An efficient diagnostic strategy for small, depressed early gastric cancer with magnifying narrow-band imaging: a post-hoc analysis of a prospective randomized controlled trial

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Background: We previously reported that magnifying narrow-band imaging (M-NBI) is a high-performance diagnostic tool for small, depressed gastric cancer. However, an efficient diagnostic strategy using endoscopic findings has not been fully elucidated.

Objective: To identify the endoscopic findings that contribute to accurate diagnosis of small, depressed gastric cancer and to propose the ideal diagnostic approach to such lesions.

Design: Post-hoc analysis of a prospective, randomized, controlled trial.

Setting: Nine hospitals.

Patients: Three hundred fifty-three patients with small, depressed gastric lesions.

Interventions: In the M-NBI group (n = 177), cancer diagnosis was made with diagnostic criteria including a demarcation line (DL) and an irregular microvascular pattern (IMVP). In the conventional white-light imaging (C-WLI) group (n = 176), diagnostic criteria were both an irregular margin and a spiny depressed area. In the C-WLI group, M-NBI was performed after C-WLI diagnosis.

Main Outcome Measurements: The diagnostic performance of each criterion in M-NBI alone, C-WLI, and M-NBI after C-WLI was investigated.

Results: M-NBI after C-WLI ultimately showed the best diagnostic performance in each diagnostic criterion. In M-NBI after C-WLI, evaluation of DL is technically easier than that of IMVP, and DL alone had a high sensitivity (95%) and negative predictive value (99%). The IMVP in M-NBI after C-WLI had a high sensitivity and specificity (95% and 96%, respectively) for diagnosis of cancer.

Limitations: Lesions were limited to the small, depressed type.

Conclusions: For a diagnosis using M-NBI after C-WLI, identification of DL is the first step, and subsequent inspection of IMVP diagnosed by DL is an efficient strategy. (Gastrointest Endosc 2014;79:55-63.)

Abbreviations: C-WLI, conventional white-light imaging; DL, demarcation line; ESD, endoscopic submucosal dissection; IM, irregular margin; IMVP, irregular microvascular pattern; M-NBI, magnifying narrow-band imaging; SDA, spiny depressed area.

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Gastric cancer is the second leading cause of cancer deaths worldwide.[1] Early detection and accurate diagnosis of depressed gastric mucosal cancer are effective ways to decrease mortality because the depressed type is the predominant morphology among gastric mucosal cancers.[2-4] Moreover, detection of mucosal cancers ≤ 20 mm in diameter is ideal because they are curable with minimally invasive treatments such as EMR and endoscopic submucosal dissection (ESD).[5,6] However, these approaches have proven difficult when using conventional white-light imaging (C-WLI) endoscopy because depressed-type cancer shows subtle morphologic changes. Accurate diagnosis is hampered by the lack of reliable diagnostic criteria. A novel endoscopic technology, magnifying narrow-band imaging (M-NBI), is a powerful tool for characterizing gastric mucosal lesions because it can visualize the microvascular architecture as well as morphology of such lesions.[7]

We performed a multicenter, prospective, randomized, controlled trial and reported that M-NBI was more useful than C-WLI in terms of the ability to diagnose small, depressed gastric cancerous lesions (UMIN-CTR 000001072).[8] In this randomized controlled trial, 2 criteria,[9,10] the presence of a demarcation line (DL) and an irregular microvascular pattern (IMVP), were used for the endoscopic evaluation of lesions using M-NBI, whereas the presence of an irregular margin (IM) and spiny depressed area (SDA) were used for C-WLI evaluation. However, the endoscopic findings that contribute to the accurate diagnosis of small, depressed gastric cancerous lesions have not been fully identified. Moreover, M-NBI still leads to misdiagnosis of some lesions, and the reasons for these misdiagnoses are unclear. Therefore, the aim of this study was to identify an efficient diagnostic strategy using the most reliable endoscopic findings to diagnose early gastric cancers and propose an ideal diagnostic approach to these cancers.

Take-home Message

- The diagnostic performance of magnifying narrowband imaging (M-NBI) after conventional white-light imaging (C-WLI) using a demarcation line (DL) and an irregular microvascular pattern (IMVP) was significantly high for small, depressed gastric lesions.
- In M-NBI after C-WLI, it is ideal to identify the DL first to diagnose small, depressed gastric cancer, and the subsequent IMVP inspection efficiently excludes false-positive lesions by the DL. The reasons for misdiagnoses include technical and cognitive factors; thus, training should involve both aspects.

METHODS

Study design and endoscopic procedure

This study was conducted as a post-hoc analysis of data collected in our randomized controlled trial.[8] The protocol of the trial was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine on February 14, 2008. The UMIN Clinical Trials Registry identification number for this study is 000001072 on March 15, 2008. In the trial, 1353 patients with concomitant gastric cancer or a history of endoscopic resection of early gastric cancer were enrolled and underwent endoscopic screening with C-WLI between June 2008 and May 2010. The target lesions were "newly detected and undiagnosed" small, depressed gastric lesions ≤ 10 mm in diameter. Only the first lesion detected in each patient was selected for examination.

Among all patients 353 previously undiagnosed lesions were found in 362 patients that were randomly assigned to the M-NBI (n = 177) and C-WLI (n = 176) groups. The diagnosis for the target lesion was made on-site by 1 endoscopist according to predetermined diagnostic criteria for C-WLI and M-NBI, and the result was recorded on a case report form. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI (M-NBI after C-WLI) to evaluate the effect of using M-NBI in conjunction with C-WLI. At least 2 endoscopic images of the target lesion in each mode were captured and stored in a computer server during the diagnosis. After compilation of all endoscopic diagnoses, at least 1 biopsy specimen was obtained from the target lesion. Lesions diagnosed as cancer or suspicious for cancer were removed by EMR/ESD to obtain a final histologic diagnosis. The demographics of the study samples are summarized in Table 1.

The biopsy and EMR/ESD specimens were evaluated based on the revised Vienna classification. Category C4 (mucosal high-grade neoplasia) and C5 (submucosal invasion by neoplasia) were diagnosed as cancerous lesions, and C1 (negative for neoplasia), C2 (indefinite for neoplasia), and C3 (mucosal low-grade neoplasia) were diagnosed as noncancerous lesions. When indeterminate lesions were encountered, we consulted with a main expert pathologist as a central review system to obtain a final diagnosis. The lesions in the M-NBI group comprised 20 cancerous and 157 noncancerous lesions, and those in the C-WLI group comprised 20 cancerous and 156 noncancerous lesions (Fig. 1). The prevalence rate was almost identical in both groups (11. 2% and 11.3%, respectively).

As described in the previous trial,[8] this study was conducted according to the Standards for the Reporting of Diagnostic Accuracy Studies initiative[11] and the Declaration of Helsinki. Randomization and masking were strictly enforced. Thirty-one endoscopists from 9 institutions in Japan participated after being trained in the acquisition of C-WLI and M-NBI images of small, depressed lesions to minimize diagnostic variation among observers. Ethical concerns were fully addressed.

Endoscopy system and setting

The video endoscopy system used in this study comprised a video processor (EVIS LUCERA CV-260SL; Olympus Medical Systems, Tokyo, Japan) and a light source

TABLE 1. Demographics of the study sample

	C-WLI group (n = 176)	M-NBI group (n = 177)	P
Median age, y	69	69	.56
Gender			
Male	138	140	.79
Female	38	37	
Mean SDL size, mm	5.6	5.6	.97
SDL location (longitudinal)			
Upper third	39	27	.21
Middle third	40	49	
Lower third	97	101	
SDL location (circumferential)			
Anterior wall	29	32	
Lessor curvature	47	68	.06
Posterior wall	60	41	
Greater curvature	40	36	
Endoscope			
GIF-Q240Z	71	65	
GIF-FQ240Z	1	3	.83
GIF-H260Z	104	109	
Histology			
Noncancerous	156	157	1.00
Cancer	20	20	

SDL, Small, depressed lesion; *M-NBI*, magnifying narrow-band imaging; *C-WLI*, conventional white-light imaging.

(EVIS LUCERA Olympus CLV-260SL; Olympus Medical Systems) that worked in both the C-WLI and NBI modes. In the NBI mode, narrow-banded short-wavelength lights (400-430 nm and 525-555 nm) were used to contrast the microvascular architecture and mucosal surface of the superficial mucosa.[12-14] High-resolution magnifying endoscopy with a capability of 80-fold optical magnification was used (GIF-Q240Z, GIF-H260Z, and GIF-FQ260Z; Olympus Medical Systems). A soft black hood (MB162 or MB46; Olympus Medical Systems) was attached at the tip of the endoscope. The structure enhancement of the endoscopic video processor was set to B-mode level 4 or 6 for C-WLI and to B-mode level 8 for M-NBI. The color mode was fixed at level 1.

Endoscopic criteria used to diagnose cancers

The 2 criteria[9,10] used in the endoscopic evaluation of lesions using M-NBI were the presence of a DL and an IMVP (Fig. 2). An IMVP refers to microvessels that differ in shape, take the shape of a closed or open loop, or are tortuous, branched, or bizarrely shaped. The vessels differ in both size and diameter, and the distribution of the microvessels is asymmetric with an irregular arrangement. The criteria used in the endoscopic evaluation of lesions using C-WLI were the presence of an IM and an SDA (Fig. 3). These findings were independently assessed and documented on a 3-point scale (present, absent, or indeterminate). Endoscopic diagnoses using both C-WLI and M-NBI were determined according to the combined visibility of the 2 findings. (1) If both findings were present, the diagnosis was cancer. (2) In the event of a combination other than pattern (1), the diagnosis was a noncancerous lesion.

Outcome measurements

Using the outlined criteria from C-WLI, M-NBI alone, and M-NBI after C-WLI, we compared the endoscopic diagnosis with the histologic diagnosis to determine the positive numbers of endoscopic findings in cancerous and noncancerous lesions, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. The diagnostic performance of each diagnostic criterion among C-WLI, M-NBI alone, and M-NBI after C-WLI was analyzed.

To clarify the reasons for incorrect diagnoses after reviewing the M-NBI findings and to extract the information that can be efficiently used in the training for M-NBI examination of early gastric cancers, the 2 experienced endoscopists who had analyzed more than 3000 endoscopic procedures using M-NBI reviewed the electronic images recorded in an image database for all facilities.

Statistical analysis

Demographics of the study samples between the C-WLI group and M-NBI group were compared using the Mann-Whitney U test for age and lesion size and the χ^2 test for gender, lesion location, endoscopy system, and histologic findings. Analyses of differences in the association between each endoscopic finding and cancer as well as analyses of differences in the diagnostic performance of the endoscopic findings provided by C-WLI, M-NBI alone, and M-NBI after C-WLI were compared using Pearson's χ^2 test and data from subjects with histopathologically confirmed diagnoses. Positive numbers of endoscopic findings in cancerous and noncancerous lesions were calculated with respect to relative risk.

In addition, all lesions diagnosed incorrectly using M-NBI were analyzed in terms of their endoscopic findings together with their histologic findings. The differences in the characteristics between correct and incorrect diagnoses were compared using the Mann-Whitney U test for lesion size and inspection time and using the χ^2 test for lesion location.

All P values were 2-sided and were not adjusted for multiple tests. $P < .05$ were considered statistically significant. All statistical analyses were performed using the Dr. SPSS II statistical software package (SPSS Japan Inc., Tokyo, Japan).

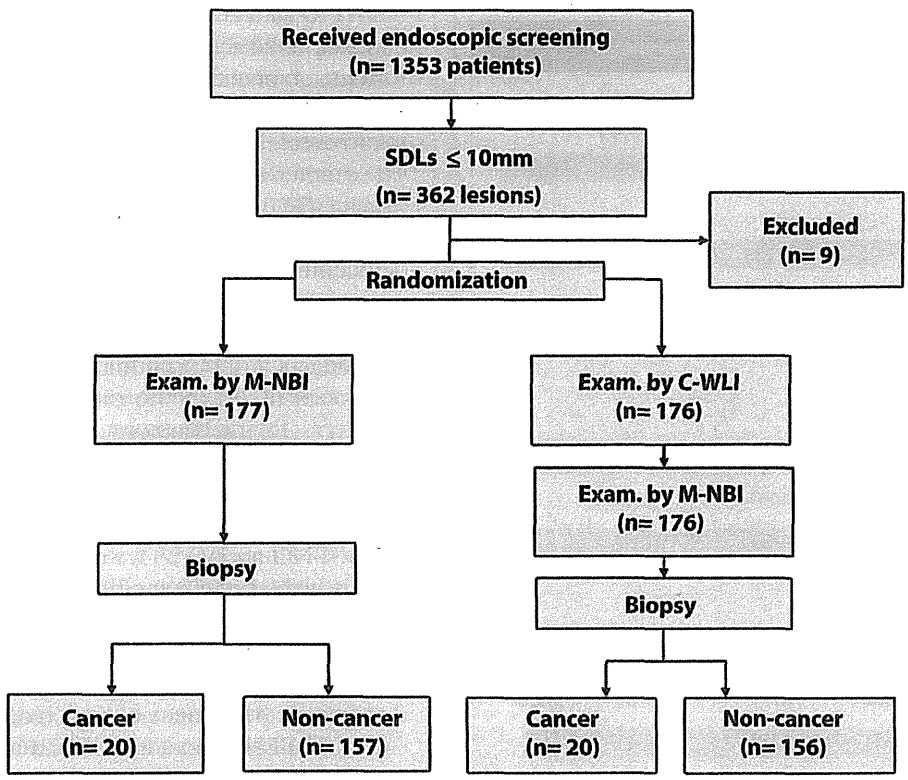

Figure 1. Trial profile, randomization, and examination. In this study, 1353 patients with concomitant gastric cancer or a history of endoscopic resection of early gastric cancer were enrolled and underwent endoscopic screening with C-WLI. Among these patients, 353 previously undiagnosed lesions were found in 362 patients that were randomly assigned to the M-NBI (n = 177) and C-WLI (n = 176) groups. *SDLs*, Small, depressed lesion; *M-NBI*, magnifying narrowband imaging; *C-WLI*, conventional white-light imaging.

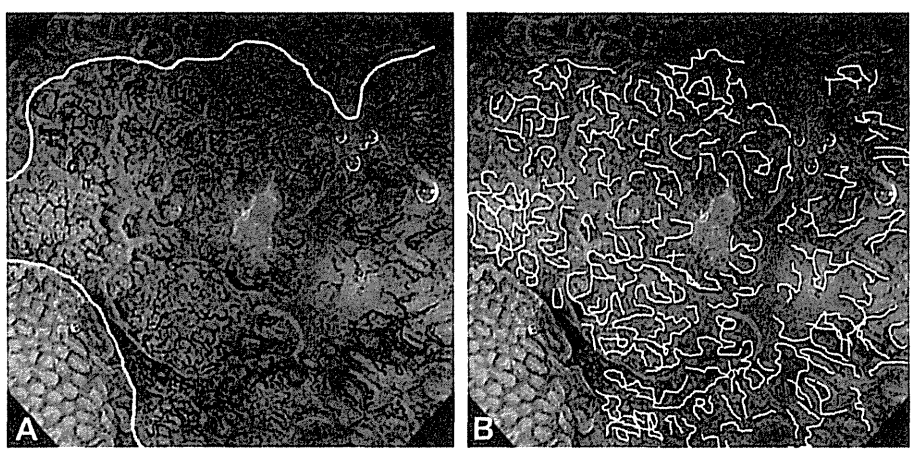

Figure 2. Endoscopic findings from magnifying narrowband imaging (M-NBI), **A,** A demarcation line (DL) is present between a depressed lesion and the surrounding mucosa (*yellow lines*). **B,** An irregular microvascular pattern (IMVP), is diagnosed if the vessels differ in shape or are a closed loop, open loop, tortuous, branched, or bizarrely shaped. The size of the vessels also varies, and their arrangement and distribution are irregular and asymmetric, respectively (*white lines*).

RESULTS

Association between each endoscopic finding and histologic result

Table 2 shows the association between each endoscopic finding in the cancerous and noncancerous lesions as diagnosed by C-WLI, M-NBI alone, and M-NBI after C-WLI. All endoscopic findings in C-WLI showed no significant differences between cancerous and noncancerous lesions. However, all endoscopic findings (DL, IMVP, and both a DL and an IMVP) in both the M-NBI alone and M-NBI after C-WLI groups were significantly associated with the diagnosis of cancerous lesions ($P < .01$ for all). In particular, IMVP and both a DL and an IMVP had strong

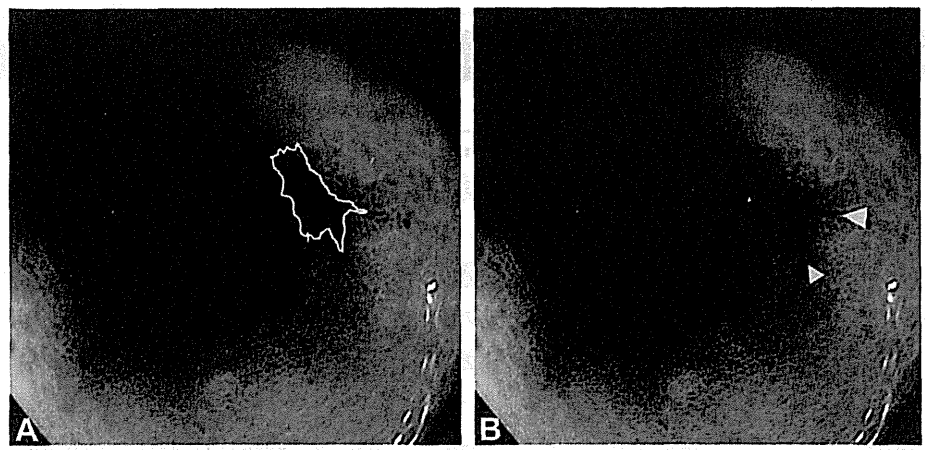

Figure 3. Endoscopic findings from conventional white-light imaging (C-WLI). **A,** An IM indicates the presence of an IM between a small, depressed lesion and the surrounding mucosa (*yellow line*). **B,** A spiny depressed area (SDA) indicates the presence of an SDA at the edge of a small, depressed lesion (*yellow arrowheads*).

associations with a cancer diagnosis (relative risks of 7.9 and 10.5 in M-NBI alone and 24.7 and 29.6 in M-NBI after C-WLI, respectively).

Diagnostic performance of each endoscopic finding

Table 3 shows the diagnostic performance according to each endoscopic finding from C-WLI, M-NBI alone, and M-NBI after C-WLI.

Accuracy. The accuracy of both M-NBI alone (90%; 95% confidence interval [CI], 85%-94%) and M-NBI after C-WLI (97%; 95% CI, 93%-99%) using a DL and an IMVP was significantly better than that of C-WLI using an IM and an SDA (65%; 95% CI, 57%-72%).

Sensitivity and specificity. Figure 4 shows the results of the comparison of the sensitivity and specificity of individual endoscopic findings provided by C-WLI, M-NBI alone, and M-NBI after C-WLI. The endoscopic findings of C-WLI were low in sensitivity (75% [95% CI, 51%-91%] for IM, 40% [95% CI, 19%-64%] for SDA, and 40% [95% CI, 19%-64%] for IM and SDA) and specificity (44% [95% CI, 36%-52%] for IM, 64% [95% CI, 56%-72%] for SDA, and 68% [95% CI, 60%-75%] for IM and SDA). The endoscopic diagnostic performance increased for C-WLI, followed by M-NBI alone; M-NBI after C-WLI ultimately showed the best diagnostic performance.

The sensitivity of an IMVP was low (60%; 95% CI, 36%-81%) in M-NBI alone, indicating that IMVP evaluation using M-NBI alone could lead to misdiagnosis of some cancers, and the sensitivity of an IMVP did not improve by combining it with evaluation of a DL (60%; 95% CI, 36%-81%). The sensitivity of an IMVP and both a DL and an IMVP in M-NBI alone significantly improved when they were evaluated after C-WLI (95% [95% CI, 75%-100%] and 95% [95% CI, 75%-100%]; $P = .02$ and $P = .02$, respectively). The specificity of an IMVP and both a DL and an IMVP was high in M-NBI alone (92% [95% CI, 87%-96%] and 94% [95% CI, 89%-97%], respectively) and M-NBI after WLI (96% [95% CI, 92%-99%] and 97% [95% CI, 93%-100%], respectively), suggesting that the presence of an IMVP indicates a high probability of cancer.

The sensitivity of a DL in M-NBI alone and M-NBI after C-WLI was high (85% [95% CI, 62%-97%] and 95% [95% CI, 75%-100%], respectively), whereas the specificity of these findings (53% [95% CI, 45%-61%] and 49% [95% CI, 41%-58%], respectively) was significantly lower than that of an IMVP (92% [95% CI, 87%-96%] and 96% [95% CI, 92%-99%]; $P = .000$ and $P = .000$, respectively). The specificity of a DL in M-NBI alone and M-NBI after C-WLI improved significantly when evaluated in combination with an IMVP (94% [95% CI, 89%-97%] and 97% [95% CI, 93%-100%]; $P = .000$ and $P = .000$, respectively). This suggests that DL is a reliable finding for identification of cancer but it needs to be evaluated with C-WLI findings and the presence of an IMVP to exclude false-positive lesions.

Positive predictive value and negative predictive value. The positive predictive value of a DL in M-NBI alone and M-NBI after C-WLI were 19% (95% CI, 11%-28%) and 19% (95% CI, 13%-29%), respectively, and were similar to those in C-WLI (15% [95% CI, 8%-23%] for IM, 13% [95% CI, 6%-23%] for SDA, and 14% [95% CI, 6%-25%] for IM and SDA). The low positive predictive value of a DL in M-NBI alone and M-NBI after C-WLI improved significantly when evaluated with IMVP ($P < .01$ and $P < .01$, respectively).

The negative predictive value of all endoscopic findings of M-NBI alone exceeded 95% (97% [95% CI, 90%-98%] for DL, 95% [95% CI, 90%-98%] for IMVP, and 95% [95% CI, 90%-98%] for both DL and IMVP). The negative predictive value of all endoscopic findings of M-NBI after C-WLI was 99% (99% [95% CI, 93%-100%] for DL, 99% [95% CI, 96%-100%] for IMVP, and 99% [95% CI, 96%-100%] for both DL and IMVP). This indicates that M-NBI findings, especially when M-NBI is performed after C-WLI, could be good markers to exclude cancer from small, depressed gastric lesions that were detected with C-WLI.

TABLE 2. Association between each endoscopic finding and cancer

Method	Endoscopic findings	Pathologic diagnosis		RR [95% CI]	P
		Cancer	Noncancerous		
C-WLI	IM	15	88	1.3 [1.0-1.8]	.11
	SDA	8	56	1.1 [.6-2.0]	.72
	IM and SDA	8	50	1.3 [.7-2.2]	.48
M-NBI alone	DL	17	74	1.8 [1.4-2.3]	<.01
	IMVP	12	12	7.9 [4.1-15.1]	<.01
	DL and IMVP	12	9	10.5 [5.1-21.7]	<.01
M-NBI after C-WLI	DL	19	79	1.9 [1.6-2.3]	<.01
	IMVP	19	6	24.7 [11.2-54.5]	<.01
	DL and IMVP	19	5	29.6 [12.4-70.6]	<.01

M-NBI, Magnifying narrow-band imaging; *C-WLI,* conventional white-light imaging; *DL,* demarcation line; *IMVP,* irregular microvascular pattern; *IM,* irregular margin; *SDA,* spiny depressed area; *RR,* relative risk; *CI,* confidence interval.

TABLE 3. Diagnostic performance according to endoscopic findings

Method	Endoscopic finding	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
C-WLI	IM	47	75	44	15	93
	SDA	61	40	64	13	89
	IM and SDA	65	40	68	14	90
M-NBI	DL	57	85	53	19	97
	IMVP	89	60	92	50	95
	DL and IMVP	90	60	94	57	95
M-NBI after C-WLI	DL	55	95	49	19	99
	IMVP	96	95	96	76	99
	DL and IMVP	97	95	97	79	99

M-NBI, Magnifying narrow-band imaging; *C-WLI,* conventional white-light imaging; *DL,* demarcation line; *IMVP,* irregular microvascular pattern; *IM,* irregular margin; *SDA,* spiny depressed area; *PPV,* positive predictive value; *NPV,* negative predictive value.

Analysis of lesions incorrectly diagnosed by M-NBI

We experienced 23 incorrect diagnoses (false positive, 14; false negative, 9) and 330 correct diagnoses for both M-NBI alone and M-NBI after C-WLI. There were no significant differences in characteristics (lesion size and location and time to establish diagnosis) between the correctly and incorrectly diagnosed lesions (Table 4). Two reviewers with experience in endoscopic diagnosis of more than 3000 cases using M-NBI reviewed the images of lesions that were misdiagnosed by M-NBI and identified the reasons for misdiagnosis as follows.

Technical factors. In 10 cases (5 false positives and 5 false negatives), the findings were judged to be indeterminate because the images were at a low magnification and/or out of focus.

Cognitive factors. Eleven cases had originally been misdiagnosed despite adequate examination. Eight cases were diagnosed as false positives, and 3 were diagnosed as false negatives. Reviewers correctly diagnosed lesions in 5 of the 8 false positives and 2 of the 3 false negatives. Thus, the reviewers posited that 1 reason for misdiagnosis was a lack of interpretive skill on the part of the endoscopist. The cases that were misdiagnosed despite adequate examination included 3 false positives and 1 false negative that the reviewers also misdiagnosed. This was presumably because of the limitations of the endoscopic criteria for diagnosing cancers used in this study.

Others. One diagnosis was mistakenly entered as a histologic noncancerous lesion on the case report form. One patient was misdiagnosed with a noncancerous lesion because of a sampling error as a result of forceps biopsy.

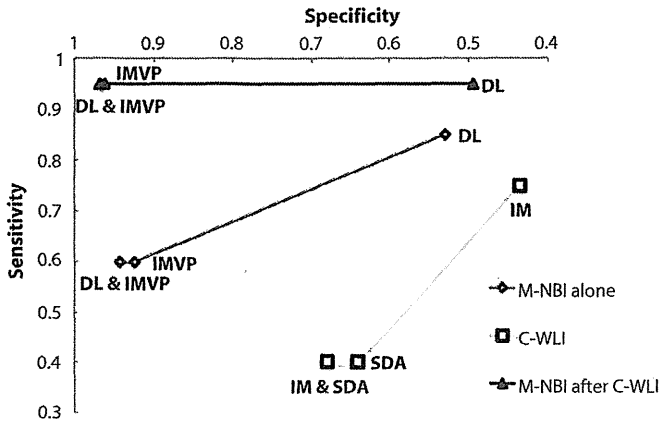

Figure 4. Comparison of the sensitivity and specificity of individual endoscopic findings in magnifying narrow-band imaging (M-NBI) alone, conventional white-light imaging (C-WLI), and M-NBI after C-WLI. Among all endoscopic findings, diagnostic performance improved significantly for C-WLI alone, followed by M-NBI alone, and then by M-NBI after C-WLI.

TABLE 4. Characteristics of correct and incorrect diagnosis by M-NBI

	Correct diagnosis (n = 330)	Incorrect diagnosis (n = 23)	*P*
Mean SDL size, mm	6	6	.67
SDL location (longitudinal)			
Upper third	61	5	
Middle third	82	7	.45
Lower third	187	11	
SDL location (circumferential)			
Anterior wall	57	4	.34
Lesser curvature	106	9	
Posterior wall	93	8	
Greater curvature	74	2	
Inspection time			
Average(s)	72	100	.15

M-NBI, Magnifying narrow-band imaging; *SDL*, small, depressed lesion.

DISCUSSION

In this study, we found that the endoscopic diagnostic performance increased for C-WLI, followed by M-NBI alone; M-NBI after C-WLI ultimately showed the best diagnostic performance for each diagnostic criterion (Fig. 4). Therefore, M-NBI should generally be performed after evaluation of C-WLI findings. The combination of DL and IMVP characterized by M-NBI after C-WLI contributed to the most reliable diagnosis for small, depressed gastric lesions and can be an ideal, simple, standard diagnostic strategy for small, depressed gastric lesions.

Based on the current results, we herein propose an efficient endoscopic diagnostic strategy for small, depressed gastric lesions, as indicated in Figure 5. In the M-NBI after C-WLI technique, both a DL and an IMVP had a high negative predictive value (99% and 99%, respectively), indicating that both criteria were sufficiently sensitive for exclusion of noncancerous lesions. A DL is technically easier to identify than an IMVP.[15] Therefore, the identification of a DL should be the first step in the diagnosis of gastric cancer because the absence of a DL alone allows for the exclusion of a noncancerous lesion. If a DL is absent, a noncancerous lesion can be diagnosed without any additional findings. Next, the presence of an IMVP is evaluated within a DL. If both a DL and IMVP are present, cancer is strongly suggested because an IMVP is sufficiently specific in the diagnosis of cancer (ie, it has a high positive predictive value) and an additional procedure with curative intent is indicated. If an IMVP is absent, the lesion can be diagnosed as a noncancerous lesion without a target biopsy sample because the negative predictive value of an IMVP is also very high. This strategy will provide a high level of accurate diagnosis for small, depressed gastric lesions. In particular, because the negative predictive value of both a DL and an IMVP is very high in M-NBI after C-WLI, the benefits of this strategy include reductions in the risk of hemorrhage, number of biopsy specimens for pathologic analysis, procedure time, and medical expenses, especially when a noncancerous lesion is diagnosed.

Analysis of lesions incorrectly diagnosed by M-NBI revealed reasons for misdiagnosis. The reasons for misdiagnosis included both technical and cognitive factors; thus, training should involve both aspects. Technical errors were mainly caused by difficulty in observation of a DL and an IMVP at maximum magnification. Attachment of a rubber cap is very helpful for capturing in-focus magnified images, but we failed to obtain sufficient images in some cases. To improve the performance of these techniques, 1 of the authors has published a book with a DVD[16] explaining the techniques necessary to perform M-NBI at maximum magnification. The role of videos in transferring information relating to endoscopic technique will be more important than that of text from now on. Cognitive factors included the lack of interpretative skill on the part of the endoscopist. In their review of the images, the 2 reviewers revised the diagnosis in 7 cases, indicating a false-positive rate of 4.5% and false-negative rate of 22.5%. These numbers could have improved with better mastery of interpretative skill. An e-learning system was developed to improve interpretative skill using M-NBI, and a multicenter study, entitled "Learning curve with an e-learning system on magnifying narrow-band imaging in endoscopic diagnosis of gastric lesions: A randomized

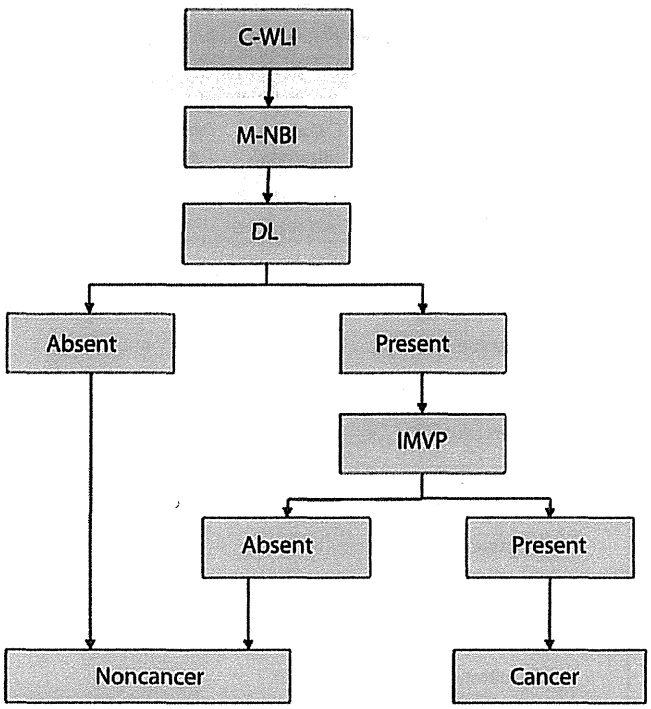

Figure 5. Strategy of using simplified criteria to make an endoscopic diagnosis of small, depressed lesions using magnifying narrowband imaging (M-NBI). When a small, depressed gastric lesion is detected by conventional white-light imaging (C-WLI), the presence or absence of a demarcation line (DL) should be the first step in diagnosing gastric cancer. If the DL is absent, a noncancerous lesion can be diagnosed. If the DL is present, the presence of an irregular microvascular pattern (IMVP) should be used for diagnosis. If an IMVP is absent, a noncancerous lesion can be diagnosed without a target biopsy sample and/or EMR/ESD. Finally, if both a DL and an IMVP are present, cancer is strongly suggested, and additional procedures are indicated.

study" (UMIN-CTR 000008569), was begun to examine the system's usefulness. After the review of recorded images by the 2 experts, there were limits of diagnosing lesions with M-NBI in 4 cases. The lesions did not fulfill the endoscopic cancerous or noncancerous diagnostic criteria of a DL and an IMVP according to M-NBI. For these lesions, development of other diagnostic equipment or another method is required to further improve the diagnostic performance.

This study has limitations. The study samples were limited to $\leq$10– mm depressed lesions. A diagnosis based on the microvascular pattern and a DL, but not the microsurface pattern, is not universally applicable to all macroscopic types of lesions. However, all small, depressed lesions in this study had a microvascular pattern that could be visualized, allowing the lesions to be diagnosed. Thus, the current authors are prospectively studying (UMIN-CTR 000004045) the ability of M-NBI to diagnose all macroscopic types of lesions using the vessel-plus-surface classification system[7] put forth by Yao et al without size or macroscopic type limitation. The vessel-plus-surface classification system uses the microsurface pattern, microvascular pattern, and DL as indices.

In conclusion, the current study suggests that although M-NBI alone provided good diagnostic performance, it is important to conduct a C-WLI evaluation before M-NBI diagnosis. When using M-NBI, identification of a DL is the first step in the diagnosis of cancer, and the subsequent identification of an IMVP is useful for excluding noncancerous lesions among the lesions that were identified to have a DL. Training in both techniques and knowledge is important to improve M-NBI diagnosis.

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Narrow-band Imaging for the Head and Neck Region and the Upper Gastrointestinal Tract

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Endoscopy is essential for the diagnosis and treatment of cancers derived from the gastrointestinal tract. However, a conventional white-light image has technical limitations in detecting small or superficial lesions. Narrow-band imaging, especially with magnification, allows visualization of microstructure patterns and microvascular patterns on the mucosal surface. These technical breakthroughs enable endoscopists to easily detect small pre-neoplastic and neoplastic lesions and to make a differential diagnosis of these lesions. Appropriate diagnosis with narrow-band imaging contributes to minimally invasive endoscopic resection.

Key words: endoscopy – narrow-band imaging – early detection – differential diagnosis

NARROW-BAND IMAGING

Narrow-band imaging (NBI) is an innovative optical technology that allows distinct visualization of microsurface patterns and microvascular patterns on the mucosal surface (1–3). The NBI system uses narrow-band illumination created with optical interference filters that generate 415 and 540 nm wavelengths, corresponding to the peaks of absorption of hemoglobin. Therefore, thin blood vessels, such as capillaries, in the epithelium or mucosal layer can be seen more distinctly than in a conventional white-light image (Fig. 1).

Currently, two types of image reconstruction systems are used for endoscopic imaging: a red–green–blue (RGB) time sequential illumination system with a monochrome charge-coupled device (CCD) and white-light illumination with a colour-chip CCD. The NBI system is applicable to both systems by placing the narrow-band light filter in front of the light source. NBI can provide the same clinical benefits with both illumination systems (Table 1), although the colour reproduction and the image resolution are somewhat different in the two systems (4).

HEAD AND NECK REGION

Head and Neck Cancer

Lugol chromoendoscopy is the standard method for detecting early squamous cell carcinoma (SCC) of the esophagus. However, Lugol dye solution cannot be applied to the oropharynx or hypopharynx because of the risk of aspiration. Moreover, the image resolution of rhinolaryngoscopy does not effectively identify superficial neoplastic lesions in the head and neck region. Therefore, early detection of cancers in the oropharynx and the hypopharynx has been difficult. This is partly attributable to the technological limitations in mounting a high-resolution CCD on the tip of a rhinolaryngoscope.

Muto et al. (5) first reported the utility of NBI combined with magnifying endoscopy (Q240Z, Olympus Medical Systems, Tokyo, Japan) in the identification of superficial SCCs in the head and neck region. Compared with white-light imaging (WLI), NBI significantly improved the visualization of the cancerous lesions by enhancing the contrast between the cancerous lesion and the background non-neoplastic epithelium and by the clear magnification of the

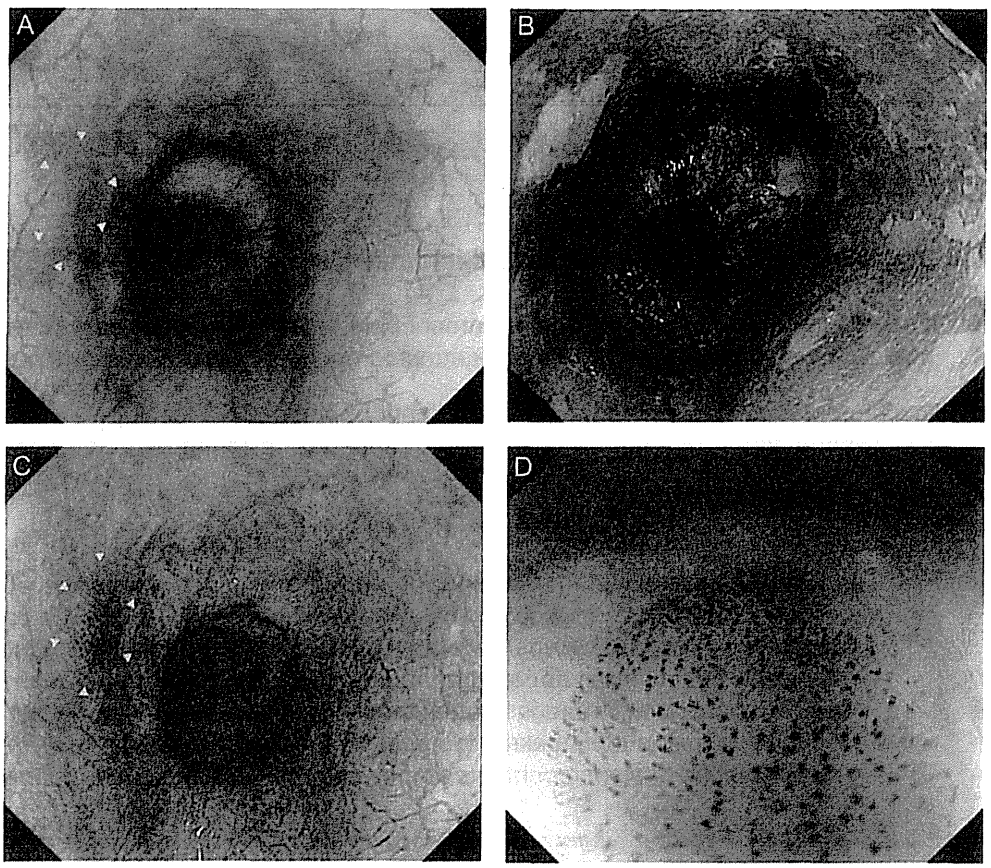

Figure 1. Superficial squamous cell carcinoma in the lower thoracic esophagus. (A) WLI shows scattered reddish spots in the slightly reddish area. (B) Lugol chromoendoscopy shows unstained area. (C) and (D) NBI shows clearly defined brownish spots indicating dilated intrapapillary capillary loops.

microvascular architecture (6). Muto et al. (1) reported that the well-demarcated brownish areas observed under NBI and the microvascular irregularities visible under magnification with NBI are useful indicators of cancerous lesions in the head and neck region. In the multicenter prospective randomized study, NBI is revealed to be superior to WLI in the detection and differential diagnosis of superficial head and neck cancer (7).

Watanabe et al. (8, 9) reported that the NBI rhinolaryngoscope (ENF-V2, Olympus Medical Systems) with a colour-chip light source (CLV-160B, Olympus Medical Systems) improved the diagnostic accuracy, and the negative predictive values for superficial lesions in the oropharynx and hypopharynx compared with those of conventional WLI. However, there is still a critical difference in the image qualities of CCDs between gastrointestinal endoscopy and rhinolaryngoscopy.

Ugumori et al. (10) prospectively compared the images taken with a colour-chip-based rhinolaryngoscope and those taken with an RGB-sequential-system-based high-resolution gastrointestinal endoscope. Whereas the conventional white-light rhinolaryngoscope identified a well-demarcated line between the neoplastic and non-neoplastic lesions in only 10% (5/51) of cases and microvascular irregularities in only 27% (14/51), the NBI rhinolaryngoscope identified these in 63% (32/51) and 94% (49/51) of cases, respectively. These results indicate that even with a rhinolaryngoscope, NBI can improve the visualization of epithelial neoplasms of the head and neck region. When combined with a high-definition television camera, the effectiveness of NBI is improved in terms of both its sensitivity and specificity (11).

NBI is also reportedly useful in detecting metachronous SCC after treatment for esophageal SCC (chemoradiotherapy, radiation therapy or surgery), unknown primary SCC of the neck and adenoid hypertrophy (12–18) (Table 1).

The early detection of cancer in this region increases the possibility of minimally invasive surgery, including endoscopic mucosal resection and endoscopic submucosal dissection methods (19, 20). The potential advantages to patients resulting from an early diagnosis, with the preservation of organ and tissue functions, are obvious.

ESOPHAGUS

Esophageal SCC

Although early detection of cancer offers the best prognosis, many esophageal SCCs (ESCCs) are still detected at a late stage, with a consequently poor prognosis. One reason is that early detection of ESCC is difficult using conventional WLI

es of NBI in contrast to WLI or CE in clinical practice in the head and neck region and the upper gastrointestinal tract

egory	Study aim	Evidence	Magnification	Study design	Diagnosis
ıamous cell :inoma	Detection	NBI >WLI (accuracy: 86.7 vs. 62.9%)	+	Prospective RCT	On site
	Differential diagnosis	NBI > WLI	+	Prospective RCT	On site
ıamous cell :inoma	Detection	NBI > WLI (accuracy: 88.9 vs. 56.5%)	+	Prospective RCT	On site
		NBI = iodine CE (accuracy: 95.1 vs. 85.9 %)	+	Prospective non-RCT	On site
	Differential diagnosis	NBI > WLI	+	Prospective RCT	On site
:nocarcinoma	Detection of HGD/early cancer	NBI = WLI + indicocalmine CE	+	Prospective non-RCT	On site
	Differential diagnosis	M-NBI > M-WLI	+	Prospective non-RCT	Review
	Grade of dysplasia	NBI > WLI	−	Prospective non-RCT	On site
rett's esophagus	Detection of SIM	NBI = indigocalmine CE > WLI (Sn.: 56 vs. 55 vs. 24%, Sp.: 90 vs. 100 vs. 40%)	+	Prospective non-RCT	Review
:nocarcinoma	Detection	No literature			
	Differential diagnosis of small depressive lesions	C-WLI + M-NBI > M-NBI > C-WLI (accuracy: 96.6 vs. 90.4 vs. 64.8%)	+	Prospective RCT	On site
	Differential diagnosis of superficial elevated lesions	M-NBI > C-WLI (accuracy: 92 vs. 74%)	+	Retrospective	Review
	Detection of lateral extent of early gastric cancer	M-NBI > indigocalmine CE	+	Prospective RCT	On site
	Diagnosis of tumour depth	No pivotal study			
:noma	Detection	No pivotal study			
:nocarcinoma	Detection	No pivotal study			
	Differential diagnosis	No pivotal study			
pullary tumour	Visualization of tumour margin	NBI > indigocalmine CE	−	Prospective non-RCT	Review

maging; WLI, white-light imaging; PPV, positive predictive value; NPV, negative predictive value; SIM, specialized intestinal metaplasia; HGD, high-grade dysplasia; Sn., se
NBI, magnifying NBI; M-WLI, magnifying WLI; CE, chromoendoscopy; C-WLI, conventional non-magnifying WLI.

endoscopy because it cannot identify the morphological changes of superficial ESCC. Although Lugol chromoendoscopy is a sensitive method for the detection of early superficial ESCC (Fig. 1A and B), iodine is an irritant and causes unpleasant reactions, such as pain, discomfort and sometimes allergic reaction. In contrast, NBI is less invasive than Lugol chromoendoscopy and enhances the clarity of the intrapapillary capillary loop (IPCL) patterns beneath the epithelium (5, 21, 22) and so it is expected to replace Lugol chromoendoscopy in this role (Fig. 1C and D).

Using an ultrathin endoscope (5 mm in diameter at the distal end; XP260N, Olympus Medical Systems), Lee et al. (23) reported the utility of NBI in the detection and accurate diagnosis of ESCC. The sensitivity of NBI was significantly better than that of conventional WLI. The specificity and positive predictive value of NBI were also better than those of Lugol chromoendoscopy, whereas their diagnostic accuracy and negative predictive value were similar. These results suggest that, even when an ultrathin endoscope is used, NBI is the best tool for screening for superficial esophageal neoplasms, as in the head and neck region.

In a multicentre prospective randomized study (7), NBI with a standard-diameter endoscope showed ~2-fold greater sensitivity than WLI. Furthermore, most of the Lugol-voiding lesions overlooked by NBI endoscopy were low-grade intraepithelial neoplasia or lesions without atypical findings (24).

In 2011, a new classification of magnified endoscopy for superficial ESCC was proposed by the Japan Esophageal Society (25), which allows differential diagnosis of ESCC, intraepithelial neoplasia and inflammation. This classification is expected to simplify the diagnosis and evaluation of the depth of invasion of superficial ESCCs.

Gastroesophageal Reflux Disease

GERD is defined by the presence of reflux esophagitis. When it causes reflux symptoms (chest pain, heartburn, discomfort, etc.), the patient's quality of life is adversely affected (26). Moreover, a significant number of patients with GERD symptoms show no endoscopic signs of esophagitis. This condition is described as 'non-erosive reflux disease' (NERD). Many NERD patients show minimal endoscopic findings, such as a whitish or reddish edematous change or erosion that is not regarded as a mucosal break (27). These minimal changes are potentially related to various GERD symptoms (28). However, the interobserver agreement when NERD is diagnosed with conventional WLI is reportedly too low to support the clinical significance of this technique (29). In contrast, NBI is expected to overcome this limitation, because it allows visualization of the superficial and slight findings attributable to NERD, which cannot be seen with conventional WLI.

Lee et al. (30) reported that the intraobserver and interobserver consistencies in grading esophagitis improved when NBI was used instead of WLI. Sharma et al. (31) reported a feasibility study of magnified endoscopy with NBI in patients with GERD. They showed that increased numbers and the dilatation of IPCLs were the best predictors of a diagnosis of GERD, with moderate-to-high interobserver agreement.

Barrett's Esophagus and Cancer

The incidence of esophageal adenocarcinoma is increasing in Western countries (32) and Barrett's esophagus (BE) is a precursor lesion of this malignancy. Surveillance of BE using WLI with random four-quadrant biopsies is the accepted practice and is recommended by the American Gastroenterological Association statement (33). Sharma et al. (34) showed in a randomized, controlled, international, crossover trial that the success of NBI in detecting intestinal metaplasia did not differ from that of the currently accepted practice of random biopsies, but required significantly fewer biopsies.

Because esophageal adenocarcinoma has a poor prognosis when detected at an advanced stage, endoscopic surveillance is recommended to detect high-grade dysplasia and mucosal neoplasia in patients with BE. However, it is difficult to identify these lesions with conventional WLI. NBI with magnifying endoscopy allows us to visualize the details of the mucosal microsurface pattern and the microvascular pattern without additional equipment or dye solutions (35).

Hamamoto et al. (36) first reported that NBI could better visualize the esophagogastric junction, net-like capillary vessels and columnar-lined esophagus (seen in BE) than conventional WLI. Kara et al. (37) reported that indigo carmine chromoendoscopy and NBI were similarly effective in the diagnosis of high-grade dysplasia or early cancer in BE. Wolfsen et al. (38) reported that high-resolution NBI can detect dysplastic lesions more efficiently, with fewer biopsy samples, than standard-resolution WLI. Singh et al. (39) reported that NBI with magnification is superior to WLI with magnification in the prediction of histology in BE.

A recent meta-analysis (40) that included 446 patients with 2194 lesions reported that NBI with magnification shows high diagnostic precision in detecting high-grade dysplasia, with a sensitivity and specificity of 96 and 94%, respectively.

STOMACH

Detection of Gastric Neoplasm by NBI

In the stomach, NBI has been considered to be used with magnification for detailed examinations. Because the light intensity under the NBI filter is low, a non-magnified image becomes dark compared with that produced under WLI. Furthermore, because the image becomes noisy with the electrical enhancement used to keep the endoscopic image bright, it is insufficient to observe the wide area of the stomach. There is also, as yet, no evidence that NBI is

superior to WLI in detecting early gastric neoplasms. To overcome these limitations, a much brighter NBI system with higher resolution will be commercially available when this review is published. Then, the evidence of other clinical benefits of NBI such as detection will be expected in future.

Differential Diagnosis of Gastric Cancer

Yao et al. (41) originally reported unique magnifying endoscopic findings of gastric cancer in 2002. This marked the beginning of the era of using magnifying endoscopy for the diagnosis of gastric cancer. The utility of magnifying endoscopic observations combined with WLI for the differential diagnosis of flat or slightly depressed gastric cancers and non-neoplastic lesions, such as gastritis, has been reported. NBI combined with magnifying endoscopy (magnifying NBI) provides better visualization of the mucosal surface and microvascular architecture than magnifying WLI (42). Several reports have compared the diagnostic yield of magnifying NBI with that of magnifying or non-magnifying WLI in distinguishing small gastric cancers from the flat or depressed benign lesions caused by chronic gastritis (43–45). However, all those reports had some limitations: they were performed at only one institution, evaluated stored images and did not involve real-time assessment or included gastric lesions with a definite pathological diagnosis. To overcome these limitations, Ezoe et al. performed a multicenter, prospective, randomized, controlled trial that targeted newly detected, undiagnosed lesions to compare and evaluate the diagnostic yields of magnifying NBI and conventional WLI. The trial revealed that magnifying NBI, especially after non-magnifying WLI, showed an extremely high diagnostic performance (46).

These lines of evidence suggest that magnifying NBI is currently one of the standard endoscopic modalities in the differential diagnosis of gastric cancers.

Determination of the Lateral Extent of Gastric Cancer

To achieve a complete resection of a mucosal gastric cancer with endoscopic resection, an accurate diagnosis of the extent of the tumour is required. By clearly visualizing the microvascular architecture and the microsurface structure inside and outside the lesion, magnifying NBI can distinguish the cancer margins from the surrounding benign mucosa, so it is expected to be useful for delineating the extent of a gastric tumour. In 2004, Sumiyama et al. (47) retrospectively described the feasibility of NBI for the guidance of *en bloc* endoscopic resection when combined with a multibending endoscope, but did not perform a formal evaluation. Kadowaki et al. compared the utility of magnifying NBI and magnifying WLI in recognizing gastric cancer demarcation. They also reported that magnifying NBI is more useful when it is combined with acetic acid (48). Kiyotoki et al. (49) and Nagahama et al. (50) reported the superiority of magnifying NBI to chromoendoscopy for determining the lateral extent of early gastric cancer. These lines of evidence suggest that magnifying NBI can be a useful modality for determining the lateral extent of gastric cancer. However, it must be emphasized that it is still difficult to accurately define the tumour margin in undifferentiated gastric cancers; the successful delineation rate was 0% for undifferentiated cancers in one study (50). Because undifferentiated gastric cancers often spread subepithelially and are covered with the non-neoplastic foveolar epithelium, observation of the mucosal surface by NBI is not useful for determining the tumour margin of this type of gastric cancer. Therefore, it is necessary to take biopsy specimens of the surrounding mucosa to define the extent of an otherwise undetectable tumour in undifferentiated gastric cancers.

Prediction of the Histological Type of Gastric Cancer

Nakayoshi et al. (51) reported that the different microvascular patterns detected with magnifying NBI images are useful in predicting the histological type of a superficial gastric cancer. Differentiated adenocarcinomas display a 'fine network pattern,' and undifferentiated adenocarcinomas display a 'corkscrew pattern' in their microvascular structures (Fig. 2). Yoshida et al. (52) reported that a 'non-

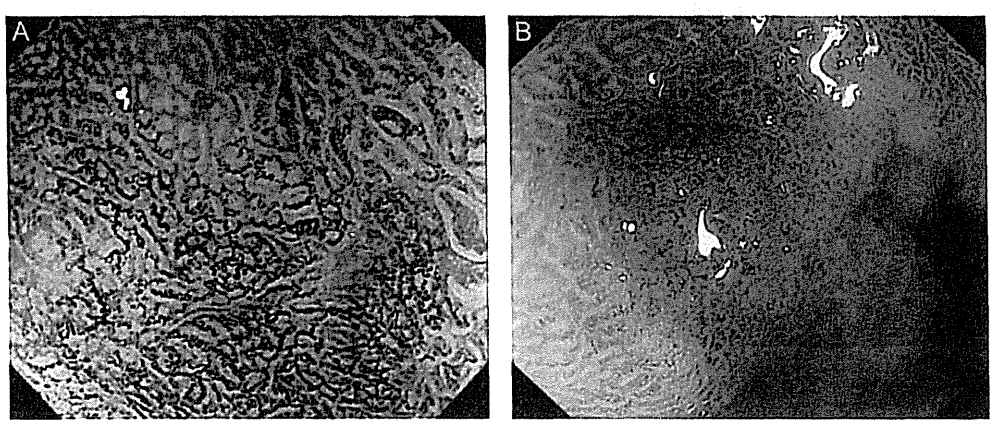

Figure 2. Microvascular patterns of gastric cancer. (A) Fine network pattern indicates differentiated adenocarcinoma. (B) Corkscrew pattern indicates undifferentiated adenocarcinoma.

structural pattern' appeared to be a useful marker of undifferentiated superficial gastric cancers.

Although these studies have indicated the utility of magnifying NBI in the prediction of the histopathological type of a gastric cancer, its reliability must be validated in a large-scale prospective study. Moreover, even if magnifying NBI can predict the histological type of a cancerous lesion, histological confirmation by biopsy is required at this time. However, the prediction of histological type could be useful to the endoscopists when selecting the site of a biopsy in a lesion because gastric cancers are usually heterogeneous.

Diagnosis of the Tumour Depth of Gastric Cancer

In contrast to ESCC, there is no evidence that NBI, with or without magnifying endoscopy, can predict the depth of tumour invasion in a patient with gastric cancer.

Diagnosis of Gastric Adenoma

Because most gastric adenomas form protruded lesions, the differential diagnosis of protruded gastric cancer and protruded adenoma is sometimes difficult (53, 54). Yao et al. reported that the characteristic finding of magnifying NBI, a white opaque substance (Fig. 3), is a relevant sign for differentiating protruded adenomas from protruded cancers (55). Tsuji et al. (56) also reported that the presence of an irregular microvascular pattern or irregular microsurface pattern with a demarcation line between the lesion and the surrounding area under magnifying NBI is useful in distinguishing cancers from adenomas. Maki et al. (57) reported that magnifying NBI appears to be useful in differentiating between cancerous and adenomatous superficial elevated lesions of the stomach with significantly higher sensitivity and accuracy. In contrast, depressed-type adenoma is rare, although it is clinically important because it has greater malignant potential than protruded adenoma (58). Tamai et al. (59) reported that depressed-type adenomas display a regular ultrafine pattern, in which the network of microvessels is composed of small and regular circles, which differs from the irregular fine network pattern of well-differentiated gastric cancers.

These reports indicate that magnifying NBI should be a useful modality for the accurate diagnosis of gastric adenoma.

DUODENUM

Small duodenal ampullary tumours are treated by surgical resection or endoscopic resection. However, the lateral margin must be precisely assessed before curative endoscopic resection. Uchiyama et al. (60) reported that magnifying NBI with a direct frontal-view magnifying endoscope can predict the histological characteristics of ampullary lesions by detecting abnormal vessels and microsurface patterns. Itoi et al. (61) reported that NBI with a conventional duodenoscope, with no magnifying capacity, allowed better visualization of the tumour margin than indigo carmine chromoendoscopy. However, these studies included only a small number of cases, so further studies with a sufficient number of patients are required to evaluate the usefulness of NBI for duodenal tumours.

CONCLUSION

NBI is now a useful endoscopic modality for the head and neck region and the upper gastrointestinal tract. It helps the endoscopists to do early detection and accurate diagnosis for the head and neck neoplasia and disease in the upper gastrointestinal diseases. Furthermore, it enables minimally invasive treatment and improves the patients' survival and quality of life. Then, standard education programme of NBI in clinical practice will be needed.

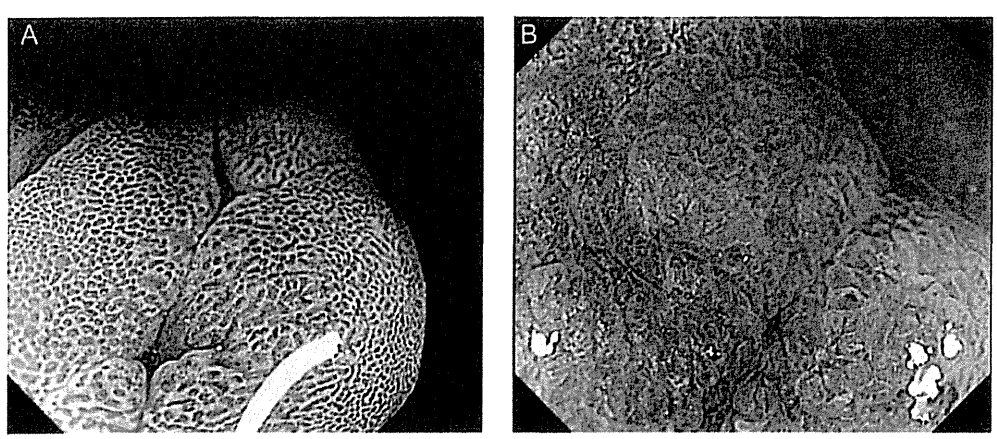

Figure 3. White opaque substance (WOS) within an elevated adenoma and well-differentiated adenocarcinoma. (A) The regular distribution of WOS indicates adenoma. (B) The irregular distribution of WOS indicates adenocarcinoma.

Conflict of interest statement

None declared.

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Review

Endoscopic diagnostic strategy of superficial esophageal squamous cell carcinoma

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The prognosis of the esophageal squamous cell carcinoma is still poor. Early detection is ideal to improve patient survival. In particular, superficial cancer limited within the mucosal layer is a good candidate for minimally invasive treatment by endoscopic resection with curative intent. However, an effective endoscopic diagnostic strategy is not established worldwide. Herein, we review the published papers on this subject.

Key words: endoscopic ultrasonography (EUS), esophagus, image-enhanced endoscopy (IEE), Lugol chromoendoscopy, narrow-band imaging (NBI), esophageal squamous cell carcinoma (ESCC)

INTRODUCTION

SQUAMOUS CELL CARCINOMA (SCC) is the predominant histological type of esophageal cancer worldwide.[1] Asia (China, Kazakhstan, Taiwan and Japan) and Eastern Africa are the areas with the highest incidence. Smoking, ethanol in alcoholic beverages and acetaldehyde associated with alcoholic beverages are definite risk factors for esophageal SCC (ESCC).[2] Because these definite risk factors are recognized, early detection of ESCC can be expected for those at risk.

Endoscopy plays an important role in the early detection of cancer in the gastrointestinal tract, which includes the esophagus. However, detection is not always easy for endoscopists, because endoscopic findings of superficial esophageal cancers are slight and minimal. Therefore, an ideal strategy for the early detection of ESCC is required.

According to the depth of the invasion, superficial ESCC is classified into Tis (carcinoma in situ/high-grade dysplasia), T1a (tumor invades the lamina propria or muscularis mucosae) or T1b (tumor invades the submucosa) by the International Union Against Cancer Classification of Malignant Tumours (7th edition) (Fig. 1).[3] Because more than half of the patients with superficial ESCC have no symptoms associated with cancer, effective screening is important for early detection. Early detection enables us to use minimally invasive treatment, such as endoscopic resection (EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection), and those with superficial ESCC can expect to be cured.

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IDEAL DIAGNOSTIC STRATEGY

(i) Identification of subject at risk:
1. drinkers;
2. smokers;
3. aldehyde dehydrogenase type 2 (ALDH2) deficiency;[4]
4. inadequate intake of green-yellow vegetables and fruits.

(ii) Detection:
1. conventional white light imaging (WLI);
2. Lugol chromoendoscopy;
3. equipment-based image-enhanced endoscopy (IEE).[5]

(iii) Differential diagnosis:
1. conventional WLI;
2. Lugol chromoendoscopy;[6–8]
3. equipment-based IEE.

(iv) Estimation of the depth of invasion:
1. conventional WLI;
2. equipment-based IEE;
3. endoscopic ultrasound (EUS).

(v) Histological confirmation by biopsy.

WHITE LIGHT IMAGING

SUPERFICIAL ESCC, ESPECIALLY Tis and T1a ESCC, sometimes lacks any changes in appearance. In these cases, early detection of superficial ESCC by

conventional WLI is difficult. Disappearance of the vascular network in the mucosa (Fig. 2), uneven surface and tiny white coating are indications of the possible presence of superficial ESCC (Fig. 3).

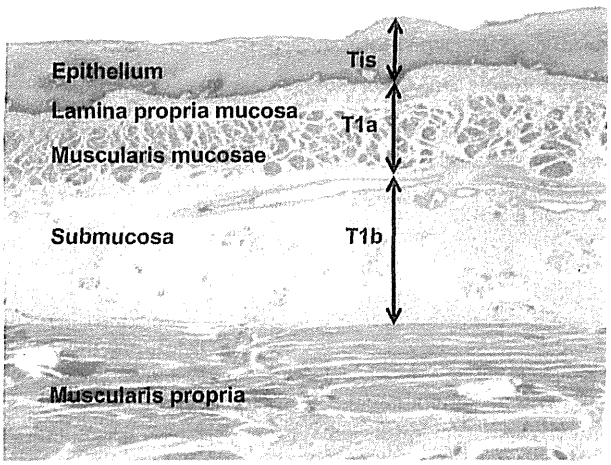

Figure 1 Histological structure of the esophageal wall. From the surface of the lumen, the esophagus comprises squamous epithelium, lamina propria mucosa, muscularis mucosae, submucosa, muscularis propria and adventitia. According to the 7th Classification of Malignant Tumors (TNM), superficial esophageal squamous cell carcinoma is classified into Tis (carcinoma in situ/high-grade dysplasia), T1a (tumor invades the lamina propria or muscularis mucosae) or T1b (tumor invades the submucosa).

LUGOL CHROMOENDOSCOPY

LUGOL CHROMOENDOSCOPY IS the standard method for detecting and identifying the margin of the lateral extension of ESCC.[6] However, it causes unpleasant reactions, such as chest pain and discomfort, in those who undergo endoscopic examination, and occasionally causes allergic reactions including flushing, asthma and iodine shock. Sodium thiosulfate solution is useful in reducing these adverse symptoms.[9] Giving i.v. steroids before examination is sometimes effective in preventing allergic reactions.

After staining with Lugol solution, a pink color change indicates ESCC (Fig. 4). The pink color change is clearly revealed after 2–3 min after Lugol staining. Shimizu *et al.* reported that when used as a diagnostic index for high-grade intraepithelial squamous neoplasia and SCC, the pink color sign shows sensitivity and specificity of 91.9% and 94.0%, respectively.[10] Ishihara *et al.* also reported that sensitivity and specificity of diagnosis of high-grade intraepithelial neoplasia or invasive cancer were 88% and 95%, respectively.[11]

The so-called 'Tatami-no-me' sign[12] is a useful indicator of the depth of invasion of ESCC (Fig. 5). 'Tatami' means traditional Japanese-style flooring and the endoscopic appearance of the 'Tatami-no-me' sign is similar to the surface pattern of Tatami (Japanese traditional floor). If the Tatami-no-me sign is not seen in a cancerous lesion, the neoplasia might have invaded the deep layer of the lamina propria. If the Tatami-no-me sign is seen, the lesion will not have invaded the deep layer of the lamina propria.

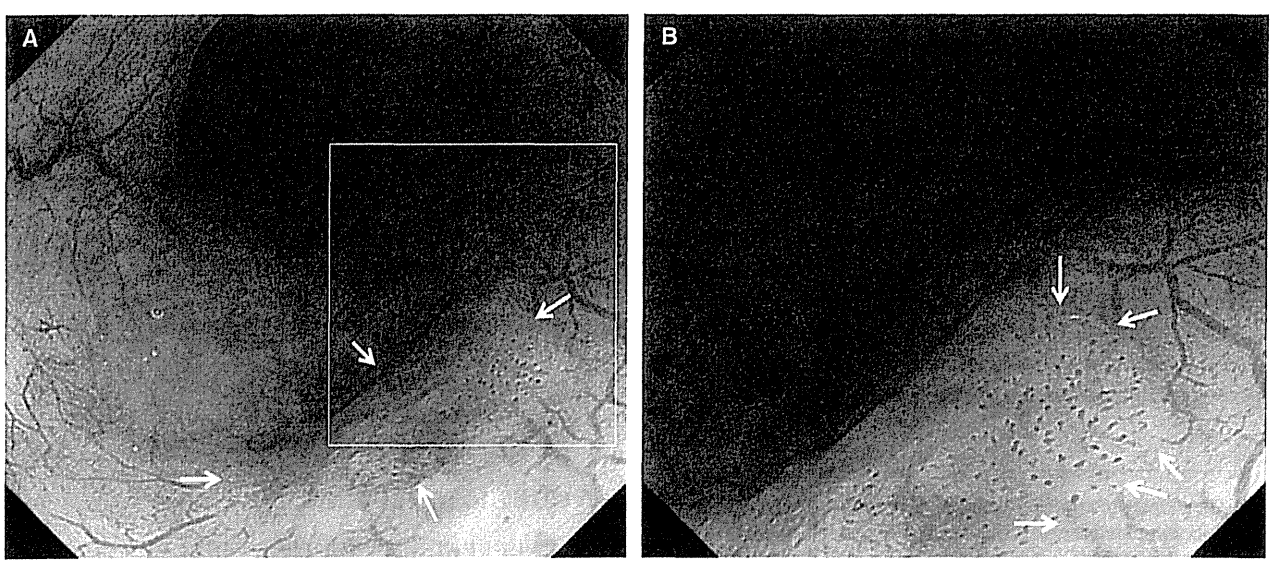

Figure 2 Superficial esophageal squamous cell carcinoma. The margin of the light reddish area (arrows in [A]) shows disappearance of the vascular network in the mucosa (arrows in B).

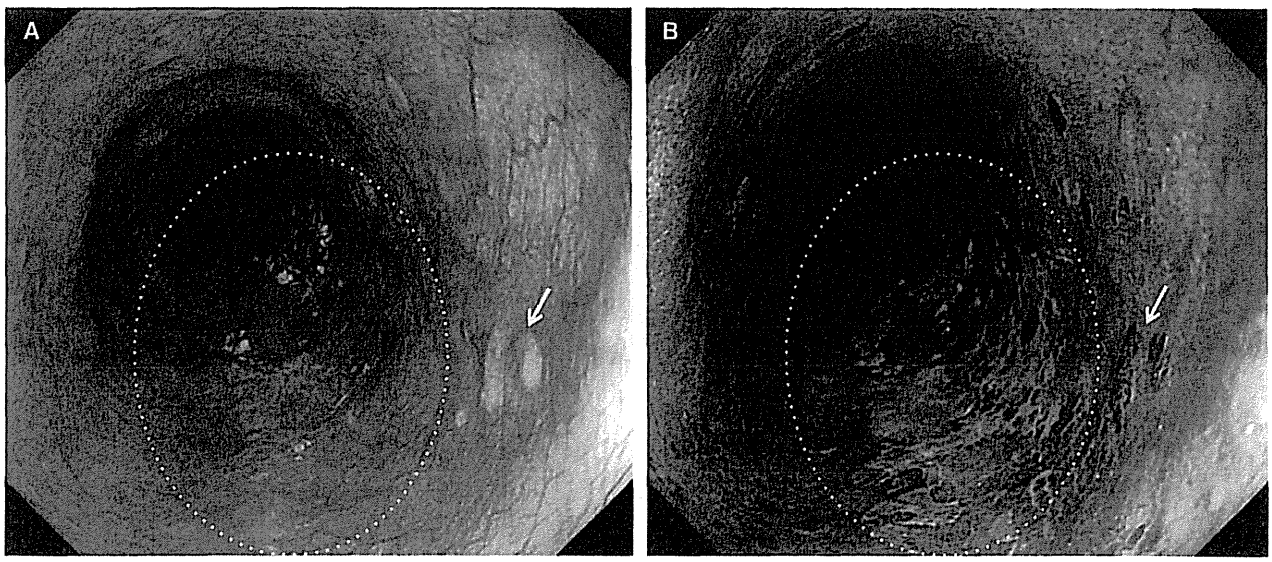

Figure 3 Superficial esophageal squamous cell carcinoma. (A) White light imaging shows uneven surface and tiny white coating in the esophageal wall. Arrow indicates glycogenic acanthosis as a landmark. (B) Lugol chromoendoscopy shows wide Lugol-voiding lesion with irregular margin. Arrow indicates glycogenic acanthosis as a landmark.

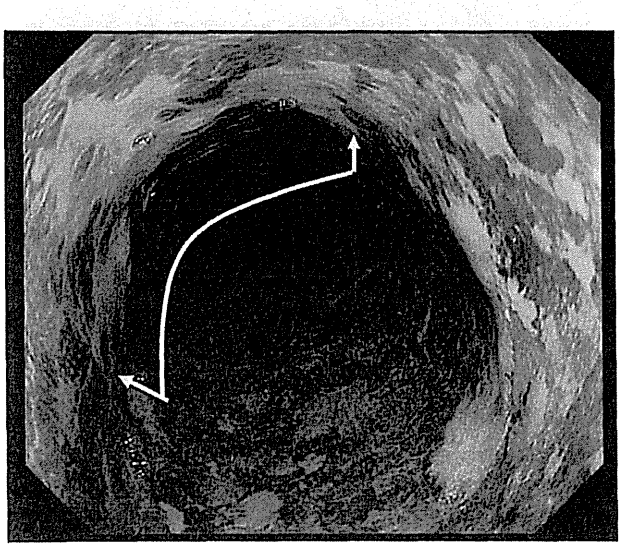

Figure 4 Lugol chromoendoscopy shows a superficial esophageal cancer: the suspicious lesion shows pink color change (arrow).

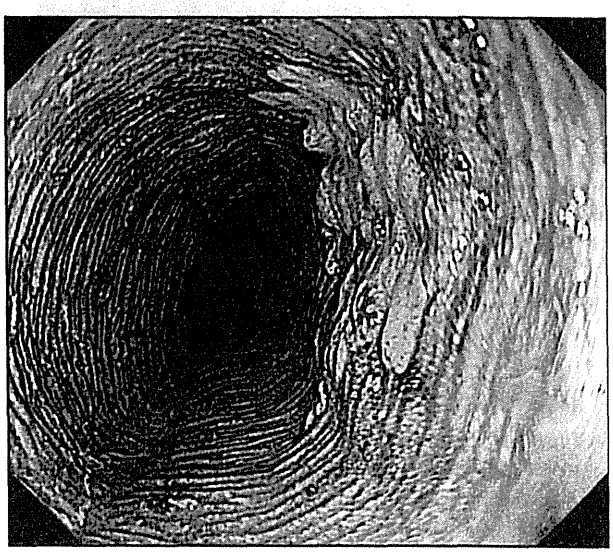

Figure 5 Lugol chromoendoscopy shows 'Tatami-no-me' sign. 'Tatami' means traditional Japanese-style flooring.

EQUIPMENT-BASED IMAGE-ENHANCED ENDOSCOPY

IMAGE-ENHANCED ENDOSCOPY[5] is expected to accurately diagnose high-grade intraepithelial neoplasia and SCC with minimal invasion of the esophagus. IEE combined with magnification is a powerful tool to characterize the lesion.

Among the IEE types, narrow-band imaging (NBI)[13,14] has been found to provide a highly accurate diagnosis of superficial ESCC. The NBI endoscopy system uses two narrow-band illuminations of 415 nm and 540 nm by the NBI filter, corresponding to the peaks of absorption of hemoglobin. Therefore, thin blood vessels, such as capillaries, in the epithelium or mucosal layer can be seen more distinctly than in conventional WLI. Under NBI observation, most of the