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ORIGINAL ARTICLE

Diagnostic performance and limitations of magnifying narrow-band imaging in screening endoscopy of early gastric cancer: a prospective multicenter feasibility study

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Abstract
Background Curative treatment of patients with gastric cancer requires reliable detection of early gastric cancer. Magnifying endoscopy with narrow-band imaging (M-NBI) is useful for the accurate preoperative diagnosis of early gastric cancer. However, the role of M-NBI in screening endoscopy has not been established. The aims of this study were to determine the feasibility and limitations of M-NBI in screening endoscopy.
Methods We conducted a multicenter prospective uncontrolled trial of patients undergoing routine screening endoscopy patients. We determined the diagnostic accuracy, sensitivity and specificity of M-NBI according to the degree of certainty and need for biopsy, as assessed using the VS (vessel plus surface) classification system. We analyzed the endoscopic and histopathological characteristics of both false negative and false positive high confidence M-NBI diagnoses. We then developed a provisional diagnostic strategy based on the diagnostic performance and limitations identified in this study.
Results A total of 1097 patients were enrolled in the study. We analyzed 371 detected lesions (20 cancers and 351 non-cancers). The accuracy, sensitivity and specificity of high confidence M-NBI diagnoses were 98.1, 85.7 and 99.4 %, respectively. The false negative case was a pale mucosal lesion with tissue diagnosis of signet-ring cell carcinoma. Exclusion of pale mucosal lesions increased the accuracy, sensitivity and specificity of high confidence M-NBI diagnoses to 99.4, 100 and 99.4 %, respectively. We therefore propose a practical strategy targeting non-pale mucosal lesions.

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Conclusions With a refined strategy considering its limitations, M-NBI can act as an "optical biopsy" in screening endoscopies.

Keywords Gastric cancer · Magnifying endoscopy · Narrow-band imaging · Screening endoscopy · VS classification

Abbreviations

M-NBI	Magnifying endoscopy with narrow-band imaging
C-WLI	Conventional endoscopy with white-light imaging
STARD	Standards for the Reporting of Diagnostic Accuracy Studies
VS	Vessel plus surface
MV	Microvascular
MS	Microsurface
CI	Confidence interval
EGD	Esophagogastroduodenoscopy

Background

Gastric cancer is the second leading cause of cancer death worldwide [1]. Detection at an early stage is important in obtaining good outcomes for patients with gastric cancer. Magnifying endoscopy with narrow-band imaging (M-NBI) is a recently developed, powerful optical image enhanced endoscopic technique that has become commonplace in the field of gastrointestinal endoscopy [2]. We previously demonstrated excellent real time diagnostic performance in making an accurate endoscopic diagnosis of early gastric cancer, in a multicenter, prospective, randomized controlled trial in which we performed M-NBI following thorough examinations using conventional endoscopy with white light imaging (C-WLI) [3]. However, the conditions differed from those in screening endoscopy in actual clinical practice in the following ways. (1) We only included patients at high risk of developing gastric cancer. (2) The diameter of the target lesions was limited to $\leq$10 mm. (3) The macroscopic type of lesions was also limited to the superficial depressed type. The validity of the clinical application of M-NBI in routine screening endoscopy has therefore yet to be confirmed. In other words, no studies have reported the feasibility and limitations of M-NBI, irrespective of size or macroscopic type, in a prospective study. Furthermore, it is not clear how M-NBI can contribute to cost effectiveness, in other words how many endoscopic biopsies are required to diagnose one cancer.

Accordingly, the first aim of this study was to investigate the real time diagnostic performance of M-NBI in screening endoscopy for circumscribed mucosal lesions of all macroscopic types and sizes. The next aims of this study were to identify the limitations of M-NBI (endoscopic and pathological characteristics of false negative and false positive cases), and to determine the number of biopsies for confirming the diagnosis of gastric cancer. Finally, we aimed to propose an efficient endoscopic diagnostic strategy for M-NBI in screening endoscopy.

Patients and methods

Study design and participants

This prospective uncontrolled multicenter feasibility study was conducted at 7 centers in Japan, in accordance with the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) initiative [4], and the Declaration of Helsinki.

Consecutive patients who underwent screening upper gastrointestinal endoscopy at each center between October 2009 and November 2010 were considered for enrollment in this study. We included patients who gave informed consent before the endoscopic examinations. We excluded patients for whom endoscopic diagnoses had already been made, those in whom biopsies were not taken for cancer screening (e.g. for detection of *Helicobacter pylori*-associated gastritis), those patients who underwent gastrectomy, those taking medicine associated with bleeding tendency, and those with severe underlying diseases.

Written informed consent was obtained from each participant, and the study was approved by the institutional review board of each participating hospital. The clinical trial number of this study was UMIN 000004045.

Participating endoscopists

All endoscopic examinations were performed at 7 centers by 20 endoscopists accredited by the Japan Gastroenterological Endoscopy Society. The median (range) duration of experience of gastrointestinal endoscopy and upper gastrointestinal M-NBI were 10 (5–16) years and 3 (0.5–5) years, respectively. All participating endoscopists underwent instruction with the textbook entitled "Zoom gastroscopy: Magnifying endoscopy in the stomach [5]", written by the lead researcher (K. Y.) before study commencement, in order to minimize diagnostic variation between participating endoscopists.

Endoscopy system and endoscopy procedures

The NBI system is an optical image-enhanced technology containing a narrow-band filter with central wavelengths of

415 and 540 nm. Since light with these wavelengths is well absorbed by hemoglobin and propagates shallowly within the mucosal tissue, the subepithelial microvascular architecture and the mucosal microsurface structure can be visualized in high contrast. Details of these principles have been described elsewhere [6, 7].

We used the electronic endoscopy system with NBI (Evis Lucera Spectrum System, Olympus Medical Systems, Tokyo, Japan), a high-resolution liquid crystal monitor (OEV191H; Olympus), and high-resolution optical magnifying endoscopes (GIF-Q240Z, GIF-H260Z; Olympus). The maximal resolution power of these scopes is 7.9 μm for the GIF-Q240Z, and 5.6 μm for the GIF-H260Z. To standardize the conditions under which magnified endoscopic images were obtained, before insertion of the scope we mounted a black soft hood attachment (MAJ-1988 for the GIF-Q240Z, MAJ-1989 for the GIF-H260Z; Olympus) on the tip of the scope, allowing the endoscopist to easily and consistently fix the distance between the tip of the scope and the target lesion at maximum magnification. The video processor was constantly set as follows: the structure enhancement function was set at the B6 level for C-WLI, and B8 for M-NBI, with the color mode fixed at level 1.

Endoscopic screenings were performed by a single endoscopist using C-WLI according to the systematic screening protocol for the stomach [8]. The patient's preparation was the same as for conventional endoscopy [9]. When a circumscribed mucosal lesion showing changes in surface or color [9, 10] was detected, the lesion was subsequently examined at maximal magnification using NBI. According to the predetermined criteria, the M-NBI examination was performed by the same endoscopist, without any consultation with other endoscopists, and the assisting physician immediately recorded the results on the uniform case record form. One target biopsy was then taken from each detected lesion. After the endoscopic examination was completed, the case record form was sent by fax to the data center at the Department of Molecular-Targeting Cancer Prevention, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, within 3 days, without waiting for the histopathological diagnosis. A full description of the endoscopic procedures followed, and evaluations, has been published elsewhere [11–13].

M-NBI diagnostic criteria

We employed the established VS (vessel plus surface) classification system for the M-NBI diagnosis of early gastric cancer (Fig. 1) [11], the most commonly applied system in clinical practice [3, 12–25]. Briefly, when we detect a mucosal lesion using C-WLI, we analyze the subsequent M-NBI findings. Firstly, using M-NBI, we determine whether a demarcation line is present between the mucosal lesion and the background surrounding mucosa. If the demarcation line is absent, a non-cancer diagnosis is made. If the demarcation line is present, we analyze the microvascular (MV) and microsurface (MS) patterns of the target lesion independently. The MV pattern is classified into 3 categories, namely a regular/irregular/absent MV pattern. Similarly, the MS pattern is classified into 3 categories, a regular/irregular/absent MS pattern. We then make the diagnosis of cancer according to the following criteria.

1. Presence of an irregular microvascular (MV) pattern with a demarcation line
2. Presence of an irregular microsurface (MS) pattern with a demarcation line

If either or both criteria are fulfilled, an endoscopic diagnosis of cancer can be made. Otherwise, an endoscopic diagnosis of non-cancer will be made. The details of the VS classification system have been reported elsewhere [9, 11].

Endoscopic diagnosis according to degree of certainty and need for biopsy

In order to determine how many biopsies are needed to diagnose one cancer, we set the grade of endoscopic diagnosis according to certainty and assessment of the need for biopsy.

Grade 1: non-cancer with high degree of confidence. The lesion can be diagnosed as non-cancer from the endoscopic findings alone. Biopsies of the lesion do not need to be taken under normal conditions.

Grade 2: non-cancer with low degree of confidence. The lesion has the appearance of non-cancer from the endoscopic findings. However, biopsies need to be taken from the lesion to confirm the diagnosis.

Grade 3: indeterminate. The lesion is indeterminate for non-cancer or cancer from the endoscopic findings alone. Therefore, biopsies need to be taken from the lesion to make a definitive diagnosis.

Grade 4: cancer with low degree of confidence. The lesion is suspicious for cancer from the endoscopic findings. However, biopsies need to be taken from the lesion to confirm the diagnosis.

Grade 5: cancer with high degree of confidence. The lesion can be diagnosed as cancer from the endoscopic findings alone. Biopsies of the lesion do not need to be taken under normal conditions.

For the purpose of this study, we reclassified Grades 1–3 as non-cancer and Grade 4 and Grade 5 as cancer, while Grade 1 and Grade 5 as "high confidence prediction" and Grades 2–4 as "low confidence prediction" [26, 27].

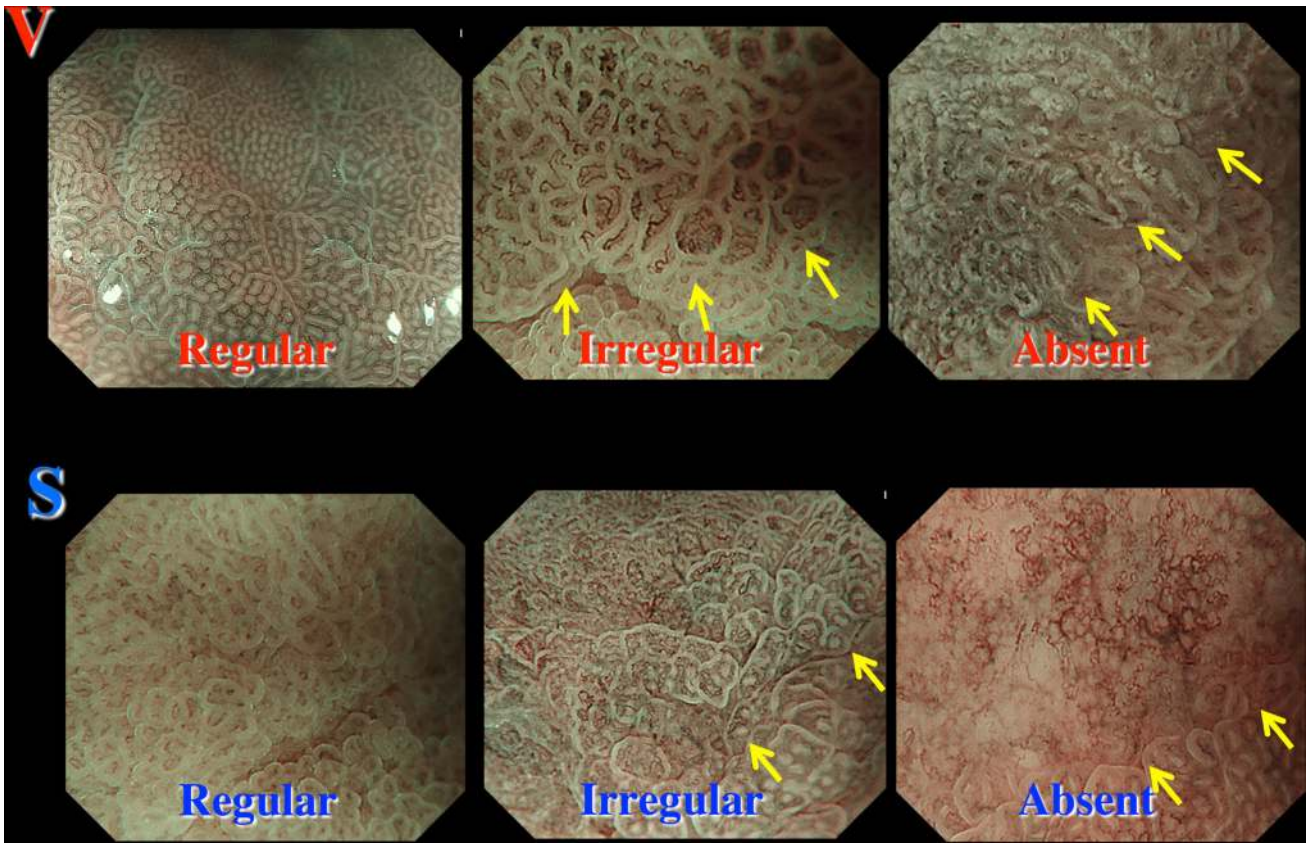


Fig. 1 VS classification using M-NBI (Reproduced with permission from Endoscopy 2009; 41:462–7 [11]). *V* microvascular pattern, classified as regular/irregular/absent. *S* microsurface pattern, classified as regular/irregular/absent

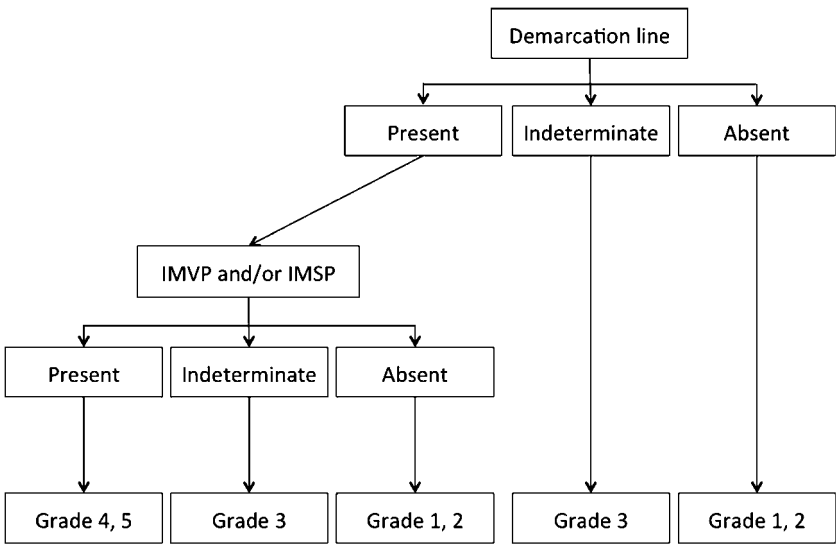


Fig. 2 Diagnostic flow diagram demonstrating the correlation between the VS (vessel plus surface) classification and Grades 1–5. *IMVP* irregular microvascular pattern, *IMSP* irregular microsurface pattern. Grade 1: non-cancer with high degree of confidence (no need for biopsies); Grade 2: non-cancer with low degree of confidence (biopsies required); Grade 3: indeterminate (biopsies required); Grade 4: cancer with low degree of confidence (biopsies required); Grade 5: cancer with high degree of confidence (no need for biopsies)

The diagnostic flow diagram shown in Fig. 2 demonstrates the correlation between the VS classification [28] and Grades 1–5. In this algorithm, when one of each finding is difficult for the endoscopist to determine whether it is present or absent, the finding is categorized as indeterminate.

Gold standard

Definitive diagnoses were made on the basis of histopathological examination of biopsy specimens or endoscopically resected specimens by highly experienced gastrointestinal pathologists in each institute, who were

blinded to the M-NBI findings. Histopathological diagnoses were made with reference to the revised Vienna classification [C1: negative for neoplasia; C2: indefinite for neoplasia; C3: mucosal low-grade neoplasia (low-grade dysplasia/adenoma); C4: mucosal high-grade neoplasia (4.1: high-grade dysplasia/adenoma; 4.2: noninvasive carcinoma (carcinoma in situ); 4.3: intramucosal carcinoma); and C5: submucosal invasion by tumor] [29, 30]. For the purpose of this study, C4 and C5 were grouped together into one category, known as cancer, and all other classifications as non-cancer [15].

End points

The primary aim of this feasibility study was to investigate the real time diagnostic performance (accuracy, sensitivity and specificity) of M-NBI, based on the degree of certainty (high or low confidence).

Another end point was the identification of the limitations of M-NBI in screening endoscopy when the endoscopist made a high confidence M-NBI diagnosis without biopsy. Limitations are defined as follows: (1) false negative cases with Grade 1 endoscopic diagnoses (non-cancer with high degree of confidence, no need for biopsies), but the pathological diagnosis was cancer, and (2) false positive cases with Grade 5 endoscopic diagnoses (cancer with high degree of confidence, no need for biopsies), but the pathological diagnosis was non-cancer. The other end points were to investigate the diagnostic performance for the subgroup of lesions after exclusion of limited cases; to identify the number of biopsies needed to diagnose one cancer, and to propose a strategy for M-NBI in screening endoscopy with reference to the above results of this prospective study.

The estimated number of biopsies needed to detect one cancer was calculated as follows:

$$\text{Number of biopsies} = \text{number of lesions Grade 2} - 4/\text{number of detected cancers}$$

Statistical analysis

Statistical analyses were performed using SPSS software version 10.5J for Windows (SPSS Inc., Chicago, IL, USA). Diagnostic accuracy, sensitivity, specificity are presented as percentages with 95 % confidence intervals (CI). Continuous valuables are expressed as median with range. Comparisons of incidences between two groups were conducted using Pearson's Chi square test or Fisher's exact test. Analyses of the difference between two groups were

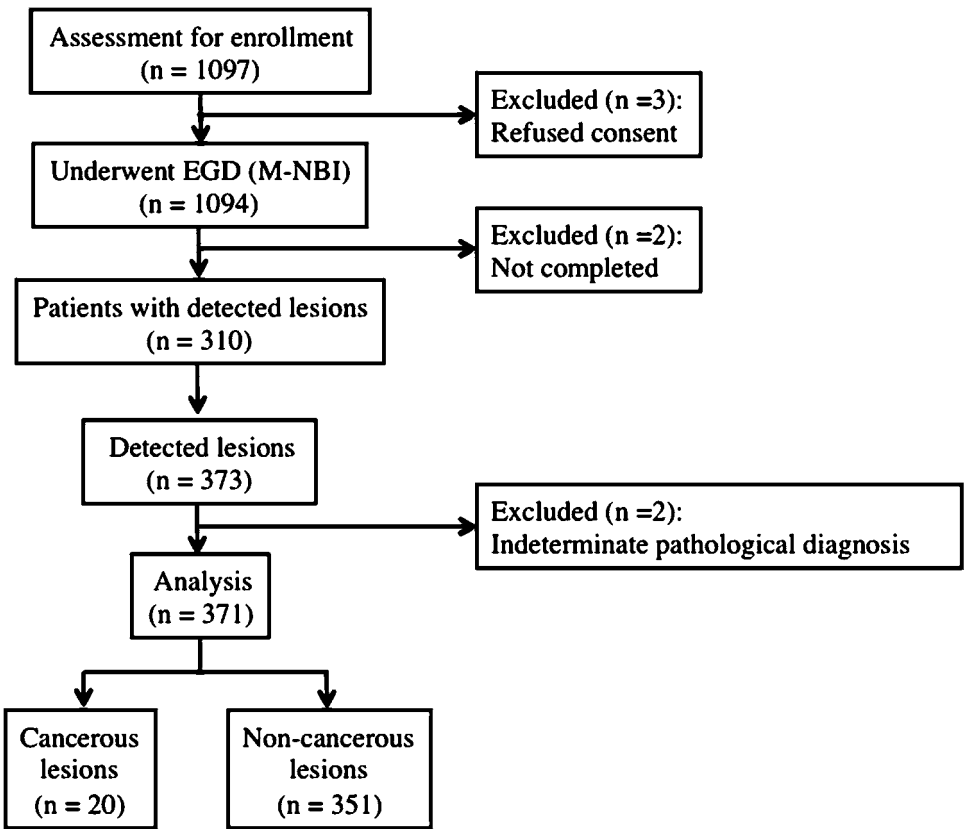


Fig. 3 Enrollment of patients and analysis of lesions. *EGD* esohagogastroduodenoscoy, *M-NBI* Magnifying endoscopy with narrow-band imaging

Table 1 Demographic characteristics of analyzed lesions according to histological diagnosis

	Cancer ($n = 20$)	Non-cancer ($n = 351$)	P value
Size (mm)			
Mean	18.8	7.3	0.002
SD	15.8	6.3	
Location			
Lower third	7	150	0.86
Middle third	8	137	
Upper third	5	64	
Macroscopic type[a]		0.39	
0 I	0	12	
0 IIa	2	61	
0 IIb	1	51	
0 IIc	14	217	
0 III	0	7	
Unclassified	3	3	
Endoscopic color			
Reddened	13	262	0.31
Same	5	50	
Pale	2	39	

[a] Macroscopic types were determined using the Paris classification

Table 2 Endoscopic diagnoses using M-NBI for all lesions according to grade of certainty

Grade	Cancer	Non-cancer	Total
1	1	170	171
2	2	116	118
3	5	58	63
4	6	6	12
5	6	1	7
Total	20	351	371

M-NBI magnifying endoscopy with narrow-band imaging, *Grade 1* non-cancer with high degree of confidence (no need for biopsies), *Grade 2* non-cancer with low degree of confidence (biopsies required), *Grade 3* indeterminate (biopsies required), *Grade 4* cancer with low degree of confidence (biopsies required), *Grade 5* cancer with high degree of confidence (no need for biopsies)

made using Student's t test. $P < 0.05$ was considered significant.

Results

Between October 2009 and November 2010, 1097 patients were enrolled in the study. Three patients refused to participate. Accordingly, 1094 patients were registered and underwent endoscopic screening. The procedure was discontinued for 2 patients because of severe vomiting reflex. Endoscopic screening was completed for 1092 patients, with no reported adverse events.

A total of 373 lesions were detected from 310 patients screened using C-WLI followed by M-NBI. No definite pathological diagnosis was possible for 2 of the 373 lesions due to inadequate biopsy specimens, leaving 371 lesions suitable for the final analysis (Fig. 3). The median age (range) of the analyzed patients was 66 (30–90) years. The male: female ratio was 183:127. The demographic characteristics of the detected lesions is shown in Table 1. The final diagnosis was cancer in 20 of the 371 lesions, from histopathological examination of biopsy or resected specimens. The histological type of the detected cancers was differentiated (intestinal) in 14 lesions, and undifferentiated (diffuse) in 6. Fourteen cancers were resected using endoscopic submucosal dissection, and 6 were resected surgically.

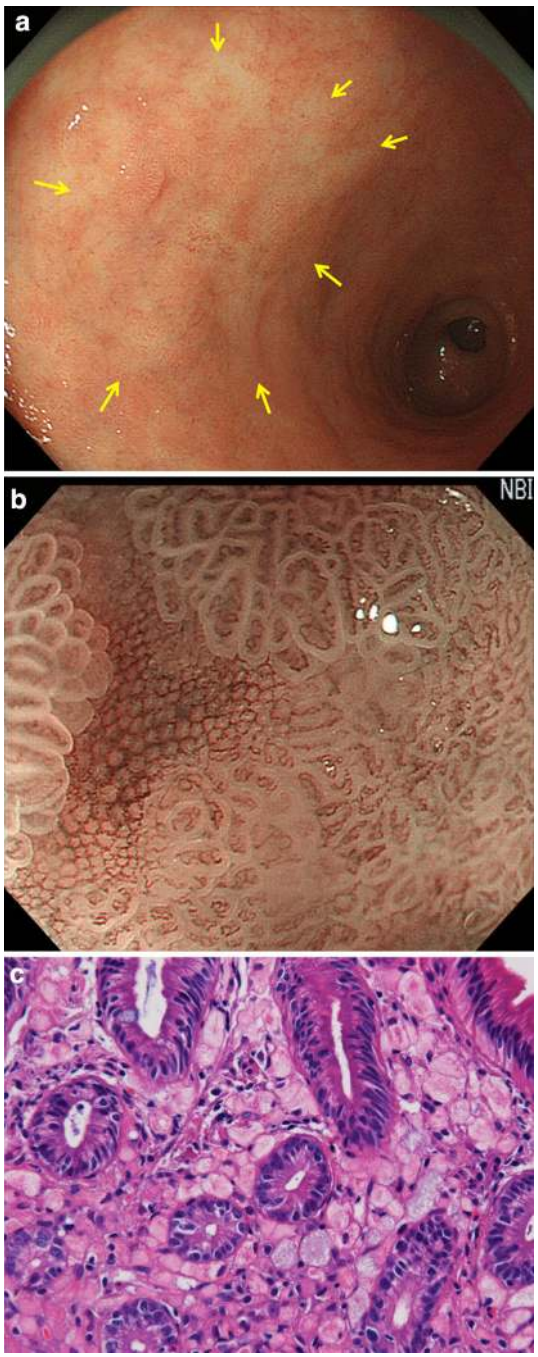
Table 2 shows the endoscopic diagnoses for all lesions according to the degree of certainty. The diagnostic performance is shown in Table 3 when we regrouped Grades 1–3 as non-cancer, and Grade 4 and 5 as cancer, and when we regrouped Grade 1 and 5 as high confidence predictions, and Grades 2–4 as low confidence predictions. The accuracy and the specificity for all lesions exceeded 95 %, while the sensitivity was only 60 %. No significant differences were seen in accuracy, sensitivity or specificity between high and low confidence prediction groups.

Referring to Table 2, there was only one false negative case, with a Grade 1 endoscopic diagnosis (non-cancer with high degree of confidence, no need for biopsies), but a pathological diagnosis of cancer, as shown in Fig. 4. When we carefully reviewed the C-WLI and M-NBI findings

Table 3 Diagnostic performance of M-NBI for all gastric lesions

	All lesions (95 % CI) ($n = 371$)		High confidence prediction (95 % CI) ($n = 178$)		Low confidence prediction (95 % CI) ($n = 193$)	
Accuracy	96.1	(94.1–98.1)	98.1	(96.6–99.6)	93.3	(89.8–96.8)
Sensitivity	60.0	(38.5–81.5)	85.7	(59.8–100)	46.2	(19.1–73.3)
Specificity	98.0	(96.5–100)	99.4	(98.2–100)	96.7	(94.1–99.3)

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



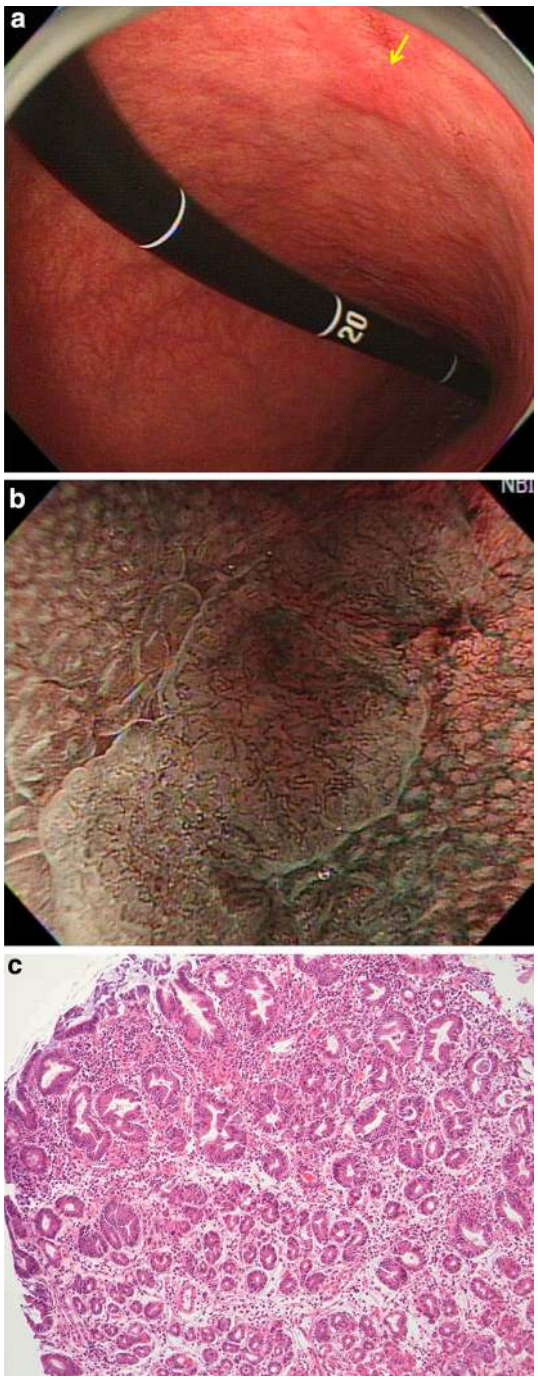
◀**Fig. 4** A false negative case with high confidence M-NBI diagnosis (Grade 1). **a** Endoscopic findings using C-WLI. A pale mucosal lesion (*arrows*) was detected during screening endoscopy. The morphology of this lesion is slightly depressed and irregularly demarcated. **b** Endoscopic findings using M-NBI. The VS classification of this lesion was regular MV pattern and regular MS pattern without a demarcation line. Therefore the M-NBI diagnosis was "Grade 1: Non-cancer with high degree of confidence. The lesion can be diagnosed as non-cancer from the endoscopic findings alone. Biopsies of the lesion do not need to be taken under normal conditions." **c** However, the histopathological findings of biopsy specimens taken from this lesion were of signet-ring cell carcinoma cells infiltrating beneath the surface epithelium showing intestinal metaplasia. The histopathological findings of the surgically resected specimen were showed a signet-ring cell carcinoma 18 mm in diameter, confined to the lamina propria mucosae. *M-NBI* Magnifying endoscopy with narrow-band imaging, *C-WLI* conventional endoscopy with white-light imaging, *VS classification* vessel plus surface classification, *MV* microvascular, *MS* microsurface

together with the histopathological findings, C-WLI shows a pale superficial depressed lesion, whereas M-NBI demonstrates a regular MV pattern plus regular MS pattern without a demarcation line. Accordingly, even after an intensive review of the M-NBI findings, the endoscopic diagnosis was non-cancer with a high degree of confidence. The histopathological findings of both biopsied and surgically resected specimens revealed a signet-ring cell carcinoma 18 mm in diameter, limited to the mucosa (Fig. 4c). There was also one false positive case, with a Grade 5 endoscopic diagnosis (cancer with high degree of confidence, no need for biopsies), with a pathological diagnosis of non-cancer, as shown in Fig. 5. When we carefully reviewed the C-WLI and M-NBI findings together with the histopathological findings, C-WLI shows a reddened superficial elevated lesion, whereas M-NBI demonstrates a regular MV pattern plus regular MS pattern with a demarcation line, although the real time M-NBI findings were recorded as an irregular MV pattern plus irregular MS pattern. The reason for this false positive result was therefore considered to be an error of interpretation.

Analysis of the false negative and false positive cases, when we exclude the 41 lesions showed as pale color using C-WLI, interestingly, there were no Grade 1 false negative lesions in the subgroup comprising 330 reddened and same colored lesions, as shown in Table 4. In this subgroup, the diagnostic performance in the high confidence prediction group ($n = 161$) was remarkably high, with accuracy, sensitivity and specificity of 99.4, 100 and 99.4 %, respectively (Table 5). Accordingly, since the diagnostic performance is excellent in the subgroup comprising reddened and same colored lesions with high confidence predictions, the number of lesions with low confidence predictions requiring biopsies was in fact 169 (Table 5). In addition, the number of cancers detected in this subgroup was 18. The number of biopsies needed to diagnose one cancer was therefore calculated to be 9.4 (169/18) when we targeted mucosal lesions with reddened/same color.

Discussion

With regard to overall diagnostic performance, the accuracy and specificity of M-NBI were excellent at 96.1 and 98.0 %, respectively, while the sensitivity was low at only 60.0 %. Nevertheless, in the high confidence prediction group, the sensitivity was 85.7 %, comparable to that in an



◀**Fig. 5** A false positive case with high confidence M-NBI diagnosis (Grade 5). **a** Endoscopic findings using C-WLI. A reddened mucosal lesion (*arrow*) was detected during screening endoscopy. The morphology of this lesion is superficial elevated. **b** Endoscopic findings using M-NBI. The VS classification of this lesion was irregular MV pattern and irregular MS pattern with a demarcation line. Therefore the real-time M-NBI diagnosis was "Grade 5: Cancer with high degree of confidence. The lesion can be diagnosed as cancer from the endoscopic findings alone. Biopsies of the lesion do not need to be taken under normal conditions." Nevertheless, when we carefully reviewed the M-NBI findings, the VS classification of this lesion was revised to a regular MV pattern plus regular MS pattern with a demarcation line. In other words, the diagnosis was corrected to "non-cancer". **c** Histopathological examination of biopsy specimens taken from this lesion revealed chronic active gastritis. *M-NBI* magnifying endoscopy with narrow-band imaging, *C-WLI* conventional endoscopy with white-light imaging, *VS classification* vessel plus surface classification, *MV* microvascular, *MS* microsurface

earlier well-designed study targeting small superficial depressed lesions [3].

One of the most clinically relevant outcomes of this study is that we could identify false negative and false positive cases in a prospectively designed multicenter feasibility study including a large number of cases. In this study, we theoretically classified endoscopic diagnoses into 5 grades according to the degree of certainty and need for biopsy, in order to determine the limitations of M-NBI and the estimated number of biopsies required to make a confirmed diagnosis. Accordingly, for Grade 1 and Grade 5 endoscopic diagnoses, biopsies were not taken. It is important for screening endoscopies to avoid false negative diagnoses. Taking into consideration the significant disadvantage, we determined the diagnostic performance after exclusion of lesions seen as pale colored using C-WLI. In this subgroup, the accuracy, sensitivity and specificity in the high confidence group were excellent at 99.4, 100 and 99.4 %, respectively. Therefore, we suggest that pale depressed lesions may be limitations of M-NBI, because early gastric cancers of the undifferentiated type/signet-ring cell type are often detected as pale flat/depressed lesions using C-WLI, and do not show any findings characteristic of cancer even with M-NBI, as we previously reported in retrospective studies [12, 27]. In other words, when we perform screening endoscopy, good indications for M-NBI are circumscribed lesions which show reddened or the same color as the background mucosa using C-WLI. Mucosal lesions seen as pale colored using C-WLI are not indications for M-NBI, but rather for taking biopsies from the target lesion.

Accordingly, from the results of this study, with consideration of the degree of diagnostic certainty and the need for biopsy, we devised a provisional strategy for screening endoscopy using M-NBI, as shown in Fig. 6. Briefly, a circumscribed mucosal lesion is detected using C-WLI. If the mucosal lesion is reddened or the same color as the background mucosa, M-NBI should be performed to make the diagnosis of either cancer or non-cancer. If the M-NBI diagnosis can be made with a high degree of confidence, this obviates the need for biopsy, but if the degree of confidence is low we need to take biopsies to obtain a histopathological diagnosis. When a mucosal lesion is pale colored, we take biopsies to make a definitive diagnosis.

When we limited the indication to mucosal lesions reddened or the same color using C-WLI, the estimated number of biopsies required to detect one cancer was 9.4.

Table 4 Endoscopic diagnoses using M-NBI for reddened/same-colored mucosal lesions according to grade of certainty

Grade	Cancer	Non-cancer	Total
1	0	154	154
2	2	100	102
3	5	52	57
4	5	5	10
5	6	1	7
Total	18	312	330

M-NBI magnifying endoscopy with narrow-band imaging, *Grade 1* non-cancer with high degree of confidence (no need for biopsies), *Grade 2* non-cancer with low degree of confidence (biopsies required), *Grade 3* indeterminate (biopsies required), *Grade 4* cancer with low degree of confidence (biopsies required), *Grade 5* cancer with high degree of confidence (no need for biopsies)

Initially, we intended to compare the number of biopsies using C-WLI with a historical control. However, after completing the trials, the number of enrolled patients in the historical control over a certain period were in fact quite different from this prospective study. Therefore, since such unbalanced data sets are not suitable for analysis, we could not compare data from this prospective study with that from the historical control. In a retrospective study, the number of biopsies required to diagnose one cancer using C-WLI with chromoendoscopy was reported as 76 [31]. This suggests that M-NBI may contribute to reducing the number of biopsies required to detect one cancer in screening endoscopy.

However, to provide further information for the selection of therapeutic strategy (e.g. endoscopic resection *vs* surgical resection), we need to take biopsies in Grade 5 cases, because endoscopic diagnosis using M-NBI has not been demonstrated to provide adequate diagnostic performance for predicting histological differentiation, i.e. differentiated *vs* undifferentiated type [9]. Therefore, clinicians should be aware of the necessity to take biopsies for the determination of histological type. On the other hand, we frequently encounter the situation where we are unable to take biopsies from a suspicious lesion in a patient on intensive antithrombotic therapy which can not be discontinued because of the high risk of thromboembolic events. In such cases, the proposed strategy may be applicable in deciding whether or not we should perform excisional biopsy after heparinization.

The limitations of this study are that this was an uncontrolled study, and the number of detected cancers was small. Therefore, in the near future we need to compare the diagnostic performance of M-NBI with other conventional endoscopy methods (e.g. chromoendoscopy) dealing with a substantial number of early gastric cancer cases. A system to ease the learning curve for M-NBI procedures has yet to be established. In order to overcome these problems, we are now developing a novel e-learning system for

Table 5 Diagnostic performance of M-NBI for reddened/same-colored mucosal lesions

	All lesions (95 % CI) ($n = 330$)		High confidence prediction (95 % CI) ($n = 161$)		Low confidence prediction (95 % CI) ($n = 169$)	
Accuracy	98.1	(96.6–99.6)	99.4	(98.2–100)	91.9	(87.8–96.0)
Sensitivity	69.2	(44.1–94.3)	100		41.7	(13.8–69.6)
Specificity	98.1	(98.2–100)	99.4	(98.2–100)	95.6	(94.2–98.8)

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

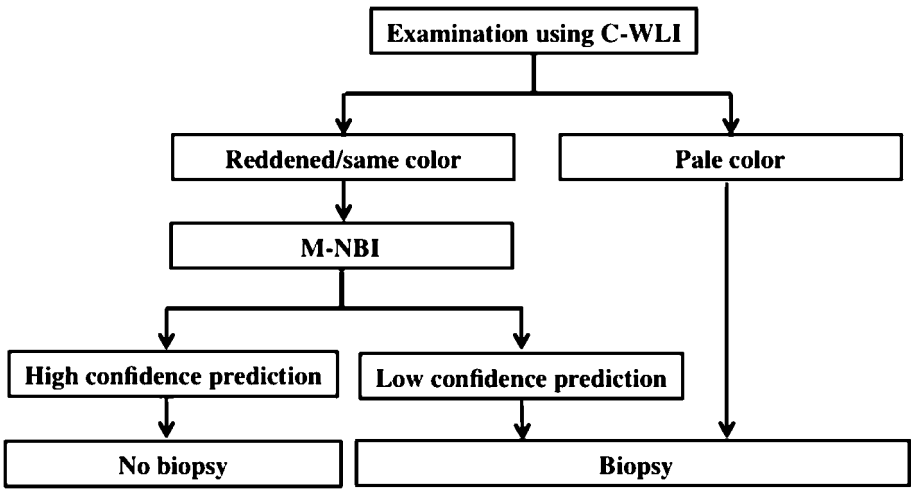


Fig. 6 A provisional strategy for M-NBI in screening gastroscopy

improving the diagnostic performance of M-NBI endoscopy (UMIN 000008569). Once it has been completed, we are planning a multicenter randomized controlled study. Once sufficient high-level evidence has been obtained that can support our provisional strategy, "optical biopsy" using M-NBI will be applied to clinical practice. The other limitations are that we have not tested the ability of NBI for detecting early gastric cancer because the image obtained by non-magnifying observation with NBI incorporated into the endoscopy system available in this study is too dark for endoscopists to detect a mucosal lesion. Recently, a new electronic endoscopy system with a bright NBI illumination (EVIS Lucera Elite, Olympus) has been launched. We are now planning a new trial to test whether NBI can detect more early gastric cancers than C-WLI. If we complete this study, it will become clear whether NBI can be helpful for detecting cancer invisible by C-WLI alone.

In conclusion, we demonstrated the high diagnostic performance and limitations of M-NBI in making a diagnosis of early gastric cancers of all macroscopic types in screening endoscopy in a multicenter prospective study, and we have proposed a provisional strategy for M-NBI in screening endoscopy for early gastric cancer that takes these limitations into consideration.

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