Can we accurately diagnose minute gastric cancers (≤ 5 mm)? Chromoendoscopy (CE) vs magnifying endoscopy with narrow band imaging (M-NBI)

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Abstract

Background Chromoendoscopy (CE) is relatively ineffective at identifying the cancer-specific morphological characteristics of minute gastric cancers less than or equal to 5 mm in diameter, and on its own is insufficient to make an accurate diagnosis. The aim of this study is to assess the diagnostic performance of magnifying endoscopy with narrow band imaging (M-NBI) for minute gastric cancers. **Methods** The minute cancer group comprised consecutive endoscopic submucosal dissection-resected minute gastric cancers histologically measured as no larger than 5 mm in diameter. The non-cancer group comprised consecutive non-cancer lesions no larger than 5 mm in diameter. The two groups were subject to retrospective analysis to evaluate the diagnostic ability (sensitivity, specificity, and diagnostic accuracy) and reproducibility of CE and M-NBI.

Results The results for CE versus M-NBI were as follows: sensitivity 43.7 % (95 % CI, 26.5–61.0 %) versus 78.0 % (95 % CI, 64.0–92.0 %); specificity 81.6 % (95 % CI, 72.6–90.6 %) versus 92.9 % (95 % CI, 87.0–98.9 %); and diagnostic accuracy 69.9 % (95 % CI, 61.0–78.6 %) versus 88.3 % (95 % CI, 82.0–94.5 %). The sensitivity and diagnostic accuracy were, therefore, significantly higher for M-NBI than for CE. The inter-observer variability was $\kappa = 0.08$ for CE and $\kappa = 0.56$ for M-NBI, while the intra-observer variability was $\kappa = 0.38$ and $\kappa = 0.65$, respectively.

Conclusions M-NBI has greater sensitivity and reproducibility than CE for the diagnosis of minute gastric cancers.

Keywords Chromoendoscopy · Minute gastric cancer · Magnifying endoscopy · Narrow band imaging · Image-enhanced endoscopy

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Introduction

Chromoendoscopy (CE) is a powerful form of image-enhanced endoscopy (IEE) that has long been considered an effective endoscopic diagnostic technique for early gastric cancer. It is used widely in Japan, where studies claim it to be the most effective technique for diagnosing early gastric cancer [1, 2]. For minute gastric cancers (≤ 5 mm), however, CE by itself is relatively ineffective at identifying the cancer-specific morphological characteristics of minute gastric cancers [3].

We previously reported that M-NBI is useful for the diagnosis of small depressed lesions [4, 5], and differentiating between adenomas and cancers in superficial elevated lesions where conventional white light imaging

(WLI) is not useful [6], as well as for margin delineation of flat early gastric cancers whose margins are unclear using conventional CE [7].

Although we have reported a specific case where magnifying endoscopy with narrow band imaging (M-NBI) has been successfully used to detect minute gastric cancers [8], to date there has been no systematic study of the usefulness of M-NBI in the diagnosis of minute gastric cancers. The aim of this study was to investigate diagnostic performance and reproducibility of M-NBI for minute gastric cancers up to 5 mm in diameter.

Patients and methods

Patients

Between January 2006 and August 2013, 30,725 esophagogastroduodenoscopies were performed at Fukuoka University Chikushi Hospital. The sample for this study comprises consecutive cases of minute gastric cancer selected from 646 cases of early gastric cancer resected using ESD endoscopic submucosal dissection. The controls comprise consecutive cases of minute non-cancer detected during esophagogastroduodenoscopies performed at Fukuoka University Chikushi Hospital during the same period. This retrospective study was approved by the Institutional Review Board of Fukuoka University Chikushi Hospital (IRB No. R12-041).

Endoscopy specification and procedure

Patients were administered the following mixture 30 min before endoscopic procedures: 100 mL of water with 20,000 units of pronase (Kaken Pharmaceutical, Tokyo, Japan), 1 g of sodium bicarbonate, and 10 mL of dimethylpolysiloxane (20 mg/mL, Horii Pharmaceutical Ind., Osaka Japan).

All procedures were performed using an Evis Lucera Spectrum system (Olympus Medical Systems Co., Tokyo, Japan) with a high-resolution upper GI zoom endoscope (GIF-Q240Z or GIF-H260Z, Olympus). The structure enhancement function of the video processor is set at level 4, 6, or 8 (level 4 or 6 for non-magnified observation and level 8 for magnified observation). Prior to the examination, a hood (MAJ-1989 for GIF-Q240Z, or MAJ-1990 for GIF-H260Z; Olympus) [9] is mounted on the tip of the endoscope to enable the endoscopist to consistently fix the mucosa at a distance of approximately 2 mm, at which maximal magnification of the endoscopic image can be obtained.

Before detailed inspection, adherent mucus is removed via water flushing. When a mucosal lesion is found during non-magnifying observation with WLI, CE with indigo

carmine is performed (Figs. 1a, 2a). After flushing out the indigo carmine dye from the lesion, the lesion is visualized using maximal magnification (Figs. 1b, 2b), employing gradual movements of the tip of the endoscope to bring the image into focus and a distally attached soft black hood to stabilize the tip of the endoscope.

Immediately after each endoscopic examination, the endoscopic findings from both CE and M-NBI were recorded on the database.

The CE and M-NBI images used in the study were taken by two endoscopists (S.F. and K.Y.), each with at least 3 years' experience in performing both CE and M-NBI procedures.

Endoscopic submucosal dissection (ESD) procedure

Endoscopic submucosal dissection procedures were performed in accordance with the previously reported method [10].

Handling of endoscopically resected specimens

Each resected specimen was placed on a flat board with the mucosal side facing upward, pinned at the edges with stainless steel pins, and fixed in a 20 % buffered formalin solution. The fixed specimen was serially sectioned at 2 mm intervals. According to the histopathological findings, the extent of the carcinoma was reconstructed on the macroscopic photograph as shown in Fig. 1c.

Histopathological examination

Final diagnoses were made after histopathological examination of biopsy specimens, or endoscopically resected specimens, by a highly experienced gastrointestinal pathologist (A.I.), who was blinded to the endoscopic findings. Histological diagnoses were made with reference to the revised Vienna classification [11] (C1: negative for neoplasia; C2: indefinite for neoplasia; C3: mucosal low-grade neoplasia [low-grade adenoma/dysplasia]; C4: mucosal high-grade neoplasia [4.1: high-grade adenoma/dysplasia; 4.2: noninvasive carcinoma (carcinoma in situ); 4.3: intramucosal carcinoma]; and C5: submucosal invasive carcinoma). For the purpose of this study, noninvasive carcinoma, intramucosal carcinoma, and submucosal invasive carcinoma were grouped together into one category, early cancer (Fig. 1d). All other categories were classified as non-cancer (Fig. 2d).

Inclusion and exclusion criteria

The inclusion and exclusion criteria for lesions in this study are given below.

Fig. 1 **a** Chromoendoscopy (CE) findings of a 2 mm 0-IIc type early gastric cancer. This lesion (arrow) was evaluated as not having an irregular margin and a spiny depressed area. **b** Magnifying endoscopy with narrow band imaging (M-NBI) findings of a 2 mm 0-IIc type early gastric cancer. A distinct DL (arrow) can be seen between the lesion and the non-cancerous mucosa, enclosing an irregular MV

pattern plus absent MS pattern. These findings are consistent with the diagnosis criteria for cancer. **c** Reconstruction of a well differentiated adenocarcinoma on the ESD resected specimen. The maximum diameter of this cancer is 2 mm. **d** Histopathological findings (HE staining) of the resected specimen show a well differentiated adenocarcinoma

Inclusion criteria for minute cancers

1. Lesion examined using CE.
2. Lesion examined using M-NBI.
3. Lesion completely resected *en bloc* using the ESD method.
4. Confirmed histological diagnosis of gastric cancer from ESD resected specimen.
5. Lesion measured histopathologically as no larger than 5 mm in greatest diameter (Fig. 1c).

Inclusion criteria for minute non-cancers

1. Lesion examined using CE.
2. Lesion examined using M-NBI.
3. Lesion diagnosed endoscopically as no larger than 5 mm (endoscopic measurement against width of open biopsy forceps).

4. Definitive histopathological diagnosis from biopsy specimen.

Exclusion criteria for minute cancers and non-cancers

1. CE and M-NBI images of the lesion are not recorded in the image filing system.
2. Morphological findings of the lesion are obscured by adherent mucous or hemorrhage associated with flushing.

Study design

A pair of images, one CE and one M-NBI, was supplied for each minute lesion, both cancerous and non-cancerous. The images were arranged in random order and

Fig. 2 **a** Chromoendoscopy (CE) findings of a 3 mm non-cancer lesion. This lesion (*arrow*) was evaluated as minute cancer using CE by the presence of both an irregular margin and a spiny depressed area. **b** Magnifying endoscopy with narrow band imaging (M-NBI) findings of a 3 mm non-cancer lesion. Although a demarcation line

(*arrow*) is identified, it encloses a regular MV pattern plus absent MS pattern. These findings are consistent with the diagnosis criteria for non-cancer. **c** Histopathological findings (HE staining) of a biopsy specimen show chronic gastritis with no malignant change

independently. An endoscopist with 7 years of experience in magnifying gastric endoscopy (T.N.) was asked to determine whether each image represented cancer or non-cancer, based on the diagnosis criteria outlined below. The endoscopist was not informed of the actual diagnoses or the number of cancers. Using the histopathological diagnosis as the gold standard, we analyzed the sensitivity, specificity, and diagnostic accuracy of both CE and M-NBI images in cancer diagnosis, and compared the diagnostic performance of the two methods. Next, an independent endoscopist (K.U.) blinded to the diagnoses from our institution was asked to determine cancer or non-cancer using the same CE and M-NBI images and the same diagnostic criteria, to provide a measure of interobserver variability. Finally, the first endoscopist (T.N.) was asked to repeat the same exercise two months later, to provide a measure of intraobserver variability.

Criteria for endoscopic diagnosis of cancer and non-cancer

The CE diagnosis criteria were defined as follows: for depressed and flat lesions, the presence of both irregular margins and spiny depressed areas [6] (Fig. 1a); for elevated lesions, both irregular surfaces and margins. The M-NBI diagnosis criteria were as per the VS classification system [9, 12] of Yao et al.: lesions presenting with (1) an irregular microvascular (MV) pattern with a demarcation line (DL) and/or (2) an irregular microsurface (MS) pattern with a demarcation line (DL) (Fig. 1b) were diagnosed as cancers.

Statistical analyses

Statistical analysis was performed using SPSS software (SPSS 16.0J for Windows).

We determined the 95 % confidence interval (CI) for comparisons of sensitivity, specificity, and accuracy between CE and M-NBI. Mann–Whitney *U* test was used to compare mean values between groups, and the McNemar test to compare frequencies between groups. A *p* value <0.05 was considered significant.

Results

Demographic baseline data

A total of 103 lesions were identified using CE and M-NBI procedures at Fukuoka University Chikushi Hospital between January 2006 and August 2013 that satisfied the inclusion criteria. These 103 lesions were identified in 99 patients (69 male, 30 female), comprising 32 minute cancer lesions in 32 patients (21 male, 11 female) and 71 minute non-cancer lesions in 67 patients (48 male, 19 female). Macroscopic classifications were made in accordance with the Paris classification system [13] (Table 1).

Diagnostic performance

From the CE images, 14 of the 32 minute cancer lesions were correctly diagnosed as cancer, while 18 were diagnosed as non-cancer. Of the 71 non-cancer lesions, 13 were diagnosed as cancer and 58 as non-cancer (Table 2).

From the M-NBI images, 25 of the 32 minute cancer lesions were correctly diagnosed as cancer and 7 as non-cancer, whereas 5 of the 71 non-cancer lesions were diagnosed as cancer and 66 as non-cancer (Table 3).

For minute cancer lesions, CE showed sensitivity of 43.7 % (95 % CI, 26.5–61.0 %), specificity of 81.6 % (95 % CI, 72.6–90.6 %), and diagnostic accuracy of 69.9 % (95 % CI, 61.0–78.6 %). The M-NBI images yielded sensitivity of 78.0 % (95 % CI, 64.0–92.0 %), specificity of 92.9 % (95 % CI, 87.0–98.9 %), and diagnostic accuracy of 88.3 % (95 % CI, 82.0–94.5 %).

The sensitivity and diagnostic accuracy of M-NBI were significantly higher than those of CE (Table 4).

Interobserver variability

The κ values for the two endoscopists T.N. and K.U. were 0.08 (slight agreement) for the CE images and 0.56 (moderate agreement) for the M-NBI images.

Intraobserver variability

The κ values for endoscopist T.N. were 0.38 (fair agreement) for the CE images and 0.65 (substantial agreement) for the M-NBI images.

Table 1 Demographic characteristics of the subjects (*n* = 103)

	Minute cancer (<i>n</i> = 32)	Minute non-cancer (<i>n</i> = 71)	<i>p</i> value
<i>Location of lesion</i>			
U	1	3	1.00*
M	12	28	
L	19	40	
<i>Size of lesion</i>			
Mean (mm)	3.8	3.3	0.012**
SD (mm)	1.13	0.92	
<i>Macroscopic type</i>			
0-IIa	11	11	0.058*
0-IIb	2	12	
0-IIc	19	48	

U upper stomach, *M* middle stomach, *L* lower stomach, *NS* not significant, *SD* standard deviation, *0-IIa* superficial elevated, *0-IIb* flat, *0-IIc* superficial shallow depressed

* Chi square test; ** Mann–Whitney *U* test

Table 2 CE diagnosis of minute gastric lesions (*n* = 103)

	CE	
	Cancer	Non-cancer
<i>Histopathological diagnosis</i>		
Cancer	14	18
Non-cancer	13	58
<i>CE chromoendoscopy</i>		

Table 3 M-NBI diagnosis of minute gastric lesions (*n* = 103)

	M-NBI	
	Cancer	Non-cancer
<i>Histopathological diagnosis</i>		
Cancer	25	7
Non-cancer	5	66
<i>M-NBI magnifying endoscopy with narrow band imaging</i>		

Table 4 Sensitivity, specificity, and diagnostic accuracy of CE and M-NBI for minute lesions (*n* = 103)

	CE	M-NBI	<i>p</i> value
Sensitivity (%)	43.7	78.0	0.003
(95 % CI)	(26.5–61.0 %)	(64.0–92.0 %)	
Specificity (%)	81.6	92.9	0.057
(95 % CI)	(72.6–90.6 %)	(87.0–98.9 %)	
Diagnostic accuracy (%)	69.9	88.3	0.000
(95 % CI)	(61.0–78.6 %)	(82.0–94.5 %)	

CE chromoendoscopy, *M-NBI* magnifying endoscopy with narrow band imaging, *CI* confidence interval

Discussion

This study demonstrated that M-NBI offers significantly greater sensitivity and diagnostic accuracy than CE for minute lesions. While CE is useful and the most popular image-enhanced endoscopic method for the diagnosis of early gastric cancer [1, 2], it is less accurate for minute lesions up to 5 mm in diameter [14–18]. Our study has shown that M-NBI is useful in the differential diagnosis between cancer and non-cancer in minute lesions up to 5 mm in diameter.

The authors have previously reported a case in which M-NBI was useful in detecting minute gastric cancers where an accurate diagnosis was not possible with CE [3]. Similarly, Sakaki et al. [19] observed gastric mucosal patterns using magnified endoscopy with white-light imaging (M-WLI) in 15 cases of flat and depressed minute gastric cancers, and were able to diagnose cancer in 12 cases based on the morphological characteristics. Since the study did not include minute non-cancers, however, it did not comprehensively test diagnostic ability. In addition, M-WLI showed poor diagnostic accuracy for moderately to well differentiated cancers with minimal structural atypia, as well as poorly differentiated adenocarcinomas or signet ring cell carcinomas with no abnormalities of the cryptal structure [20].

Several studies have reported the usefulness of magnifying chromoendoscopy for minute lesions of the colon measuring up to 5 mm [21–23]. Tung et al. [21] for example, reported that pit pattern analysis of colorectal lesions using magnifying colonoscopy is a useful and objective tool for differentiating neoplastic from non-neoplastic lesions of the large bowel. Meanwhile, M-NBI has also been used successfully on small epithelial tumors of the colon. Sano et al. [24] reported that observation of surface microcapillary vessels using M-NBI was a useful and simple method for differentiating non-neoplastic and neoplastic colorectal polyps smaller than 10 mm.

As far as the authors are aware, however, the present study is the first to conclusively demonstrate the superior diagnostic ability of M-NBI compared to CE in diagnosing gastric cancers and non-cancerous lesions of the stomach up to 5 mm in diameter.

In this study, 7 cancer lesions were incorrectly diagnosed as non-cancers using M-NBI. We analyzed the associated endoscopic images, histopathological findings, and attending physicians' notes to determine why these diagnoses were incorrect. We found that in five of the seven cases, examinations had been performed by the attending physician after taking biopsies. In other words, the appearance was of a biopsy scar, with no visible cancerous characteristics by M-NBI. In other words, minute cancers are so small that a post-biopsy examination will

only reveal a deficit in the mucosal epithelium or benign regenerating epithelium in the healing stage, causing misdiagnosis. In the case of another lesion, even though a DL was detected using M-NBI, the irregularities in the microvascular pattern were so mild that a diagnosis of cancer could not be made, causing the misdiagnosis. The remaining lesion was signet ring cell carcinoma. The surface of the carcinoma was covered with noncancer. Therefore neither irregular microvascular pattern nor irregular microsurface pattern was seen. These particular lesions are considered to be at the limits of the diagnostic criteria used in the study.

Similarly, we investigated the reasons five non-cancerous lesions were incorrectly diagnosed as cancers using M-NBI. In two of these lesions, the finding of minor irregularities in the microvascular pattern prompted a cancer diagnosis. In another lesion, the magnified endoscopic images were not taken in the on-face view, and the low magnifying ratio also contributed to the error. The remaining two errors were considered genuine errors of interpretation.

Notwithstanding its limitations as a retrospective study, this study did show that minute cancers are relatively uncommon, at just 32 lesions out of more than 30,000 upper gastrointestinal endoscopies performed.

As a tertiary referral hospital, our institution handles referrals of post-biopsy gastric cancer patients. As a result, 29 of the 32 minute gastric lesions in the present study had undergone biopsy before endoscopic imaging. Investigation limited solely to naïve lesions would require a prospective study, but the incidence of minute gastric cancer is low (32 of 30,725 upper gastrointestinal endoscopy cases at our institution). Accordingly, this retrospective study can be considered a necessary precursor to a prospective study. An evaluation of the true usefulness of M-NBI will require a joint prospective trial involving multiple institutions with large subject numbers, based on the current findings.

In the routine clinical setting, M-NBI examinations follow conventional and CE examinations, and all of these findings are used to make endoscopic diagnoses. In this study, however, we used previously obtained CE and M-NBI images as the basis for independent differential diagnoses of cancer versus non-cancer. A possible limitation of this study is therefore its lack of consistency with actual clinical practice. On the other hand, independent evaluations using CE and M-NBI mean that we do not have to consider any carrying-over effect, an advantage of the study method we employed.

The κ value for interobserver variability for CE examination of minute lesions was 0.08 (slight agreement). The corresponding value for M-NBI was considerably higher at 0.56 (moderate agreement). The κ values for intraobserver variability were 0.38 (slight agreement) for CE, and

considerably higher at 0.65 (moderate agreement) for M-NBI. When observer agreement is greater than chance, the κ value ranges from 0 (absence of agreement) to 1 (complete agreement), with 0.00–0.20 corresponding to slight agreement, 0.21–0.40 to fair agreement, 0.41–0.60 to moderate agreement, 0.61–0.80 to substantial agreement, and 0.81–1.00 to almost perfect agreement. According to our results, M-NBI shows greater reproducibility than CE for the diagnosis of minute gastric cancers.

In conclusion, this study is the first to demonstrate that M-NBI is superior to CE for the diagnosis of minute gastric cancers. Our findings also suggest that M-NBI has greater reproducibility than CE for the endoscopic diagnosis of minute gastric cancers.

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