Real-time diagnostic yield of white light endoscopy, chromoendoscopy and magnifying endoscopy with narrow band imaging in the undiagnosed gastric lesions after Helicobacter pylori eradication

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Abstract

Background: Early-stage gastric cancer (EGC) after Helicobacter pylori (H. pylori) often confuse endoscopic diagnosis. We prospectively evaluated the real-time diagnostic yield of combining white light endoscopy (WLE), chromoendoscopy (CE), and magnifying endoscopy with narrow band imaging (ME-NBI) for undiagnosed gastric lesions after H. pylori eradication. Methods: Using a retrospective data set, we conducted a consensus meeting to learn ME-NBI features of EGC after H. pylori eradication associated with diagnostic difficulty. Then, we prospectively evaluated the real-time diagnostic yield of WL, followed by CE, and ME-NBI in the diagnosis of 166 newly identified gastric lesions from 219 patients after H. pylori eradication. Results: A consensus meeting characterized ME-NBI feature of EGC with diagnostic difficulty, as having irregular vessel patterns in only tiny area of the lesion. Among 166 undiagnosed gastric lesions in the prospective study, 22 neoplastic lesions (18 adenocarcinomas and 4 adenomas) were identified. In these lesions, diagnosed case was dramatically increased when combined with ME-NBI (98%) compared to WLE alone (54%) and CE with WLE (63%) (WLE+CE+ME-NBI vs. others, all P<0.0001). In the diagnosed cases, the diagnostic accuracy was also improved when combined with ME-NBI (99.4%) compared to WLE alone (92.2%: P=0.004) and CE with WLE (95.1%: P=0.03). Conclusions: WLE combined with ME-NBI can improve the diagnostic yield of EGC in patients after H. pylori eradication. For precise diagnosis of EGC by ME-NBI, it is essential to detect irregular vessels.

Background

Gastric cancer (GC) is one of the most common malignancies and the second causal of cancer death worldwide [1]. *Helicobacter pylori* (*H. pylori*) infection is known risk for the development of GC [2,3]. A prospective study in Japan demonstrated that *H. pylori* eradication reduced the incidence of metachronous GC after endoscopic resection of early-stage gastric cancer (EGC) [4]. The Japanese national health insurance system has covered the cost for the eradication therapy for patients with *H. pylori*-associated gastritis. However, GC is discovered in patients even after successful *H. pylori* eradication [5]. It has been reported that EGC found after *H. pylori* eradication sometimes appears with indistinct forms, such as tiny and flattened lesions [6-10]. Histopathological findings of such cases are highlighted as having either regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors [9,10], which may confuse endoscopic as well as histologic diagnosis [7]. Moreover, endoscopic examination in patients after *H. pylori* eradication often reveals gastric lesions such as patchy redness and/or map-like redness, which need to be distinguished from EGC [11,12]. Previous studies have demonstrated that magnifying endoscopy with narrow band imaging (ME-NBI), combined with conventional white light endoscopy (WLE) can improve the diagnostic yield of EGC [13]. However, recent retrospective studies reported that about 10 % of EGCs after *H. pylori* eradication were difficult to demarcate from surrounding mucosa even by using ME-NBI [14,15]. Moreover, the diagnostic strategy of combining WLE, chromoendoscopy (CE), and ME-NBI for distinguishing EGC from benign gastric lesions has not been established in patients after *H. pylori* eradication. In the present study, we retrospectively investigated ME-NBI features of EGC after *H. pylori* eradication associated with

diagnostic difficulty. Based on this, we conducted a prospective study to evaluate the real-time diagnostic yield of combining WLE, chromoendoscopy (CE), and ME-NBI for undiagnosed gastric lesions in patients after *H. pylori* eradication.

Methods

Retrospective study

Initially, we conducted a consensus meeting to learn ME-NBI features of EGC after *H. pylori* eradication associated with diagnostic difficulty. For this consensus meeting, we consulted an EGC cohort in our retrospective study [14]. This cohort consisted of 71 EGCs from 61 patients after *H. pylori* eradication (eradication group) and 115 EGCs with current *H. pylori* infection (control group). All patients attended the endoscopy center of Fujita Health University for the ESD between April 2011 and December 2016. All endoscopic photographs of EGC were reviewed by two expert endoscopists (TT and NH) and the ME-NBI features of EGCs were evaluated using the vessel plus surface (VS) classification system [13]. In this system, endoscopic diagnosis of EGC is performed in terms of microvascular (MV), microsurface (MS) patterns and presence of demarcation line (DL). Diagnosis of EGC using the ME-NBI was based on the presence of irregular MV and/or MS with clear DL, while no or poor evidence of such findings was defined as the lesion with difficult diagnosis. Factors associated with diagnostic difficult was further explored using the ME-NBI photographs. Fujita Health University School of Medicine approved the protocol of the retrospective study, and written informed consent was obtained from all participating subjects.

Prospective study

Based on the consensus meeting, we prospectively evaluated the real-time diagnostic yield of combining WLE, chromoendoscopy (CE) using indigo carmine, and ME-NBI in undiagnosed gastric lesions in patients after successful *H. pylori* eradication. For this prospective study, 219 patients who had at least 6 months of post-eradication were enrolled.

Between December 2016 and September 2018, 298 upper endoscopic examinations were performed for these patients by two expert endoscopists (TT and NH). For all examinations, endoscopy was performed with the GIF-H260Z or the GIF-H290Z (Olympus Corporation, Tokyo, Japan). After inserting the endoscopy into the stomach, screening was performed using WLE. If the newly detected and undiagnosed gastric lesions were identified in the screening endoscopy, lesion was diagnosed by 1) WLE, followed by 2) CE using indigo carmine dye (0.2%) and 3) ME-NBI. If an endoscopist could diagnosed the lesion as either neoplastic or non-neoplastic, we considered it as a diagnosed case and diagnostic results (neoplastic or non-neoplastic) were recorded based on the real-time observation. As a rule, these results were not changed if a different diagnosis was made by other modalities. Diagnostic criteria of EGC using the conventional WLE and the CE was based on the presence of well–demarcated, depressed, or elevated lesions with an irregular margin and an irregular mucosal area with a color change (reddish or whitish),

while no evidence of such findings was considered to be a noncancerous lesion by the conventional WLE and the CE. Although, the diagnostic criteria of EGC using ME-NBI was made by the VS classification system [13], based on the consensus meeting, we especially tried to evaluate irregular MV using high power magnification. After endoscopic observation, at least biopsy was taken from the lesion. The biopsy specimens were evaluated using H&E staining. The diagnostic pathological criteria were based on the Japanese Classification of Gastric Carcinoma, 14th edition [16]. Groups 3, 4 and 5 were diagnosed as neoplastic lesions and group 1 was diagnosed as non-neoplastic lesions. If the biopsy result was group 2 (indefinite for neoplasia), additional examination was scheduled for the conclusive pathological diagnosis. Fujita Health University School of Medicine approved the protocol of the prospective study, and written informed consent was obtained from all participating subjects. This study was registered with the University Hospital Medical Information Network (UMIN000033100).

Statistical analysis

Diagnostic yields of WL, CE and M-NBI were evaluated in terms of sensitivities, specificities, and diagnostic accuracies were calculated by reference to the pathological diagnosis of endoscopic biopsy. Diagnostic accuracy was defined as (true positive+ true negative)/total number of cases). Statistical differences of continuous and categorical variables between the two groups were determined using the Student‘s t-test and the Chi-square Test, respectively. $P<0.05$ was considered significant.

Results

Retrospective study

We used an EGC cohort in our retrospective study [14]. The cohort consisted of 71 EGCs from 61 patients after *H. pylori* eradication (eradication group) and 115 EGCs with current *H. pylori* infection (control group). Diagnostic yield of EGC by using ME-NBI was 88.7% (63/71) in the eradication group, which was significantly lower than that of control group (98.2%: 113/115, $P=0.01$) [14]. This result seemed to be similar to those reported in others study, reporting that approximately 10 % of EGCs after *H. pylori* eradication were difficult to diagnose using ME-NBI [15]. We further reviewed all endoscopic photographs of EGC lesions in eradication group to explore factors associated with diagnostic difficult using the ME-NBI. 8 EGCs (11.3%) in the eradication group that was considered to be diagnostic difficult showed relatively regular MS with unclear DL, which was undistinguishable from surrounding mucosa, while irregular MV was found at least within the small area of the lesion (Fig. 1), suggesting that to detect irregular MV would be essential for the precise diagnosis of these cases.

Prospective study

The clinic-pathological characteristics of 219 participants in the prospective study at the study enrollment are shown in the Table 1. During the study period, 73, and 3 patients underwent one, and two times follow up endoscopy. In total, 298 upper endoscopic examinations were performed and 166 undiagnosed gastric lesions were identified in 95 patients. In the 166 undiagnosed gastric lesions, 22 neoplastic lesions (18 adenocarcinomas and 4 adenomas) were identified in 18 patients based on the endoscopic biopsy. 20 out of 22 neoplastic lesions were identified as the second lesions from patients with EGC, or as the metachronous lesions after endoscopic resection of EGC. 2 neoplastic lesions were identified in cancer-free patients. Majority of undiagnosed gastric lesions were appeared as reddish (138/166) and depressed (118/166) morphology and the median size was 8 mm (Table 2). We then evaluated the real-time diagnostic yield of combining WLE, CE, and ME-NBI for these undiagnosed gastric lesions in the reference to pathological diagnosis of the endoscopic biopsy. The retrospective study showed that the ME-NBI feature of EGC with difficult diagnosis in the eradication group was characterized as having irregular MV in tiny area of the lesion. We defined this issue to diagnose the lesion as neoplastic by using the ME-NBI. Initially, we investigated the frequencies of confident case among different modalities. The result showed that frequency of diagnosed case was dramatically increased when combined with ME-NBI compared to WLE alone and CE with WLE, while it was not significantly different in the comparison of WLE alone and CE with WLE (WLE *vs. WLE+*CE *vs. WLE+CE+*ME-NBI, 54% *vs.* 63% *vs.* 98%; WLE *vs. WLE+*CE, P=0.19; WLE *vs. WLE+CE+*ME-NBI, WLE+CE *vs. WLE+CE+*ME-NBI, both P<0.0001) (Table 3). Next, we compared the diagnostic yield of combining three endoscopic modalities in the diagnosed cases. Sensitivity, specificity and accuracy was 92.3%, 92.2% and 92.2% for the WLE; 92.3%, 95.5% and 95.1% for the CE+WLE; 100%, 99.3% and 99.4% for the *WLE+CE+*ME-NBI. The diagnostic accuracy was significantly improved when combined with ME-NBI compared to WLE alone and CE with WLE, while it was not significantly different in the comparison of WLE alone and CE with WLE (WLE *vs.* WLE+CE, P=0.41; WLE *vs.* WLE+CE+ME-NBI, P=0.004; WL+CE *vs.* WLE+CE+ME-NBI, P=0.03) (Table 4). The identified neoplastic lesions included 4 adenoma lesions but we applied VS classification system [13] for such adenoma lesions. 2 out of 4 adenoma lesions could be diagnosed as neoplastic lesions by using ME-NBI, while remaining 2 lesions could not be diagnosed by using ME-NBI.

Discussion

The retrospective consensus meeting highlighted the ME-NBI feature of EGCs with diagnostic difficulty in the eradication group. ME-NBI feature of these cases was characterized as having relatively regular MS with unclear DL, which was difficult ro distinguish from surrounding mucosa. Histopathological findings of EGC after *H. pylori* eradication are reported as either regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors [9,10], which may confuse endoscopic as well as histologic diagnosis [7]. If considerable part of the EGC lesion was covered by such distinct histological changes, the diagnosis of EGC would become difficult. On the other hand, we also found that irregular MV was found at least within the small area of such lesions. This suggest that it is essential to detect irregular MV for the precise diagnosis of these cases. The prospective study in undiagnosed

gastric lesions based on this consensus meeting demonstrated that combining ME-NBI with other modalities improved the frequency of confidence case compared to WLE alone and CE with WLE. The diagnostic accuracy in the confident cases was also higher when combined with ME-NBI with other modalities compared to WLE alone and CE with WLE. Our result suggest that ME-NBI, combined with other modalities contributes to precise diagnosis of EGC after *H. pylori* eradication. The 298 upper endoscopic examinations in 219 patients in the prospective study identified 166 undiagnosed gastric lesions in 95 patients, which was more frequent compared to other previous study [13]. This difference would be depends of the prevalence of patients after *H. pylori* eradication included in the study. Since endoscopic examination in patients after *H. pylori* eradication often reveals gastric lesions such as patchy redness and/or map-like redness, which sometimes difficult to distinguish from EGC [11,12], it is possible that endoscopists have to diagnose more lesions per examination after *H. pylori* eradication. Our result indicate that combining ME-NBI with WLE can predict pathological findings of gastric lesions in such clinical conditions with higher sensitivity, specificity and high confidence, which can reduce the number of endoscopic biopsy and can shorten the examination time. We showed that frequency of diagnosed case, as well as diagnostic yield of EGC, were not improved when combining CE with WLE compared to WLE alone, which was in line with our previous retrospective study [14]. Since the diagnosis of EGC using the conventional WLE and the CE is based on endoscopic findings of irregularly shaped depression or unevenness elevation, which are often accompanied with a color change (reddish or whitish). Compared to the conventional WLE, the CE can more enhance the depression or elevation in the EGC lesions by using the indigo carmine dye, while the information of color would become indistinct by its dark blue color. Since the EGC lesions in the eradication group often appear as a red color depressed lesion [6,7,14], it would be important to detect such color change by using the WLE to diagnose EGC after *H. pylori* eradication. On the other hand, it is possible that histological changes such as normal epithelium and/or surface differentiation covering the tumor tissue would make the depression or elevation unclear in the eradication cases. Therefore, it should be noted that, in considerable EGCs in eradicated cases, the endoscopic diagnosis would become rather difficult by using indigo carmine dye and it would be rather ideal to only use WLE and ME-NBI for efficient diagnosis of these cases.

Conclusions

In summary, we showed that ME-NBI, combined with WLE can improve the diagnostic yield of undiagnosed gastric lesions in patients after *H. pylori* eradication. Since this would be a first prospective study reporting usefulness of combining ME-NBI with WLE in the diagnosis of undiagnosed gastric lesions after *H. pylori* eradication. Our study cohort was only from single center and consisted of both cancer and cancer-free patients. This issue should be noted as the limitation. Our result need to be confirmed by larger studies in various cohorts with both high and low risks for developing GC.

Declarations

Ethics approval and consent to participate

Fujita Health University School of Medicine approved the protocol of the prospective study, and written informed consent was obtained from all participating subjects. This study was registered with the University Hospital Medical Information Network (UMIN000033100).

Consent for publication

All authors have approved the manuscript and agree with publication our study to BMC gastroenterology.

Availability of data and material

All data and material related to this study was included in the manuscript.

Competing interests

The authors declare that they all have no conflict of interest.

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Authors' contributions

Tomomitsu Tahara designed the study protocol, collected patients, performed endoscopic examination, analyzed the data and wrote the manuscript.

Noriyuki Horiguchi performed endoscopic examination.

Tsuyoshi Terada, Dai Yoshida and Masaaki Okubo collected patients.

Kohei Funasaka, Yoshihito Nakagawa, Tomoyuki Shibata and Naoki Ohmiya advised about the study design and data analysis.

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Tables

Table 1 Clinicopathological characteristics of patients in the prospective study

Variables	
Age (range)	70 (40-87)
Female/male	59/160
Post-eradication period (range)	45 (6-240) months
Cancer-free patients	81
Patients with EGC	32
Post-endoscopic resection	106
Reason for H. pylori eradication	
Duodenal ulcer	6
Gastric ulcer	25
Gastritis	88
Gastric polyp	3
After or before endoscopic resection	67
Others	30

Table 2 Summary of gastric lesions detected in the prospective study

Variables	
Lesions	166
Cases	95
Neoplastic lesions	22
Cases with neoplastic lesions	18
Color	
Reddish	138
Whitish	21
Same as surroundings	7
Morphology	
Depressed	118
Protruded	27
Flat	21
Size (range)	8 (3-35) mm

Table 3 Diagnosed cases in three different endoscopic modalities

Modalities	Diagnosed case
WL	54% (90/166)
CE	62% (102/164)
ME-NBI	98% (162/166)

WL *vs.* CE, P=0.19;

WL *vs.* NBI, CE *vs.* ME-NBI, *P*<0.0001;

Statistical analysis was performed by the fisher's exact test.

CE could not performed for 3 cases.

Table 4 Diagnostic yields of different endoscopic modalities in diagnosed cases

Endoscopic	Pathologic	WLE	CE	ME-NBI
Neoplastic	Neoplastic	12	12	19
	Non-neoplastic	6	4	1
Non-neoplastic	Neoplastic	1	1	0
	Non-neoplastic	71	85	142
Sensitivity		92.3%	92.3%	100%
Specificity		92.2%	95.5%	99.3%
Accuracy #		92.2% (83/90)	95.1% (97/102)	99.4% (161/162)

WL *vs.* CE, *P*=0.41; WL *vs.* NBI, *P*=0.004; CE *vs.* NBI, *P*=0.03;

Figures

Figure 1

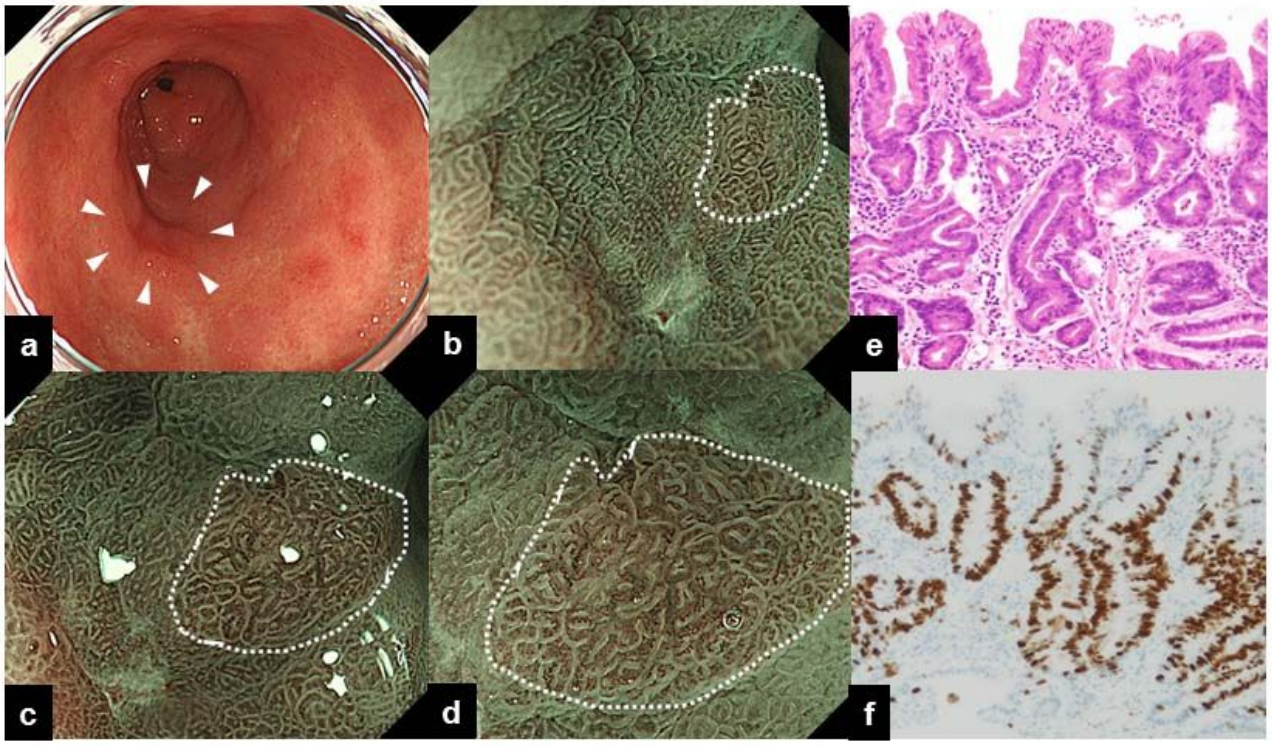

Figure 1

A representative case of EGC after H. pylori eradication that was considered to be difficult to diagnose. (a) A reddish depressed lesion was detected in the WLE in the gastric antrum (white arrow heads). (b~d) ME-NBI showed relatively regular MS with unclear DL, which was difficult to distinguish from surrounding mucosa, while irregular MV was found within the small area of the lesion by middle and high power magnification (white dotted line). (e) Histological examination with Hematoxylin-Eosin staining showed that atypical degree of cancerous crypts became lower due to surface differentiation of tumors. (f) Lower expression of MIB-1 in the surface area of the tumor was also observed.

Figure 2

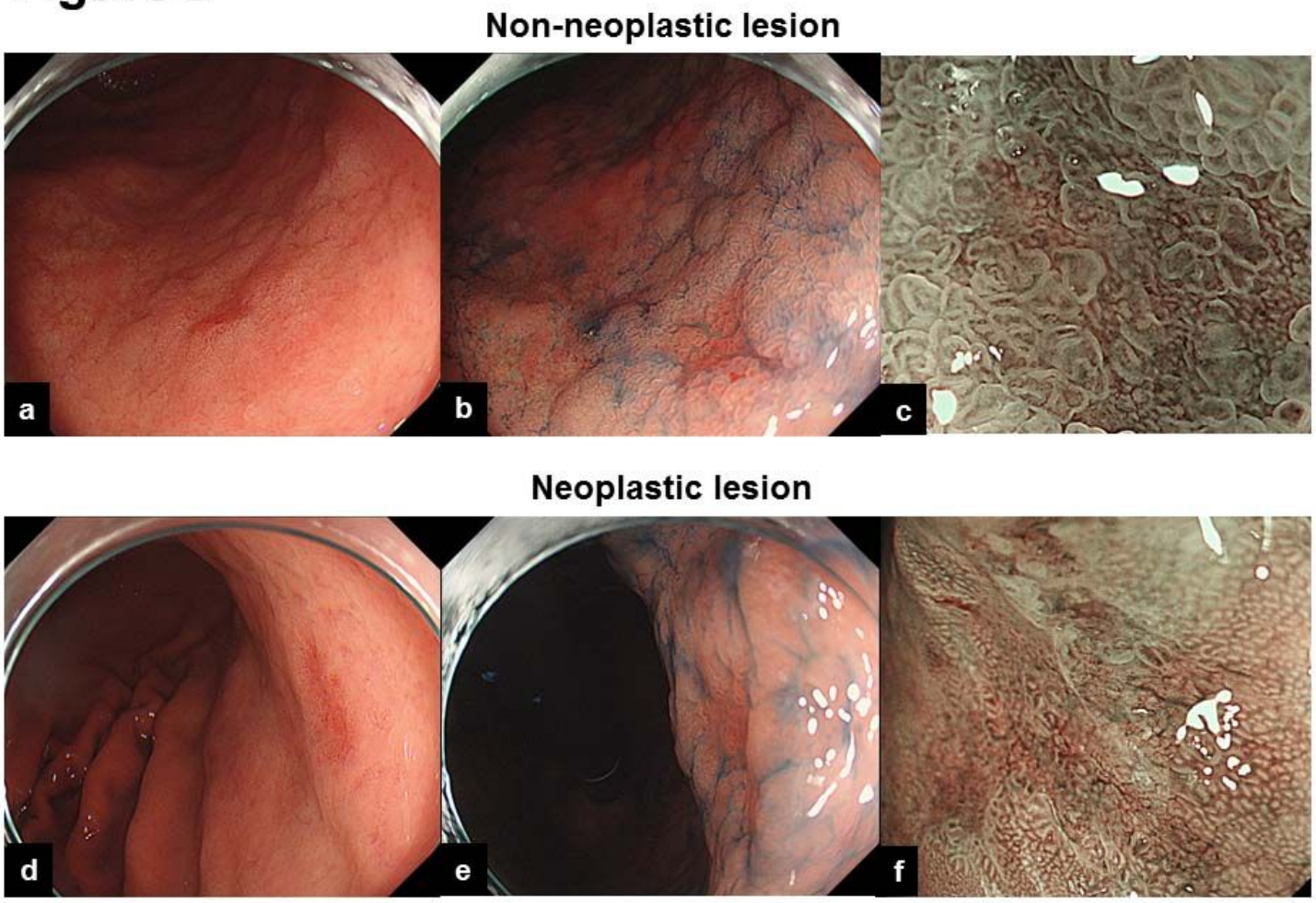

Figure 2

Undiagnosed gastric lesions detected in the prospective study. A non-neoplastic lesions (a~c) and a cancer (d~f). Both were appeared as 6mm sized reddish depressed lesions, and could not been diagnosed by an endoscopist using WLE and CE (a, b, d, and e). ME-NBI showed irregular MV within the lesion in below lesion (f), not in the upper lesion (c). An endoscopist could diagnosed upper and below lesions as non-neoplastic and cancer, respectively.