

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Endoscopic mucosal resection (EMR) is being increasingly accepted as one of the standard treatment for superficial esophageal cancer because of its minimal invasiveness and excellent survival rate.[1,2] Furthermore, the endoscopic submucosal dissection (ESD) technique has made it possible to carry out *en-bloc* resection of widespread neoplasia, such as a superficial spreading-type of esophageal squamous cell carcinoma and Barrett esophageal cancer.[3–7] However, extended removal of the esophageal mucosa frequently causes severe stricture.[8,9]

Esophageal stricture may markedly interfere with the oral intake of food and fluids, and thus affect the patients' quality of life adversely. In addition, once severe esophageal stricture has developed, it is difficult to resolve the condition. Although endoscopic balloon dilation (EBD) is usually indicated for benign stricture including the cicatricial stricture caused by EMR/ESD, the effect of EBD is sometimes only temporary and the stricture would reappear.[10,11]

Before 2002, we carried out EBD only when the patients complained of dysphagea by postEMR/ESD stricture, and EBD was repeated until the dysphagea was completely resolved. In 2003, we reported that mucosal defects greater than three-fourths of the circumference of the esophagus after EMR are at high risk of developing esophageal stricture.[12] Since then, we started preventive EBD not to develop stricture, before postEMR/ESD mucosal defects develop scarring.

In this study, we evaluated the effectiveness of preventive EBD for the patients with superficial widespread esophageal cancer who developed mucosal defect extending more than three-fourths of the circumference of the esophagus by EMR/ESD.

PATIENTS AND METHODS

Patients

From February 1993 to June 2008, we experienced 64 consecutive patients with widespread mucosal defects greater than three-fourths of the esophageal circumference as a result of EMR/ESD for esophageal cancer. Written informed consent was obtained from all patients before carrying out EMR/ESD and EBD.

Endoscopic Resection Technique

To remove the lesions endoscopically, EMR[13,14] or ESD[5–7] were carried out.

EBD Technique

All patients received administration of 17.5 to 35 mg of pethidine hydrochloride to reduce the suffering from EBD

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procedure. All EBD procedures were carried out using direct visualization and fluoroscopic monitoring. The balloon was positioned across the stenotic site, and then it was inflated carefully with double-diluted contrast agent. During the procedure, patients were closely observed with pulse, blood pressure, and oxygen saturation. When a patient experienced pain during the dilation or when a notch of the balloon placed on the stricture was gradually disappeared, dilation was stopped, and then the balloon was maintained in its inflated state and held close to the tip of the endoscope, and was pushed through the stenotic site as a bougie technique. If the notch of the balloon was rapidly expanded, suggesting a tear at the stenotic site, dilation is immediately stopped and the balloon was deflated, and then the endoscope and deflated balloon were removed.

Four CRE balloon dilators (Boston Scientific Corp. Natick, MA, USA) of different sizes (10 to 12 mm, 12 to 15 mm, 15 to 18 mm, and 18 to 20 mm) were used according to the severity of the stricture. A single balloon was used in each EBD session. When the endoscope could be passed through the site of the mucosal defect, a balloon of 18 to 20 mm was used. When the stricture was less than 10 mm in diameter and larger than 5 mm, a 15 to 18 mm balloon was used. When the stricture was less than 5 mm in diameter and larger than 2 to 3 mm, a 12 to 15 mm balloon was used. When the stricture was a pinhole stricture, a 10 to 12 mm balloon was used. We did not carry out preventive EBD when the luminal diameter was estimated to be greater than 20 mm because the diameter of the lumen would have been greater than that of the fully expanded balloon.

In this study, we defined the EBD procedure carried out immediately after EMR/ESD as "preventive EBD" and that after the development of postEMR/ESD cicatricial stricture as "conventional EBD."

Protocol of the Preventive EBD and Conventional EBD

Preventive EBD was commenced within 1 week after the EMR/ESD and repeated weekly until the complete healing of mucosal defect was observed (Fig. 1). Patients consumed a regular diet during the period of mucosal healing and weekly preventive EBD.

If the postEMR/ESD mucosal defects became scarred with stricture despite repeated preventive EBD, conventional EBD was given repeatedly until the stricture was completely resolved. The time interval of conventional EBD depended on patients' symptom such as dysphagea (usually 2 to 4 wk). The strategy of conventional EBD has not been changed throughout this study period, therefore, the time interval of conventional EBD is not different between 2 groups.

Definition of the Stricture

"Stricture" was defined when a standard 11-mm-diameter endoscope (Q240, 1T240; Olympus Optical Co. Ltd., Tokyo, Japan) could not be passed through the site, or when the patients complaint of dysphagea. Whereas, "complete resolution of the stricture" was defined when a standard diameter endoscope could be passed through the site, and patients' symptoms of dysphagia were completely relieved.

In each EBD sessions in all cases, diameter of stricture was measured by comparing with the diameter of inflated balloon under the fluoroscopic monitoring, and it was classed into 3 groups: more than equal to 2 mm; more than 2 mm and, more than equal to 5 mm; more than 5 mm. The duration required for resolving the stricture was defined as the time interval between the day when the stricture was first observed and the day of complete resolution.

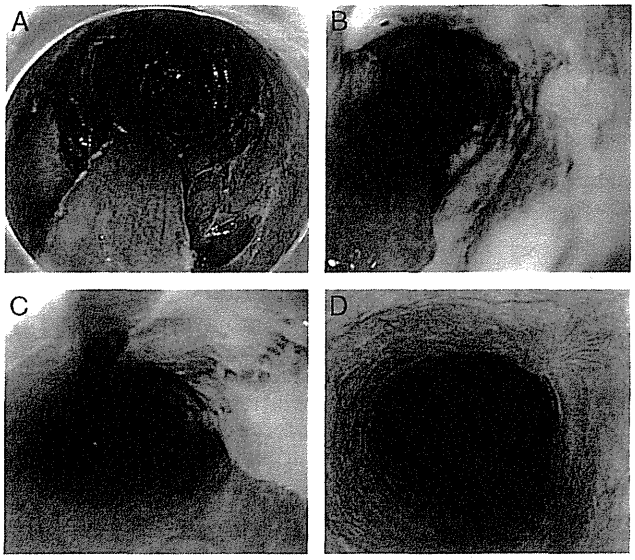

FIGURE 1. A representative case who received preventive endoscopic balloon dilation after a semicircumferential endoscopic submucosal dissection(ESD). A, Semicircumferential mucosal defect immediately after the ESD. B, Mucosal defect 1 week after the ESD. The site gradually developed scarring with mild stricture. C, Mucosal defect 1 month after the ESD. The site developed scarring furthermore, but the stricture was mild. D, PostESD site 2 months after the ESD. The complete healing of the postESD mucosal defect was observed without stricture. The endoscope could be passed through the site and the patient did not complain of any symptom with esophageal stricture.

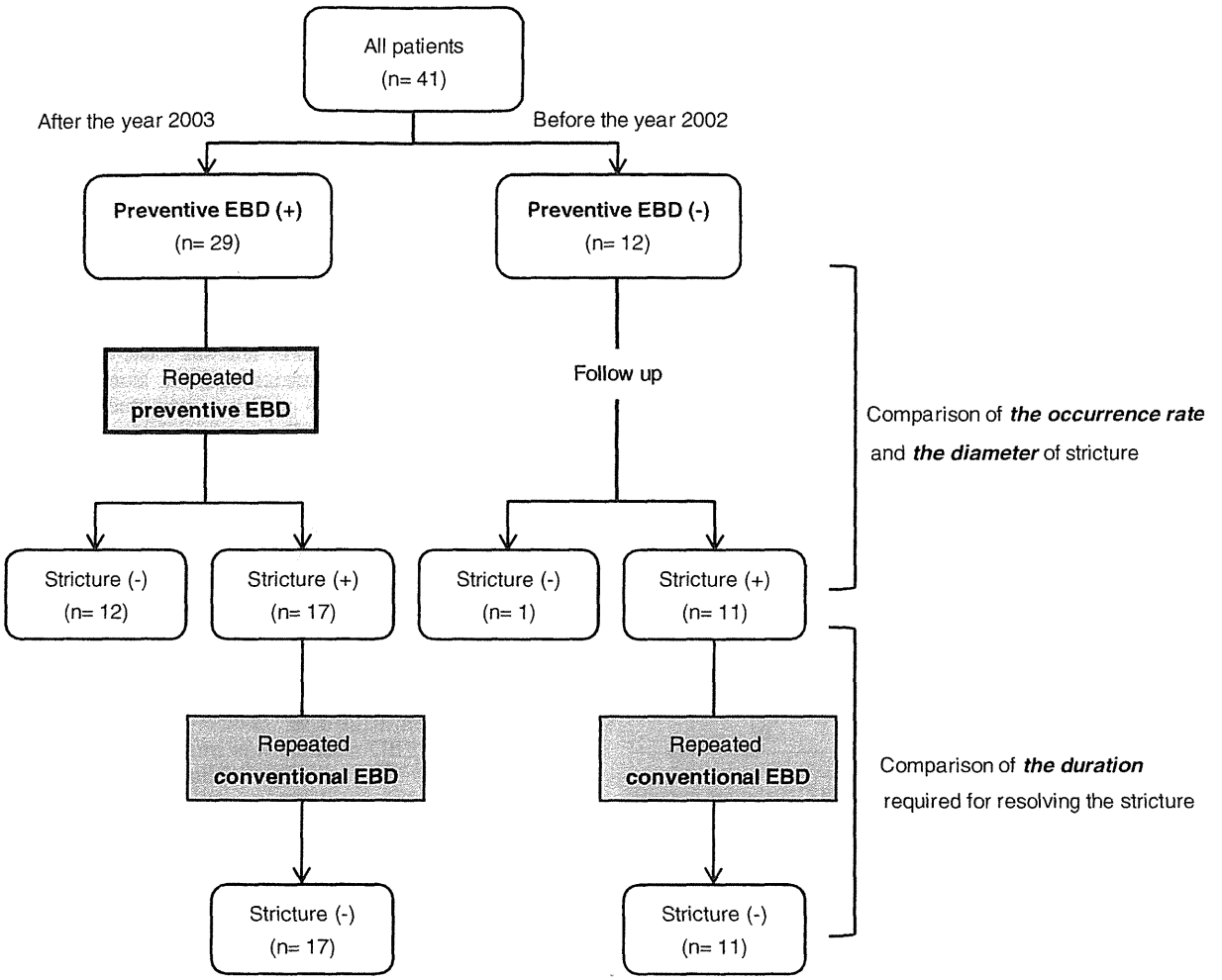

FIGURE 2. Diagram of patients flow.

Evaluation of Preventive EBD

The efficacy of preventive EBD was evaluated retrospectively by comparing the following 3 points between the patients with preventive EBD and those without it (Fig. 2); the occurrence rate of stricture, the diameter of stricture, and the duration required for resolving the stricture by repeated conventional EBD.

Statistical Analysis

Fisher exact test, or its extension when there were more than 2 categories, was used for categorical variables and the Mann–Whitney U test was used for continuous variables. Cox proportional hazard model was used for the multivariate analysis. A P value of more than equal to 0.05 was considered significant. All statistical analyses were carried out using the Dr SPSS II Statistics software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Background

Among the 64 patients with mucosal defects greater than three-fourths of the circumference of the esophagus after EMR/ESD, 3 patients did not attend follow-up consultations, 17 received additional treatment for primary lesions (chemoradiation for deep invasion of the carcinoma or EMR/ESD for local recurrence and incomplete resection), and 3 underwent surgical resection for metachronous gastric cancer immediately after EMR/ESD. We excluded these 23 patients because additional treatments had the potential to make the stricture worse. Finally, we used data from 41 lesions in 41 patients to evaluate the efficacy of the preventive EBD.

Thirty-six lesions were removed by EMR and 5 lesions were removed by ESD procedure. A histopathological diagnosis of squamous cell carcinoma was found in all lesions and 40 lesions were mucosal cancers but 1 submucosal cancer.

Of the 41 patients, 29 underwent preventive EBD and 12 did not. There were no statistical differences in the characteristics of the patients and the mucosal defects except for the endoscopic resection method between patients who underwent preventive EBD and those who did not. Because the ESD was recently established technique, there are no patients treated by ESD in the historical control group. Although the difference was not statistically significant, the rate of circumferential resections tended to be greater in

TABLE 1. Comparison of the Characteristics of Mucosal Defects After Endoscopic Resection in Patients With and Without Preventive EBD

	Preventive EBD		
	(+) n = 29	(−) n = 12	P
Sex			
Male	28	11	0.50
Female	1	1	
Age			
Median (range)	64 years (50-74)	60 years (48-80)	0.21
Circumference of the lumen			
Circumferential	10	6	0.49
Semi-circumferential	19	6	
Depth of resected lesion			
Mucosa	28	12	0.34
Submucosa	1	0	
Location			
Upper	3	1	0.30
Middle	13	5	
Lower	13	6	
Length of mucosal defect			
30 mm or less	6	4	0.30
More than 30 mm	23	8	
Median (range)	40 mm (10-110)	45 mm (20-70)	0.38
Endoscopic resection procedure			
EMR	24	12	< 0.001
ESD	5	0	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

conventional EBD group [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] (Table 1).

Profile of Preventive EBD Sessions

Among the 29 patients who underwent preventive EBD, the median number of preventive EBD sessions was 6 (range, 3 to 9) and the period of preventive EBD was 45 days (range, 16 to 65) (Table 3).

Efficacy of Preventive EBD

The number of patients who developed stricture after EMR/ESD was significantly lower in patients who were given preventive EBD than those who were not given preventive EBD [12/29 (59%) vs. 11/12 (92%), $P = 0.04$] (Table 2).

TABLE 2. Comparison of the Occurrence Rate and the Diameter of Esophageal Stricture Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	P
No. patients who developed stricture	17/29 (59%)	11/12 (92%)	0.04
The narrowest diameter of the stricture			
≤2 mm	1/17 (6%)	4/11 (36%)	0.01
2 mm < and ≤5 mm	2/17 (12%)	4/11 (36%)	
5 mm <	14/17 (82%)	3/11 (28%)	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation.

The narrowest diameter of stricture in each patient was significantly larger in patients who were given preventive EBD than those who were not given preventive EBD [(≤2 mm; > 2 mm and ≤5 mm; > 5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] (Table 2).

The number of days to development of stricture was 23 days (21 to 49) in patients without preventive EBD. Similarly, in patients who were given preventive EBD, tendency of stricture development was observed within 2 weeks after EMR/ESD. However, preventive EBD could prevent the patients' symptom such as dysphagea because dilation was carried out at short intervals (once a week) in all patients. Therefore, no patients suffered from dysphagea during the preventive EBD period in this study. Since the patients with preventive EBD complained the symptom of dysphagia after the completion of weekly preventive EBD, the number of days to development of stricture was 51 days (30 to 72). It was significantly longer in patients who underwent preventive EBD than those who did not ($P < 0.001$).

Seventeen patients with preventive EBD and 11 patients without preventive EBD developed esophageal stricture. Then, they were given conventional EBD repeatedly until the stricture was completely relieved. Among them, the duration required conventional EBD was significantly shorter in patients given preventive EBD than in those not given it (29 d vs. 78 d; $P = 0.04$). The number of conventional EBD sessions was smaller in patients with preventive EBD than in those without it, although the difference was not statistically significant (2 times vs. 4.5 times; $P = 0.5$) (Table 3).

The number of total EBD sessions was greater in patients with preventive EBD than in those without it, however, the difference was not statistically significant (8 times vs. 4.5 times; $P = 0.42$) (Table 3).

Safety of EBD Procedure

Among a total of 166 preventive EBD sessions for 29 patients, no complication occurred during the procedure (complication rate of preventive EBD: 0%). Among a total of 189 conventional EBD sessions for 28 patients, a perforation was occurred in 1 conventional EBD session in 1 patient (0.5% per total conventional EBD sessions, 3.6% per patient). The patient was immediately hospitalized and administered intravenous antibiotics. The patient had no symptoms or signs of mediastinitis. The fasting period was 3 days and hospital stay was only 1 week after causal EBD. No other major complication occurred.

Clinical Course of all Patients After EMR/ESD

Follow up period was calculated between the day of EMR/ESD and the day of patients' final visit. After the complete resolution of stricture, endoscopic examination was carried out every 6 months in all patients. Median follow up period of all patients was 84 months. There were no patients who suffered from dysphagea owing to the recurrence of stricture.

RISK OF STRICTURE

Risk Factors for Stricture Among Patients With Preventive EBD

The method of EMR and the longitudinal length of mucosal defect (> 30 mm in length) were significantly

TABLE 3. Comparison of the Duration and the Number of EBD Sessions Required for Resolving the Stricture by Conventional EBD Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	*P*
Period of preventive EBD*	45 d (16-65)	(−)	(−)
Number of days to development of the stricture*	51 d (30-72)	23 d (21-49)	< 0.001
Duration required for resolving the stricture*	29 d (15-169)	78 d (8-1093)	0.04
No. preventive EBD sessions*	6.0 sessions (3-9)	(−)	(−)
No. conventional EBD sessions*	2.0 sessions (2-20)	4.5 sessions (2-35)	0.5
No. total EBD sessions*	8.0 sessions (3-29)	4.5 sessions (0-35)	0.42
No. patients whose stricture was relieved	17/17 (100%)	11/11 (100%)	1

Number of patients are shown unless specified.
*Median (range).
EBD indicates endoscopic balloon dilation.

associated with the increased risk for development of stricture by multivariate analysis (Odds ratio: 20.8, 95% CI: 1.3-328.9 and 12.7, 95% CI: 1.3-126.9, respectively). Circumferential mucosal defects showed a higher rate of stricture than semicircumferential mucosal defects; however, the difference was not statistically significant (Odds ratio: 3.0, 95% CI: 0.2-40.5) (Table 4).

DISCUSSION

Technically, extended esophageal mucosal resection could be carried out. However, the development of the esophageal stricture is one of the most important problem to be solved. To date, there are no well-established methods to prevent the stricture after EMR/ESD. If we can prevent the development of the stricture after EMR/ESD by preventive EBD, the ability of the patients oral intake would be dramatically improved.

In this study, we showed that the preventive EBD reduced the incidence of esophageal stricture in patients who underwent an extensive EMR/ESD. In our preventive EBD protocol, EBD was carried out once a week for about 6 weeks [median; 44 days (16 to 65 d)] until the mucosal defect completely developed scar. Because of this strategy, the number of EBD sessions tended to be greater. Although it did not reach statistical significance ($P = 0.42$), the total number of EBD sessions was nearly twice as high compared with the conventional EBD group (8.0 vs. 4.5). However, the narrowest diameter of stricture was significantly mild in the preventive EBD group compared with the group without it (Table 2), whereas 60% of the patients in the preventive EBD group develop stricture. Clinically, the severity of the stricture is very important, because it critically affects the oral intake condition. Furthermore, the preventive EBD shortened the period to relieve the stricture even when the stricture was developed. These data indicated that the preventive EBD was a beneficial method, and thus should be considered to carry out for the patients who underwent extensive EMR/ESD as a supportive treatment.

TABLE 4. Predictive Factors for Development of Stricture After Endoscopic Resection in Patients who Received Preventive EBD

	Odds Ratio (95% CI)	*P*
Method of endoscopic resection		
ESD	1.0 (reference)	0.03
EMR	20.8 (1.3-328.9)	
Longitudinal length of mucosal defect involving over three-fourth of the esophageal circumference		
≤30 mm	1.0 (reference)	0.03
>30 mm	12.7 (1.3-126.9)	
Circumference of mucosal defect		
Semi-circumferential	1.0 (reference)	0.4
Circumferential	3.0 (0.2-40.5)	

EBD indicates endoscopic balloon dilation.

Perforation and massive bleeding were the most severe complications during the EBD procedure. However, there was no complication associated with preventive EBD procedure in this study. Thus, we could conclude that the preventive EBD was a feasible procedure. Not to develop perforation, we carefully carried out preventive EBD under fluoroscopic monitoring, to confirm with both the size of the stricture and the inflated balloon. When the patients complained of pain or when the balloon expanded exponentially, we stopped dilating the balloon immediately not to develop deep tear or perforation.

There were some imbalances of the characteristics of mucosal defect between 2 groups; the rate of circumferential resections [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] and the rate of ESD resections [5/29 (17%) vs. 0/12 (0%), $P < 0.001$]. Although the difference of the rate of circumferential resections was not statistically significant, the possibility that the results of this study might be influenced by the difference cannot be denied. However, the "circumferential resection" and "noncircumferential resection" were not associated with the risk of development of stricture by the multivariate analysis even in the preventive EBD group. Therefore, it seemed that the imbalance about the rate of circumferential resection between 2 groups was not a major problem. As for the different rate of ESD resections, there are no patients treated by ESD in the historical control group because the ESD was recently established technique. These imbalances between 2 groups are unavoidable limitations of the retrospective review with small sample size.

The rate for stricture was lower in patients who underwent ESD than those who received EMR [1/5 (20.0%) vs. 16/24 (66.7%), $P = 0.03$]. Although the reason for this difference is unknown, 1 possibility is that the potent cautery effect of EMR compared with that of ESD might cause more severe submucosal injury resulting in an

increased risk for development of stricture.[15] Clarification of the precise mechanisms for developing stricture after EMR/ESD is warranted in future studies. In addition, the difference of rate for stricture between 2 groups might be influenced by the lower rate for stricture in ESD patients. However, there are no ESD patients who did not undergo preventive EBD, it is therefore impossible to evaluate real influence from ESD patients for the results of this study.

Temporary stent placement may also be a promising strategy for preventing postEMR/ESD stricture. Self-expandable removable stents or biodegradable stents have been reported to be useful for the treatment of benign stricture such as anastomotic stricture and cicatricial stricture by esophagitis.[16] However, there has been no report on the use of self-expandable removable stents for preventing the postEMR/ESD stricture. Although the biodegradable stents have been reportedly applied for prevention of the postEMR/ESD stricture, a small number of patients, short-term follow-up periods, and a high frequency of stent migration obscured its usefulness.[17,18] Thus, further evaluation of these methods is required to compare their usefulness with the EBD.

The multivariate analysis in patients with preventive EBD showed that the longer longitudinal mucosal defects (>30 mm) was the significant risk factor for development of the stricture; in contrast, the circumferential mucosal defect was not a significant risk factor. To avoid the treatment induced esophageal stricture, these data are informative when we select the treatment modalities for the extended esophageal cancer; such as EMR/ESD, chemoradiotherapy, radiotherapy, or surgical resection. If patients prefer the remaining the sufficient ability of oral intake, extensive EMR/ESD should not be indicated, because the long term EBD would be needed and the symptom of dysphagia afflicts the patients.

In conclusion, preventive EBD could be a useful and acceptable strategy to reduce the incidence of postEMR/ESD stricture. Because there is no other effective method to prevent stricture after extensive EMR/ESD at present, preventive EBD should be considered for all patients who undergo extensive EMR/ESD. Although almost 60% of patient developed stricture despite the preventive EBD, the severity of the stricture was clearly reduced even when the stricture was developed. Since the number of patients in this study is rather small, and moreover, this was the retrospective study, a prospective study with a large number of cases is required to confirm the effectiveness of preventive EBD procedure for the prevention of postEMR/ESD stricture in patients with early stage esophageal cancer.

REFERENCES

1. Inoue H, Tani M, Nagai K, et al. Treatment of esophageal and gastric tumors. *Endoscopy*. 1999;31:47–55.
2. Fujita H, Sueyoshi S, Yamana H, et al. Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. *World J Surg*. 2001; 25:424–431.
3. Satodate H, Inoue H, Yoshida T, et al. Circumferential EMR of carcinoma arising in Barrett's esophagus: case report. *Gastrointest Endosc*. 2003;58:288–292.
4. Seewald S, Akaraviputh T, Seitz U, et al. Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. *Gastrointest Endosc*. 2003;57:854–859.
5. Soetikno R, Kaltenbach T, Yeh R, et al. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. *J Clin Oncol*. 2005;23:4490–4498.
6. Fujishiro M, Yahàgi N, Kakushima N, et al. En bloc resection of a large semicircular esophageal cancer by endoscopic submucosal dissection. *Surg Laparosc Endosc Percutan Tech*. 2006;16:237–241.
7. Fujishiro M, Yahagi N, Kakushima N, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol*. 2006;4:688–694.
8. Chiu YC, Hsu CC, Chiu KW, et al. Factors influencing clinical applications of endoscopic balloon dilation for benign esophageal strictures. *Endoscopy*. 2004;36:595–600.
9. Kim SH, Lee SO. Circumferential intramural esophageal dissection successfully treated by endoscopic procedure and metal stent insertion. *J Gastroenterol*. 2005;40:1065–1069.
10. Lew RJ, Kochman ML. A review of endoscopic methods of esophageal dilation. *J Clin Gastroenterol*. 2002;35:117–126.
11. Pereira-lima JC, Ramires RP, Zamin I Jr, et al. Endoscopic dilation of benign esophageal strictures: Report on 1043 procedures. *Am J Gastroenterol*. 1999;94:1497–1501.
12. Katada C, Muto M, Manabe T, et al. Esophageal stricture after endoscopic mucosal resection of superficial esophageal lesions. *Gastrointest Endosc*. 2003;57:165–169.
13. Monma K, Sakaki N, Yoshida M. Endoscopic mucosectomy for precise evaluation and treatment of esophageal intraepithelial cancer (in Japanese with English abstract). *Endoscopia Digestiva*. 1990;2:501–506.
14. Makuuchi H. Endoscopic mucosal resection for early esophageal cancer-Indications and techniques. *Digestive Endoscopy*. 1996;8:175–179.
15. Conio M, Sorbi D, Batts KP, et al. Endoscopic circumferential esophageal mucosectomy in a porcine model: an assessment of technical feasibility, safety, and outcome (short communication). *Endoscopy*. 2001;33:791–794.
16. Karbowski M, Schembre D, Kozarek R, et al. Polyflex self-expanding, removable plastic stents: assessment of treatment efficacy and safety in a variety of benign and malignant conditions of the esophagus. *Surg Endosc*. 2008;22: 1326–1333.
17. Saito Y, Tanaka T, Andoh A, et al. Usefulness of biodegradable stents constructed of poly-l-lactic acid monofilaments in patients with benign esophageal stricture. *World J Gastroenterol*. 2007;13:3977–3980.
18. Saito Y, Tanaka T, Andoh A, et al. Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. *Dig Dis Sci*. 2008;53:330–333.

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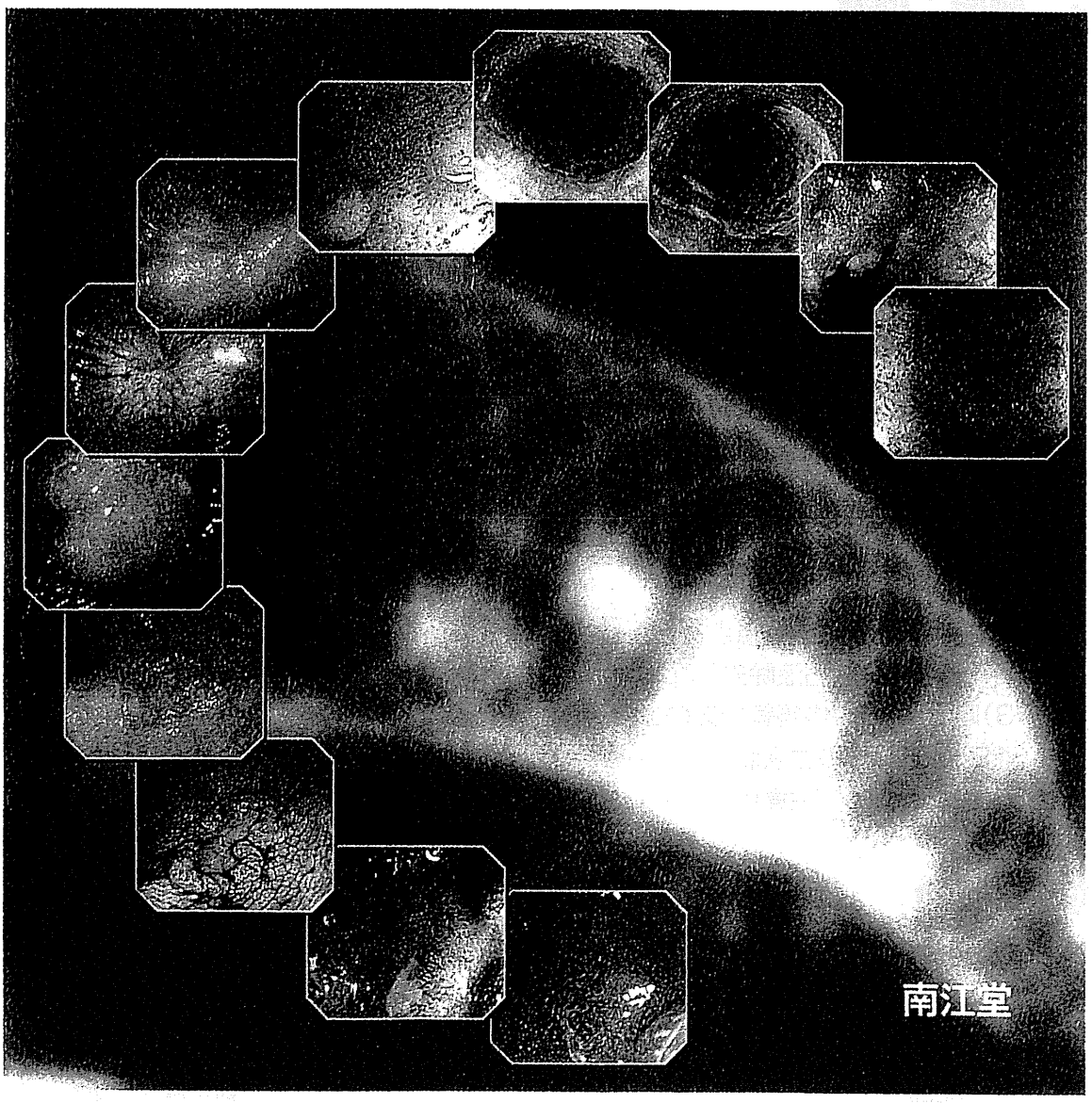

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SIDE MEMO

4）経鼻内視鏡のメリット・デメリット

内視鏡検査は消化器診療に不可欠なモダリティとして日常臨床に普及している．しかし，その苦しいイメージから，検査を受けることに消極的な患者は少なくない．健常者にとってはその傾向はなおさらであり，わが国の検診受診率が低調であることの1つの理由でもあろう．

たとえば，実際に上部消化管内視鏡検査の際には，嘔気をもよおすことが少なくない．これはスコープが舌根部を圧迫することにより生じる咽頭反射によるものであるが，近年注目を集めている経鼻内視鏡では舌根部を圧迫しないため咽頭反射は起こりにくい．実際に経鼻内視鏡に対する患者の評価は非常に高い．

しかし，画質は経口内視鏡に比べ劣っており，導入に躊躇する施設は少なくない．国立がん研究センターでは2004年からがん予防・検診研究センターで内視鏡検診を行っているが，開設以来，経鼻内視鏡の導入にはあまり関心はなかった．その主たる理由はやはり画質にあった．

ところが，最新式の経鼻内視鏡(EG-530NW，富士フィルムメディカル社製)のデモに上司の勧めで立ち会う機会があり，これを契機にこの概念が変わった．技術は進歩し，想像以上に画質がよくなっていた．光量も視野角も向上していた．もちろんHi-visionには及ばないが，かなりのレベルにまで向上していた．これなら当センターの人間ドックに導入するのに支障はない，と確信できた．経鼻内視鏡を導入して半年足らず，まだ経験は浅いが，それでも受診者の評価は高く，それ以上に受診者が"ゲーゲー"しないため，検査医はじっくり落ちついて観察できる安心感がある．

筆者は大学卒業以来，鼻腔の解剖学を勉強する機会がほとんどなかったが，1時間弱，書物を紐解き，付属DVDで何度かイメージトレーニングをすることで解剖学的構造はほとんど把握できた．実際の手技も3日で慣れた．今では全くストレスなく検査を遂行できている．

表1に経鼻内視鏡のメリット・デメリットを示す．たしかにデメリットは存在する．レンズ洗浄を契機とする水はけの悪さはデメリットの1つである．ひとたびレンズ洗浄を行うと，水がポタポタと出るため画像が見えにくくなる．レンズ洗浄の後は，送気をしばらく行い，その後吸引ボタンを押すことで解決するが，やや煩雑である．これは1つの例であるが，初学者にとって消化管の画像以外に気をとられる要素が増えることは好ましいことではない．まずは通常径経口内視鏡で基本操作と診断学をしっかり習得し，余裕が出てきた後に取り組むほうが望ましい．今後，内視鏡機器の精度・技術がさらに向上した際には，こういったデメリットも徐々に解消されていくだろう．

経鼻内視鏡は低迷する検診受診率向上の1つの契機になりうるモダリティである．今後さらなる技術の進歩が期待される．

図1 経鼻内視鏡像：上部消化管内視鏡検査にて，胃体中部前壁に12mm大の発赤した不整形の陥凹性病変を認めた．肉眼型は表面陥凹型(0-IIc)，深達度は粘膜内(M)の病変と考え生検施行．病理学的にwell and moderately differentiated adenocarcinomaと診断され，後日ESDにより根治的な切除がなされた．

表1

メリット	デメリット
苦痛が少ない(咽頭反射が起こりにくい)	挿入できない例がある
鎮痛，鎮静薬を使わなくてもよい	鼻の違和感，鼻出血
身体への負担が少ない	画質が劣る，視野角，光量が劣る
会話ができる	レンズ洗浄の際の水はけの悪さ
検査医がじっくりと落ちついて検査できる	生検しづらい部位がある

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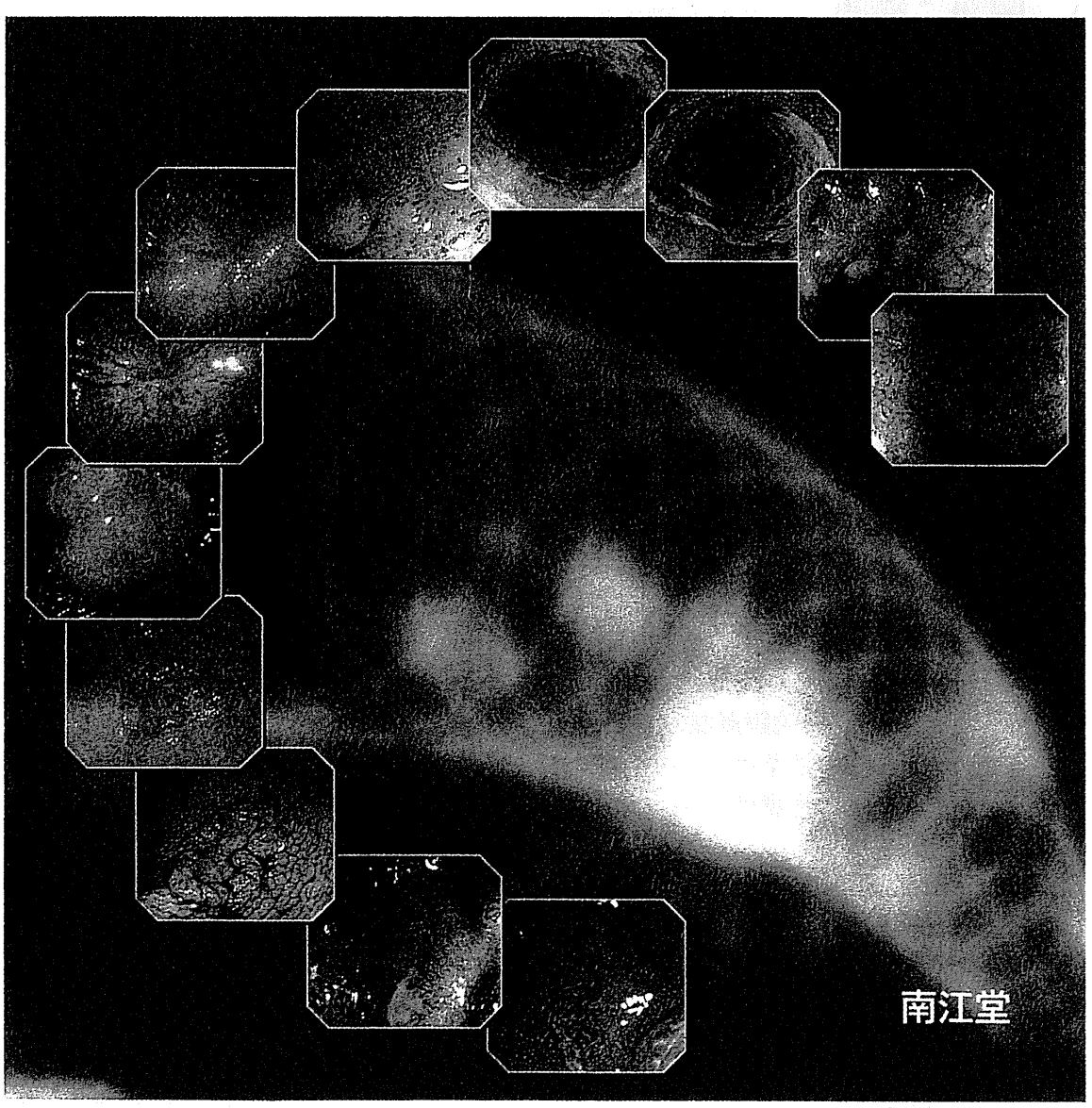

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