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METHODOLOGY

Study design and patient recruitment for the Japan Polyp Study

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Background: The Japan Polyp Study (JPS) Workgroup was established in 2000 to evaluate colonoscopic follow-up surveillance strategies. The JPS was a multicenter randomized controlled trial designed to evaluate follow-up surveillance strategies in patients who had undergone two complete colonoscopies for control of colorectal cancer, with removal of all detected polyps. The aim of the present analysis was to assess the patient recruitment and whether the clinical characteristics were adequate for enrollment at the participating centers.

Materials and methods: Among referrals for colonoscopy at the eleven participating centers, all patients who were 40–69 years old, without a family or personal history of familial polyposis, Lynch syndrome, inflammatory bowel disease, or a personal history of polypectomy with unknown histology, and had no invasive colorectal cancer or colectomy, were considered for inclusion from February 2003.

Results: Among 4,752 referrals, a total of 3,926 patients with a mean age of 57.3 (range 40–69) years, including 2,440 (62%) males, were included in the JPS. The participation rate was 83%. Among them, a total of 2,757 patients who had undergone two complete colonoscopies with removal of all detected polyps were eligible, giving an eligibility rate of 70% (2,757 of 3,926). Among the eligible patients, 2,166 were assigned to randomized groups, and 591 patients to a nonrandomized group. The last steps of data lock, analysis, and complete histopathological assessment based on a pathology review are ongoing.

Conclusion: Eligible patients recruited for the JPS were successfully assigned on the basis of the expected sample-size calculation.

Keywords: colonoscopy, follow-up surveillance strategies, Japan Polyp Study (JPS), study design, multicenter randomized controlled trial

Introduction

Colorectal cancer is the third-most important cause of cancer mortality in Japan.[1] Identification and removal of adenomatous polyps and postpolypectomy surveillance are considered to be important for control of colorectal cancer.[2,3] However, there have been no established recommendations for postpolypectomy colonoscopic surveillance in Japan. In current practice, the intervals between colonoscopies after polypectomy are variable, often being up to a year, and not based on data from randomized clinical trials.

The evolution of colorectal cancer from its precursor lesion, adenoma, was first reported by Morson as the adenoma–carcinoma sequence.[4] The introduction of colonoscopy provided an opportunity for clarifying this sequence, because of its ability to examine the entire colon and remove polyps for pathological examination. The epidemiology and natural history of adenomas are not only important for choosing

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the optimal follow-up policy after polypectomy but also for evaluating endoscopic screening for colorectal adenomas and cancer. On the other hand, depressed lesions, including some with advanced histology, have been demonstrated in a number of recent series from several Western countries and Japan.[5–9] However, the clinical significance of depressed lesions in the evolution of colorectal cancer, ie, the so-called de novo pathway, is still controversial.[10]

In the US, the National Polyp Study (NPS), which has been ongoing since 1980, has recommended an interval of at least 3 years between colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination.[2,3,11] Although long-term evaluation of colonoscopic polypectomy in the NPS demonstrated a 53% reduction in mortality due to colorectal cancer, the study was conducted prior to recent epidemiologic studies documenting the importance of nonpolypoid lesions. Therefore, such techniques as chromoendoscopy, required for diagnosis of nonpolypoid lesions, were not used in the NPS, and this may at least partly explain the discrepancy between the results of the NPS and subsequent epidemiological studies.[12,13]

The Japan Polyp Study (JPS) Workgroup was established in 2000 to evaluate follow-up colonoscopic surveillance strategies, partly supported by a Grant for Scientific Research Expenses for Health and Welfare Programs.[14] The JPS was a multicenter randomized controlled trial designed to evaluate follow-up surveillance strategies in patients who have undergone two complete colonoscopies for control of colorectal cancer, with the removal of all detected polyps by high-resolution chromoendoscopy, including nonpolypoid lesions. From 2000 to 2002, we confirmed whether randomization was feasible after one complete colonoscopy as far as the cecum, with removal of all detected adenomatous polyps, as was the case in the NPS. Initially, we had investigated a retrospective cohort study to estimate the incidence of advanced neoplasia after initial colonoscopy at six institutes of the JPS Workgroup.[14,15] Unexpectedly, the study showed higher cumulative incidences of index lesions, which were defined as large adenomatous polyps measuring >10 mm, adenomas with high-grade dysplasia, or invasive cancer (1 year after initial colonoscopy, 3.2%, including seven invasive cancers; 3 years after initial colonoscopy, 7.5%, including 13 invasive cancers).[16] Based on these results, the JPS Workgroup considered it necessary to perform two complete colonoscopies before randomization in order to avoid overlooking any clinically significant lesions. All of the institutional review boards finally agreed that randomization into two groups undergoing either 1) follow-up examination at 1 year and 3 years or 2) follow-up examination at 3 years after two complete colonoscopies as far as the cecum, with removal of all adenomatous polyps detected, was acceptable (Figure 1).[16]

The primary end point of the JPS was to address the hypothesis that after two complete colonoscopies with the removal of all detected polyps, the incidence of index lesions would not be different between patients undergoing two further follow-up examinations and those undergoing just one. The aim of the present analysis was to assess the patient recruitment of the JPS and to determine whether the clinical characteristics were adequate for enrollment at the participating centers.

Materials and methods

Organization

This multicenter prospective study was initiated by the JPS Workgroup, which was established in 2000 in Japan. Eleven participating centers accrued patients for the JPS (Table 1). All entries and follow-up examinations were the responsibility of the study investigators. Quality-assurance programs were instituted in each of the disciplines encompassed by the study. An independent pathology-review team was established at the National Cancer Center (Tokyo, Japan) to examine all resected polyps prospectively, and for each polyp a consensus among the three pathology reviewers (TS, TF, and YA) was reached. The pathologic classification adopted for the JPS was based on the World Health Organization classification.[17] All depressed lesions and index lesions were reviewed independently by the endoscopic review team at the National Cancer Center. The endoscopic classification was based on the Japanese Society for Cancer of the Colon and Rectum system.[18] All data obtained on the basis of the JPS protocol were overseen by Medical Support Research (Osaka, Japan).

Sample-size calculation

For determining the sample size required for a noninferiority trial, we set the incidence of index lesions at 3% at 3 years after initial examination of a clean colon. We also set the noninferiority margin at 2% (considered as clinically relevant), the one-sided alpha at 2.5% (one-sided), and the statistical power at 80%. For each group, 1,142 patients were required, and a total of 2,284 patients were required for the trial. Considering the patient dropout rate (20%) and patients who did not have polyps (who were not eligible for the randomized trial: 20%), we planned to recruit at least 4,000 patients for the study.

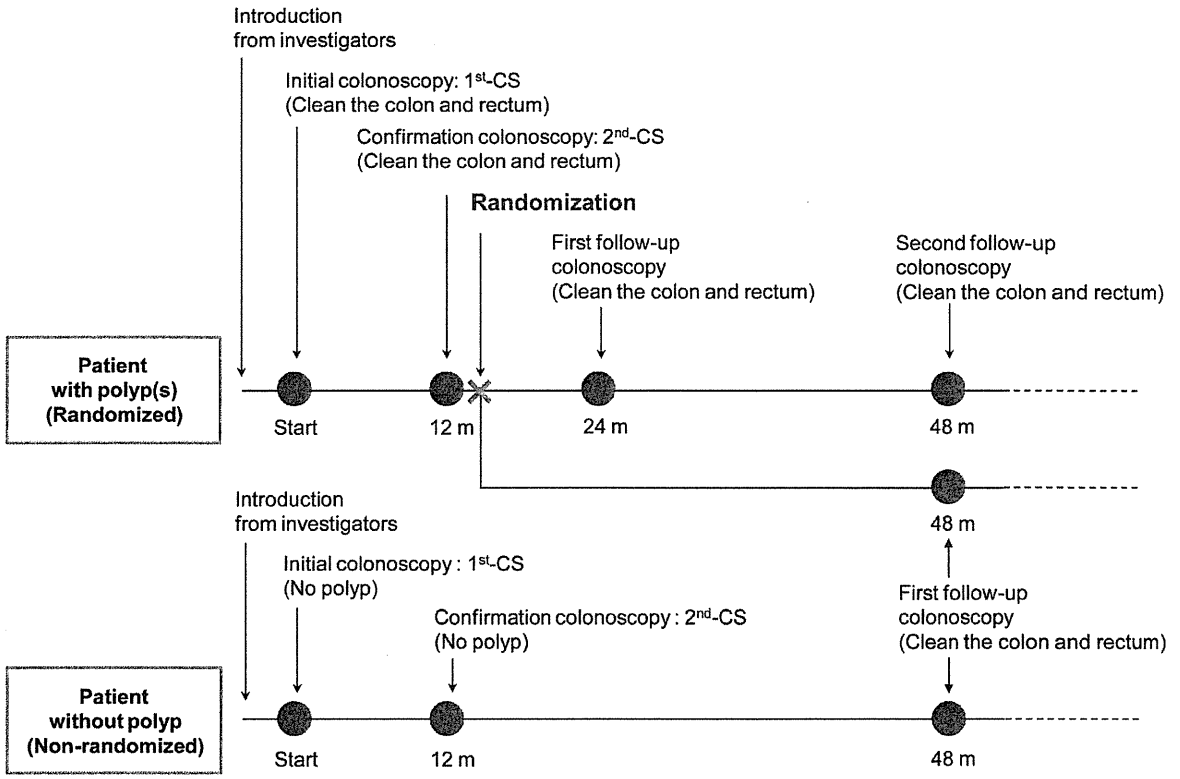

Figure 1 Design of the Japan Polyp Study.
Abbreviations: CS, colonoscopy; m, months.

Table 1 Participating, review, and data centers in the Japan Polyp Study

	Location (prefecture)
Participating center	
1. National Cancer Center Hospital	Tokyo
2. National Cancer Center Hospital East	Chiba
3. Saku Central Hospital	Nagano
4. Showa University Hospital	Tokyo
5. Showa University Northern Yokohama Hospital	Kanagawa
6. Kitasato University East Hospital	Kanagawa
7. Shizuoka Cancer Center	Shizuoka
8. Hattori GI Endoscopy and Gastroenterology Clinic	Kumamoto
9. Osaka Medical Center for Cancer and Cardiovascular Diseases	Osaka
10. Takahiro Fujii Clinic	Tokyo
11. Tochigi Cancer Center*	Tochigi
Pathology review	
1. National Cancer Center Hospital	Tokyo
2. Dokkyo Medical University	Tochigi
3. Niigata Medical University	Niigata
Endoscopic review	
1. National Cancer Center Hospital	Tokyo
Data Center	
1. Medical Research Support	Osaka

Note: *Since 2005.

Informed consent

Information on the protocol was given to all patients, and informed consent was secured after the respective interventions. In regular checkups, there was no discrimination according to agreement/refusal to take part in the study, or any drawback resulting from withdrawal. Only patients who gave informed consent were included in the study.

Patient accrual

All patients referred for colonoscopy at the eleven participating centers shown in Table 1, who were 40–69 years old, without a family or personal history of familial polyposis, Lynch syndrome, or inflammatory bowel disease, or a personal history of polypectomy with unknown histology, and without invasive colorectal cancer or colectomy, were considered for inclusion from February 2003.

Patients were excluded if colonoscopy revealed colorectal cancer invading beyond the muscularis mucosae, or a sessile adenoma with a base exceeding 3 cm in diameter. The data collected for these patients consisted of the reason for referral, the outcome of the examination, and certain items of

demographic information. Patients were eligible if they had undergone two complete colonoscopies (first CS and second CS) as far as the cecum, with removal of all polyps detected. The patients were assigned to two groups: 1) a nonrandomized group (patients without polyps), and 2) a randomized group (patients with polyps). Data for all patients in these two groups included detailed demographics, medical history, and information on the procedure employed and the individual polyp(s) resected. Nonrandomized patients included those who had no neoplastic lesions were enrolled at 3 years only after undergoing two complete colonoscopies (first CS and second CS).

All randomized patients were randomly assigned to undergo follow-up colonoscopy at 1 and 3 years, or at 3 years only. For randomization, we used a dynamic allocation scheme to ensure balance between the two groups over time.[19] There were five prognostic factors: 1) institution, 2) sex (male/female), 3) age category ($\geq$65 years and $<$65 years), 4) risk stage of colon cancer – a) patients with polyps measuring $\leq$5 mm only on two complete colonoscopies (first CS and second CS), b) patients with polyps measuring $\geq$6 mm on two complete colonoscopies, independently of the presence of polyps measuring $\leq$5 mm, and c) patients with any intramucosal cancer, independently of the presence and size of the polyp on colonoscopy – and 5) history of colonoscopy, chosen for balance between the groups. The study design of the JPS is shown in Figure 1.

Follow-up

All patients were contacted by post 2 months before their scheduled follow-up month, with a request to undergo the follow-up examination.

Statistical analysis

Basic descriptive analyses of the pool of patients referred for colonoscopy and those eligible for the surveillance study are presented. The percentages were recorded in the categorical data (eg, sex and reason for referral) for each center. Means and standard deviation were used for quantitative data (eg, age).

Ethical considerations

The protocol was reviewed a priori and approved by the institutional review boards at all of the participating hospitals in 2003. This trial is registered, and details are available at http://www.umin.ac.jp (UMIN C000000058), where the trial protocol can be accessed.

Funding

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Results

A flowchart for the JPS is shown in Figure 2.

Patient recruitment for the JPS

Patient accrual began in February 2003 and ended in December 2006. A total of 4,752 patients were referred to the eleven participating centers for colonoscopy, and none of them had a history of familial polyposis, Lynch syndrome, or inflammatory bowel disease, a personal history of polypectomy with unknown histology, or had had invasive colorectal cancer or colectomy. A total of 3,926 patients with a mean age of 57.3 (range 40–69) years, including 2,440 (62%) males, who consented to join the study were included in the JPS (Table 2). The participation rate was 83% (3,926 of 4,752).

Reason for referral

Although most patients were referred for a number of reasons, each patient was categorized according to the main finding on which the referral was based (Table 3). The predominant reason for referral was a positive result for fecal occult blood testing (FOBT; 37.2%), followed by overt symptoms (16.9%).

First colonoscopy

A total of 3,895 patients underwent colonoscopy, among whom 178 were excluded due to 1) invasive cancers (109 patients: 45 with advanced cancer, 66 with submucosal invasive cancer, and three with intramucosal cancer, with a certain degree of overlap), 2) lesions more than 30 mm in diameter, or for which surgery was indicated (16 patients: nine with adenoma, seven with intramucosal cancer), 3) carcinoid tumor (seven patients), and 4) other reasons (46 patients: inflammatory bowel disease/poor bowel preparation/failure to clean the colon or total colonoscopy). A total of 930 patients dropped out before receiving the second CS in spite of postal notification. The prevalence of patients with invasive colorectal cancer was 2.8% (109 of 3,895).

Second colonoscopy

A total of 2,787 patients underwent colonoscopy at 1 year after the first CS. A total of 30 patients were excluded due to 1) invasive cancer (four patients: one with advanced cancer,

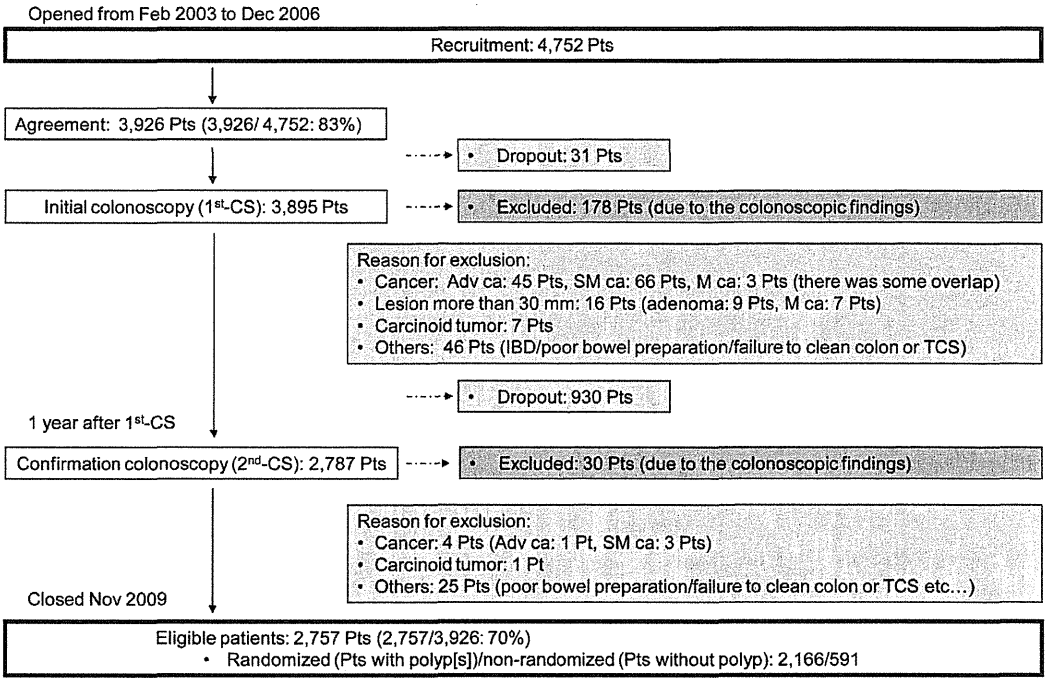

Figure 2 Japan Polyp Study flow.
Abbreviations: Pts, patients; CS, colonoscopy; Adv, advanced; ca, cancer; SM, submucosal invasive; M, intamucosal; IBD, inflammatory bowel disease; TCS, total colonoscopy.

three with submucosal invasive cancer), 2) carcinoid tumor (one patient), and 3) other reasons (25 patients: poor bowel preparation/failure to clean the colon or total colonoscopy). The prevalence of patients with interval invasive colorectal cancer was 0.14% (four of 2,787).

Patients eligible for the JPS

A total of 2,757 patients who underwent two complete colonoscopies (first CS and second CS) as far as the cecum, with removal of all polyps detected, were eligible. The eligibility rate was 70% (2,757 of 3,926). Among the eligible patients, 2,166 were assigned to randomized patient groups (patients with polyp[s]) and 591 patients to a nonrandomized patient group (patients without polyp).

Discussion

The NPS, which was started in the USA in 1980, showed that the removal of all polyps by colonoscopy reduces the incidence of colorectal cancer, and recommended an interval of at least 3 years between colonoscopic removal of newly diagnosed adenomatous polyps and subsequent follow-up examination.[2,3] In Japan, however, there are no established recommendations for postpolypectomy colonoscopic surveillance based on reliable evidence.

The JPS Workgroup was established in 2000 to evaluate colonoscopic follow-up surveillance strategies under a Grant for Scientific Research Expenses for Health and Welfare Programs. The JPS is the largest clinical study conducted in ethnic Japanese communities, documenting for the first time follow-up surveillance strategies for patients who have undergone two complete colonoscopies for control of colorectal cancer, with the removal of all detected polyps.[16] It will provide preexisting comorbidity data, including the prevalence of both flat and depressed colorectal lesions, the quality of colonoscopy, and the risk of colon cancer. Furthermore, these follow-up data will help to clarify the long-term impact of colonoscopic removal on mortality due to colorectal cancer. The evidence will form a basis for the surveillance and management of colorectal cancer in community-dwelling individuals who undergo colonoscopy in Japan.

Although the subjects in the JPS underwent two complete colonoscopies before randomization, the participation rate was high (83%). However, 24.5% (961 of 3,926) of the patients dropped out from the study before randomization, mostly after the first CS. One possible reason for the high dropout rate was that all examinations were performed under the national health insurance scheme. Patients had to pay expenses ranging from US$35 to $80 per colonoscopy, or $100–$300

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Table 2 Patient characteristics for referral at each participating center

	Participating center*											
	1	2	3	4	5	6	7	8	9	10	11	Total (%)
Males	341	281	281	332	167	123	80	197	55	429	154	2,440 (62.1)
Females	211	165	98	206	97	36	64	158	25	313	113	1,486 (37.9)
Mean age, (range)	59.2 (40–69)	58.6 (40–69)	55.8 (40–69)	57.3 (40–69)	54.7 (40–69)	59.4 (40–69)	58.2 (41–69)	57.4 (41–69)	57.8 (40–69)	56.0 (40–69)	58.0 (40–69)	57.3 (40–69)

Note: *Numbers for participating centers are indicated in Table 1.

Table 3 Reasons for referral at each participating center

Reason for referral, n (%)	Participating center*											
	1	2	3	4	5	6	7	8	9	10	11	Total (%)
FOBT+	95 (17.2)	164 (36.8)	308 (81.3)	256 (47.6)	98 (37.1)	23 (14.5)	67 (46.5)	92 (25.9)	43 (53.8)	118 (15.9)	196 (73.4)	1,460 (37.2)
Overt symptoms+	62 (11.2)	89 (20.0)	12 (3.2)	105 (19.5)	86 (32.6)	11 (6.9)	19 (13.2)	100 (28.2)	8 (10.0)	155 (20.9)	18 (6.7)	665 (16.9)
Surveillance after polypectomy	59 (10.7)	56 (12.6)	33 (8.7)	83 (15.4)	25 (9.5)	82 (51.6)	5 (3.5)	34 (9.6)	0 (0)	154 (20.8)	36 (13.5)	567 (14.4)
Screening (no symptoms)	47 (8.5)	81 (18.2)	23 (6.1)	63 (11.7)	37 (14.0)	4 (2.5)	8 (5.6)	96 (27.0)	0 (0)	184 (24.8)	9 (3.4)	552 (14.1)
Referred for endoscopic treatment	226 (40.9)	32 (7.2)	1 (0.3)	5 (0.9)	4 (1.5)	38 (23.9)	33 (22.9)	22 (6.2)	20 (25.0)	107 (14.4)	5 (1.9)	493 (12.6)
Others	63 (11.4)	24 (5.4)	2 (0.5)	26 (4.8)	14 (5.3)	1 (0.6)	12 (8.3)	11 (3.1)	9 (11.3)	24 (3.2)	3 (1.1)	189 (4.8)

Note: *Numbers for participating centers are indicated in Table 1.
Abbreviations: FOBT, fecal occult blood test; +, positive.

for polypectomy. However, we had to consider whether two colonoscopies are realistically tolerable for Japanese patients after completing the JPS. Finally, a total of 2,166 patients were assigned to randomized patient groups, and these eligible patients recruited for the JPS were successfully assigned in line with the expected sample-size calculation.

The sex distribution of the JPS subjects, with a mean age of 57.3 years, showed a male predominance at all participating centers. A recent study reported that male sex was associated with an increase in adenoma detection, with a statistically significant odds ratio of 1.89 (95% confidence 1.78–1.99) compared to females.[20] The first reason for the male predominance was that most of the patients had some risk factors with one or more adenomas for referral ($FOBT^+$, 37.2%; surveillance after polypectomy, 14.4%; referred for endoscopic treatment, 12.6%). The second reason was that the sex distribution of patients mentioned earlier accidentally showed a male predominance. The incidence of male sex was 63% in $FOBT^+$, 67% in surveillance after polypectomy, and 72% in referred for endoscopic treatment, respectively. However, the sex distribution and mean age of the patients (male/female/age: 59.1%/40.9%/60 years) recruited for the NPS were almost the same as for the JPS.[11] The final results of the JPS should be compared with the outcome of the NPS to assess the effectiveness of two colonoscopies with removal of all polyps before randomization for reduction of the incidence of advanced neoplasia.

This study had some limitations. We often used high-magnification endoscopes, because these are commonly available at Japanese academic centers.[5,6] However, there was no disease entity of sessile serrated adenoma/polyps (SSA/P) at the beginning of the JPS, and we did not evaluate the criteria for distinguishing SSA/P from hyperplastic polyps, because no pathologic gold standard for diagnosis has yet been fully established.[21] Recently, serrated lesions of the colorectum were considered as the precursors of perhaps a third of colorectal cancers. Cancers arising in serrated lesions are usually in the proximal colon, and account for a disproportionate fraction of cancer identified after colonoscopy. Rex et al with an expert panel recommended complete removal of all serrated lesions, except for diminutive sigmoid or rectal lesions.[22] Interval cancers arising in serrated lesions may not be prevented completely in the JPS, because serrated lesions, including SSA/P, were not always removed.

Conclusion

All patients recruited for the JPS were successfully assigned in line with the expected sample-size calculation. The last steps of data calculation/statistical processing at the data center and complete histopathological assessment by pathology review are ongoing. It is anticipated that the data will help to establish not only effective surveillance strategies after removal of all detected polyps but also reveal details of preexisting comorbidity, including prevalence of colorectal lesions, quality of colonoscopy, and the risk of colon cancer. Surveillance continues to evaluate the long-term effect of colonoscopic polypectomy in the JPS on mortality from colorectal cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL ARTICLE

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

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

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

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

Abbreviations

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

Background

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

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

Patients and methods

Study design and participants

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

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

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

Participating endoscopists

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

Endoscopy system and endoscopy procedures

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

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

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

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

M-NBI diagnostic criteria

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

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

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

Endoscopic diagnosis according to degree of certainty and need for biopsy

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

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

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

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

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

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

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

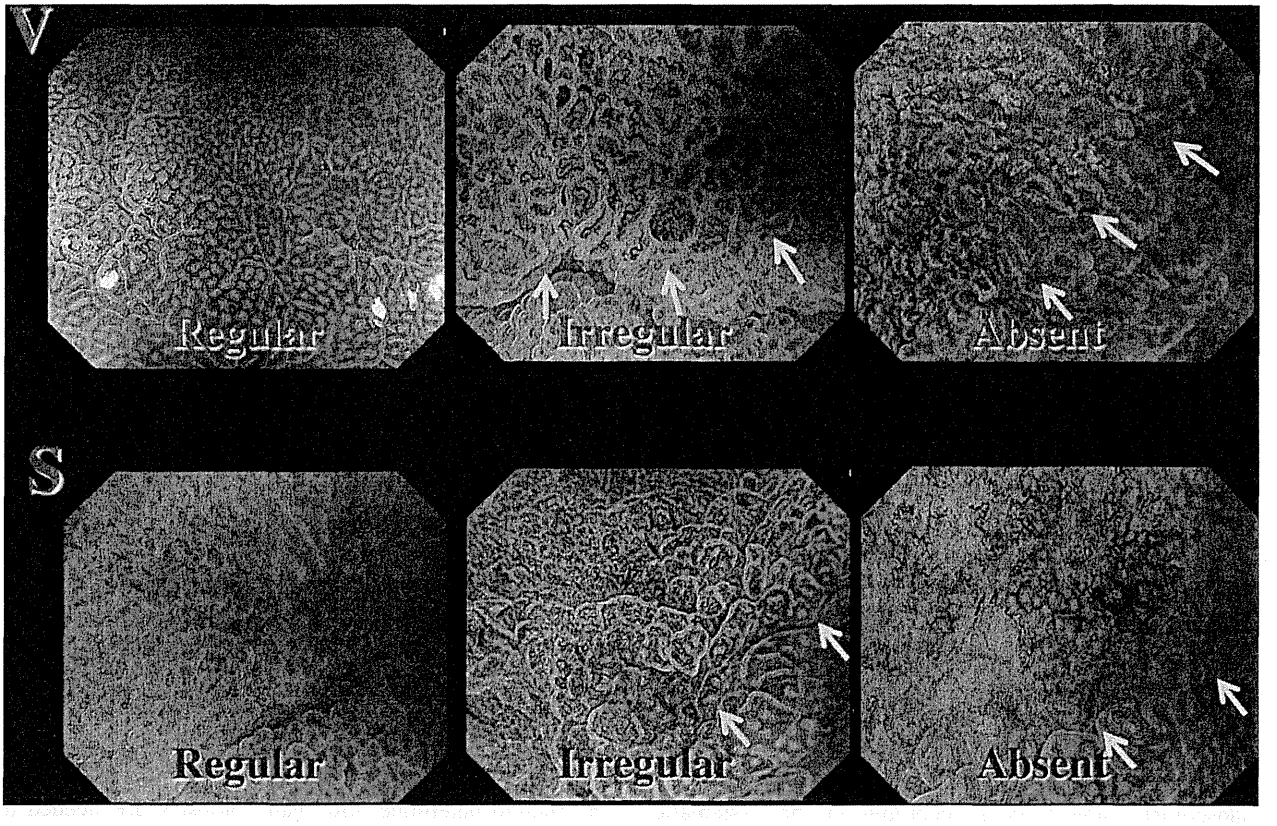


Fig. 1 VS classification using M-NBI (Reproduced with permission from Endoscopy 2009; 41:462–7 [11]). *V* microvascular pattern, classified as regular/irregular/absent. *S* microsurface pattern, classified as regular/irregular/absent

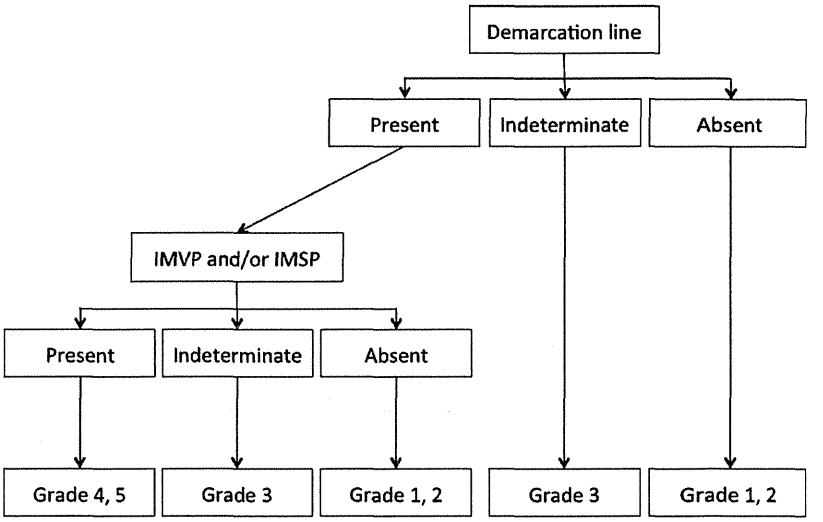


Fig. 2 Diagnostic flow diagram demonstrating the correlation between the VS (vessel plus surface) classification and Grades 1–5. *IMVP* irregular microvascular pattern, *IMSP* irregular microsurface pattern. Grade 1: non-cancer with high degree of confidence (no need for biopsies); Grade 2: non-cancer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

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

Gold standard

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

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

End points

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

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

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

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

Statistical analysis

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

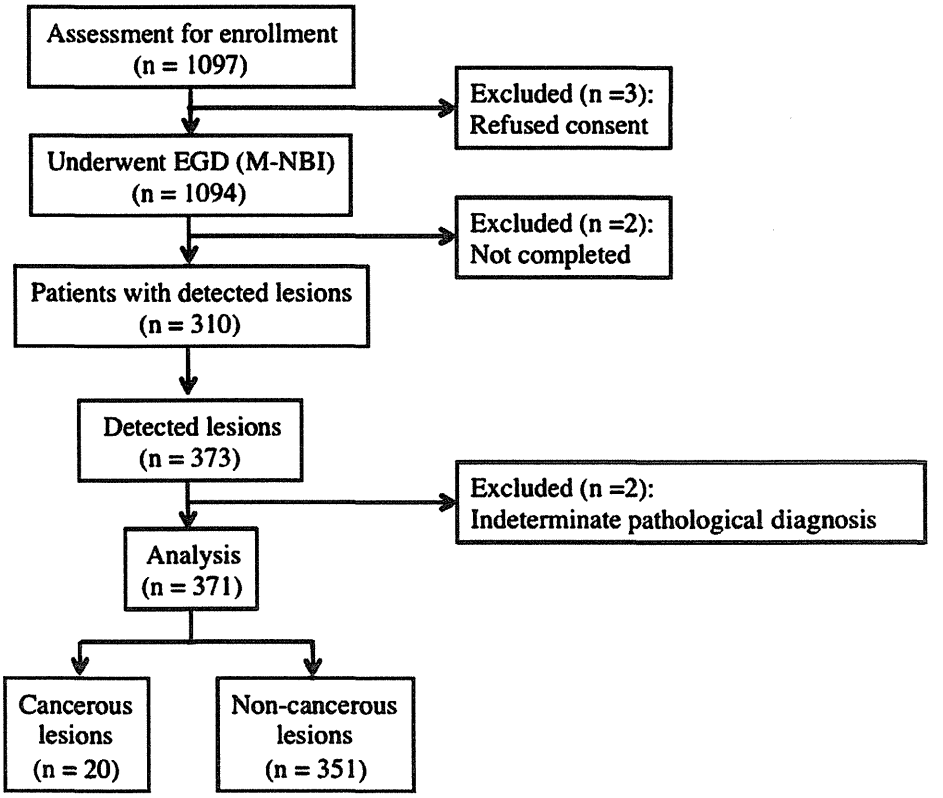


Fig. 3 Enrollment of patients and analysis of lesions. *EGD* esohagogastroduodenoscoy, *M-NBI* Magnifying endoscopy with narrow-band imaging

Table 1 Demographic characteristics of analyzed lesions according to histological diagnosis

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

[a] Macroscopic types were determined using the Paris classification

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

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

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

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

Results

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

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

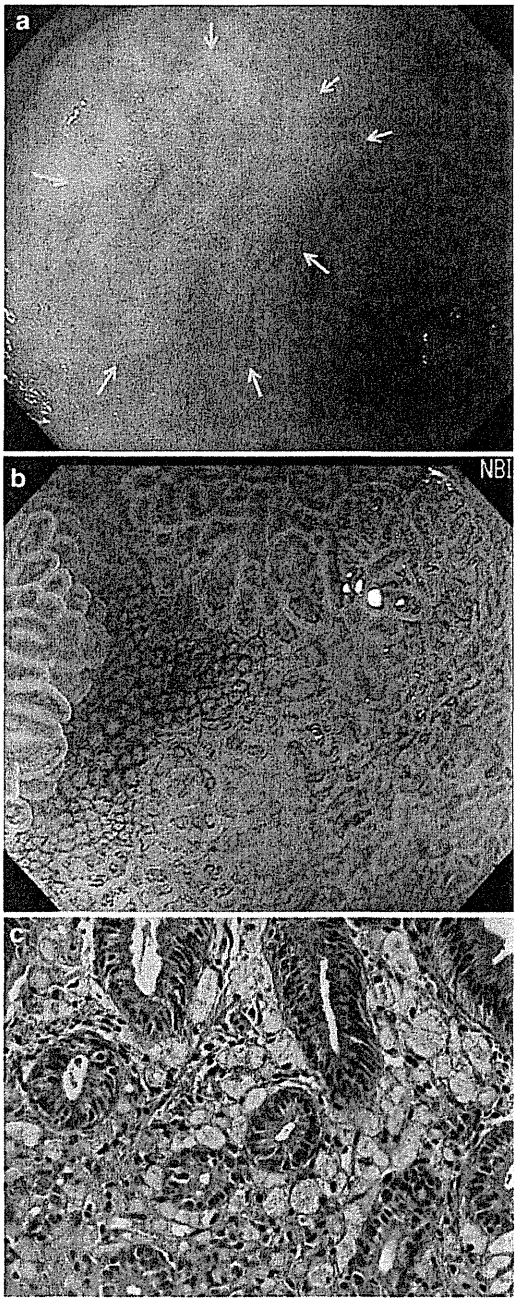
Table 2 shows the endoscopic diagnoses for all lesions according to the degree of certainty. The diagnostic performance is shown in Table 3 when we regrouped Grades 1–3 as non-cancer, and Grade 4 and 5 as cancer, and when we regrouped Grade 1 and 5 as high confidence predictions, and Grades 2–4 as low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

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

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

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

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



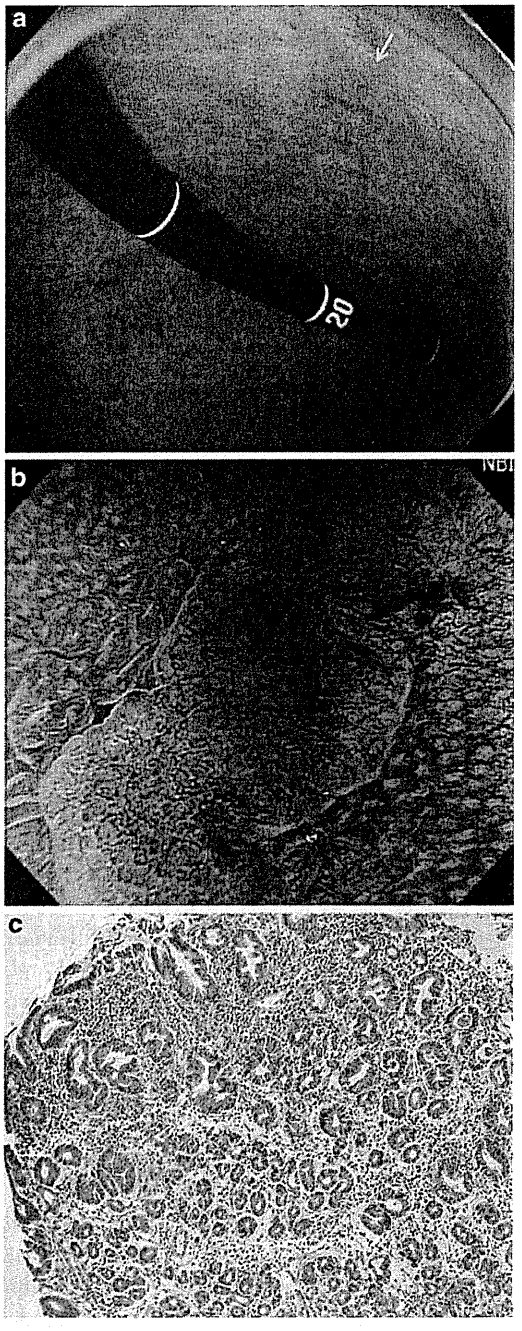
◀**Fig. 4** A false negative case with high confidence M-NBI diagnosis (Grade 1). **a** Endoscopic findings using C-WLI. A pale mucosal lesion (*arrows*) was detected during screening endoscopy. The morphology of this lesion is slightly depressed and irregularly demarcated. **b** Endoscopic findings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

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

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

Discussion

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

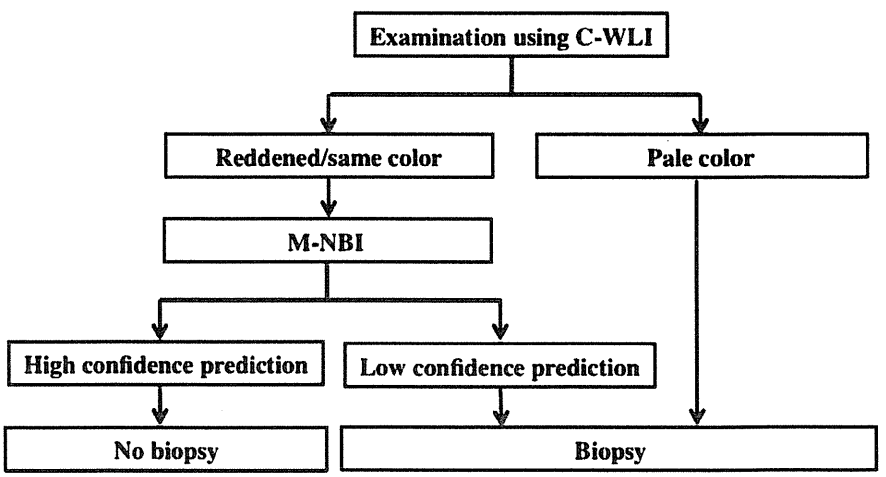


Fig. 6 A provisional strategy for M-NBI in screening gastroscopy

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

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

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Conflict of interest The authors have no potential conflicts of interest relevant to this article to declare.

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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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