Magnifying endoscopy with narrow-band imaging is more accurate for determination of horizontal extent of early gastric cancers than chromoendoscopy

Authors Itsuko Asada-Hirayama[1], Shinya Kodashima[1], Yoshiki Sakaguchi[2], Satoshi Ono[1], Keiko Niimi[3], Satoshi Mochizuki[4], Yosuke Tsuji[2], Chihiro Minatsuki[2], Satoki Shichijo[1], Keisuke Matsuzaka[5], Tetsuo Ushiku[6], Masashi Fukayama[6], Nobutake Yamamichi[1], Mitsuhiro Fujishiro[1,7], Kazuhiko Koike[1]

Institutions Institutions are listed at the end of article.

submitted
5. December 2015
accepted after revision
11. April 2016

Bibliography
DOI http://dx.doi.org/10.1055/s-0042-107068
Endoscopy International Open 2016; 04: E690–E698

E-ISSN 2196-9736

Corresponding author
Shinya Kodashima, MD PhD
Department of Gastroenterology
Graduate School of Medicine
The University of Tokyo
7-3-1
Hongo
Bunkyo-ku
Tokyo 113-8655
Japan
Fax: +81-3-58008806
kodashima-tky@umin.ac.jp

Background and study aims: Although magnifying endoscopy with narrow-band imaging (ME-NBI) is reported to be useful for delineating the horizontal extent of early gastric cancers (EGCs), there are few reports which have objectively demonstrated the superiority of ME-NBI over chromoendoscopy with indigo carmine for this purpose. We conducted an exploratory comparison of the diagnostic accuracy of both modalities for the delineation of EGCs using prospectively collected data, and clarified the clinicopathological features related to inaccurate evaluation of the horizontal extent of EGCs.

Patients and methods: EGCs were assigned to the oral narrow-band imaging (O-NBI) group or the oral chromoendoscopy (O-CE) group before endoscopic submucosal dissection (ESD). The oral border was observed according to assignment, and the anal border with the other modality. The horizontal extent of the tumor was evaluated by each modality and a marking dot was placed on the visible delineation line. After ESD, the marking dots were identified pathologically and defined as "accurate evaluation" if they were located within 1 mm of the pathological tumor border. We compared the rate of accurate evaluation of ME-NBI and chromoendoscopy, and analyzed the clinicopathological features related to inaccurate evaluation.

Results: A total of 113 marking dots evaluated by ME-NBI and 116 evaluated by chromoendoscopy were analyzed. The rate of accurate evaluation by ME-NBI was significantly higher than that by chromoendoscopy (89.4% vs 75.9%, $P=0.0071$). The EGCs with flat borders and large EGCs were significantly related to inaccurate evaluation using ME-NBI. There were no significant factors related to inaccurate evaluation with chromoendoscopy.

Conclusions: The accurate evaluation rate of the horizontal extent of EGCs by ME-NBI is significantly higher than that by chromoendoscopy.

Study registration: UMIN000007641

Introduction

With the recent development of endoscopic submucosal dissection (ESD), en bloc resection of mucosal gastric cancer is now theoretically possible regardless of the size, shape, or location of the tumors [1]. Additionally, ESD enables en bloc resection of lesions with submucosal fibrosis such as lesions with ulcer scarring or residual lesions after endoscopic treatment [1]. However, the number of complications related to ESD is reported to be higher than that of endoscopic mucosal resection (EMR) [2] because of the technical difficulties of ESD. In particular, the size of mucosal resection has been reported to be significantly associated with the incidence of complications such as delayed bleeding, perforation, and stricture [3–9]. Making the extent of resection in ESD as small as curatively possible is important to reduce the number of procedure-related complications. Therefore, precise evaluation of the horizontal extent of early gastric cancers (EGCs) during ESD is necessary.

In Japan, conventional endoscopy with white light imaging (WLI) and chromoendoscopy with indigo carmine are widely used for endoscopic evaluation of the horizontal extent of EGCs [10]. Recently, magnifying endoscopy with narrow-band imaging (ME-NBI) has been reported to be useful for distinguishing cancerous lesions from non-cancerous lesions and for delineating the horizontal extent of EGCs [11–14]. However, there are few reports which have objectively demonstrated the superiority of ME-NBI over chromoendoscopy for this purpose.

Nagahama et al. reported that, among EGCs with unclear margins through chromoendoscopy with indigo carmine, the entire horizontal margin

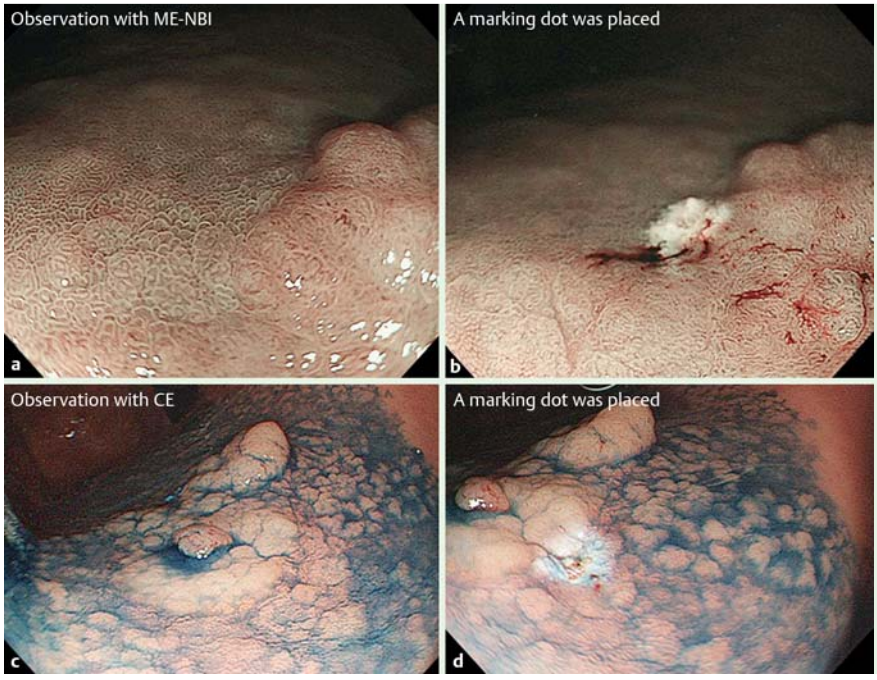

Fig. 1 The oral or anal border of the tumor was observed with magnifying endoscopy with narrow-band imaging (ME-NBI) according to assignment, and a marking dot was placed on the visible delineation line. The other side of the tumor border was observed with chromoendoscopy, and a marking dot was placed on the visible delineation line.

could be accurately delineated in 72.6% of these lesions using ME-NBI [12]. However, their study was limited by the fact that it was not a direct comparison between the diagnostic accuracy of ME-NBI and chromoendoscopy, and by the fact that the accuracy of tumor delineation was not objectively assessed. The aim of this study was to objectively compare the accuracy of both modalities for determining the horizontal extent of EGCs.

Patients, materials and methods

This study was begun after approval by the Medical Ethics Committee of the University of Tokyo Hospital and registration in the University Hospital Medical Network Clinical Trial Registry (UMIN000007641) on 2 April 2012. Written informed consent for participation in this study was obtained from all subjects by their own free will.

Study subjects

The study subjects had EGCs treated by ESD, after giving informed consent, at the University of Tokyo Hospital between 11 April 2012 and 30 November 2013. The exclusion criteria were as follows: (1) adenocarcinomas of the esophagogastric junction, (2) cancers of a remnant stomach or a gastric tube, (3) residual cancers after endoscopic treatment, (4) type 0-I lesions (lesions which were composed of two or more elements, such as type 0-I+IIa, were included in the analysis), (5) cancers located in the greater curvature of the gastric body, (6) cancers which extended to the duodenum, (7) cancers less than 10 mm in diameter. ESD was indicated for EGCs or adenomas with a suspicion of adenocarcinoma (Group 4 by biopsy) that met the Gotoda criteria [15]. The subjects were assigned to the oral-NBI (O-NBI) group or the oral-CE (O-CE) group by the envelope method. Two hundred sealed envelopes were prepared, 100 for the O-NBI group and 100 for the O-CE group, and an envelope was randomly picked from the box before ESD. There was no prior research showing the appropriate prediction of sample size so we determined the timing of study termination when the analyzable subjects exceeded 50 lesions in each arm.

Endoscopic procedure for delineation of EGCs

All patients received preoperative endoscopic examination with ME-NBI and/or chromoendoscopy with indigo carmine before the treatment date, and biopsies were performed from the perilesion area unless they took anticoagulants. The tumor location, circumference, and macroscopic type were determined using conventional endoscopy with white light just before ESD and were described according to the Japanese Classification of Gastric Carcinoma – 3 rd Edition [16]. If the tumor was composed of two or more elements, the predominant macroscopic type was adopted.

In the O-NBI group, we first observed the oral side of the tumor with ME-NBI. We mainly used middle zoom observation, and the horizontal extent of the tumor was carefully determined based on changes in the microvascular patterns and/or microsurface patterns [13] and a marking dot was placed on the oral delineation line of the tumor using the DualKnife (KD-650, Olympus, Tokyo, Japan). After that, 0.2% indigo carmine was sprayed and we observed the anal side of the tumor with chromoendoscopy without magnification and determined the horizontal extent of the tumor. A marking dot was placed on the anal delineation line of the tumor (**Fig. 1**).

In the O-CE group, we first observed the anal side of the tumor with ME-NBI using middle zoom observation and a marking dot was placed on the anal delineation line of the tumor. After 0.2% indigo carmine was sprayed, we observed the oral side of the tumor with chromoendoscopy and placed a marking dot on the oral delineation line.

The number of marking dots was determined according to the diameter of the tumor in the short axial direction, with one mark per centimeter. After that, ESD was performed as described in previous reports [11, 17]. A GIF-H260Z video gastroscope (Olympus, Tokyo, Japan) was used for evaluation of the horizontal extent of EGCs. A VIO 300 D electrosurgical generator (Erbe Elektromedizin, Tubingen, Germany) was used as the high frequency

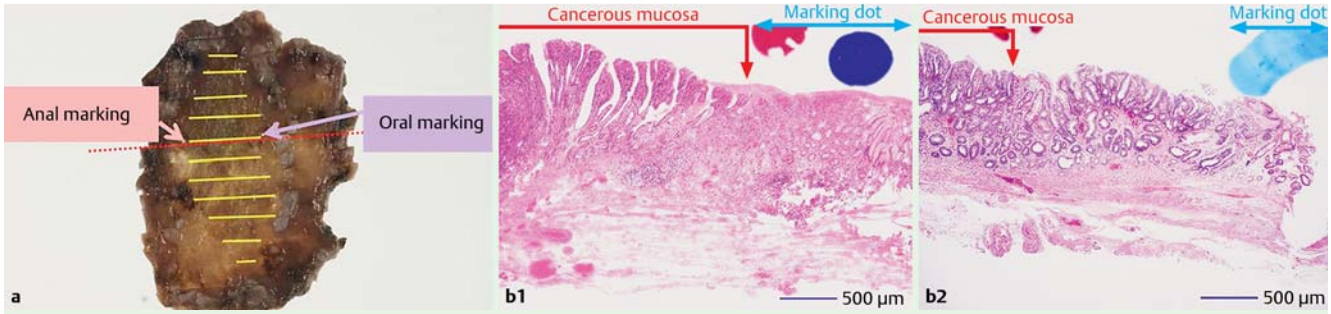

Fig. 2 Judgment of accurate or inaccurate evaluation. **a** The section was made in a direction linking the marking dots on the oral and anal side of the tumor border. The marking dots were identified under microscopic observation. **b1** Marking dots which were located within 1 mm of the tumor border were defined as "accurate evaluation" of tumor delineation. **b2** If a marking dot was located more than ±1 mm from the tumor border, it was defined as "inaccurate evaluation".

electrical generator. The delineation of tumor borders and placement of marking dots on tumor edges were performed by endoscopists who had certification from the Japan Gastroenterological Endoscopy Society.

Pathological assessment and judgment of accurate or inaccurate evaluation

After ESD, we identified the marking dots on the tumor borders of the resected specimens and inserted 23G needles on those markings to assist the microscopic recognition. Then the resected specimens were fixed in a formalin solution and were serially cut at 2-mm intervals. The section was made in a direction linking the marking dots on the oral or anal tumor border. However, lesions which required serial cuts in a different direction to evaluate the resection margin accurately were excluded from analysis. The marking dots were identified under microscopic observation. Marking dots which were located within 1 mm of the border of the tumor were defined as "accurate evaluation" of tumor delineation. If a marking dot was located more than ±1 mm from the tumor border, it was defined as "inaccurate evaluation" (**Fig. 2**). We set the cutoff value which separated accurate or inaccurate evaluation as ±1 mm in view of the technical limitation of putting the marking dot on the endoscopically determined tumor border.

Histological type, tumor size, tumor depth, ulceration, lymphovascular infiltration, and horizontal tumor extent were assessed pathologically according to the Japanese Classification of Gastric Carcinoma – 3rd Edition [16]. If the tumor exhibited multiple histological types, the predominant histological type was adopted. We also assessed the presence of a flat (0–IIb) component, the presence of diffuse-type adenocarcinoma, the presence of mixed histology, the difference in the mucosal height at the tumor border compared with the adjacent non-neoplastic mucosa (i.e. macroscopic type of the tumor border: elevated, flat, or depressed), the histological type of the tumor border, and the presence of marginal elevation. The presence of a flat (0–IIb) component meant that a tumor contained a flat component which could be recognized macroscopically on the resected specimen (e.g. 0–IIa+0–IIb); on the other hand, macroscopic type of tumor border was defined based on the histological finding for the area where the marking dot was placed. The presence of diffuse-type adenocarcinoma meant that the lesion was comprised of poorly differentiated adenocarcinoma or signet ring cell carcinoma. The presence of mixed histology meant that the lesion was comprised of more than two histological types (e.g. well-differentiated adenocarcinoma and moderately differentiated adenocarcinoma). A pathologist who was blinded to which group each specimen was assigned performed the judgment of accurate or inaccurate evaluation and detailed assessment of the tumor border.

Outcome measurement

Based on the definition previously described, we calculated the rate of accurate evaluation of ME-NBI and chromoendoscopy. As a subgroup analysis, the rates of accurate evaluation according to macroscopic type of EGCs were also calculated and compared. We also analyzed the clinicopathological features of EGCs related to inaccurate endoscopic evaluation of the horizontal extent of the tumor by ME-NBI or by chromoendoscopy.

Statistical analysis

This was performed using the chi-squared test or Fisher's exact test for nominal variables. Student's *t* test was used for analysis of continuous variables. All analyses were performed using JMP version 10 (SAS Institute, Tokyo, Japan). *P* values <0.05 were considered statistically significant.

Results

A total of 130 lesions (124 patients) out of 276 EGCs (261 patients) treated by ESD in our hospital were enrolled in this study; 67 lesions were assigned to the O-NBI group and 63 to the O-CE group (**Fig. 3**). One lesion in the O-NBI group and three lesions in the O-CE group were excluded from analysis because the final pathological results of these lesions indicated that they were not adenocarcinoma. Three lesions in the O-NBI group and four lesions in the O-CE group were excluded because sections made in different directions from the direction linking the marking dots on the oral or anal tumor borders were required to assess the resection margins. Five lesions in the O-NBI group and five lesions in the O-CE group were excluded because the marking dots on the tumor border could not be identified by optical microscopy. So the final numbers of analyzable lesions in the O-NBI group and O-CE groups were 58 and 51, respectively.

There were no statistically significant differences between the background characteristics of the two groups (**Table 1**).

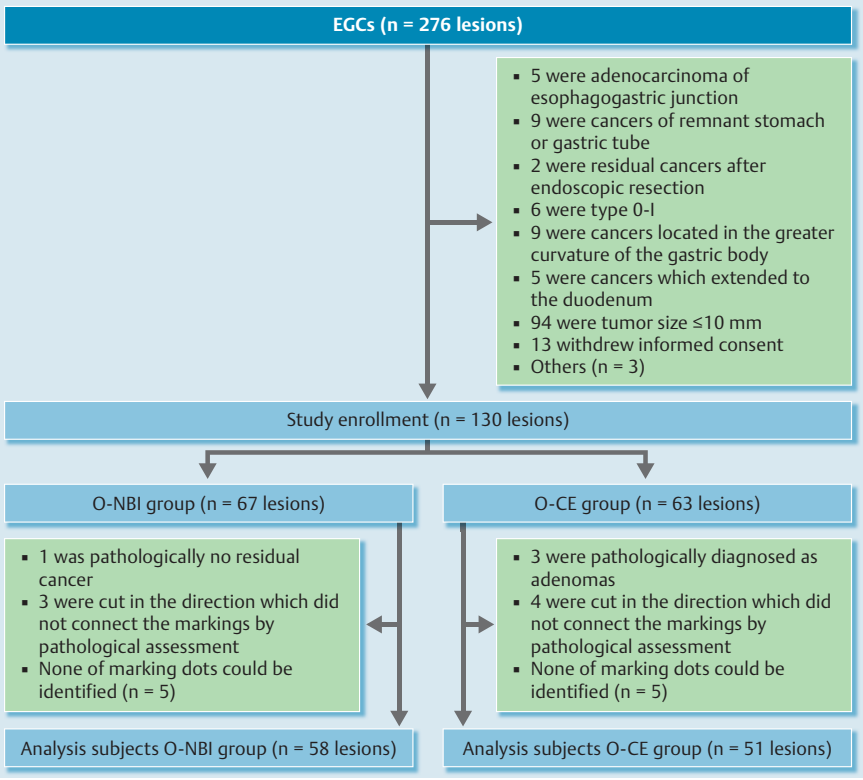

Fig. 3 Study enrollment flow chart. One hundred and thirty lesions out of 276 early gastric cancers (EGCs) treated by endoscopic submucosal dissection (ESD) were enrolled in this study; 67 lesions were assigned to the oral narrow-band imaging (O-NBI) group and 63 to the oral chromoendoscopy (O-CE) group. We analyzed the results of 109 lesions (58 lesions from the O-NBI group and 51 lesions from the O-CE group).

Comparison of the accurate evaluation rate of ME-NBI and chromoendoscopy

After excluding the marking dots which could not be recognized on the resected specimens, 113 marking dots evaluated by ME-NBI and 116 marking dots evaluated by chromoendoscopy were analyzed. The rate of accurate evaluation by ME-NBI (101/113, 89.4%) was significantly higher than that by chromoendoscopy (88/116, 75.9%) (P=0.0071) (**Fig. 4**). In a subgroup analysis, the rates of accurate evaluation according to macroscopic type of the EGCs were also calculated. There was no significant difference in the rates of accurate evaluation (37/43, 86.1% by ME-NBI vs 33/41, 80.5% by chromoendoscopy, P=0.4944) in the Type 0–IIa group. However, in the Type 0–IIc group, the rate of accurate evaluation by ME-NBI (63/69, 91.3%) was significantly higher than that by chromoendoscopy (54/74, 73.0%) (P=0.0045).

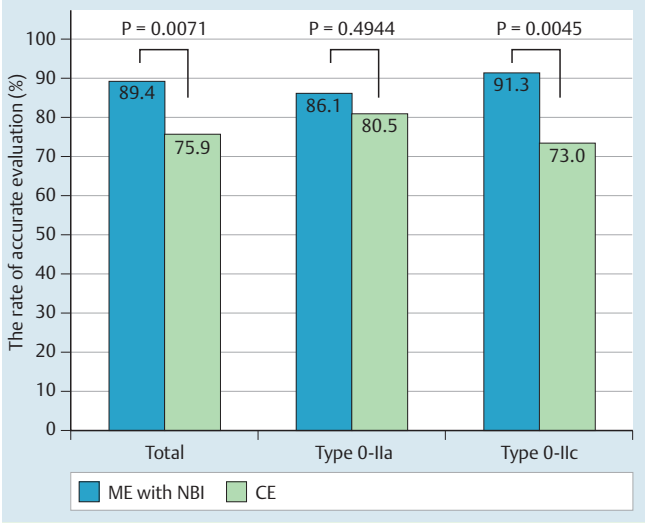

Fig. 4 Comparison of the rate of accurate evaluation. The rate of accurate evaluation by ME-NBI (101/113, 89.4%) was significantly higher than that by chromoendoscopy (88/116, 75.9%) (P=0.0071). There was no significant difference in the rates of accurate evaluation (37/43, 86.1% by ME-NBI vs 33/41, 80.5% by chromoendoscopy, P=0.4944) in the Type 0-IIa group. However, in the Type 0-IIc group, the rate of accurate evaluation by ME-NBI (63/69, 91.3%) was significantly higher than that by chromoendoscopy (54/74, 73.0%) (P=0.0045).

Factors related to inaccurate evaluation

The rate of inaccurate evaluation by ME-NBI was 10.6% (12/113). Through univariate analysis, the lesions with flat tumor borders as well as large lesions were significantly more likely to have inaccurate margin assessment (**Table 2**). Multivariate analysis could not be performed because the number of inaccurate markings was insufficient for accurate analysis. The rate of inaccurate evaluation by chromoendoscopy was 24.1% (28/116). There were no significant factors related to inaccurate evaluation by chromoendoscopy (**Table 3**).

Discussion

Recently, ME-NBI has gradually become popular in the clinical setting. In this study, we objectively compared the usefulness of ME-NBI and chromoendoscopy for determining the horizontal extent of EGCs through precise correlation between endoscopic and pathological findings. As a result, the rate of accurate evaluation by ME-NBI was significantly higher than that by chromoendoscopy. The delineation of tumor borders with chromoendoscopy is performed based on mucosal elevation/depression enhanced by indigo carmine, but these findings often arise as a consequence of inflammation or intestinal metaplasia.

Table 1 Patient and lesion characteristics.

	O-NBI group (n = 58 lesions)	O-CE group (n = 51 lesions)	*P* value
Age (mean ± SD)	72.8 ± 8.1	73.3 ± 9.7	0.7774
Gender (male/female)	44/12	29/18	0.0605
Tumor size, mean ± SD, mm	19.9 ± 13.9	20.7 ± 11.8	0.7474
Location			0.6038
Upper	11	7	
Middle	30	25	
Lower	17	19	
Circumference[1]			0.4754
Less	30	27	
Gre	4	6	
Ant	10	11	
Post	14	7	
Macroscopic type			0.2011
0–I	1	0	
0–IIa	25	16	
0–IIb	0	0	
0–IIc	32	35	
Presence of a flat component			0.4968
Yes	4	2	
No	54	49	
Histological type[2]	1		0.6270
pap	45	0	
tub1	10	36	
tub2	2	13	
por/sig		2	
Mixture of diffuse-type			0.8273
Yes	10	8	
No	48	43	
Mixed histology			0.7969
Yes	31	26	
No	27	25	
Ulceration			0.4649
Yes	7	4	
No	51	47	
Depth			0.3194
M	46	38	
SM1	5	9	
SM2	7	4	
Helicobacter pylori infection[3]			0.8139
Positive	23	19	
After eradication	13	11	
Negative	15	15	
Snare use rate, n/%	1/1.72	0/0.0	0.3462
En bloc resection rate, %	100.0	100.0	
Complete resection rate, %	93.1	94.1	0.8294
Curative resection rate, %	77.59	82.35	0.5361
Delayed bleeding, n/%	4/7.1	5/10.6	0.5315
Perforation, n/%	1/1.8	0/0.0	0.3573

O-NBI, oral narrow-band imaging; O-CE, oral chromoendoscopy.
Age, gender, delayed bleeding rate, and perforation rate were calculated based on the number of patients, and all remaining items were calculated based on the number of the lesions.
[1] Less = lesser curvature, Gre = greater curvature, Ant = anterior wall, Post = posterior wall.
[2] pap = papillary adenocarcinoma, tub1 = well-differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, por/sig = poorly-differentiated adenocarcinoma/signet-ring cell carcinoma.
[3] The conditions of *Helicobacter pylori* infection were unclear in five patients in the O-NBI group and two patients in the O-CE group.

In contrast, the delineation of tumor borders with ME-NBI is performed based on the specific findings of the tumor, such as microvascular or microsurface pattern. So observation with ME-NBI might be able to delineate EGCs more accurately than with chromoendoscopy.

Our study suggested that a large tumor size and a flat tumor border were significant factors which were related to inaccurate endoscopic evaluation of the horizontal extent of EGCs using ME-NBI.

These factors may lead to inaccurate evaluation due to the technical aspects of ME-NBI. For ME-NBI at full magnification, the endoscope must come in contact with the surface of the gastric mucosa. Thus, during the process of delineating the tumor border with ME-NBI, the endoscope inevitably comes in continuous contact with the surrounding mucosa, leading to contact bleeding and other mucosal damage. In addition, observation using ME-NBI is time-consuming because, at a magnification of × 80, only a small area can be observed at one time. The influence of mucus

Table 2 Factors related to inaccurate evaluation with ME-NBI (univariate analysis).

	Accurate evaluation n = 101 (89.4 %)		Inaccurate evaluation n = 12 (10.6 %)		*P* value
	n	%	n	%	
Gender					0.7955
Male	71	89.9	8	10.1	
Female	30	88.2	4	11.8	
Location					0.3531
Upper	16	84.2	3	15.8	
Middle	49	87.5	7	12.5	
Lower	36	94.7	2	5.3	
Circumference					0.3755
Less	48	84.2	9	15.8	
Gre	10	100.0	0	0.0	
Ant	21	91.3	2	8.7	
Post	22	95.7	1	4.4	
Macroscopic type					0.5810
0–I	1	100.0	0	0.0	
0–Iia	37	86.1	6	14.0	
0–IIc	63	91.3	6	8.7	
Presence of a flat component					0.6212
Yes	5	83.3	1	16.7	
No	96	89.7	11	10.3	
Histological type[1]					0.4615
pap	1	100.0	0	0.0	
tub1	68	90.7	7	9.3	
tub2	26	83.8	5	16.1	
por/sig	6	100.0	0	0.0	
Mixture of diffuse-type					0.7362
Yes	21	87.5	3	12.5	
No	80	89.9	9	10.1	
Mixed histology					0.9002
Yes	57	89.1	7	10.9	
No	44	89.8	5	10.2	
Ulceration					0.3915
Yes	9	81.8	2	18.2	
No	92	90.2	10	9.8	
Depth					1.0000
M	75	89.3	9	10.7	
SM1	15	88.2	2	11.8	
SM2	11	91.7	1	8.3	
Helicobacter pylori infection[2]					1.0000
Positive	39	88.6	5	11.4	
After eradication	23	92.0	2	8.0	
Negative	34	89.5	4	10.5	
Macroscopic type of tumor border[3]					0.0111*
Elevated	25	100.0	0	0.0	
Flat	54	83.1	11	16.9	
Depressed	22	100.0	0	0.0	
Histological type of tumor border					1.0000
pap	2	100.0	0	0.0	
tub1	69	88.5	9	11.5	
tub2	24	88.9	3	11.1	
por/sig	6	100.0	0	0.0	
Marginal elevation[3]					0.7188
Yes	13	92.9	1	7.1	
No	88	89.8	10	10.2	
Age, mean ± SD	73.3 ± 9.0		72.8 ± 7.5		0.8339
Tumor size, mean ± SD, mm	21.5±13.7		31.0±17.7		0.0301[4]

ME-NBI, magnifying endoscopy with narrow-band imaging.

[1] pap = papillary adenocarcinoma, tub1 = well-differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, por = poorly-differentiated adenocarcinoma, sig = signet ring cell carcinoma.

[2] The conditions of *Helicobacter pylori* infection were unclear in five patients in the accurate evaluation group and one patient in inaccurate evaluation group.

[3] Macroscopic type of tumor border and marginal elevation were not able to be judged in one lesion in the inaccurate evaluation group because of the burning effect.

[4] $P < 0.05$.

Table 3 Factors related to inaccurate evaluation with chromoendoscopy (univariate analysis).

	Accurate evaluation n = 88 (75.9 %)		Inaccurate evaluation n = 28 (24.1 %)		*P* value
	n	%	n	%	
Gender					0.4936
Male	60	74.1	21	25.9	
Female	28	80.0	7	20.0	
Location					0.2181
Upper	16	84.2	3	15.8	
Middle	40	69.0	18	31.0	
Lower	32	82.1	7	18.0	
Circumference					0.4379
Less	43	71.7	17	28.3	
Gre	10	83.3	2	16.7	
Ant	20	87.0	3	13.0	
Post	15	71.4	6	28.6	
Macroscopic type					0.6183
0–I	1	100.0	0	0.0	
0–IIa	33	80.5	8	19.5	
0–IIc	54	73.0	20	27.0	
Presence of a flat component					0.9673
Yes	3	75.0	1	25.0	
No	85	75.9	27	24.1	
Histological type					0.1153
pap	1	100.0	0	0.0	
tub1	65	80.3	16	19.8	
tub2	20	69.0	9	31.0	
por/sig	2	40.0	3	60.0	
Mixture of diffuse-type					0.3497
Yes	15	68.2	7	31.8	
No	73	77.7	21	22.3	
Mixed histology					0.7530
Yes	47	77.1	14	23.0	
No	41	74.6	14	25.5	
Ulceration					0.0809
Yes	8	57.1	6	42.9	
No	80	78.4	22	21.6	
Depth					0.7013
M	68	77.3	20	22.7	
SM1	12	70.6	5	29.4	
SM2	8	72.7	3	27.3	
Helicobacter pylori infection[1]					0.6861
Positive	31	70.5	13	29.6	
After eradication	20	76.9	6	23.1	
Negative	29	78.4	8	21.6	
Macroscopic type of tumor border[2]					0.2770
Elevated	20	87.0	3	13.0	
Flat	54	77.1	16	22.9	
Depressed	14	66.7	7	33.3	
Histological type of tumor border					0.6024
pap	2	100.0	0	0.0	
tub1	67	77.0	20	23.0	
tub2	18	72.0	7	28.0	
por/sig	1	50.0	1	50.0	
Marginal elevation[2]					0.6766
Yes	13	81.3	3	18.8	
No	75	76.5	23	23.5	
Age, mean ± SD	72.9 ± 8.5		71.4 ± 9.9		0.4367
Tumor size, mean ± SD, mm	21.6 ± 13.5		24.9 ± 15.3		0.2744

[1] The conditions of *Helicobacter pylori* infection were unclear in eight patients in the accurate evaluation group and one patient in the inaccurate evaluation group.
[2] Macroscopic type of tumor border and marginal elevation were not able to be judged in two lesions in the inaccurate evaluation group because of the burning effect.

secretion from gastric mucosa caused by water flushing and contact of the scope may become greater with time. Large lesions generally require close-up observation of a wider area and long observation time for delineation, which may lead to contact bleeding and/or mucus secretion, complicating endoscopic evaluation. Lesions with a flat tumor border may also tend to require observation of a wider area and long observation time for delineation because of the difficulty to decide where to observe by ME-NBI. Thus, these lesions might be more open to the influence of contact bleeding and/or mucus secretion.

On the other hand, with chromoendoscopy, endoscopists identify the tumor borders from a middle distance view during a relatively short time, which may be why the results of chromoendoscopy were not influenced by these factors.

Among lesions with an elevated or depressed tumor border, the rate of accurate evaluation by ME-NBI was 100 %. However, with chromoendoscopy, evaluation was inaccurate in 13 % of elevated types and 33 % of depressed types. Although mucosal elevation/depression at the tumor border and intralesional mucosal irregularity is enhanced by indigo carmine, the background gastric mucosa surrounding EGC is often uneven because of inflammation or intestinal metaplasia. It may have been difficult to distinguish the elevation/depression of the tumor border from those due to inflammation or intestinal metaplasia by chromoendoscopy. On the other hand, ME-NBI may be able to distinguish these mucosal alterations by observation of microvascular and microsurface patterns.

It has been reported that the tumor borders of diffuse-type EGCs are often difficult to delineate even with ME-NBI, although no diffuse-type lesion was inaccurately evaluated in our study. By pathological assessment, tumor cells were observed at the surface of the mucosa at the tumor edge in all cases. This was one reason why we could accurately delineate the diffuse-type EGCs. The number of diffuse-type EGCs was too small in our study, thus a systematic analysis of the usefulness of ME-NBI in delineating diffuse-type EGCs is required.

The limitations of this study are as follows. First, it is possible that the operators marked the most easily distinguishable delineation point of the tumor border within the range of oral or anal side, because the protocol for the location of marking was not strictly established. The objectivity of this study may have been improved if the location of the marking had been defined as the most oral or anal edge of the tumor.

Second, the subjects of this study did not cover all EGCs. We excluded EGCs located in the greater curvature of the gastric body to remove the influence of inaccurate marking due to respiratory fluctuation. However, we have previously reported that the rate of accurate evaluation of the horizontal extent of EGCs was not influenced by tumor location or the circumference [18]. Thus, it would appear that it is possible to extrapolate the results of this study to EGCs located in the greater curvature of the gastric body. We also excluded EGCs less than 10 mm in diameter because the entire tumor border would be visible during evaluation with ME-NBI, influencing the evaluation with chromoendoscopy. In addition, this exclusion criterion could also prevent the underestimation of chromoendoscopy accuracy due to contact bleeding during the observation with ME-NBI. There is a high possibility that the results of this study can be extrapolated to these EGCs because tumor delineation is easier in small EGCs as we have also reported previously [18]. We excluded cancers of a remnant stomach or a gastric tube and residual cancers after endoscopic treatment to remove the influence of previous treatment and to focus only on the clinicopathological features of EGCs. The usefulness of ME-NBI and chromoendoscopy for determining the horizontal extent of these lesions is a subject of future investigation.

In conclusion, the rate of accurate evaluation of the horizontal extent of EGCs by ME-NBI is significantly higher than that by chromoendoscopy. However, accurate evaluation is still difficult in large EGCs and EGCs with flat tumor borders, even with ME-NBI. A more careful approach using more than one modality may be advisable for these EGCs.

Competing interests: Yosuke Tsuji: Paid speaker (GUNZE medical, CSL Behring, HOYA Pentax, Olympus Medical Systems, Eisai Corporation, and Astrazeneka Pharmaceutical)
Mitsuhiro Fujishiro: Consulting fee (Nihon PHarmaceutical), Collaboration research grant (HOYA pentax)

Institutions
[1] Department of Gastroenterology, The University of Tokyo, Tokyo, Japan
[2] Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[3] Department of Gastroenterology, Center for Epidemiology and Preventive Medicine, The University of Tokyo, Tokyo, Japan
[4] Department of Gastroenterology, Tokatsu-Tsujinaka Hospital, Chiba, Japan
[5] Department of Pathology, Chiba University Hospital, Chiba, Japan
[6] Department of Pathology, The University of Tokyo, Tokyo, Japan
[7] Department of Endoscopy & Endoscopic Surgery, The University of Tokyo, Tokyo, Japan

Acknowledgments

We are grateful to Mr Takeshi Shimamoto (Kameda Medical Center Makuhari, Chiba-city, Japan) for his valuable assistance with the statistical analyses. This work was supported by JSPS KAKENHI Grant Number 24790680.

References

1 *Gotoda T, Yamamoto H, Soetikno RM*. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929 – 942
2 *Park YM, Cho E, Kang HY* et al. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc 2011; 25: 2666 – 2677
3 *Oda I, Gotoda T, Hamanaka H* et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 2005; 17: 54 – 58
4 *Sugimoto T, Okamoto M, Mitsuno Y* et al. Endoscopic submucosal dissection is an effective and safe therapy for early gastric neoplasms: a multicenter feasible study. J Clin Gastroenterol 2012; 46: 124 – 129
5 *Nakamura M, Nishikawa J, Hamabe K* et al. Risk factors for delayed bleeding from endoscopic submucosal dissection of gastric neoplasms. Scand J Gastroenterol 2012; 47: 1108 – 1114
6 *Chung IK, Lee JH, Lee SH* et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointest Endosc 2009; 69: 1228 – 1235
7 *Mannen K, Tsunada S, Hara M* et al. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. J Gastroenterol 2010; 45: 30 – 36
8 *Imagawa A, Okada H, Kawahara Y* et al. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. Endoscopy 2006; 38: 987 – 990
9 *Iizuka H, Kakizaki S, Sohara N* et al. Stricture after endoscopic submucosal dissection for early gastric cancers and adenomas. Dig Endosc 2010; 22: 282 – 288
10 *Sakai Y, Eto R, Kasanuki J* et al. Chromoendoscopy with indigo carmine dye added to acetic acid in the diagnosis of gastric neoplasia: a prospective comparative study. Gastrointest Endosc 2008; 68: 635 – 641
11 *Kakushima N, Fujishiro M*. Endoscopic submucosal dissection for gastrointestinal neoplasms. World J Gastroenterol 2008; 14: 2962 – 2967

12 *Nagahama T*, *Yao K*, *Maki S* et al. Usefulness of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy (with video). Gastrointest Endosc 2011; 74: 1259 – 1267
13 *Yao K*, *Anagnostopoulos GK*, *Ragunath K*. Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy 2009; 41: 462 – 467
14 *Nonaka K*, *Namoto M*, *Kitada H* et al. Usefulness of the DL in ME with NBI for determining the expanded area of early-stage differentiated gastric carcinoma. World J Gastrointest Endosc 2012; 4: 362 – 367
15 *Gotoda T*, *Yanagisawa A*, *Sasako M* et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219 – 225
16 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101 – 112
17 *Tanaka M*, *Ono H*, *Hasuike N* et al. Endoscopic submucosal dissection of early gastric cancer. Digestion 2008; 77: 23 – 28
18 *Asada-Hirayama I*, *Kodashima S*, *Goto O* et al. Factors predictive of inaccurate determination of horizontal extent of intestinal-type early gastric cancers during endoscopic submucosal dissection: a retrospective analysis. Dig Endosc 2013; 25: 593 – 600