Thieme

Delineation of the extent of early gastric cancer by magnifying narrow-band imaging and chromoendoscopy: a multicenter randomized controlled trial

Authors

Takashi Nagahama[1], Kenshi Yao[1], Noriya Uedo[2], Hisashi Doyama[3], Tetsuya Ueo[4], Kunihisa Uchita[5], Hideki Ishikawa[6], Takashi Kanesaka[2], Yasuhito Takeda[3], Kurato Wada[4], Kentaro Imamura[1], Hisatomi Arima[7], Toshio Shimokawa[8]

Institutions

1 Department of Endoscopy, Fukuoka University Chikushi Hospital, Fukuoka, Japan
2 Department of Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan
3 Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan
4 Department of Gastroenterology, Oita Red Cross Hospital, Oita, Japan
5 Department of Gastroenterology, Kochi Red Cross Hospital, Kochi, Japan
6 Department of Molecular-targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan
7 Department of Preventive Medicine and Public Health, Fukuoka University Hospital, Fukuoka, Japan
8 Department of Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan

submitted 23.3.2017
accepted after revision 19.12.2017

Bibliography
DOI https://doi.org/10.1055/s-0044-100790
Published online: 13.2.2018 | Endoscopy 2018; 50: 566–576

ISSN 0013-726X

Corresponding author
Takashi Nagahama, MD, PhD, Department of Endoscopy, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino City, Fukuoka 818-8502, Japan
Fax: +81-92-9292630
nagahamagogo@gmail.com

Supplemental Fig. e6
Online content viewable at:
https://doi.org/10.1055/s-0044-100790

ABSTRACT

Background Accurate delineation of tumor margins is necessary for curative resection of early gastric cancer (EGC). The objective of this multicenter, randomized, controlled study was to compare the accuracy with which magnifying narrow-band imaging (M-NBI) and indigo carmine chromoendoscopy delineate EGC margins.

Methods Patients with EGC ≥ 10 mm undergoing endoscopic or surgical resection were enrolled. The oral-side margins of the lesions were first evaluated with conventional white-light endoscopy in both groups and then delineated by either chromoendoscopy or M-NBI. Biopsies were taken from noncancerous and cancerous mucosa, each at 5 mm from the margin. Accurate delineation was judged to have been achieved when the histological findings in all biopsy samples were consistent with endoscopic diagnoses. The primary end point was the difference in rate of accurate delineation between the two techniques.

Results Data on 343 patients were analyzed. The accurate delineation rate (95 % confidence interval) was 85.7 % (80.4 – 91.0) in the chromoendoscopy group (n = 168), and 88.0 % (83.2 – 92.8) in the M-NBI group (n = 175; $P = 0.63$). Lower third tumor location (odds ratio [OR] 2.9; $P = 0.01$), nonflat macroscopic type (OR 4.4; $P < 0.01$), and high diagnostic confidence (OR 3.6; $P < 0.001$) were associated with accurate delineation, whereas use of M-NBI was not (OR 1.2; $P = 0.39$). Even after adjustment for identified confounders, the difference in accurate delineation between the groups was not significant (OR 1.0; $P = 0.82$).

Conclusions M-NBI does not offer superior delineation of EGC margins compared with chromoendoscopy; the two methods appear to be clinically equivalent.

University Hospital Medical Network Clinical Trials Registry UMIN000014628
TRIAL REGISTRATION: multicenter, randomized, controlled study UMIN000014628 at http://www.umin.ac.jp

Introduction

Accurate delineation of cancer margins is necessary for deciding on a treatment plan for early gastric cancer (EGC) and for achieving complete resection by endoscopic or open surgery [1–3]. In Japan, conventional white-light imaging followed by chromoendoscopy using indigo carmine solution is now widely used for delineating the margins of gastric cancers [4–7]. Chromoendoscopy is an effective means of delineating margins and determining the detailed surface structure of the gastric mucosa associated with cancer infiltration [4–7]. However, several studies that evaluated the ability of chromoendoscopy to delineate the margins of EGCs found that chromoendoscopy failed to delineate the entire margin in 18.9%–21.6% of patients [8, 9]. Margin delineation by chromoendoscopy using high resolution endoscopy thus appears to be inaccurate in about 20% of patients.

Recently, magnifying endoscopy with narrow-band imaging (M-NBI) has enabled observation of the microvascular and microsurface patterns of gastric mucosa [10,11]. Yao et al. have devised a vessel-plus-surface classification system for diagnosing gastric cancer by magnifying endoscopy that uses both microvascular and microsurface morphological findings [12]. EGC is widely diagnosed by M-NBI based on the vessel-plus-surface classification system in clinical practice, and its superiority to conventional white-light endoscopy in differentiation between cancers and noncancers has been demonstrated in a multicenter, randomized, controlled trial [13]. M-NBI is also reportedly useful for delineating the margins of EGC [8,9,14–16], and strong consensus has been reached regarding the utility of this technique [17]. However, to date there is insufficient evidence to determine the usefulness of M-NBI in delineating the margins of EGC [17]. Therefore, the aim of this multicenter, randomized, controlled trial was to investigate superiority of M-NBI in terms of accurate delineation rate compared with chromoendoscopy, which is the standard method in Japanese current practice.

Methods

Study design

This was a multicenter, randomized, controlled trial. In line with the standards for reporting diagnostic accuracy studies [18], chromoendoscopy was used for the index test in this study. Its accuracy in margin delineation was compared with that of M-NBI, a newer diagnostic method, using histological diagnosis as the reference standard. This study was conducted at five Japanese institutions that are high-volume centers for EGC.

Inclusion and exclusion criteria

The inclusion criteria were: 1) age ≥20 years; 2) EGC with a tumor size of ≥10 mm as determined by endoscopy at the time of detection; 3) Category 4 (mucosal high grade neoplasia) or Category 5 (submucosal invasion of neoplasia) disease diagnosed by histological evaluation of a biopsy specimen according to the revised Vienna classification [19]; and 4) planned endoscopic (endoscopic submucosal dissection [ESD]) or surgical resection. If multiple target lesions were found, only the oral-most lesion was evaluated.

Exclusion criteria were: 1) remnant stomach; 2) high risk of bleeding during endoscopic biopsy; and 3) refusal to provide informed consent.

The current trial complied with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of each participating institution. All patients provided written informed consent prior to enrollment. The study was registered as UMIN000014628.

Randomization

After study enrollment, participants were allocated to either the chromoendoscopy or M-NBI group in a 1:1 ratio via a minimization method using the following pre-adjustment factors: institution (A, B, C, D, and E), tumor location (upper, middle, and lower third), and histological type (differentiated and undifferentiated). Briefly, randomization was provided via a web response system in which the allocation sequence was computer generated at a data center (Medical Research Support, Osaka, Japan).

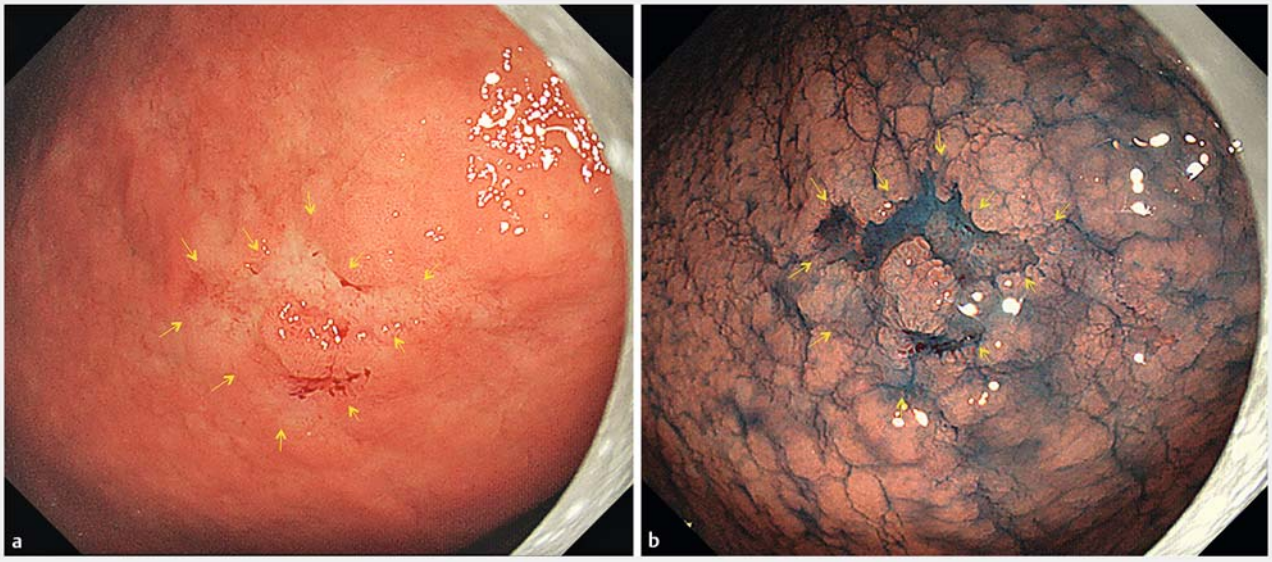
Examination protocol

Endoscopic procedures

An upper gastrointestinal endoscope with optical zoom function (GIF-Q240Z, GIF-FQ260Z, GIF-H60Z, or GIF-H290Z; Olympus, Tokyo, Japan) was used in the study.

After a target lesion had been identified by conventional white-light imaging, the margin on the most proximal (oral-most) side of the lesion was first evaluated with conventional white-light imaging, after which it was completely delineated in accordance with the endoscopic diagnostic criteria using the method of assessment to which the patient had been allocated. For patients allocated to the chromoendoscopy group, 0.1% indigo carmine solution was sprayed through the working channel using a spray catheter (PW-5L-1; Olympus) or an injection syringe. Once the solution had been dispersed, the margin was delineated [9]. For patients allocated to the M-NBI group, the tip of the endoscope was fitted with a soft black hood (MAJ-1989 for the GIF-Q240Z and GIF-H290Z, and MAJ-1990 for the GIF-FQ260Z and GIF-H260Z; Olympus), and the lesion was examined at maximum magnification to delineate the margin [9]. The protocol for this procedure has been described previously [11].

Endoscopists with at least 5 years' endoscopy experience, which is the period required for application of board-certified fellow of the Japan Gastroenterological Endoscopy Society (JGES), performed endoscopy in the study. Endoscopists with less than 5 years' experience were requested to perform the examination under the supervision of a board-certified fellow of the JGES.



▶ **Fig. 1** Examination in the chromoendoscopy group. **a** Endoscopic image of early gastric cancer using conventional white-light imaging. A 0-IIc type early gastric cancer is evident on the anterior wall of the gastric angle. The pale area in the center of the image is cancerous mucosa, and the line along which the mucosal color suddenly changes is the suspected margin of the lesion (yellow arrows). **b** Endoscopic image of early gastric cancer using chromoendoscopy. The cancerous area is the region in which the regular surface structures of the background mucosa are not visible and there is an irregular surface structure. The line along which the surface structure changes abruptly is the suspected tumor margin (yellow arrows).

Diagnostic criteria for cancer margins by chromoendoscopy and M-NBI

For patients allocated to the chromoendoscopy group, cancer margins were determined by: 1) absence of regular features in the background mucosa; and 2) detection of an irregular surface structure inside the marginal line (▶ **Fig. 1**) [6, 7]. For patients allocated to the M-NBI group, margins were determined by: 1) abrupt changes in the regular microvascular and microsurface patterns in the background mucosa (demarcation line); and 2) detection of irregular microvascular or microsurface patterns inside the demarcation line (▶ **Fig. 2**) [10 – 12].

The level of confidence in the accuracy of margin delineation was determined according to the following criteria: 1) the endoscopist was confident of having accurately determined the cancer margin; and 2) the endoscopist deemed that no mapping biopsies were needed in addition to endoscopic delineation. High confidence was defined as meeting both criteria; all other diagnoses were recorded as low confidence.

Biopsy procedure

Biopsy specimens were taken from two locations: noncancerous mucosa 5 mm outside the margin on the oral-most side, and cancerous mucosa 5 mm inside the margin (▶ **Fig. 3**), as determined by the endoscopic method used for that patient. Biopsy forceps with an aperture of ≤ 5 mm (FB-231K, FB-19K-1, or FB-34K-1 – Olympus; or Radial Jaw 4P – Boston Scientific, Marlborough, Massachusetts, USA) were used for the biopsies. The distance between the site of biopsy and the margin was measured by comparing with opened biopsy forceps. Endoscopic images were taken before and after the biopsy procedures to justify the biopsy site.

The histological diagnosis of the biopsy specimen was used as the reference standard. In accordance with the revised Vienna classification [19], Category 4 (mucosal high grade neoplasia) and Category 5 (submucosal invasion of neoplasia) were classified as "cancer," and Category 1 (negative for neoplasia), Category 2 (indefinite for neoplasia), and Category 3 (mucosal low grade neoplasia) were classified as "not cancer."

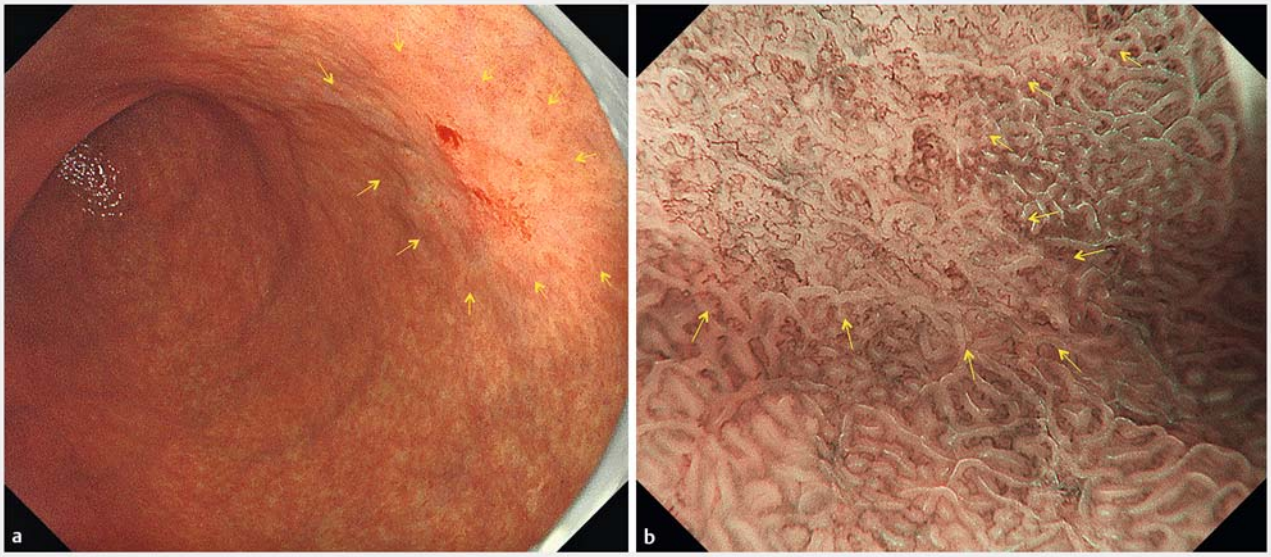
Determination of *Helicobacter pylori* infection status

The presence or absence of *H. pylori* infection was investigated by serum antibody concentration, urea breath test, rapid urease test, histology, culture, urinary antibody, or fecal antigen. A patient was reported as being positive for *H. pylori* if any one of these tests showed positive findings. If all tests that had been performed in any one patient were negative, the patient was deemed to be *H. pylori* negative.

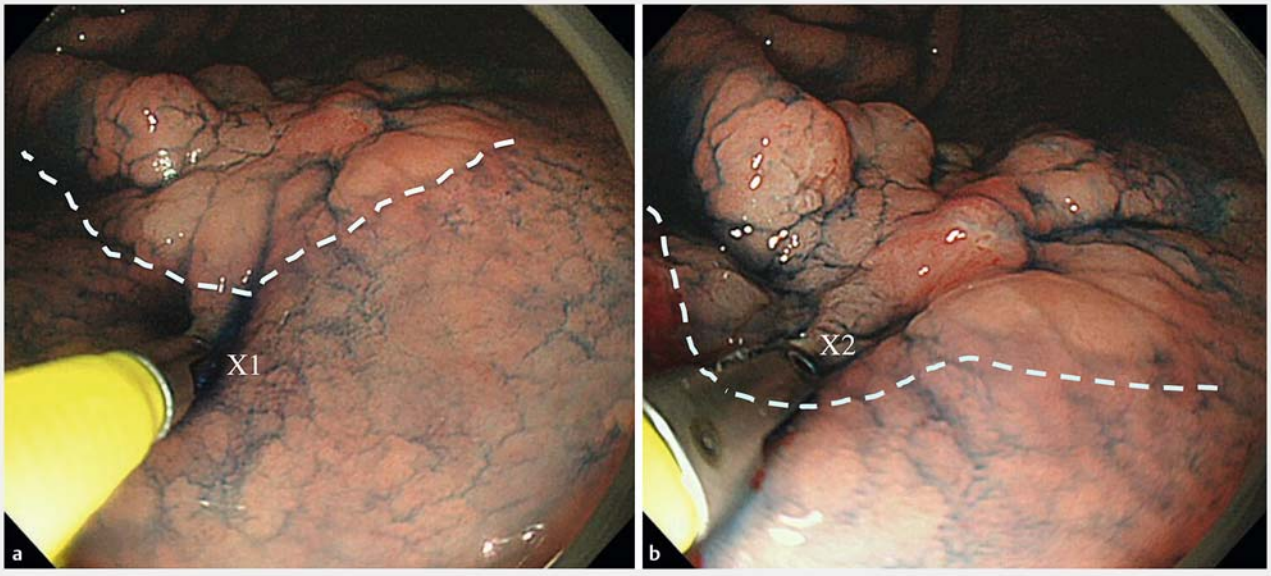
Outcome measurement

Primary end point

The primary end point was the rate of accurate delineation, which was defined as follows. Margin delineation is the act of using endoscopy to identify cancerous mucosa as "cancer" and noncancerous mucosa as "not cancer" on the basis of differences in the morphological features of the cancerous and noncancerous areas. Agreement between the histological diagnoses from cancerous (X2) and noncancerous (X1) mucosa in all biopsy samples and the endoscopic diagnosis, was defined as accu-



▶ **Fig. 2** Examination in the magnifying narrow-band imaging group (M-NBI). **a** Endoscopic image of early gastric cancer using conventional white-light imaging. A type 0-IIc early gastric cancer is evident on the posterior wall of the lower gastric body. The pale area is cancerous mucosa, and the line along which the color suddenly changes is the suspected margin of the lesion (yellow arrows). **b** M-NBI image. The area in which the regular microvascular and microsurface patterns on the background mucosa are absent and there is an irregular microvascular or microsurface pattern is the suspected cancerous mucosa. The line along which the patterns change abruptly is the suspected demarcation line (yellow arrows).

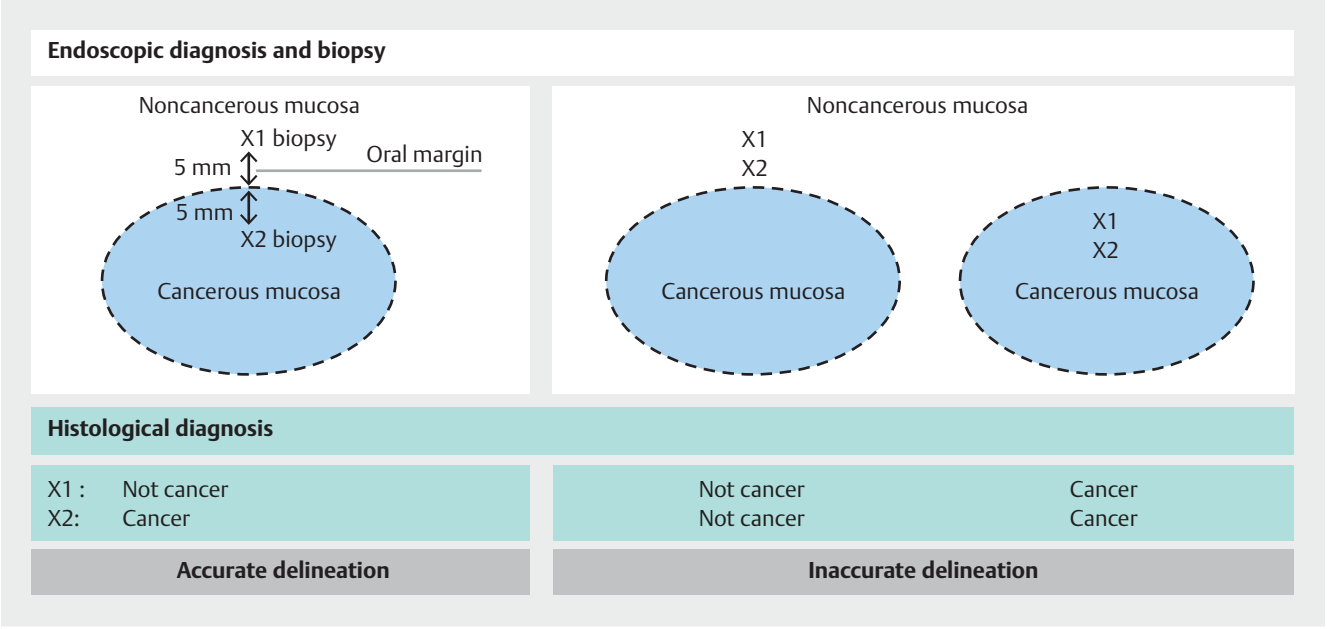


▶ **Fig. 3** Forceps biopsy for histological diagnosis. **a** The biopsy specimens were taken from 5 mm outside (X1) the oral-most margin (dotted line) of the cancer. **b** The biopsy specimens were taken from 5 mm inside (X2) the oral-most margin (dotted line) of the cancer.

rate delineation (▶ **Fig. 4**). One or more inconsistencies between histological and endoscopic diagnoses were judged as inaccurate delineation. The rate of accurate delineation was calculated as the number of patients with accurate delineation divided by the total number of patients.

Secondary end points

Clinicopathological factors that were associated with accurate delineation were determined and then used to adjust for such confounders; the resultant adjusted difference between the groups was used to assess the accurate rates of delineation for chromoendoscopy and M-NBI.



▶ **Fig. 4** Definition of accurate delineation. Agreement between the histological diagnoses of cancerous (X2) and noncancerous (X1) mucosa in all biopsy samples and the endoscopic diagnosis was defined as accurate delineation. One or more inconsistencies between histological and endoscopic diagnoses was defined as inaccurate delineation.

The rate of correct diagnosis of biopsies from cancerous and noncancerous mucosa was compared between the chromoendoscopy and M-NBI groups.

Histological findings in inaccurate delineated lesions were reviewed and examined by pathologists. Histological findings underlying inaccurate delineation were classified into the following major characteristics, which are reportedly responsible for the limits of endoscopic diagnosis of tumor extent [9]: 1) undifferentiated type adenocarcinoma infiltrating into the glandular neck zone covered with non-neoplastic epithelium; 2) differentiated type adenocarcinoma infiltrating the mucosa mixed with non-neoplastic epithelium; and 3) differentiated type adenocarcinoma with low grade atypia. The proportions of these characteristic histological findings were compared between the chromoendoscopy and M-NBI groups.

As subgroup analyses, rates of accurate delineation were compared between the chromoendoscopy and M-NBI groups according to *H. pylori* infection status (negative vs. positive), tumor size (< 20 mm vs. ≥ 20 mm), location (upper, middle vs. lower third), macroscopic type (flat vs. elevated/depressed), histological type (differentiated vs. undifferentiated), invasion depth (T1a vs. T1b), treatment (ESD vs. surgery), institution (A – E), endoscopists' experience (less experienced [endoscopy experience of < 5 years] vs. experienced [endoscopy experience of ≥ 5 years]), and level of confidence in diagnosis (low confidence vs. high confidence).

Sample size

On the basis of results of previous studies [8, 9, 15], the rate of accurate delineation was estimated as 95 % for the M-NBI group and 85 % for the chromoendoscopy group. The minimum required sample size was calculated as 322 for both groups using a power of 80 % and an alpha level of 0.05 for the study overall. A target sample size of 340 in total was therefore set, taking discontinuations and withdrawals into account.

Data collection and analysis

Patient enrollment, randomization, and recording of data were all performed on site, and data were collected at a single data center (Medical Research Support) within 3 days of examination – that is, before the histological diagnoses of the biopsies had been determined. Once the number of enrolled cases had reached the target sample size, collected data were fixed at the data center and analyzed using the methods described below.

Statistical analysis was performed using Pearson's chi-squared or Fisher's exact test for comparison of categorical variables, and Student's *t* test for comparison of continuous variables. A logistic regression model was used for multivariate analysis to assess associations between clinicopathological characteristics and rate of accurate delineation. Variables found to be significantly associated by univariate analysis were used as covariables in the multivariate analysis. All analyses were considered exploratory, and therefore no correction for multiple testing was done. All analyses were performed using SPSS software version 20.0 (IBM, Armonk, New York, USA). Values of $P < 0.05$ were considered to denote statistical significance.

Results

Patient enrollment and background

The required sample size was set to 340 patients. However, at the point when 256 patients had been enrolled, 21 patients had already dropped out, which was more than the predicted 5 %. Therefore, with the aim of approximating the predicted frequency, the protocol was revised and the sample size increased by 40 patients. Finally, a total of 384 patients were enrolled between November 2014 and March 2016. Of these, 191 were assigned to the chromoendoscopy group and 193 to the M-NBI group. The following numbers of patients were excluded from the study: 4 in the chromoendoscopy group and 5 in the M-NBI group before the protocol-determined examination; 9 in the chromoendoscopy group and 5 in the M-NBI group during the protocol-determined examination; and 10 in the chromoendoscopy group and 8 in the M-NBI group after the protocol-determined examination. Finally, 168 patients in the chromoendoscopy group and 175 in the M-NBI group were eligible for analysis (▶ **Fig. 5**).

Background characteristics according to study group are shown in ▶ **Table 1**. The groups were balanced in terms of sex, age, *H. pylori* status, tumor size, location, macroscopic type, histological type, invasion depth, treatment method, institution, and endoscopists' experience.

Rates of accurate delineation

The rates of accurate delineation were 85.7 % (95 % confidence interval [CI] 80.4 % – 91.0 %) in the chromoendoscopy group and 88.0 % (95 %CI 83.2 % – 92.8 %) in the M-NBI group; this difference was not statistically significant ($P = 0.63$) (▶ **Table 2**).

The level of confidence in diagnosis was greater in the M-NBI group than the chromoendoscopy group (rate of high confidence 90.8 % vs. 81.5 %; $P = 0.01$); however, this was not reflected in the difference in rate of accurate delineation. No patient in either group had positive resection margins after ESD or surgery.

Adjustment of differences in rate of accurate delineation between study groups

According to univariate analysis, lower third tumor location (odds ratio [OR] 2.9, 95 %CI 1.2 – 6.6; $P = 0.01$), nonflat macroscopic type (OR 4.4, 95 %CI 1.5 – 13; $P < 0.01$), and high confidence in diagnosis (OR 3.6, 95 %CI 1.8 – 7.5; $P < 0.001$) had statistically significant associations with accurate delineation (▶ **Table 3**). The use of M-NBI was not significantly associated with accurate delineation (OR 1.2, 95 %CI 0.65 – 2.3; $P = 0.39$). After adjustment for identified confounders by multivariate analysis, the difference between groups in rate of accurate delineation was not significant (OR 1.1, 95 %CI 0.55 – 2.1; $P = 0.82$).

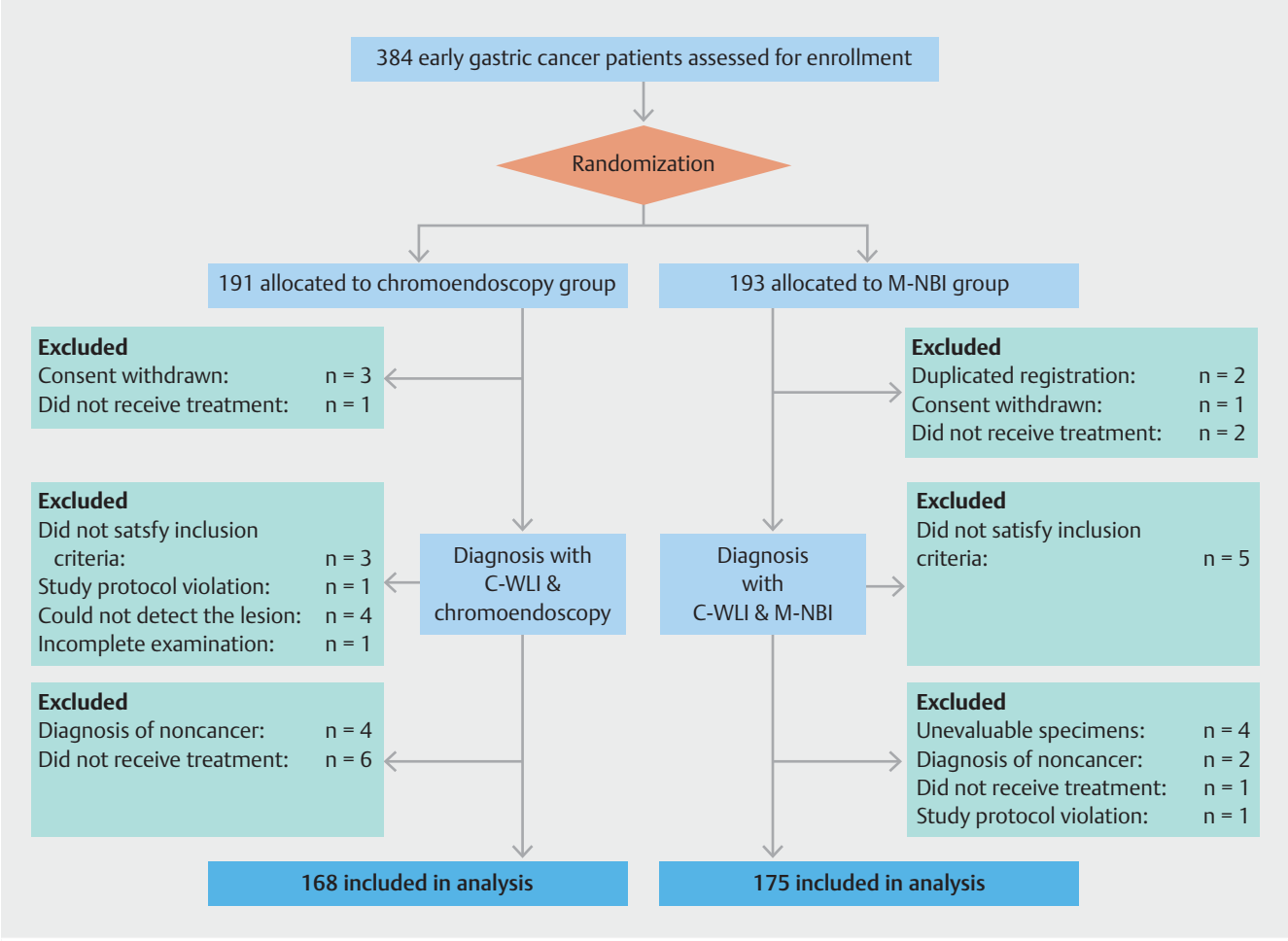
Rates of correct diagnosis of noncancerous and cancerous mucosa

The rate of correct diagnosis of noncancerous mucosa (X1) as "not cancer" was 89.3 % (95 %CI 84.6 % – 94.0 %) in the chromoendoscopy group and 92.0 % (95 %CI 88.0 % – 96.0 %) in the M-

▶ **Table 1** Characteristics of the participants according to study group.

	Chromoendoscopy n = 168	M-NBI n = 175
Sex, n		
▪ Male	118	118
▪ Female	50	57
Age, mean ± SD, years	69 ± 10	69 ± 9
H. pylori status, n		
▪ Positive	100	96
▪ Negative	67	77
▪ Unknown	1	2
Tumor size, mean ± SD, mm	24 ± 14	24 ± 15
Location, n		
▪ Upper third	35	35
▪ Middle third	77	86
▪ Lower third	56	54
Macroscopic type, n		
▪ Elevated	50	36
▪ Depressed	111	130
▪ Flat	7	9
Histological type, n		
▪ Differentiated	135	142
▪ Undifferentiated	33	33
Invasion depth, n		
▪ T1a	134	138
▪ T1b and deeper	34	3
Treatment, n		
▪ ESD	122	123
▪ Surgery	46	52
Institution, n		
▪ A	65	67
▪ B	52	55
▪ C	25	29
▪ D	15	14
▪ E	11	10
Endoscopists' experience*, n		
▪ Experienced	74	83
▪ Less experienced	94	92

M-NBI, magnifying narrow-band imaging; T1a, mucosal cancer; T1b, submucosal cancer; ESD, endoscopic submucosal dissection.
* Experienced, > 8 years of endoscopy experience; less experienced, < 8 years of endoscopy experience.



▶ **Fig. 5** Flow chart showing enrollment of participants, randomization, and examination. C-WLI, conventional white-light imaging; M-NBI, magnifying narrow-band imaging.

▶ **Table 2** Rates of accurate delineation of extent of early gastric cancer according to study group.

	Chromo-endoscopy (n = 168)	M-NBI (n = 175)	*P* value
Accurate delineation rate (95 %CI), %	85.7 (80.4 – 91.0)	88.0 (83.2 – 92.8)	0.63

M-NBI, magnifying narrow-band imaging; CI, confidence interval.

NBI group ($P = 0.46$) (▶ **Table 4**). The rate of correct diagnosis of cancerous mucosa (X2) as "cancer" was 96.4 % (95 %CI 93.6 % – 99.2 %) in the chromoendoscopy group and 96.0 % (95 %CI 93.1 % – 98.9 %) in the M-NBI group ($P > 0.99$).

Histological findings in inaccurately delineated lesions

Histological findings for inaccurately delineated lesions according to study group are shown in ▶ **Table 5**. "Undifferentiated type adenocarcinoma infiltrating into the glandular neck zone covered with non-neoplastic epithelium" was the most common (29.2 %) histological finding for inaccurately delineated lesions in the chromoendoscopy group, whereas "differentiated type adenocarcinoma with low grade atypia" was the most common (28.6 %) in the M-NBI group.

Subgroup analysis of rate of accurate delineation in the study groups

There was no statistically significant difference in the rate of accurate delineation between the chromoendoscopy and M-NBI groups according to *H. pylori* infection status, tumor size, location, macroscopic type, histological type, invasion depth, treatment, institution, endoscopists' experience, or level of confidence in diagnosis (see ▶ **Supplemental Fig. e 6**, available online).

▶ **Table 3** Adjustment of differences in rate of accurate delineation between the chromoendoscopy and magnifying narrow-band imaging groups.

	Accurate n = 298	Inaccurate n = 45	Univariate analysis		Multivariate analysis	
			OR (95 %CI)	*P* value	Adjusted OR (95 %CI)	*P* value
Group, n				0.39		0.82
▪ Chromoendoscopy	144	24	1		1	
▪ M-NBI	154	21	1.2 (0.65 – 2.3)		1.1 (0.55 – 2.1)	
H. pylori status, n				0.99		
▪ Negative	170	19	1			
▪ Positive	125	26	1.0 (0.53 – 1.9)			
Tumor size, n				0.75		
▪ < 20, mm	138	22	1			
▪ ≥ 20, mm	160	12	1.1 (0.59 – 2.1)			
Location, n				0.01		0.02
▪ Upper/Middle third	195	38	1		1	
▪ Lower third	103	7	2.9 (1.2 – 6.6)		2.5 (1.1 – 6.4)	
Macroscopic type, n				< 0.01		0.03
▪ Flat	10	6	1		1	
▪ Elevated/Depressed	288	39	4.4 (1.5 – 13)		3.7 (1.1 – 11)	
Histological type, n				0.18		
▪ Undifferentiated	54	12	1			
▪ Differentiated	244	33	1.6 (0.80 – 3.4)			
Invasion depth, n				0.36		
▪ T1a	234	38	1			
▪ T1b or deeper	64	7	0.67 (0.29 – 1.6)			
Treatment, n				0.76		
▪ ESD	212	33	1			
▪ Surgery	86	12	1.1 (0.55 – 2.3)			
Institution, n				0.73		
▪ A	114	18				
▪ B	94	13				
▪ C	45	9				
▪ D	25	4				
▪ E	20	1				
Endoscopists' experience, n				0.64		
▪ Experienced	55	7	1			
▪ Less experienced	243	38	0.8 (0.3 – 1.9)			
Confidence level of diagnosis, n				< 0.001		< 0.01
▪ Low confidence	33	14	1		1	
▪ High confidence	265	31	3.6 (1.8 – 7.5)		3.1 (1.4 – 6.7)	

M-NBI, magnifying narrow-band imaging; ESD, endoscopic submucosal dissection; OR, odds ration; CI, confidence interval.

▶ **Table 4** Rate of correct diagnosis of biopsies for cancerous and non-cancerous mucosa according to study group.

	Chromo-endoscopy (n = 168)	M-NBI (n = 175)	*P* value
Correct diagnosis rate (95 %CI), %			
Noncancerous mucosa	89.3 (84.6 – 94.0)	92.0 (88.0 – 96.0)	0.46
Cancerous mucosa	96.4 (93.6 – 99.2)	96.0 (93.1 – 98.9)	> 0.99

M-NBI, magnifying narrow-band imaging.

▶ **Table 5** Histological findings in inaccurately delineated lesions according to study group.

	Chromo-endoscopy (n = 24)	M-NBI (n = 21)
Histological finding, n (%)		
Undifferentiated type adenocarcinoma infiltrating the glandular neck zone covered with non-neoplastic epithelium	7 (29.2)	4 (19.0)
Differentiated type adenocarcinoma infiltrating the mucosa mixed with non-neoplastic epithelium	4 (16.7)	3 (14.3)
Differentiated type adenocarcinoma with low grade atypia	2 (8.3)	6 (28.6)
Others	11 (45.8)	8 (38.1)

M-NBI, magnifying narrow-band imaging.

Discussion

We herein report our results of a multicenter, prospective, randomized, controlled trial. We hypothesized that M-NBI would be superior to chromoendoscopy for margin delineation of EGC; however, we failed to identify a significant difference in accuracy of margin delineation between the two methods.

Several studies have reported that M-NBI is useful for delineating the tumor margins of EGC. In their multicenter cohort study (n = 31), Nonaka et al. showed a diagnostic accuracy of 100 % for delineation of superficial depressed- or flat-type EGCs by M-NBI [8]. In their retrospective cohort study (n = 356), Nagahama et al. reported that performing M-NBI after chromoendoscopy increased diagnostic accuracy of delineation from 81.1 % to 94.8 % [9], but these were not comparative data between M-NBI and chromoendoscopy. Another prospective randomized trial (M-NBI n = 38 vs. chromoendoscopy n = 45) demonstrated that M-NBI delineated margins accurately more frequently than chromoendoscopy (97.4 % vs. 77.8 %; *P* < 0.001) [16]. However, in that study, the endoscopists were free to select sites for delineation of the margins of a lesion, suggesting potential selection bias. Moreover, the reference standard was the stereoscopic appearance of the mucosa and not histology. Another single-center, prospective, randomized trial (n = 109) of EGCs treated by ESD reported that margins were accurately delineated significantly more frequently by M-NBI than by chromoendoscopy (89.4 % vs. 75.9 %; *P* = 0.007) [20]. However, in that study, M-NBI and chromoendoscopy were used on different sides (oral and anal) of the same lesion, and M-NBI was always used prior to chromoendoscopy, suggesting a possible carry-over effect. To the best of our knowledge, the present study is the first large-scale, multicenter, head-to-head, comparative, randomized, controlled trial to investigate the possible superiority of M-NBI over chromoendoscopy in accuracy of delineation of EGC margins.

In the present study, the rate of accurate delineation was similar in the chromoendoscopy (85.7 %) and M-NBI (88.0 %) groups. Moreover, after adjustment for confounding factors that were significantly associated with accurate delineation, the rates of accurate delineation between the groups were very similar (OR 1.1, 95 %CI 0.55 – 2.1); thus, our data did not reveal any difference between chromoendoscopy and M-NBI in their ability to accurately delineate the margins of EGCs. We expected the rate of accurate delineation by M-NBI to be 95 %, excluding undifferentiated-type adenocarcinoma; however, the actual accuracy of M-NBI for all types of EGC was lower than expected. Most reference data used to calculate the expected accuracy were derived from retrospective studies with expert endoscopists and may accordingly have been biased, whereas our results represent data obtained from less-experienced endoscopists as well as expert endoscopists in M-NBI. The crucial role of M-NBI in lesion delineation has recently been emphasized. It is, of course, more accurate than conventional white-light endoscopy; however, its diagnostic performance appears equivalent to that of chromoendoscopy. We therefore believe that our findings suggest that, when chromoendoscopy is appropriately used, even endoscopists who do not have access to novel image-enhancing technology or magnifying endoscopy can achieve similar outcomes regarding delineation of lesions, enabling optimal treatment decisions to be made for patients with EGC.

The rates of correct diagnosis (according to biopsy findings) of cancerous mucosa as “cancer” were > 95 % for both the chromoendoscopy and M-NB groups (96.4 % and 96.0 %, respectively), whereas the rates for accurate diagnosis of noncancerous mucosa as “not cancer” were around 90 % (89.3 % and 92.0 %, respectively), indicating the possibility of underestimation of lesion extent and positive resection margins. Review of the histological findings of the inaccurately delineated lesions in this study revealed that more than half of them featured previously reported histological reasons for difficulty in delineation of EGC margins. In the chromoendoscopy group, the commonest histological type of inaccurately delineated lesion was undifferentiated type adenocarcinoma infiltrating the glandular neck zone covered with non-neoplastic epithelium (29.2 %), whereas in the M-NBI group it was differentiated type adenocarcinoma with low grade atypia (28.6 %). These findings suggest that it is

difficult to accurately delineate EGCs with certain histological characteristics, even when using the best currently available techniques, namely chromoendoscopy and M-NBI. However, in some ways, different methods may complement each other. In general clinical practice, chromoendoscopy facilitates an overview of the gross morphological characteristics and color of a lesion, whereas M-NBI enables detailed evaluation of the micro-mucosal appearance of small, targeted areas. In this study, patients whose lesions had been inaccurately delineated were treated after the boundaries had been ascertained by any endoscopic examination method and biopsy. Moreover, particularly when the margins were indistinct, the operator excised a slightly larger area. We therefore encountered no positive resection margins after ESD and surgery in either group. This suggests that using another endoscopic method or mapping biopsies for lesions with unclear margins is a practical way of avoiding incomplete (R1) resection.

It has recently been reported that some gastric cancers detected after *H. pylori* eradication have unclear margins [21, 22]. In this study, 42.2 % of patients (144 / 341) were *H. pylori* negative. Although we did not collect data on history of *H. pylori* eradication therapy, almost all *H. pylori*-negative patients can be regarded as having undergone intentional or spontaneous eradication because the prevalence of *H. pylori* infection-naïve patients among all gastric cancer patients is reportedly about 1 % [23, 24]. We found no statistically significant association between accurate delineation and *H. pylori* status (OR 1.0, 95 %CI 0.53 – 1.9) in the current study. Therefore, we suspect that *H. pylori* eradication has little impact on accuracy of the delineation of EGC margins.

This study had some limitations. First, we designed it to target only the proximal margins of the lesions. In other words, the superiority or inferiority of M-NBI or chromoendoscopy over the entire infiltration margin for ESD remains unclear. Second, only lesions 10 mm or larger were included. Therefore, the difference in diagnostic ability between the two methods for smaller lesions is unknown. Further studies to investigate the usefulness of M-NBI in delineation of specific lesions are warranted.

In conclusion, this study did not verify the superiority of M-NBI over chromoendoscopy for delineating the margins of EGC, indicating that chromoendoscopy and M-NBI have equivalent accuracy in clinical practice.

Acknowledgments

The authors are grateful to Professor Akinori Iwashita, Dr. Hirohiko Tomita, Dr. Hirosi Kurumaya, Dr. Hirotoshi Yonematsu, and Dr. Naoto Kuroda for pathological diagnosis.

Competing interests

None

References

[1] Suzuki H, Oda I, Sekiguchi M et al. Factors associated with incomplete gastric endoscopic submucosal dissection due to misdiagnosis. Endosc Int Open 2016; 25: 88 – 93

[2] Kakushima N, Ono H, Tanaka M et al. Factors related to lateral margin positivity for cancer in gastric specimens of endoscopic submucosal dissection. Dig Endosc 2011; 23: 227 – 232

[3] Sekiguchi M, Suzuki H, Oda I et al. Risk of recurrent gastric cancer after endoscopic resection with a positive lateral margin. Endoscopy 2014; 46: 273 – 278

[4] Mashimoto A, Akazawa K, Isobe Y et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. Gastric Cancer 2013; 16: 1 – 27

[5] Tsuda Y. A study in the diagnosis of gastric lesions using the fibergastroscope combined with a new staining process. Gastroenterological Endoscopy (Tokyo) 1967; 9: 189 – 195

[6] Ida K, Hashimoto Y, Takeda S et al. Endoscopic diagnosis of gastric cancer with dye scattering. Am J Gastroenterol 1975; 63: 316 – 320

[7] Yao T, Fujiwara A, Watanabe H et al. Endoscopic diagnosis of the extent of infiltration in gastric cancer (in Japanese with English abstract). Stomach and Intestine 1972; 7: 725 – 738

[8] 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

[9] Nagahama T, Yao K, Maki S et al. Useful of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy. Gastrointest Endosc 2011; 75: 1259 – 1267

[10] Yao K, Oishi T. Microgastroscopic findings of mucosal microvascular architecture as visualized by magnifying endoscopy. Dig Endosc 2002; 13: 27 – 33

[11] Yao K, Ohishi T, Matsui T et al. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. Gastrointest Endosc 2002; 56: 279 – 284

[12] Yao K, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy 2009; 41: 462 – 467

[13] Ezoe Y, Muto M, Uedo N et al. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. Gastroenterology 2011; 141: 2017 – 2025

[14] Yao K, Yao T, Iwashita A. Determining the horizontal extent of early gastric carcinoma: two modern techniques based on differences in the mucosal microvascular architecture and density between carcinomatous and non-carcinomatous mucosa. Dig Endosc 2002; 14: 83 – 87

[15] Nakayoshi T, Tajiri H, Matsuda K et al. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology. Endoscopy 2004; 36: 1080 – 1084

[16] Kiyotoki S, Nishikawa J, Satake M et al. Usefulness of magnifying endoscopy with narrow-band imaging for determining gastric tumor margin. J Gastroenterol Hepatol 2010; 25: 1636 – 1641

[17] Uedo N, Fujishiro M, Goda K et al. Role of narrow band imaging for diagnosis of early-stage esophagogastric cancer: current consensus of experienced endoscopists in Asia–Pacific region. Dig Endosc 2011; 23: 58 – 71

[18] Bossuyt PM, Reitsma JB, Bruns DE et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Clin Chem 2003; 49: 1 – 6

[19] Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 2002; 51: 130 – 131

[20] Asada-Hirayama I, Kodashima S, Sakaguchi Y et al. Magnifying endoscopy with narrow-band imaging is more accurate for determination of horizontal extent of early gastric cancers than chromoendoscopy. Endosc Int Open 2016; 4: 690 – 698

[21] Ito M, Tanaka S, Takata S et al. Morphological changes in human gastric tumours after eradication therapy of Helicobacter pylori in a short-term follow-up. Aliment Pharmacol Ther 2005; 21: 559 – 566

[22] Kobayashi M, Hashimoto S, Nishikura K et al. Magnifying narrow-band imaging of surface maturation in early differentiated-type gastric cancers after Helicobacter pylori eradication. J Gastroenterol 2013; 48: 1332 – 1342

[23] Ono S, Kato M, Suzuki M et al. Frequency of Helicobacter pylori-negative gastric cancer and gastric mucosal atrophy in a Japanese endoscopic submucosal dissection series including histological, endoscopic and serological atrophy. Digestion 2012; 86: 59 – 65

[24] Matsuo T, Ito M, Tanaka S et al. Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. Helicobacter 2011; 1: 415 – 419