

A comparative study of magnifying endoscopy with narrow-band image and endocytoscopy in the diagnosis of gastric neoplasm: a pilot study

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Background/aims Endoscopic technologies have recently advanced to optimize the detection and diagnosis of gastric lesions. Endocytoscopy aids in the virtual realization of histology. Herein, we aimed to investigate gastric lesions using single-stain endocytoscopy and compare them using magnifying endoscopy with narrow-band imaging (ME-NBI) in terms of diagnostic yield *in vivo*.

Methods and methods In the present prospective study, we registered 24 patients with gastric neoplasms and retrospectively reviewed their images. Three endoscopists reviewed the images of gastric neoplasms using white light, ME-NBI, and endocytoscopy. The diagnostic yield of endocytoscopy in early gastric cancer (EGC) was assessed using histopathology as the gold standard.

Results Endocytoscopy was performed in 24 patients with gastric neoplasms. Of these, 15 patients had adenocarcinomas, while nine patients had low-grade dysplasia. The sensitivity, specificity, and accuracy of endocytoscopy for EGC detection were reported as 80.0% [95% confidence interval (CI), 51.9–95.7], 66.7% (95% CI, 58.4–91.9), and 75.0% (95% CI, 53.3–90.2) by endoscopist A; 80.0% (95% CI, 51.9–95.7), 44.4% (95% CI, 13.7–78.8), and 66.7% (95% CI, 44.7–84.4) by endoscopist B; and 93.3% (95% CI, 68.1–99.8), 55.6% (95% CI, 21.2–86.3), and 79.2% (95% CI, 57.9–92.8) by endoscopist C; these findings were not inferior to NBI. The inter-observer agreement, κ statistic = 0.67 (95% CI, 0.43–0.90) was favorable.

Conclusion Endocytoscopy aid in the diagnosis of EGC because of its better sensitivity and accuracy compared to NBI or white-light imaging. However, further large-scale studies are required to confirm our findings. *Eur J Gastroenterol Hepatol* 35: 530–536

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Introduction

Gastric cancer is one of the leading causes of cancer-related deaths. Although its prevalence is decreasing, it is

still ranking as the fifth most common cancer worldwide [1]. Histopathological examination is essential for the early diagnosis and detection of gastric cancer. Recent advances in endoscopic imaging technology have enabled real-time histological diagnoses during endoscopy.

During the early development of gastric cancer, surface mucosal microvessels dilate and become tortuous [2,3]. These subtle morphological changes cannot be identified through the conventional white-light imaging (WLI) examination. Image-enhanced endoscopy (IEE) has advanced and technological improvements are being made to the magnification of superficial lesions over the last 3 decades [4].

Magnification of lesions was obtained by performing experiments that helped in the examination of the micro-surfaces of lesions using stereoscopic microscopy [5]. This strategy was followed by the development of high-power optical magnification in the modern era of endoscopy. Presently, endoscopes manufactured by a range of companies enable up to 80–100 times magnification. Magnification allows the examination of small areas of the gastrointestinal tract without loss of resolution; however, it needs to be used in combination with other equipment for the detection of gastric neoplasms.

Narrow-band imaging (NBI) is a type of equipment-based IEE that uses optical filters in sequential lighting video endoscopes to spectral narrow-band filters [6]. Combining magnification and NBI techniques improves

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the diagnosis of early gastric cancer (EGC) because magnifying endoscopy with NBI (ME-NBI) has the capacity to detect subtle morphological changes in the gastric mucosa that WLI cannot identify [7].

Endocytoscopy is an ultra-high magnification real-time endoscopy that magnifies the surface of the digestive mucosa by more than 520 times, enabling the observation of the nucleus, cytoplasm, and gland structures at the cellular level. As endocytoscopy provides real-time microscopic images *in vivo*, its application in histological diagnosis for virtual biopsy (without the need to perform biopsy) is promising. Endocytoscopy uses a high-power, fixed-focus objective lens, which is connected to a light source and an imaging device, similar to that in a conventional endoscope. Cellular staining is required for observation of the target site; 1% methylene blue for the nucleus and 0.1% crystal violet for the cytoplasm are used [8].

Endocytoscopy is a safe and effective technique for increasing the accuracy of diagnoses of the biopsy specimens as it helps in obtaining histological images *in vivo* from the esophagus and colon. The effectiveness of endocytoscopy has been reported in previous studies; however, its application for the detection of gastric cancer is difficult as the stomach is mainly composed of secretory cells, and staining is difficult due to the presence of mucus and inflammatory products. As a result, very few studies have been conducted on testing the efficacy of cell microscopy in gastric lesions. A small-scale study in Japan used endocytoscopy for the detection of gastric cancer. However, no study has been conducted on this front in Korea.

The aim of the present study was to evaluate the sensitivity, specificity, and accuracy of single-stain endocytoscopy in diagnosing gastric neoplasms and compare the accuracy of these findings with those of white endoscopy or ME-NBI.

Materials and methods

Patients

Twenty-four patients who were referred for endoscopic resection for dysplasia or EGC at three tertiary hospitals between December 2020 and July 2021 were enrolled in the study. This was a multicenter, open-label study that involved prospective data collection and retrospective analysis. Fifteen patients diagnosed with EGC and nine patients diagnosed with low-grade gastric adenoma underwent endoscopic submucosal dissection (ESD). The local Ethics Committee approved the study protocol. The study adhered to the principles of the Declaration of Helsinki. (IRB Registration No. 17T7040). Informed consent was obtained from all patients enrolled in the study.

Endocytoscopy examination

A magnifying endoscope (GIF-Q240Z; Olympus Optical, Inc., Tokyo, Japan) combined with the NBI system and an integrated-type endocytoscope (GIF-H290EC; Olympus Medical Systems Corp., Tokyo, Japan) set at a magnification of 500X was used in the present study. All examinations were performed under intravenous sedation induced using propofol (200 mg/20 mL). In the endocytoscopy examination, the lesion was rinsed with water and pronase to remove as much mucus as possible.

The lesion and surrounding mucosa were sprayed with 0.1% methylene blue. One minute later, the lesion was irrigated with water and observed under the endocytoscope. Methylene blue was reapplied if the cells and nuclei were not properly stained. All assessments were performed by two endoscopists (W.S.L. and J.C.P.) who have at least 30 cases of experience in endocytoscopy examinations.

Assessment before endoscopic resection

A total of 24 patients underwent an endoscopic examination before undergoing ESD. Routine upper endoscopic procedures were performed on each patient. WLI and ME-NBI were performed for patients with gastric lesions that were referred for ESD. Photographs were obtained for the retrospective analysis. Subsequently, an endocytoscopy evaluation was performed for each patient. During endocytoscopy examination, photographs were obtained to evaluate the efficiency of the use of endocytoscopy in the differential diagnosis of early EGC and low-grade adenoma. The mucosa around the neoplastic lesions was also assessed using endocytoscopy by endoscopists, and biopsy samples were extracted from areas presumed to be intestinal metaplasia. ESD was performed for each of the 24 patients, and ESD specimens were sent for histopathological analysis. The flowchart of the study is shown in Fig. 1.

Assessment after endoscopic submucosal dissection

After the first procedure, WLE, NBI, and endocytoscopy images of gastric lesions were obtained and sent to three expert independent endoscopists with at least 5 years of experience, who were not involved in the first procedure and were blinded to the study details. The selected endoscopists evaluated a training set of images composed of five cases of adenoma and gastric cancer by scrutinizing the endocytoscopy images of gastric lesions in accordance with the endocytoscopic diagnosis based on the ‘EC classification of gastric mucosa’ [9]. Then, endoscopists assessed the pathologic findings of the WLE, NBI, and endocytoscopy images for lesions that were suitable for analysis. The ESD specimen obtained was the gold-standard final pathological diagnosis.

Statistical analyses

The Shapiro–Wilk test and distributional plots were used to assess normality. Continuous data are presented as mean \pm SD. The sensitivity, specificity, and accuracy of the

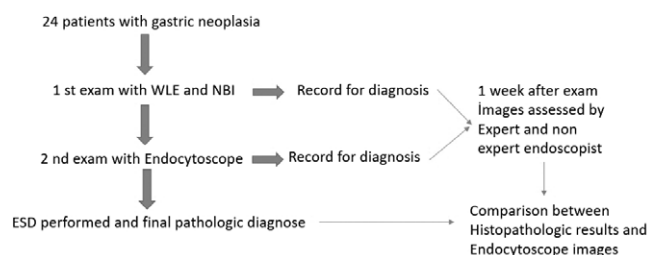


Fig. 1. Flowchart for study process.

EGC diagnosis made by the three endoscopists were calculated. The κ statistic was used to estimate the inter-observer agreement. κ values ≤ 0.40 , $0.41\text{--}0.75$, and ≥ 0.75 were considered poor, good, and excellent, respectively. The Wilson method was used to calculate the 95% confidence intervals (CIs). All analyses were performed using the STATA software version 14.1 (StataCorp., Texas, USA).

Results

Patients' characteristics

A total of 24 patients (mean age \pm SD, 66.6 ± 9.8 years) were enrolled. Of the 24 patients, 12 (50%) were men and 12 (50%) were women. The patient characteristics are presented in Table 1. On the basis of histopathology, 15 patients were diagnosed with adenocarcinomas and nine with adenomas. No complications were observed in NBI or endocytoscopy use. After single staining with methylene blue, all the samples were observed using endocytoscopy for 20–30 min or more to obtain clear images.

Findings of endocytoscopic view

The characteristics of the 24 analyzed lesions are illustrated in Figs. 2–8. Images of EGC obtained using endocytoscopy were markedly different from the images of low-grade dysplasia (LGD).

Gastric cancer

Cancer cells showed irregularly arranged lumen or varied lumen widths. In particular, the nuclei exhibited three typical features: swelling, disarrangement, and shape heterogeneity. From well to poorly differentiated, the nuclei were more overlapped and the glands tended to break. However, it was difficult to describe objective findings to distinguish the degree of cancer differentiation in endocytoscopy (Figs. 2–4).

Low-grade dysplasia

The endocytoscopy findings of LGD were characterized by dense and slit lumens and mild irregularities in the gland structure. Figures 5 and 6 show representative cases of LGD in endocytoscopy.

Intestinal metaplasia

As shown in Figs. 7 and 8, the epithelium exhibited a villous architecture and vacuoles, suggestive of goblet cells. Nuclei were stained more intensely in these cells than in the normal mucosa but demonstrated no atypia.

Evaluation of endocytoscopy images

The diagnostic yields of WLI, ME-NBI, and endocytoscopy for EGC are presented in Table 2. On the basis of these data, the sensitivity, specificity, and accuracy of each endoscopy given by the three experts in EGC were calculated. Average sensitivity, specificity, and accuracy of endocytoscopy were 84.4%, 55.6%, and 73.6%, respectively. Inter-observer agreement, κ statistic = 0.67 (95% CI, 0.43–0.90) was good. Endocytoscopy showed a high sensitivity between 80 and 93% compared with other modalities. Moreover, compared to other endoscopic imaging modalities, the median accuracy of endocytoscopy was much higher than that of NBI, although the difference was not statistically significant.

Endocytoscopy contributes diagnostic yield in uncertain cases of magnifying endoscopy with narrow-band imaging

NBI and endocytoscopy images of the same lesions were compared to assess the contribution of endocytoscopy in uncertain cases. On the ME-NBI image, the microsurface and microvascular of the lesion appeared relatively ambiguous (Figs. 9 and 10), which made the differentiation of non-cancerous lesions from cancerous lesions difficult. However, non-cancerous and cancerous lesions were clearly distinguishable on endocytoscopy images (Figs. 11 and 12). The endocytoscopy image in Fig. 11 shows small, round, and regularly arranged nuclei suggestive of LGD. The endocytoscopy image in Fig. 12, which is significantly different from Fig. 11, shows hyperchromatic, disarranged nuclei with heterogeneity in size and shape, suggestive of cancerous lesions. Therefore, endocytoscopy would

Table 1. Patient demographics and clinicopathological characteristics of gastric tumors

Characteristic	Adenoma (n=9)	Malignancy (n=15)	
Sex, male, number (%)	5/9	7/15	$P > 0.99$
Age, mean (SD), years	66.7 ± 7.6	66.6 ± 11.3	$P > 0.79$
Tumor location, number (%)			
Corpus	4	7	
Antrum	3	6	$P = 0.84$
Cardia	2	2	
Macroscopic type			
0-IIa	6	4	
0-IIb	2	5	$P = 0.25$
0-IIc	1	5	
0-III	0	1	
Tumor size, mean (SD), cm	12.4 ± 4.4 mm	20.1 ± 12.5 mm	$P = 0.08$

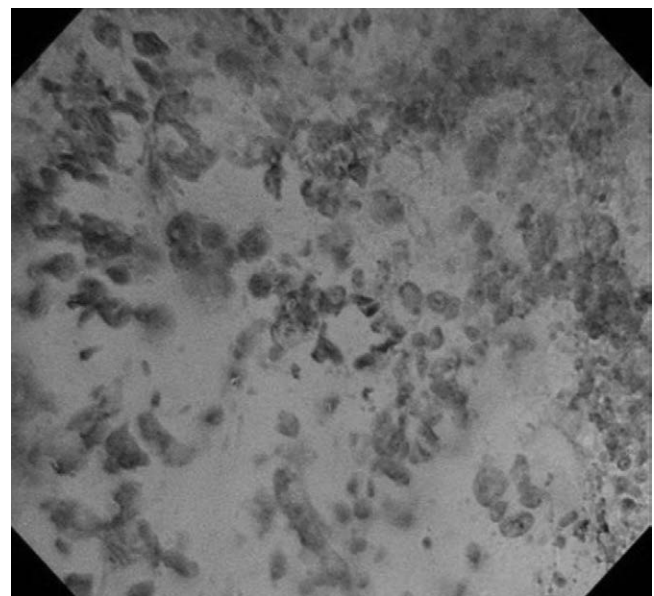


Fig. 2. Endocytoscopy image of adenocarcinoma well differentiated.

enhance diagnostic yield, especially in cases with unclear ME-NBI patterns.

Discussion

This study examined the diagnostic yield of single-stain endocytoscopy in EGC by comparing the single-stain endocytoscopy findings with those of ME-NBI. The present study showed that visualized cellular changes were correlated with the pathological diagnosis.

ME-NBI is often used to predict the histology of EGC based on observations of vascular and surface structures. Although a diagnostic system for ME-NBI has not yet been established, the vascular surface classification proposed by Yao in 2009 is the preferred classification method. The vascular surface classification is based on

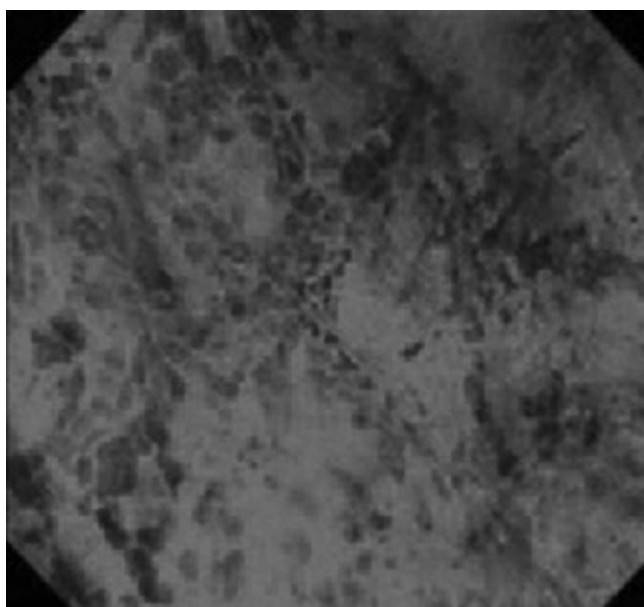


Fig. 3. Endocytoscopy image of adenocarcinoma moderately differentiated.

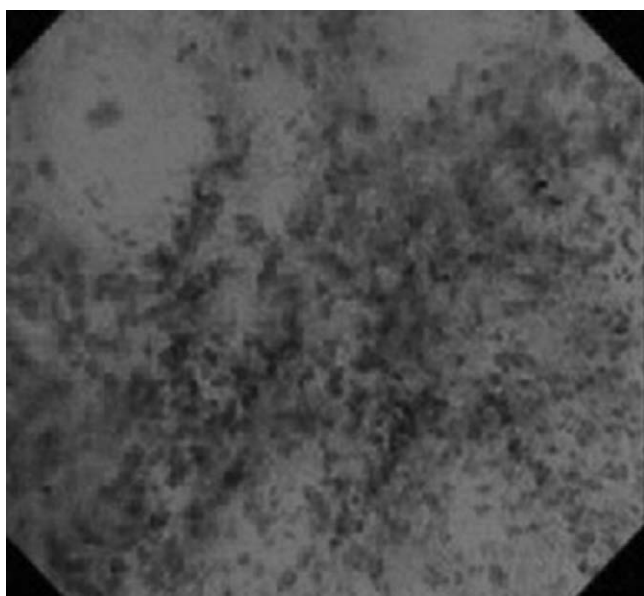


Fig. 4. Endocytoscopy image of adenocarcinoma poorly differentiated.

the presence of a demarcation line of superficial lesions and the detection of microvascular and microsurface patterns inside the demarcation line. Previous studies have reported that the ME-NBI method using vascular surface classification has an accuracy rate of between 79 and 95%, a sensitivity of 95%, and a specificity of 96% [9,10].

Although the ME-NBI method has shown excellent sensitivity and specificity, it has limitations. Unlike the esophagus or colon, the gastric lumen has a large internal space, which poses a limitation because the space cannot be illuminated with sufficient light intensity [11]. Besides, some uncertain lesions, especially flat discolored lesions of the undifferentiated type, cannot be identified using ME-NBI.

The clinical efficacy of endocytoscopy is highly anticipated to overcome this issue, which enables in-vivo ultra-high magnification (520X) for direct visualization at the cellular level and allows precise pathological prediction. The usefulness of endocytoscopy in evaluating the colon and esophagus has been reported previously [12,13]; however, the diagnostic yield of endocytoscopy in detecting EGC is insufficient owing to its limitations. When compared with endocytoscopy, NBI is easier to perform and does not require advanced image-capturing skills. Endocytoscopy requires more time owing to its staining, and bleeding due to contact with the lens prevents the acquisition of suitable images to detect EGC. Performing endocytoscopy, particularly in the stomach is difficult as gastric mucosa contains more mucus compared with other parts of the gastrointestinal tract.

Our results reiterate the findings of previous studies. One study reported that the overall accuracy for diagnosing gastric cancer had a sensitivity ranging from 78.4 to 86% and a specificity ranging from 93.3 to 100% for endocytoscopy. Kaise *et al.* investigated the accuracy of cellular atypia as a predictor of gastric cancer. They defined high-grade cellular atypia as a predictor of gastric cancer. Absence or fusion of lumen and irregularities of nuclei were defined as components of atypia. Cellular atypia was detected using endocytoscopy in 86% of gastric cancer patients; however, it was not detected in adenoma or non-neoplastic patients [14,15].

One study enrolled 30 patients with gastric cancer, whose endocytoscopy images were assessed by an endoscopist and pathologist who were blinded to the patients' clinical information. The diagnostic accuracy, sensitivity, and specificity rates were 88%, 92.9%, and 90.6% for endoscopists, and 88.9%, 91.3%, and 90.0% for pathologists, respectively. There was no statistically significant difference between the two observers, and the inter-observer agreement (κ -value = 0.745) was similar to that in the present study [16].

The present study is the first to compare the diagnostic performance and accuracy of NBI and endocytoscopy for EGC detection in Korea. Our study had some limitations. First, as mentioned previously, the presence of viscous mucus and dense ulcer plaques on the stomach are the main obstacles to obtaining a clear view in endocytoscopy. All lesions were stained and examined according to the study protocol. Although lesions with mucus were washed and stained to obtain clear images, some were poorly visible during endocytoscopy

examination. In addition, it takes at least 20–30 min to wash the lesions and observe them. This may have influenced the interpretation of the results. Second, the enrolled patients and participating endoscopists were relatively small in number, suggesting that future studies may need the involvement of a larger number of patients and expert endoscopists to substantiate the results of this study.

The standard endocytoscopy method uses double staining with crystal violet and methylene blue; however, crystal violet cannot be used in Korea for safety reasons. Although we used only one type of staining method, the results were comparable to those of previous studies.

The present study showed statistically significant differences between ME-NBI and single-stain endocytoscopy

methods in terms of nuclear morphology assessment for differentiating between cancerous and non-cancerous areas in the stomach. The early detection and diagnosis of gastric lesions are key factors that increase the prognosis and survival rates of patients with gastric cancer. The use of technologies, such as endoscopy, has improved the detection and diagnosis of EGC. Diagnosis of gastric tumors using magnification and NBI is based on detection of irregularities in the gland structure rather than cytological structure; however, endocytoscopy can be used to diagnose gastric tumors by observing the nucleus and cytoplasm.

A clear classification method for endocytoscopy in gastric cancer has not yet been established, which affects the reproducibility of results. However, in our study, the ‘EC classification of gastric mucosa’ was used for diagnosing

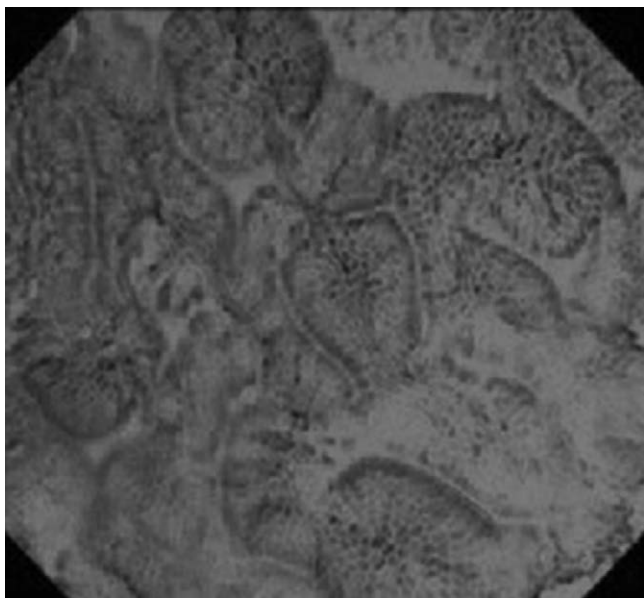


Fig. 5. A representative case of low-grade dysplasia. Mild irregularities in gland structure with no nuclear atypia.

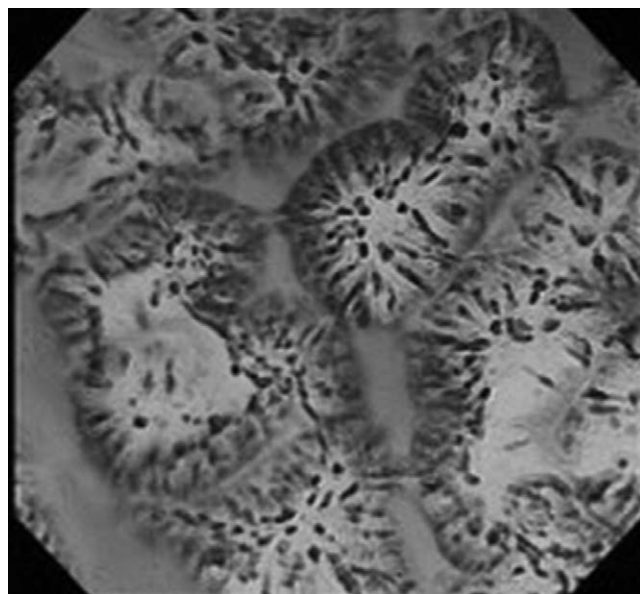


Fig. 7. A representative case of intestinal metaplasia. The epithelium exhibits a villous architecture.

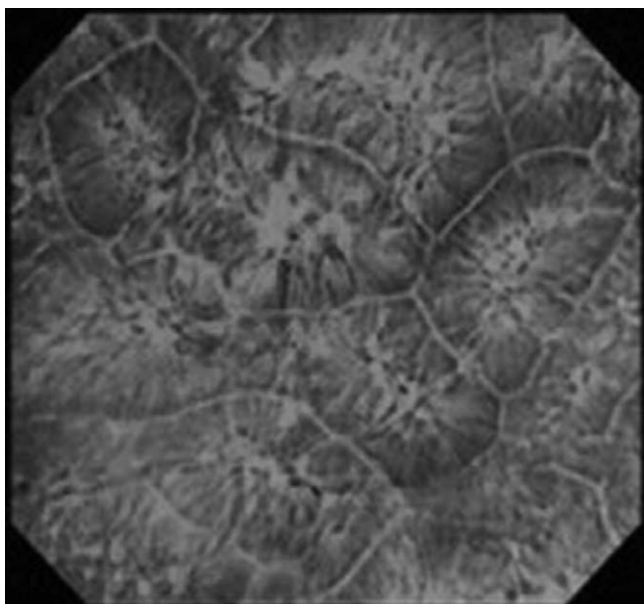


Fig. 6. Another example of low-grade dysplasia.

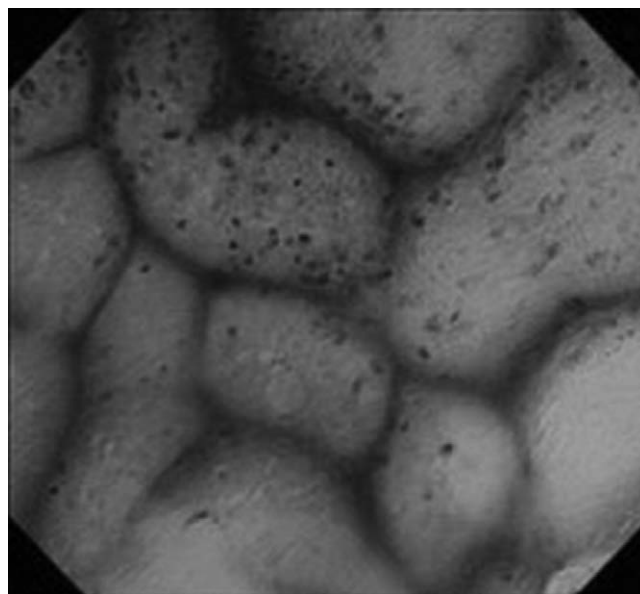
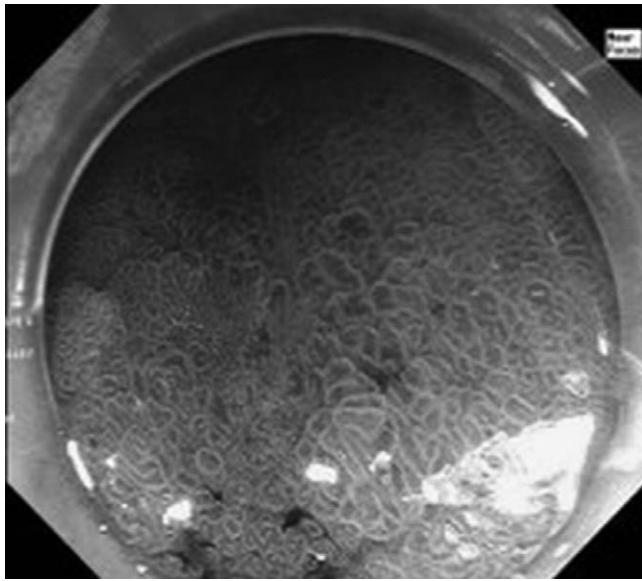
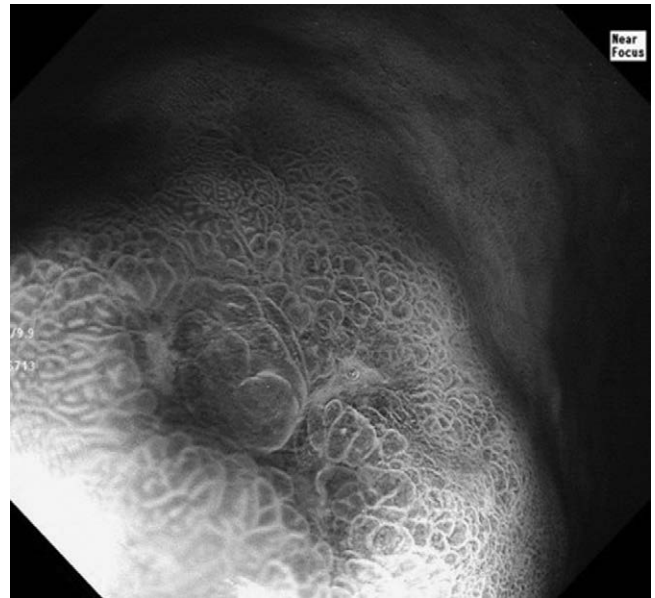
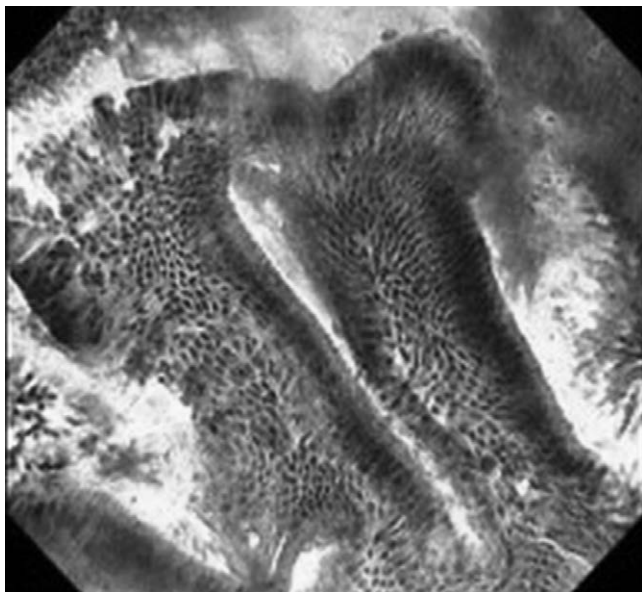
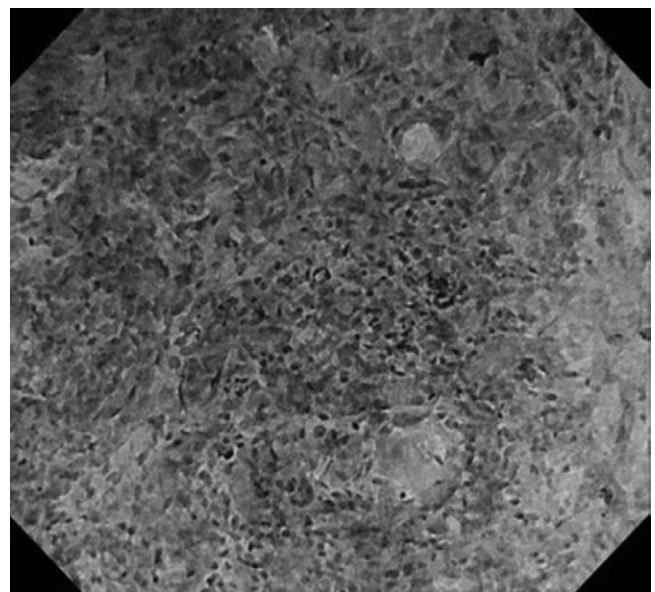


Fig. 8. A representative case of intestinal metaplasia. Some epithelial cells had vacuoles, suggestive of goblet cells.

Table 2. Diagnostic yields of each endoscopist for early gastric cancer

	Endoscopist A	Endoscopist B	Endoscopist C
WLE	Result (95% CI)		
Sensitivity	46.7 (21.3–73.4)	66.7 (38.4–88.2)	46.7 (21.3–73.4)
Specificity	77.8 (39.9–97.2)	66.7 (29.9–92.5)	88.9 (51.8–99.7)
Accuracy	58.3 (36.6–77.9)	66.7 (44.7–84.4)	62.5 (40.59–81.2)
NBI			
Sensitivity	60 (32.3–83.7)	73.3 (44.9–92.2)	60 (32.3–83.7)
Specificity	55.6 (21.2–86.3)	66.7 (29.9–92.5)	66.7 (29.9–92.5)
Accuracy	58.3 (36.6–77.9)	70.8 (48.9–87.4)	62.5 (40.6–81.2)
Endocytoscopy			
Sensitivity	80 (51.9–95.7)	80 (51.9–95.7)	93.3 (68.1–99.8)
Specificity	66.7 (29.9–92.5)	44.4 (13.7–78.8)	55.6 (21.2–86.3)
Accuracy	75 (53.3–90.2)	66.7 (44.7–84.4)	79.2 (57.9–92.8)

CI, confidence interval; NBI, narrow-band imaging; WLE, white-light endoscopy.

**Fig. 9.** NBI image of low-grade dysplasia. NBI, narrow-band imaging.**Fig. 11.** Endocytoscopy image of low-grade dysplasia.**Fig. 10.** NBI image of adenocarcinoma. NBI, narrow-band imaging.**Fig. 12.** Endocytoscopy image of adenocarcinoma.

suspicious lesions [9]. On the basis of the endocytoscopy classification, normal and dysplasia groups were divided by assessing cellular and glandular morphology, lumen changes, loss of polarity of nuclei, and nuclear structural changes. The presence of the 'enlarged nuclear sign' was critical in dividing cancer and adenoma (positive 'enlarged nuclear sign' depicts cancer). According to the present study, endocytoscopy may help in identifying parts that appear ambiguous in NBI. Further classification methods that can easily differentiate endoscopic observation findings and have high diagnostic accuracy and agreement among endoscopists are required.

In summary, single-stain endocytoscopy presents a quite superior diagnostic yield for cancerous and non-cancerous lesions compared to NBI. Additional benefits of examining EGC using endocytoscopy must be validated through a well designed prospective comparison trial in the future.

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None.

Conflicts of interest

There are no conflicts of interest.

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