ORIGINAL ARTICLE

Magnifying endoscopy for the diagnosis of specialized intestinal metaplasia in short-segment Barrett's esophagus

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Abstract

AIM: To determine whether magnified observation of short-segment Barrett's esophagus (BE) is useful for the detection of specialized intestinal metaplasia (SIM).

METHODS: Thirty patients with suspected short-segment BE underwent magnifying endoscopy up to × 80. The magnified images were analyzed with respect to their pit-patterns, which were simultaneously classified into five epithelial types [Ⅰ (small round), Ⅱ (straight), Ⅲ (long oval), Ⅳ (tubular), Ⅴ (villous)] by Endo's classification. Then, a 0.5% solution of methylene blue (MB) was sprayed over columnar mucosa. The patterns of the magnified image and MB staining were analyzed. Biopsies were obtained from the regions previously observed by magnifying endoscopy and MB chromoendoscopy.

RESULTS: Three of five patients with a type Ⅴ (villous) epithelial pattern had SIM, whereas 21 patients with a non-type Ⅴ epithelial patterns did not have SIM. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of pit-patterns in detecting SIM were 100%, 91.3%, 92.3%, 60% and 100%, respectively (*P* = 0.004). Three of the 12 patients with positive MB staining had SIM, whereas 14 patients with negative MB staining did not have SIM. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of MB staining in detecting SIM were 100%, 60.9%, 65.4%, 25% and 100%, respectively (*P* = 0.085). The specificity and accuracy of pit-pattern evaluation were significantly superior compared with MB staining for detecting SIM by comparison with the exact McNemar's test (*P* = 0.0391).

CONCLUSION: The magnified observation of a short-segment BE according to the mucosal pattern and its classification can be predictive of SIM.

Key words: Short-segment; Barrett's esophagus; Magnifying endoscopy; Methylene blue chromoendoscopy; Specialized intestinal metaplasia; Dysplasia; Esophageal adenocarcinoma; Diagnosis

Core tip: Various endoscopic approaches and advancements have shown great promise. However, careful endoscopic observation and stepwise four quadrant bi-

opsy still represent the standard for the surveillance of Barrett's esophagus (BE). In our study, we investigated the usefulness of magnifying endoscopy for the diagnosis of specialized intestinal metaplasia (SIM) in patients with short-segment BE compared with methylene blue chromoendoscopy. We found that the magnified observation of a short-segment BE according to its mucosal pattern and classification can be predictive of SIM.

INTRODUCTION

Barrett's esophagus (BE) is important clinically as the link between one of the most common gastrointestinal diseases, gastroesophageal reflux disease (GERD), and the most rapidly increasing cancer of the gastrointestinal (GI) tract, esophageal adenocarcinoma (EAC). For an adenocarcinoma to develop in the esophagus, the squamous epithelium must transition to columnar epithelium and subsequently become dysplastic. This metaplasia-dysplasia-carcinoma sequence is attributed to the repeated injury of the esophagus by gastroesophageal reflux[1-3]. According to the Montreal consensus from 2006, BE is characterized by the replacement of the squamous epithelia in the distal esophagus by columnar epithelia (gastric metaplasia), irrespective of the presence of specialized intestinal metaplasia (SIM)[4]. Controversy exists regarding the absolute requirement of intestinal metaplasia to define BE, primarily because long-term follow-up studies are not available to assess the risk of progression for each histologic subtype. However, cross-sectional and descriptive studies suggest that SIM either coexists with or precedes a significant majority of EAC cases and is likely the precursor lesion[5,6]. Therefore, histologic confirmation of SIM in BE is required. Because of the latent period of transition to high grade dysplasia, EAC is significantly shorter for patients with low grade dysplasia (median of 2.75 years) than for patients without low grade dysplasia (median of 9.88 years)[1].

Patients with SIM are currently recommended to undergo periodic endoscopic surveillance to determine the progression to dysplasia at an early, potentially curable stage[5,7].

Discerning SIM and obtaining satisfactory target biopsies at the region of interest by standard endoscopic observation is difficult[8,9]. Thus, to identify the presence of SIM and dysplasia according to the Seattle protocol, specimens are obtained using a predefined four-quadrant sampling technique[10]. The major disadvantages of this method are the need for multiple biopsies, random choice of biopsy places, and the high cost.

Chromoendoscopy and magnifying endoscopy have been improving mucosal visualization to allow for better differentiation of the SIM and dysplasia from the columnar epithelium during endoscopy[11,12]. These techniques provide more accurate biopsies as well as reduce the number of biopsies[13,14]. Chromoendoscopy involves the use of dyes sprayed over the mucosa. Methylene blue (MB) stains actively absorbing cells, such as the intestinal epithelium and intestinal metaplasia[11]. The sensitivity and specificity of MB staining for SIM detection in BE is still under discussion[15,16]. Magnifying endoscopy, which provides images of fine mucosal detail that correspond to histologic structure, is now widely accepted for the study of GI disorders. After magnification, a characteristic relief called a pit-pattern is visible on the surface of the esophageal epithelium. The most widely known classification of esophageal pit-patterns in relation to histology were described by Endo *et al*[17]. The usefulness of this classification is its ability to predict the presence of SIM based on the structure of the mucosal surfaces.

BE can be subdivided into long-segment BE ($\geq$ 3 cm) and short-segment BE (< 3 cm)[18]. Just as for long-segment BE, histologic confirmation of SIM in short-segment BE is also needed; not only long-segment BE but also short-segment BE, have been known as major risk factors for the development of EAC[19,20]. Furthermore, small areas of dysplasia can be difficult to diagnose.

The aim of this study was to determine whether the magnified observation of short-segment BE is useful for the detection of SIM and for the prediction of histological diagnosis compared with MB chromoendoscopy.

MATERIALS AND METHODS

Patients with short-segment BE were prospectively enrolled into this study at Soonchunhyang University Hospital in South Korea between March 2002 and June 2002 (Figure 1). Patients underwent magnifying endoscopy, which could enhance the image up to × 80 (Olympus GIF-Q240Z, Japan) (Figure 2). Mucus was removed by a 10% solution of acetylcysteine instillation. The magnified images were analyzed with respect to pit-patterns, which were simultaneously classified into five epithelial types [I (small round), II (straight), III (long oval), IV (tubular), V (villous)] by Endo's classification (Figure 3). Then, a 0.5% solution of methylene blue was sprayed over the columnar mucosa. The excess of dye was flushed away with 50 mL of water after 2 min. The patterns of the magnified image and MB staining were analyzed. Biopsies were obtained from the regions previously observed by magnifying endoscopy and MB chromoendoscopy (Figure 4). If the biopsies were unsatisfactory or inaccurately targeted, other biopsies were performed. Every biopsy was classified into three types of epithelium by a pathologist: the fundic type, cardiac type and SIM (Figure 5). The study was performed after receiving approval from the Institutional Review Board of the Soonchunhyang University in Seoul, South Korea.
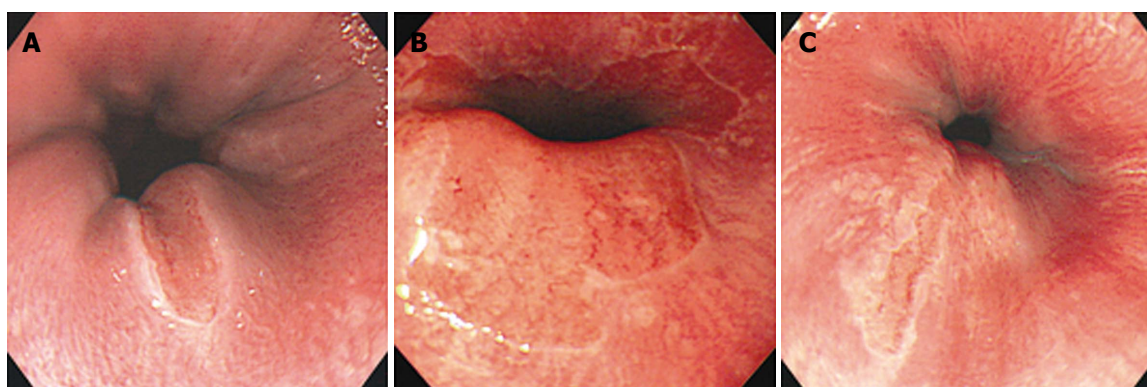
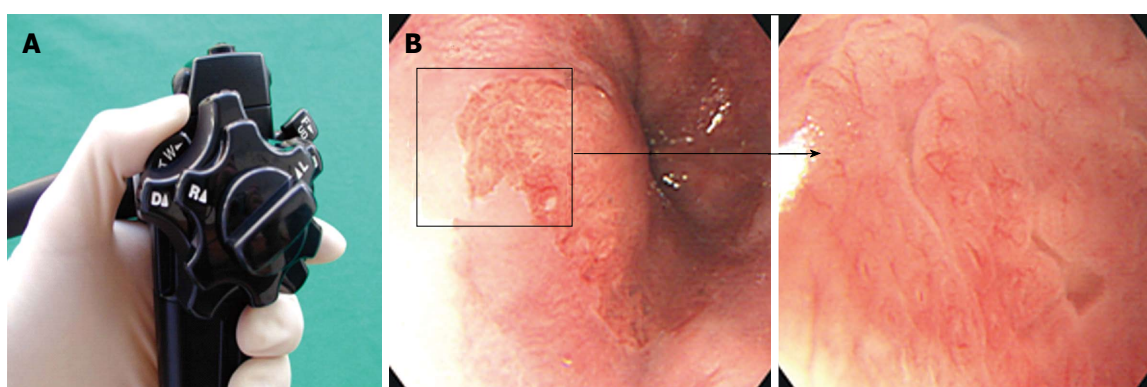**Figure 1 Screening endoscopy.** A-C: Endoscopically suspected short-segment Barrett's esophagus (< 3 cm).

Figure 2 Magnifying endoscopy. A: Magnifying endoscopy up to × 80 (Olympus GIF-Q240Z, × 80); B: Magnified image of the short-segment Barrett's esophagus.
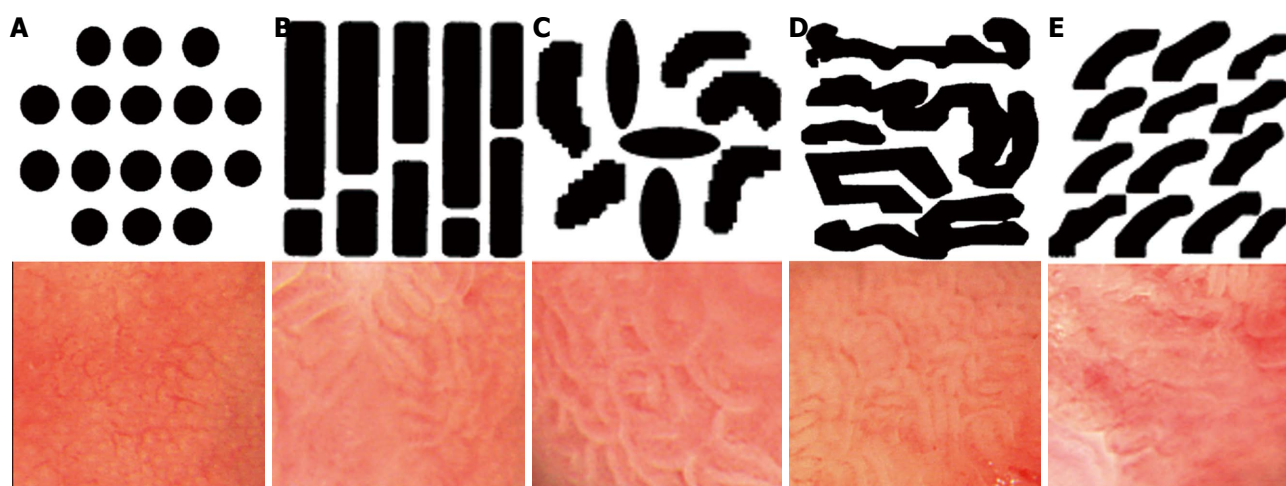

Figure 3 Classification of pit-pattern of Barrett's esophagus by Magnifying endoscopy (Endo's classification). A: I (small round); B: II (straight); C: III (long oval); D: IV (tubular); E: V (villous).

Statistical analysis

To analyze the relationships among the variables, Fisher's exact test was used. We performed an exact McNemar's test to compare the diagnostic value of MB chromoendoscopy and magnifying endoscopy for detection of SIM. Data analysis was performed using SPSS 14.0. All statistical hypotheses were verified at a significance level of $P < 0.05$.

RESULTS

Patient characteristics

Thirty patients, 16 men and 14 women, with an average age of 44.8 years (range 17-75 years), were enrolled into this study. All of the patients had tongue-like columnar epithelium in the tubular esophagus within 3 cm from the
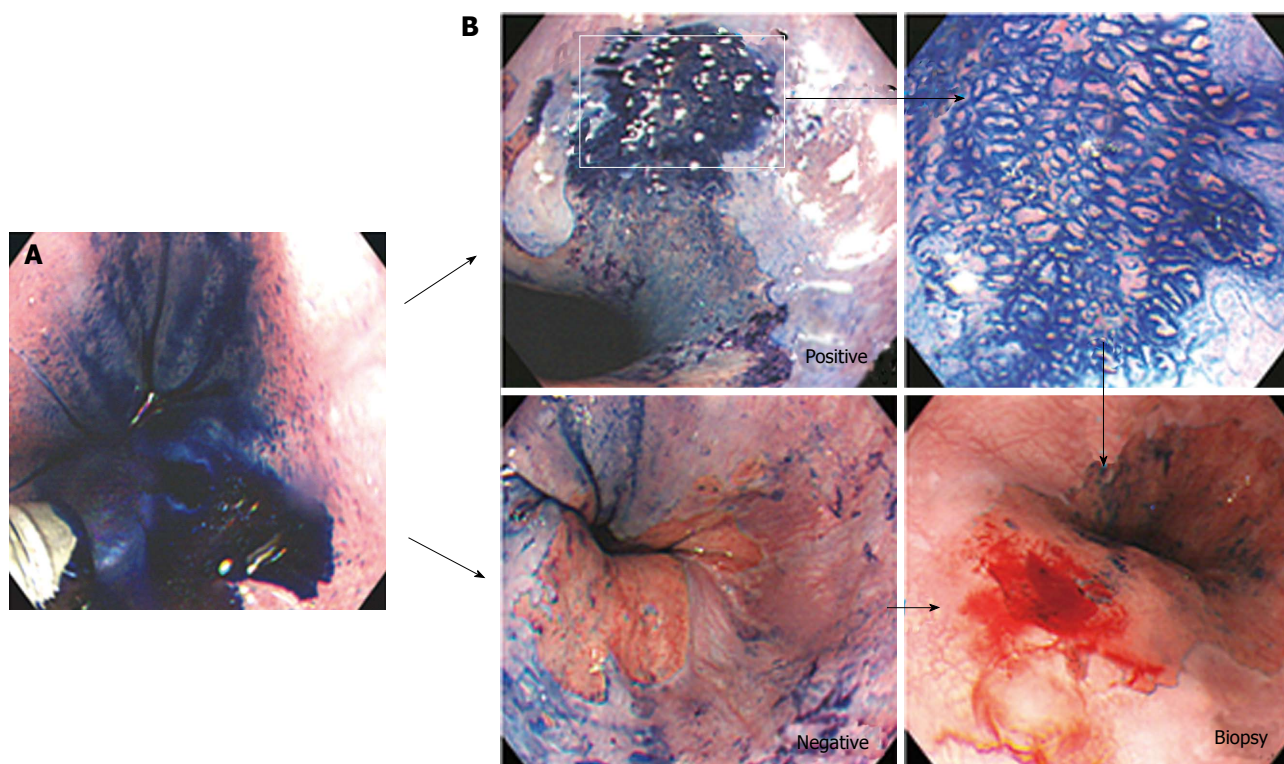
Figure 4 Methylene blue chromoendoscopy. A: 0.5% solution of methylene blue (MB) was sprayed over the columnar mucosa; B: Biopsies were obtained from the regions previously observed by magnifying endoscopy and MB chromoendoscopy.
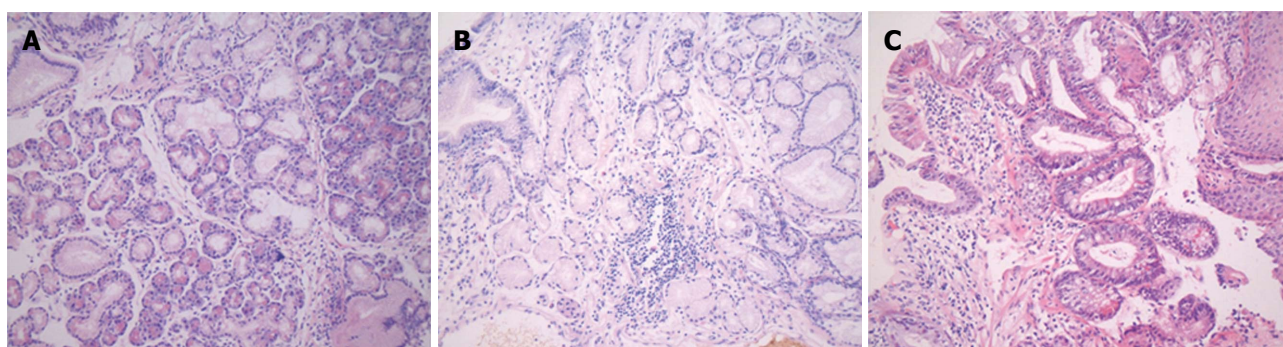

Figure 5 Histological diagnosis. A: Fundic type (HE stain, × 200); B: Cardiac type (HE stain, × 200); C: Specialized intestinal metaplasia (HE stain, × 400).
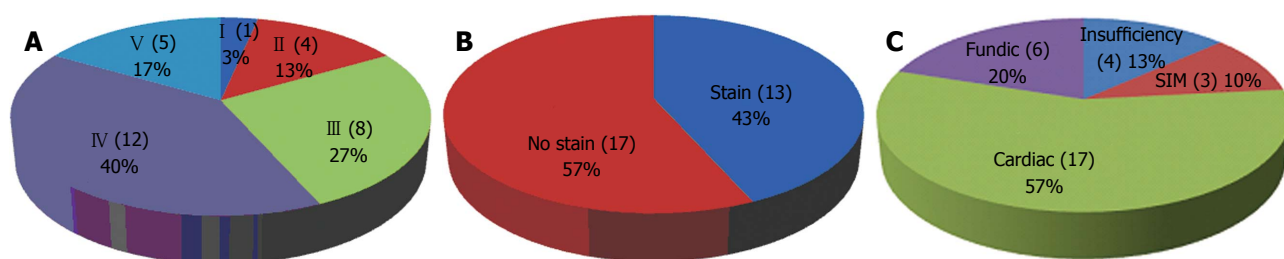
Figure 6 Distributions of pit-pattern, methylene blue staining, histologic diagnosis. A: Pit-pattern; B: Methylene blue staining; C: Histologic diagnosis. SIM: Specialized intestinal metaplasia.

Esophagogastric junction, as identified by previous standard endoscopy. No patient had previous histologically proven SIM in the columnar lined epithelium.

The results for individual patients, including the pit-pattern, MB staining, histologic diagnosis and reflux esophagitis, are listed in Table 1. Distributions of the types of pit-pattern, MB staining, and histologic diagnosis are shown in Figure 6.

Table 1 Individual results

Patient	Type	Stain	Histology	Reflux	Patient	Type	Stain	Histology	Reflux
1	Villous	Yes	SIM	Yes	16	Tubular	No	Insufficiency	Yes
2	Oval	No	Cardiac	No	17	Villous	Yes	SIM	Yes
3	Oval	No	Cardiac	No	18	Oval	No	Fundic	Yes
4	Straight	No	Fundic	No	19	Tubular	No	Insufficiency	No
5	Straight	Yes	Fundic	No	20	Oval	Yes	Fundic	Yes
6	Tubular	No	Cardiac	No	21	Villous	Yes	SIM	No
7	Oval	No	Cardiac	No	22	Tubular	No	Insufficiency	No
8	Tubular	Yes	Cardiac	No	23	Tubular	Yes	Cardiac	Yes
9	Tubular	No	Cardiac	No	24	Villous	Yes	Cardiac	Yes
10	Small round	Yes	Fundic	No	25	Oval	No	Cardiac	Yes
11	Tubular	No	Cardiac	Yes	26	Villous	No	Cardiac	No
12	Tubular	No	Cardiac	No	27	Straight	No	Cardiac	No
13	Tubular	No	Fundic	No	28	Tubular	No	Cardiac	No
14	Tubular	Yes	Insufficiency	No	29	Oval	Yes	Cardiac	Yes
15	Tubular	Yes	Cardiac	No	30	Oval	yes	Cardiac	Yes

SIM: Specialized intestinal metaplasia.

Table 2 Relationship between specialized intestinal metaplasia and variables

Variables	SIM (+)	SIM (-)	Total
Reflux esophagitis	2	9	11
No-Reflux esophagitis	1	14	15
Total[1]	3	23	26
Villous	3	2	5
Non-villous	0	21	21
Total[2]	3	23	26
MB stain	3	9	12
Non-MB stain	0	14	14
Total[3]	3	23	26

[1]Fisher's exact test: P = 0.538; [2]Sensitivity = 100%, specificity = 91.3%, accuracy = 92.3%, PPV = 60%, NPV =100%, Fisher's exact test: P = 0.004; [3]Sensitivity = 100%, specificity = 60.9%, accuracy = 65.4%, PPV = 25%, NPV = 100%, Fisher's exact test: P = 0.085. SIM: Specialized intestinal metaplasia; PPV: Positive predictive value; NPV: Negative predictive value; MB: Methylene blue.

Histologic examination revealed SIM in 3 of 26 patients (11.5%). The remaining four patients could not be diagnosed due to the insufficiency of the specimens for histologic examination. Reflux esophagitis was diagnosed by histologic examination in 11 of 26 patients (42.3%). The patients without RE did not have a history of GERD. SIM in BE was not more common in patients with reflux esophagitis (2 patients, 18.1%) than in those without it (1 patient, 5.2%; P = 0.538, Table 2).

Relationship between type of pit-pattern and SIM

The fine mucosal patterns (pit-pattern) of 30 patients were recorded and classified according to Endo's classification. The specimens obtained previously from the regions observed by magnification without MB staining underwent histologic examinations to determine the relationship between the type of pit-pattern and SIM by magnifying endoscopy.

Of the 30 patients, one case was type I (small round);

four cases were type II (straight); eight cases were type III (long oval); 12 cases were type IV (tubular); and five cases type were V (villous). Type IV (tubular) was the most common epithelial type. As shown in Table 1 and Figure 6, three of five patients with a type V (villous) epithelial pattern had SIM. Twenty-one patients without type V epithelial patterns did not have SIM (P = 0.004). These results suggest that a type V (villous) epithelial pattern is compatible with SIM, and the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of type V pit-pattern in detecting SIM were 100%, 91.3%, 92.3%, 60% and 100%, respectively (Table 2).

Relationship between MB staining and SIM

Out of 30 patients, 13 patients (43.3%) had positive MB staining, and 17 patients (56.7%) had negative MB staining. One of the 13 patients with positive MB staining and three of the 17 patients with negative MB staining did not receive a histological diagnosis due to insufficient specimens. As shown in Table 1 and Figure 6, three of 12 patients with positive MB staining had SIM, whereas 14 patients with negative MB staining did not have SIM (P = 0.085). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of MB staining in detecting SIM were 100%, 60.9%, 65.4%, 25% and 100%, respectively (Table 2).

Diagnostic value of pit-pattern evaluation and MB staining for detecting SIM

In comparison with MB staining, pit-pattern evaluation according to Endo's classification had much higher specificity (91.3% *vs* 60.9%), accuracy (92.3% *vs* 65.4%), and positive predictive value (60% *vs* 20%) for the detection of SIM in BE; however, it had a similar sensitivity (both 100%) and negative predictive value (both 100%). The exact McNemar's test revealed that the specificity and accuracy of pit-pattern evaluation was significantly superior to that of MB staining for detecting SIM by (P = 0.0391;

Table 3 Diagnostic value of pit-pattern evaluation and metaplasia staining for detection of specialized intestinal metaplasia (n = 3)

	TP	TN	*P* value
Pit-pattern	3	21	
MB stain	3	14	
	Pit-pattern	MB stain	
Sensitivity	100.00%	100.00%	
Specificity	91.30%	60.90%	0.0391[1]
Accuracy	92.30%	65.40%	0.0391[1]
PPV	60.00%	25.00%	0.1643[1]
NPV	100.00%	100.00%	

[1]*P* value by exact McNemar's test. TP: True positive; TN: True negative; PPV: Positive predictive value; NPV: Negative predictive value; MB: Methylene blue.

Table 3).

DISCUSSION

SIM in BE is a risk factor for EAC. A strong relationship has been established between the presence of SIM and the subsequent development of adenocarcinoma[5,6].

Detecting esophageal neoplasias at an earlier stages will allow for the possibility of intervening more quickly and lowering the mortality from EAC. However, the effectiveness of the screening and surveillance of BE has not been studied in randomized, controlled trials. For example, various endoscopic approaches and advancements have shown great promise, yet the confirmation of their utility in high-quality clinical trials has yet to occur[21,22].

Canto *et al*[11] found that the overall accuracy of MB staining for detecting SIM was 95%. However, the same level of accuracy was not achieved in other studies. Dave *et al*[16] reported that MB staining was associated with prolonged endoscopy, increased patient discomfort, and potentially serious adverse events; furthermore, it was neither very sensitive nor specific for SIM. According to Horwhat *et al*[13], chromoendoscopy might decrease the number of biopsies without an improving the overall detection rate of dysplasia compared with a conventional four-quadrant biopsy. Wasielica-Berger *et al*[14] and Ferguson *et al*[23] found no convincing data indicating that pit-pattern evaluations may replace multiple biopsies, according to the Seattle recommendations for the detection of SIM in BE. Therefore, the aim of this study was to determine whether the magnified observation of short-segment BE is useful for the detection of SIM or for the prediction of histological diagnosis, compared with MB chromoendoscopy.

Oberg *et al*[3] showed that a long duration of reflux symptoms (RR = 1.3; 95%CI: 1.2-1.7) were independently associated with an increased risk of developing high-grade dysplasia or esophageal adenocarcinoma. However, SIM in BE was not more common in patients with reflux esophagitis who had a history of GERD compared with those without such a history (*P* = 0.538).

Endo's study found that the type IV (tubular) and type V (villous) classifications were characteristic of SIM. Similarly, we found a significant correlation between pit-patterns evaluated according to Endo's classifications and histology. The differences in the frequency of SIM were related to the particular mucosal pit-pattern types. We frequently found SIM in places with a type V (villous) epithelial pattern (3 of 5 patients). SIM did not coexist in any case with a non-type V epithelial pattern. Therefore, the surface structure of type V (villous) epithelial pattern is compatible with SIM (*P* = 0.004).

MB is a vital stain that is taken up by actively absorbing tissues, such as the small intestinal and colonic epithelium. In BE, areas of intestinal metaplasia are positively stained, whereas non-absorptive epithelia, such as those found in squamous or gastric mucosa, remain unstained. We found SIM in places with MB-positive stained epithelium (3 of 12 patients). No case of SIM was associated with MB-negative stained epithelium. However, MB-positive staining cannot be considered characteristic of SIM, as the difference was not significant (*P* = 0.085).

Compared with MB staining, the pit-pattern evaluation by magnifying endoscopy according to Endo's classification had much higher specificity (91.3% *vs* 60.9%) and positive predictive value (60% *vs* 20%) for the detection of SIM in BE, despite similar sensitivity (100% *vs* 100%) and negative predictive values (100% *vs* 100%). The specificity and accuracy of pit-pattern evaluations were significantly superior, according to McNemar's exact test, to those of MB staining for the detection of SIM (*P* = 0.0391).

There were some limitations to our study. First, we found no sites with dysplasia or cancer cells, which may be attributed to the relatively small number of patients. In addition, the present study enrolled too few patients (3 out of 5 patients with type V pit-pattern). However, this study was very difficult regarding the recruitment of patients due to the refusal of many of the patients and the quite rare prevalence of this condition in Korea[24,25]. Second, long-segment BEs were excluded in our study. The risk of progression to malignancy appears to increase significantly with increasing lengths of BE[26,27]. It would be worth knowing about pit-patterns in long-segment, salmon-colored mucosa and also pit-pattern correlation with histological diagnosis of BE. However, there is conflicting evidence in the literature[28]. Short-segment and long-segment BE are biologically identical and have significant if not equivalent malignant potential. In addition, Kim *et al*[29] showed that patients with long-segment BE are very rare in South Korea. So, we focused on short-segment BE in this study. Third, we did not address whether the simultaneous use of magnifying endoscopy and MB staining might improve the diagnostic yield. Sharma *et al*[12] reported that high magnification chromoendoscopy might be a useful clinical tool for the increased detection of patients with intestinal metaplasia. Statistically, there is no doubt that the results are improved when magnifying endoscopy is performed with MB staining simultaneously, if both are characteristics of SIM. In our study, MB-positive staining could not be considered a characteristic of SIM. Therefore, we did not

try to demonstrate that the simultaneous performance of magnifying endoscopy and MB staining could improve the results. Fourth, we did not count the total number of biopsies. Thus, we could not show that the magnifying endoscopy might decrease the number of biopsies, generating an overall improvement in the detection rate of dysplasia compared with a conventional, four-quadrant biopsy.

In summary, we identified the usefulness of magnifying endoscopy for the diagnosis of SIM in patients with short-segment BE from preceding studies. However, we were still unable to demonstrate the usefulness of MB chromoendoscopy. Because we did not count the total number of biopsies, we could not confirm that both of the endoscopic examinations decreased the number of biopsies, costs and inspection time. We found that both methods were time-consuming and caused patient discomfort. These are among the disadvantages of the other studies.

Various endoscopic approaches and advancements have shown great promise. Still, careful endoscopic observation and stepwise four quadrant biopsy still represent the standard for the surveillance of BE[21,30]. In our study, the evaluation of mucosal surfaces under magnification has potential to allow the selection of the biopsy site according to the pit-pattern. In conclusion, the magnified observation of short-segment BE according to the mucosal pattern and its classification can be predictive for SIM.

COMMENTS

Background
Crosssectional and descriptive studies suggest that specialized intestinal metaplasia (SIM) either coexists with or precedes a significant majority of esophageal adenocarcinoma (EAC) cases and is the likely precursor lesion.

Research frontiers
Detecting esophageal neoplasia at an earlier stage will allow for the possibility of intervening more quickly and the lowering mortality due to EAC. However, the effectiveness of screening and surveillance of Barrett's esophagus (BE) has not been studied in randomized controlled trials. In addition, discerning SIM and obtaining satisfactory target biopsies at the region of interest by standard endoscopic observation is difficult.

Innovations and breakthroughs
The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of pit pattern in detecting SIM were 100%, 91.3%, 92.3%, 60% and 100%, respectively ($P = 0.004$). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of methylene blue (MB) staining in detecting SIM were 100%, 60.9%, 65.4%, 25% and 100%, respectively ($P = 0.085$). The specificity and accuracy of the pit-pattern evaluation were significantly superior compared with MB staining for detecting SIM by comparison of exact McNemar's test ($P = 0.0391$).

Applications
The study results suggests that the magnified observation of short-segment BE according to the mucosal pattern and its classification can be predictive for SIM.

Terminology
BE is characterized by the replacement of the squamous epithelia in the distal esophagus by columnar epithelia (gastric metaplasia), irrespective of the presence of specialized intestinal metaplasia.

Peer review
The paper found that the magnified observation of a short-segment BE according to its mucosal pattern and classification can be predictive of SIM. It's an informative manuscript, nicely written.

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