None of the patients showed extrathyroid extension corresponding to T3 or T4 or lymph node metastasis corresponding to N1 in the UICC TNM classification [13] based on preoperative and intraoperative findings. On pathological examination, all patients were node-negative. To date, two patients with FAP-associated CMV, who underwent hemithyroidectomy at the initial surgery (one in Kuma hospital and one in another hospital) and were diagnosed as having polyposis thereafter, showed recurrence to the remnant thyroid 86 and 90 months after initial surgery, respectively. These patients underwent a second surgery and further recurrence has not been detected to date. Furthermore, one patient died of colorectal carcinoma 64 months after thyroid surgery and one died of lung suppuration unrelated to PTC or colorectal carcinoma 28 months after surgery. The other patients have survived without any evidence of PTC recurrence to date.

Discussion

There are two types of CMV etiology; FAP-associated and sporadic. Furthermore, there are two initial manifestations of FAP-associated CMV detection: thyroid nodule and FAP. We compared clinicopathological features between the two groups.

CMV can be diagnosed by preoperative cytological findings [12]. In our series, 75% of FAP-associated CMV and 37% of sporadic CMV were diagnosed as or highly suspected of CMV on cytology. The higher incidence in FAP-associated CMV is definitely because we ordered immunocytochemistry for beta-catenin and ER for patients who were known to have FAP.

Since it is well-known that CMV can be associated with FAP, screening of colonic polyposis by total colonoscopy should be recommended for patients who were diagnosed as having CMV. We demonstrated that FAP-associated CMV showed multiple tumors more frequently than sporadic CMV both on preoperative imaging studies and on pathological examination, indicating that the presence of FAP is highly suspected especially for patients with multiple CMV. In the subset of FAP-associated CMV, patients in the polyposis precedent group were younger and had smaller tumors than those in the thyroid precedent group. It is therefore suggested that thyroid screening for FAP patients contributes to early detection of CMV, even before patients become aware of thyroid nodule.

All patients in our series were node-negative and lacked extrathyroid extension. Furthermore, none of these patients died of carcinoma. These findings indicate that CMV normally shows an indolent character regardless of whether it is FAP-associated, which was not discrepant with previous studies [8, 9, 10, 16]. There is one report of CMV in an older (42 years) male patient who died of carcinoma only 17 months after surgery, but this seems atypical because neuroendocrine differentiation and a poorly differentiated component were present [17]. To date, however, 2 patients who underwent hemithyroidectomy for FAP-associated CMV recurred to the remnant thyroid during follow-up. Based on these findings, total thyroidectomy is recommended for CMV patients with multiple carcinoma lesions, a family history of colonic polyposis or colorectal carcinoma or diagnosed as having colonic polyposis before thyroid surgery. In contrast, none of the sporadic patients showed recurrence to the remnant thyroid, even though they underwent hemithyroidectomy, indicating that total thyroidectomy may not be mandatory for such patients. In our department, prophylactic MND has been performed for PTC patients having tumor larger than 3 cm, because these patients are likely to develop recurrence in regional lymph nodes [18]. However, such an extensive prophylactic node dissection is not needed for patients who were preoperatively diagnosed as having CMV.

Taken together, we showed that FAP-associated CMV showed multiple tumors more frequently than sporadic CMV. Total thyroidectomy is recommended at least for CMV patients associated with FAP, but extensive lymph node dissection is not necessary.

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Magnifying Narrowband Imaging Is More Accurate Than Conventional White-Light Imaging in Diagnosis of Gastric Mucosal Cancer

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CLINICAL AT

BACKGROUND & AIMS: It is difficult to accurately diagnose patients with depressed gastric mucosal cancer based on conventional white-light imaging (C-WLI) endoscopy. We compared the real-time diagnostic yield of C-WLI for small, depressed gastric mucosal cancers with that of magnifying narrow-band imaging (M-NBI). **METHODS:** We performed a multicenter, prospective, randomized, controlled trial of patients with undiagnosed depressed lesions ≤10 mm in diameter identified by esophagogastroduodenoscopy. Patients were randomly assigned to groups that were analyzed by C-WLI (n = 176) or M-NBI (n = 177) immediately after detection; the C-WLI group received M-NBI after C-WLI. We compared the diagnostic accuracy, sensitivity, and specificity between C-WLI and M-NBI and assessed the diagnostic yield of M-NBI conducted in conjunction with C-WLI. **Results:** Overall, 40 gastric cancers (20 in each group) were identified. The median diagnostic values for M-NBI and C-WLI were as follows: accuracy, 90.4% and 64.8%; sensitivity, 60.0% and 40.0%; and specificity, 94.3% and 67.9%, respectively. The accuracy and specificity of M-NBI were greater than those of C-WLI ($P < .001$); the difference in sensitivity was not significant ($P = .34$). The combination of M-NBI with C-WLI significantly enhanced performance compared with C-WLI alone; accuracy increased from (median) 64.8% to 96.6% ($P < .001$), sensitivity increased from 40.0% to 95.0% ($P < .001$), and specificity increased from 67.9% to 96.8% ($P < .001$). **CONCLUSIONS: M-NBI, in conjunction with C-WLI, identifies small, depressed gastric mucosal cancers with 96.6% accuracy, 95.0% sensitivity, and 96.8% specificity. These values are better than for C-WLI or M-NBI alone.**

Keywords: Gastric Cancer; Early Detection; Benign; Malignant; Neoplasm; Biopsy.

Gastric cancer is the fourth most common malignancy and the second leading cause of death from cancer worldwide.[1] Early detection and curative treatment are the best strategies for improving patient survival. Esophagogastroduodenoscopy is the most sensitive method of early detection of gastric cancers. However, an accurate early diagnosis of gastric mucosal cancer is difficult with conventional white-light imaging (C-WLI) endoscopy; nevertheless, it remains the standard endoscopic examination modality worldwide.

Detection of mucosal cancers ≤20 mm in diameter is ideal, because they are curable using minimally invasive treatments such as endoscopic mucosal resection and endoscopic submucosal dissection.[2,3] Among the gastric mucosal cancers, the depressed type is the predominant morphology.[4-6] However, small depressed cancers (≤10 mm in diameter) are more difficult to distinguish from benign abnormalities (such as inflammation) compared with elevated cancers. Although chromoendoscopy using indigo carmine has contributed to an improvement in the diagnosis of gastric mucosal cancers,[7] there is no evidence of the superiority of chromoendoscopy over C-WLI. Therefore, C-WLI endoscopy remains the standard imaging modality for diagnosing gastric mucosal cancers.

Histologic evaluation of biopsy specimens from suspicious lesions is conventionally used to confirm a diagnosis. A highly accurate diagnosis without the need for a biopsy is the ultimate goal of endoscopists, because this would decrease the number of unnecessary biopsies, especially when confirming a negative biopsy of any suspicious cancerous lesion. This could reduce the risk of postbiopsy bleeding, costs associated with the procedure, and the workload on pathologists.

Magnifying narrow-band imaging (M-NBI), a recently developed advanced endoscopic imaging technology, was reported to be useful for the accurate diagnosis of gastric abnormalities such as cancers,[8-13] adenomas,[14] and intestinal metaplasia.[15] However, no randomized trials have been conducted to compare M-NBI with C-WLI. The present study was designed to assess and compare the real-time diagnostic yield of C-WLI for depressed gastric mucosal

Abbreviations used in this paper: CI, confidence interval; C-WLI, conventional white-light imaging; M-NBI, magnifying narrow-band imaging; NPV, negative predictive value; PPV, positive predictive value.

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cancers with that of M-NBI when performed by skilled endoscopists.

Patients and Methods

Study Design and Participants

This randomized, controlled, open-label, multicenter trial was conducted at 9 centers in Japan. This study was conducted according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) initiative[16] and the Declaration of Helsinki.

The frequency of synchronous or metachronous multiple gastric cancers was reported as 3 to 5 per 100 patient-years,[17-19] which is higher than the incidence of gastric cancer in the general population. In other words, patients with gastric cancer might constitute a cancer-enriched population, which may be a more suitable model for screening of potential gastric cancers than the general population. Therefore, we recruited patients aged 20 years or older with untreated gastric cancers and patients with a history of gastric cancer. Patients who had been treated with endoscopic mucosal resection or endoscopic submucosal dissection were included in the latter group, because their stomachs were preserved with minimum injury. We excluded patients who had been treated with surgical resection, because the stomach was either removed or was reduced in size. Other exclusion criteria were serious complications that could interfere with the examination protocol and the use of medication that might interfere with the collection of a biopsy specimen. Written informed consent was obtained, and the institutional review board of each participating hospital approved the study. The clinical trial number of this study was UMIN-CTR000001072.

To detect a target lesion, screening was performed using C-WLI endoscopy. Previously undetected lesions were considered ideal potential targets for evaluating the diagnostic yield without bias. Therefore, the target lesions for this study were "newly detected and undiagnosed" small, depressed gastric lesions ≤10 mm in diameter. We did not target lesions that had been analyzed histologically. Small, depressed lesions with apparent erosion or ulceration were also not evaluated, because it is difficult to visualize surface changes in these lesions. If the patient had multiple such lesions, only the first lesion detected was selected for examination. The diameter of each lesion was estimated by comparing it with the size of the biopsy forceps.

Randomization and Masking

When a target small, depressed lesion was detected by C-WLI screening, patients were immediately assigned randomly to undergo detailed examination using C-WLI or M-NBI at a 1:1 ratio. After the randomization, all endoscopists knew which imaging method would be used for the detailed examination when making a diagnosis of the target lesion. Randomization was performed promptly on-site using tables of random numbers stratified by hospital, and the results thereof were kept in sealed, numbered envelopes. The random allocation sequence was prepared at the data management center. Both the assignment result and the corresponding envelope number were recorded by the data management center. At each participating hospital, sealed envelopes were stored by a third party who was not involved in the study, and the envelopes were opened by an assistant physician in serial order only when randomization was performed. The assigned patient identification number, envelope number, and assignment result were recorded on-site and faxed to the data management center on the day of the examination.

Procedure and End Points

The study design and the protocol examination are outlined in Supplementary Figure 1 and Supplementary Materials and Methods. The diagnosis for the target lesion was made by one endoscopist according to predetermined diagnostic criteria for C-WLI and M-NBI without any consultation with other physicians, and an assistant physician immediately recorded the results using a case report form. For each modality, the interval between the start of the observation and the time at which an endoscopic diagnosis was made was measured using a stopwatch. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI. This procedure was used to evaluate the effect of using M-NBI in conjunction with C-WLI. After all records were compiled, at least one biopsy specimen was obtained from the target lesion.

The primary aim of the study was to compare the diagnostic accuracy between C-WLI and M-NBI. The secondary aim was to compare diagnostic sensitivity, specificity, and examination time between C-WLI and M-NBI and to evaluate the effects of an additional M-NBI study after the initial C-WLI in terms of diagnostic accuracy, sensitivity, specificity, and examination time. Histopathology diagnosis of obtained biopsy specimens was used as a gold standard for the diagnosis.

Endoscopy System

The NBI system is an innovative optical image-enhanced technology that involves a narrow-bandwidth NBI filter in the video endoscopy system. The central wavelengths of the NBI filters are 415 nm and 540 nm, and each has a bandwidth of 30 nm. Because 415-nm and 540-nm light are well absorbed by hemoglobin, the microvascular architecture of the mucosal surface can be visualized readily. Details of this system have been reported elsewhere.[20-22]

We used high-resolution magnifying endoscopy with a capability of 80-fold optical magnification (GIF-Q240Z, GIF-H260Z, and GIF-FQ260Z; Olympus Medical Systems, Tokyo, Japan) and a high-resolution liquid-crystal monitor (OEV191H; Olympus Medical Systems). We alternated between the 2 imaging modalities (C-WLI and M-NBI) by pushing a button on the endoscope (Evis Lucera Spectrum System; Olympus Medical Systems). We used a fixed structure enhancement setting and color tone for the video processor.

Participating Endoscopists

All examinations were performed by 31 endoscopic specialists accredited by the Japan Gastroenterological Endoscopy Society in 9 institutes. Before the onset of the study, all participating endoscopists were trained using images of small, depressed lesions to minimize diagnostic variation between them.

Diagnostic Criteria for C-WLI and M-NBI

Figure 1 shows a representative endoscopic image of a small, depressed gastric cancer and a small, depressed benign lesion. The diagnostic method based on endoscopic findings is outlined in Supplementary Materials and Methods.

The endoscopic diagnostic criteria for small, depressed gastric cancers using C-WLI were defined based on previous reports of C-WLI findings: an irregular margin and a spiny depressed area.[23] The observation of 2 findings (irregular margin and spiny

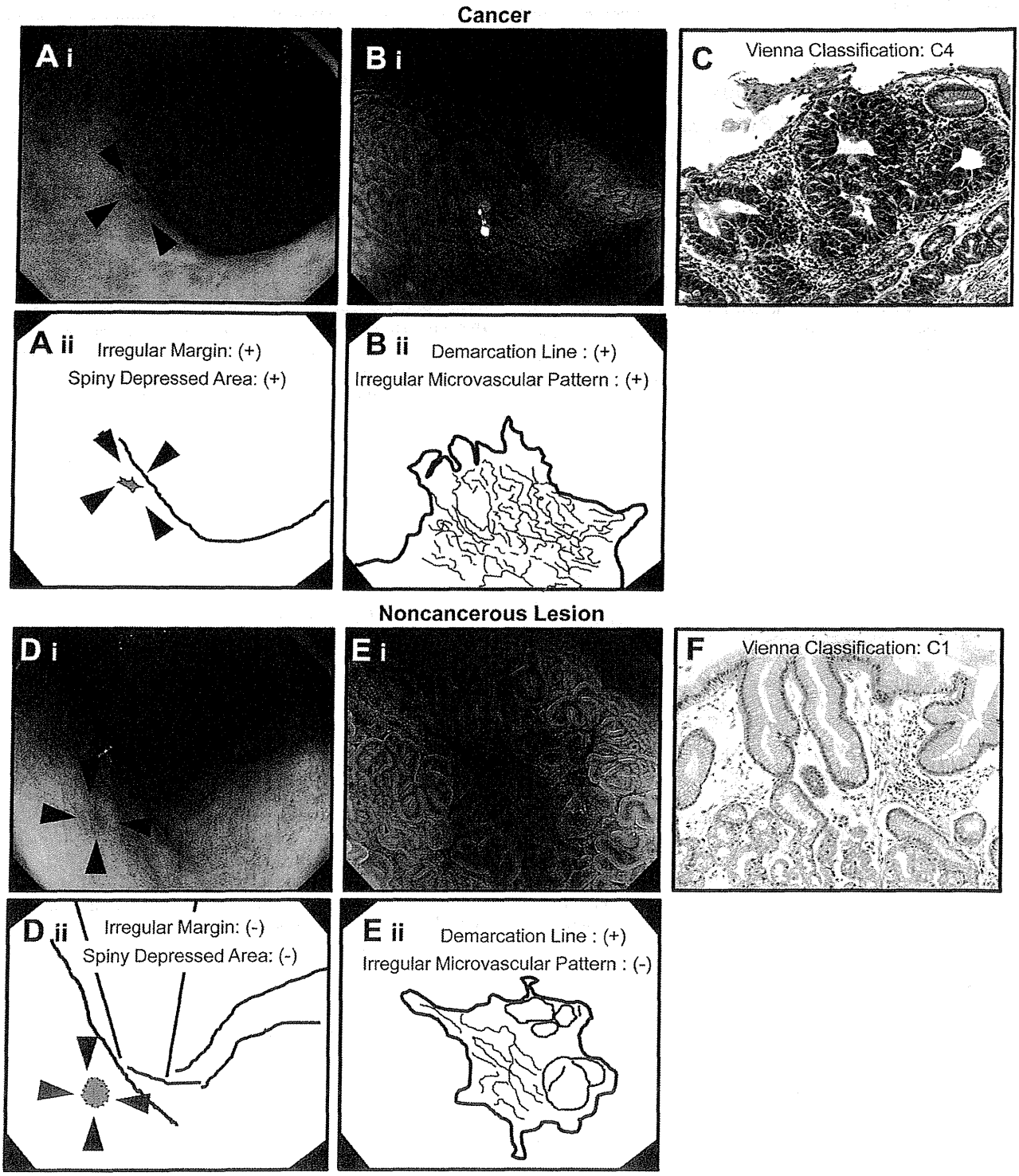

Figure 1. Representative endoscopic findings for gastric small, depressed lesions. *A–C* show a case of cancer, and *D–F* show a case of noncancerous lesions. *A* shows an endoscopic image obtained using C-WLI. A small, depressed lesion (*arrowheads*) is evident in the anterior wall of the lower part of the gastric body. This lesion was evaluated as having an irregular margin and a spiny depressed area. *B* shows an endoscopic image obtained using M-NBI, which enabled clear visualization of the demarcation line and an irregular microvascular pattern. *A′* and *B′* are schematic representations of the images shown in *A* and *B*, respectively. *C* shows a lesion that was histologically diagnosed as a differentiated adenocarcinoma, Vienna Classification C4. *D* shows an image obtained using C-WLI. A small reddish area (*arrowheads*) is evident in the anterior wall of the upper part of the gastric body. Because the depressed area was not "spiny" and because a definite margin was not apparent, this case was evaluated as not having a spiny depressed area or an irregular margin. *E* shows an image obtained using M-NBI, which enabled clear visualization of a demarcation line and the absence of an irregular microvascular pattern. *D′* and *E′* are schematic representations of the images shown in *D* and *E*, respectively. *F* shows a lesion that was histologically diagnosed as gastritis, Vienna Classification C1.

depressed area) in the target lesion was classified according to 3 categories: present, absent, or indeterminate.

The endoscopic diagnostic criteria for small, depressed gastric cancers using M-NBI were defined based on previous reports by Yao et al: a demarcation line between the depressed cancerous lesion and the surrounding noncancerous area and an irregular microvascular pattern inside the lesion.[24] Observations of 2 findings (demarcation line and irregular microvascular pattern) in the target lesion were also classified according to 3 categories: present, absent, or indeterminate.

Endoscopic diagnoses were determined according to the combined visibility of the 2 findings as follows (Supplementary Figure 2). (1) If both findings were present, the diagnosis was "cancer." (2) If either finding was indeterminate, the diagnosis was "inconclusive." (3) If either or both findings were absent, the diagnosis was "noncancerous."

For analyzing diagnostic accuracy, sensitivity, and specificity, lesions diagnosed as "inconclusive" were considered as endoscopic "noncancerous" lesions.

Pathology Diagnosis

The biopsy specimens were evaluated using H&E staining. The diagnostic pathology criteria were based on the revised Vienna classification.[25] C4 (mucosal high-grade neoplasia) or C5 (submucosal invasion by neoplasia) were diagnosed as cancer, and C1 (negative for neoplasia), C2 (indefinite for neoplasia), or C3 (mucosal low-grade neoplasia) were diagnosed as noncancerous lesions. In this study, we used a central system of consultation with a main expert pathologist. If an indeterminate lesion were to be encountered, it was scheduled to be reviewed by this consulting pathologist in making a final diagnosis.

Statistical Analysis

We assumed that the accuracy, sensitivity, and specificity of C-WLI and M-NBI compared with histologic diagnosis would be 60% and 85%, respectively. To set a probability for error of 0.05 and attain a power of 80% for testing the superiority of M-NBI, 108 patients including at least 43 cancerous lesions were needed. Next, we calculated how many patients would need to be screened. Because the frequency of small depressed lesions was reported to be 8.1% in the general population,[9] the required size of the screening sample was 1100 patients.

Statistical analysis was performed using SPSS software, version 17 (SPSS Inc, Chicago, IL). For diagnostic performance, accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented as percentages with 95% confidence intervals (CIs). Continuous variables are expressed as medians and interquartile ranges. Analyses of the difference in diagnostic performance between C-WLI and M-NBI were conducted using the population whose diagnoses had been confirmed by pathology using Pearson's χ^2 test. Analyses of the effect of additional M-NBI after the initial C-WLI on diagnostic performance were conducted using the population whose diagnoses had been confirmed by pathology and McNemar testing. Analysis of the examination duration was conducted using the population who completed protocol examination and the Mann–Whitney nonparametric test for comparisons between C-WLI and M-NBI, as well as the Wilcoxon signed rank test for comparisons between C-WLI and C-WLI plus M-NBI. All probability values calculated in this analysis were 2 sided, and $P < .05$ was considered significant.

Results

Between June 2008 and May 2010, 1365 patients were enrolled in the study. Eight patients refused to participate and 4 were registered twice; therefore, the remaining 1353 patients were registered correctly and underwent endoscopic screening. Screening was discontinued for 2 patients because of a large amount of residual digesta in the stomach and a severe vomiting reflex. Endoscopic screening was completed for the remaining 1351 patients.

Of the screened patients, 362 (26.8%) had newly detected and undiagnosed small, depressed lesions and were randomly assigned to one of 2 groups: (1) 180 patients were examined using C-WLI followed by M-NBI, and (2) 182 patients were examined using M-NBI alone. Four patients in the C-WLI group (one patient's lesion was >10 mm in diameter, one was discontinued from the examination because of Mallory–Weiss syndrome, and 2 had a missed biopsy) and 5 patients in the M-NBI group (one was examined with an unpermitted endoscope and 4 missed biopsy) were excluded. Data for 176 patients in the C-WLI group and 177 patients in the M-NBI group were used for the final analysis (Figure 2). The demographic and lesion characteristics of the 2 groups were balanced. In both groups, 13% of patients had newly diagnosed gastric cancer (20 per group; Table 1).

Table 2 shows endoscopic diagnoses for all lesions. Inconclusive diagnoses were obtained for 3 lesions (1.7%) using M-NBI, for 6 lesions (3.4%) using C-WLI, and for 2 lesions (1.3%) using C-WLI followed by M-NBI. These lesions were considered endoscopic "noncancerous" lesions for analysis.

The real-time diagnostic accuracy of M-NBI was significantly greater than that of C-WLI (90.4% [95% CI, 85.1%–94.3%] and 64.8% [95% CI, 57.2%–71.8%], respectively; $P <$ .001; Table 3). Real-time M-NBI diagnosis had greater specificity than C-WLI diagnosis (94.3% [95% CI, 89.4%–97.3%] and 67.9% [95% CI, 60.0%–75.2%], respectively; $P <$ .001; Table 3). The diagnostic sensitivities of M-NBI and C-WLI did not differ significantly (60.0% [95% CI, 36.1%–80.9%] and 40.0% [95% CI, 19.1%–63.9%], respectively; $P =$ .34; Table 3). M-NBI in conjunction with C-WLI significantly enhanced the diagnostic performance of the latter; accuracy increased from 64.8% (95% CI, 57.2%–71.8%) to 96.6% (95% CI, 93.5%–99.1%; $P <$ .001), sensitivity increased from 40.0% (95% CI, 19.1%–63.9%) to 95.0% (75.1%–99.9%; $P <$ .001), and specificity increased from 67.9% (95% CI, 60.0%–75.2%) to 96.8% (92.7%–99.0%; $P <$ .001; Table 3).

The median durations of the C-WLI and M-NBI procedures were 21 seconds (interquartile range, 12–40 seconds) and 55 seconds (interquartile range, 23–97 seconds), respectively, and this difference was highly significant ($P <$ .001). The median total duration of C-WLI followed by M-NBI (72 seconds [interquartile range, 40–144 seconds]) was significantly longer than that of

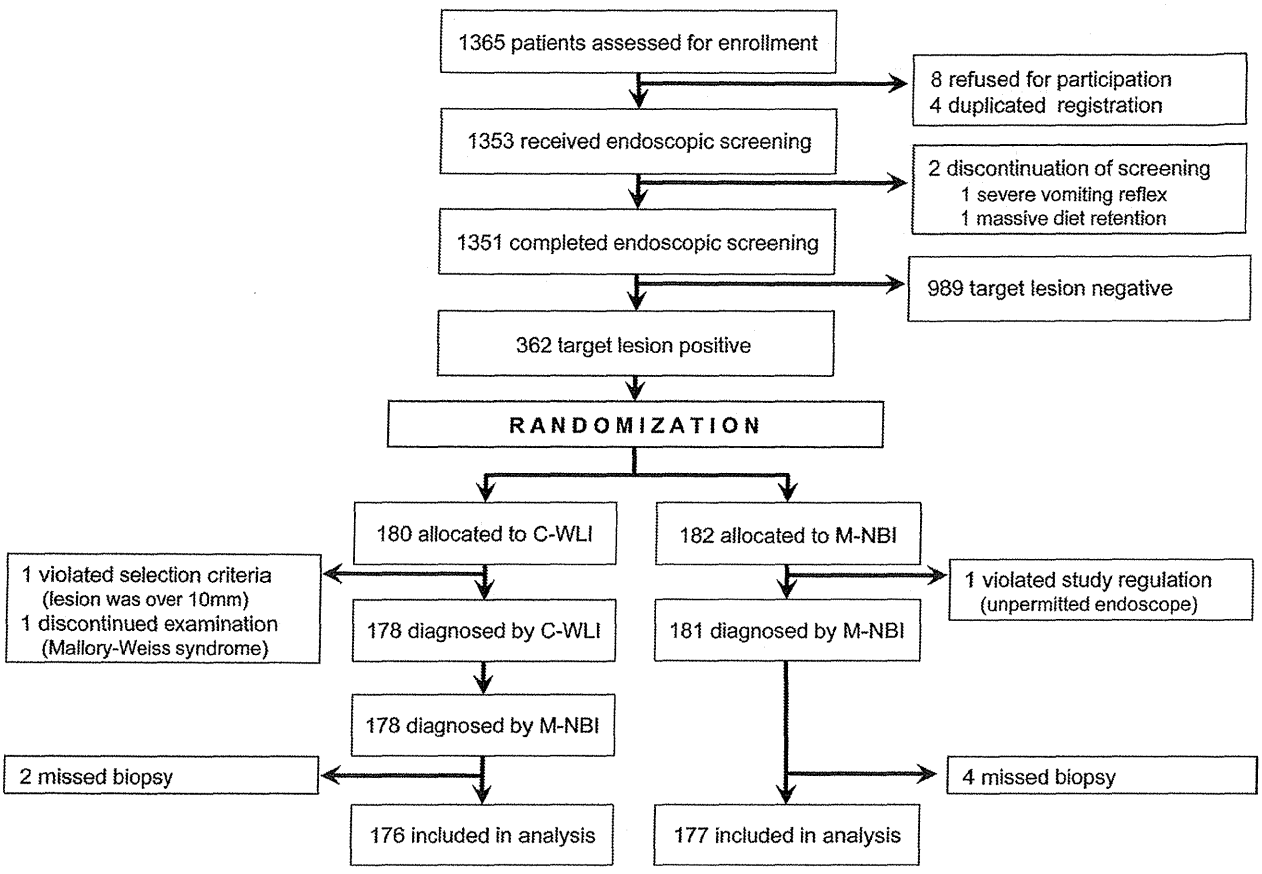

Figure 2. Patient enrollment, randomization, and examination.

C-WLI alone ($P < .001$). All patients tolerated the procedures well (Table 3).

Figure 3 shows the PPV and NPV data for each examination. M-NBI significantly improved the PPV compared with C-WLI alone to 57.1% (95% CI, 36.0%–78.3%) from 13.8% (95% CI, 2.9%–22.7%; $P = .001$). Furthermore, C-WLI followed by M-NBI dramatically improved the PPV from 13.8% (95% CI, 2.9%–22.7%) to 79.2% (95% CI, 62.9%–95.4%; $P < .001$). Similarly, the NPV of C-WLI of 89.8% (95% CI, 84.4%–95.3%) was improved by M-NBI to 94.9% (95% CI, 91.4%–98.3%; $P = .16$) and by C-WLI followed by M-NBI to 99.3% (95% CI, 98.1%–100%; $P < .001$).

Detailed C-WLI examination was discontinued during the procedure in one patient (1/362; 0.3%) because of bleeding associated with Mallory–Weiss syndrome. Although the bleeding stopped spontaneously without any endoscopic hemostatic treatment, a biopsy specimen was not obtained because the suspicious target lesion was missed. Two patients (2/362; 0.6%) were hospitalized on the day after examination because of bleeding from the biopsy site; although one patient needed a blood transfusion, both patients were discharged within a few days. None of the 3 patients experienced prolonged adverse effects. There were no serious adverse events directly related to the endoscopic observations.

Table 4 summarizes the clinical courses and pathologic diagnoses of 40 gastric cancers in 40 patients. Thirty-two patients were treated endoscopically (by endoscopic mucosal resection or endoscopic submucosal dissection). Five patients underwent surgical resection for synchronous advanced gastric cancers. The remaining 3 patients did not receive any treatment; 2 had other concomitant noncurable malignancies, and one refused treatment. Histologically, 39 lesions were of the intestinal type and one lesion was of the diffuse type. Regarding the depth of the 37 lesions that were removed, 35 were mucosal cancers, 2 of which were accompanied by submucosal invasion (0.3 mm and 0.8 mm). The depths of the 3 untreated lesions were estimated endoscopically as 2 mucosal cancers and one submucosal cancer.

Discussion

In this multicenter randomized trial, we compared the diagnostic yield of C-WLI with that of M-NBI for small gastric cancers. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities. One was the worldwide standard method of C-WLI; the other was M-NBI, which is the most advanced imaging method at present. This end point is the most impor-

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group

	C-WLI (n = 176)	M-NBI (n = 177)	*P* value
Age (*y*)			
Median (range)	69 (45–93)	69 (37–87)	.56
Sex			
Male	138	140	.79
Female	38	37	
Endoscope			
GIF-Q240Z	71	65	.83
GIF-H260Z	104	109	
GIF-FQ260Z	1	3	
Size of lesion (*mm*)			
≤5	74	71	.75
>5	102	106	
Mean	5.6	5.6	.97
Location of lesion			
Upper third			
Anterior wall	4	2	.51
Lesser curvature	9	10	
Posterior	22	12	
Greater curvature	4	3	
Middle third			
Anterior wall	7	7	
Lesser curvature	13	25	
Posterior	12	11	
Greater curvature	8	6	
Lower third			
Anterior wall	18	23	
Lesser curvature	25	33	
Posterior	26	18	
Greater curvature	28	27	
Histopathology diagnosis			
Cancer	20	20	1.00
Noncancerous	156	157	

tant aspect of this study, because if C-WLI proves superior to M-NBI, such advanced methods are not needed in practice. However, if M-NBI is indeed better than C-WLI, it should be used more in daily practice. The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI. This end point is also important, because in daily practice M-NBI is usually performed after C-WLI. Therefore, the results might reflect the practical diagnostic potential. To evaluate these aims, we used a strictly controlled randomized study. Furthermore, the endoscopic diagnosis in each method (C-WLI and M-NBI) was made on-site and independently to avoid any bias.

M-NBI, especially when used in conjunction with C-WLI, significantly enhanced real-time sensitivity, specificity, and accuracy of diagnosis; therefore, we concluded that M-NBI is an essential modality for diagnosing small gastric mucosal cancer. Although there are reports on the diagnostic yield of M-NBI for differential diagnosis of gastric lesions, some were performed at only one institute,[9,10,12,13] one was evaluated by several expert endoscopists using stored images and did not involve real-time assessment,[12] and one included gastric lesions with a definite diagnosis.[13] To overcome these limitations, our study targeted newly detected and undiagnosed gastric superficial lesions, which were evaluated on-site. For these reasons, the present results are the most reliable and could be a milestone in the field of endoscopic diagnosis of early gastric cancers.

Regarding accuracy and specificity, M-NBI alone yielded excellent results (90.4% and 94.3%, respectively), which were significantly better than those obtained with C-WLI. However, the sensitivities of M-NBI alone (60.0%) and C-WLI alone (40.0%) were lower than the estimated values: 85% for M-NBI and 60% for C-WLI. The low sensitivity of C-WLI might be acceptable considering the difficulty of diagnosing small gastric cancers in daily clinical practice. Although the reason for the low sensitivity of the M-NBI group is unknown, it might be associated with the examination protocol in this study; M-NBI observation was performed without evaluating a gross finding of lesions using C-WLI. In daily practice, magnifying examinations are usually performed after C-WLI. Actually, when performed after the C-WLI observation, M-NBI yielded excellent diagnostic performance in terms of accuracy, sensitivity, and specificity (all values were >95%). In addition, M-NBI and C-WLI followed by M-NBI significantly improved the PPV and NPV compared with C-WLI alone. This has enormous significance in clinical practice, because the examination with high PPV and high NPV might enable the clinician to make appropriate judgments as to which lesion needs pathology to confirm the diagnosis. When the lesion is suspected to be a neoplasm by C-WLI followed by M-NBI, taking a biopsy specimen is highly recommended to confirm the pathology. On the other hand, when the lesion is not suspected to be a neoplasm by M-NBI alone or by C-WLI followed by M-NBI, we could avoid a negative biopsy. These results have the potential to enable so-called "optic biopsy." Taken together, C-WLI followed by M-NBI might be the best

Table 2. Endoscopic Diagnoses for All Small Depressed Lesions

		Cancerous lesion (%)			Noncancerous lesion (%)		
Group	Method	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis
M-NBI	M-NBI	12/20 (60.0)	7/20 (35.0)	1/20 (5.0)	146/157 (93.0)	9/157 (5.7)	2/157 (1.3)
C-WLI	C-WLI	8/20 (40.0)	12/20 (60.0)	0/20 (0)	100/156 (64.1)	50/156 (32.1)	6/156 (3.8)
	C-WLI+M-NBI	19/20 (95.0)	1/20 (5.0)	0/20 (0)	149/156 (95.5)	5/156 (3.2)	2/156 (1.3)

Table 3. Diagnostic Performance of C-WLI and M-NBI for Gastric Small Depressed Lesions

Group	Method	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Examination time (s), median (interquartile range)
M-NBI	M-NBI	90.4[a] (85.1–94.3)	60.0 (36.1–80.9)	94.3[a] (89.4–97.3)	55[a] (23–97)
C-WLI	C-WLI	64.8 (57.2–71.8)	40.0 (19.1–63.9)	67.9 (60.0–75.2)	21 (12–40)
	C-WLI + M-NBI	96.6[b] (93.5–99.1)	95.0[b] (75.1–99.9)	96.8[b] (92.7–99.0)	72[b] (40–144)

[a]$P < .001$ for M-NBI vs C-WLI; [b]$P < .001$ for C-WLI vs C-WLI + M-NBI.

approach for making accurate diagnoses of small gastric cancers.

The durations of the M-NBI and C-WLI followed by M-NBI examinations were 34 seconds and 51 seconds, respectively, significantly longer than that required for C-WLI alone. However, these durations are clinically acceptable, because we managed to make accurate diagnoses without having to insert a spraying catheter or use indigo carmine. The importance of simple methods and accurate diagnoses for clinical practice is indisputable. Thus, Li et al showed that confocal laser endomicroscopy can be used to identify gastric superficial cancers with high validity and reliability.[26] However, confocal laser endomicroscopy requires the intravenous administration of a contrast agent. In contrast, M-NBI can be used by simply pushing a button on the endoscope. In addition, evaluation of demarcation lines and irregular microvascular patterns is sufficient for diagnosis with M-NBI, whereas confocal laser endomicroscopy requires knowledge of histopathology procedures for diagnosis.

Major bleeding caused by an endoscopic biopsy is rarely reported.[27] However, in our study, 2 patients experienced bleeding from the biopsy site. The best way of avoiding such bleeding is to avoid unnecessary biopsies. M-NBI, especially when used in conjunction with C-WLI, could help to reduce the number of unnecessary biopsies.

Our study has some limitations. First, the number of cancerous lesions was small, and it was less than the required sample size. This might be associated with insufficient power to evaluate sensitivity adequately. Then, further large numbers of patients for screening are needed to evaluate the sensitivity for diagnosing small gastric mucosal cancers of each modality. Second, this study was open labeled because the endoscopists knew which imaging modality was in use. Thus, a blinded study was impossible. Third, there is no arm that includes a dye-based imaging method such as indigo carmine or acetic acid. Indigo carmine and acetic acid are useful, but these dyes are only used in a few countries and institutes, and the standard worldwide endoscopic method to diagnose early gastric cancer is still C-WLI without any dye use. In addition, if we added a chromoendoscopy arm in this study, the required sample size would need to be enlarged and the study design and statistical analyses would be excessively complex. For these reasons, we did not include the dye-based imaging method.

Early detection of small gastric cancers makes it possible to effect a cure using minimally invasive treatments such as endoscopic mucosal resection and endoscopic

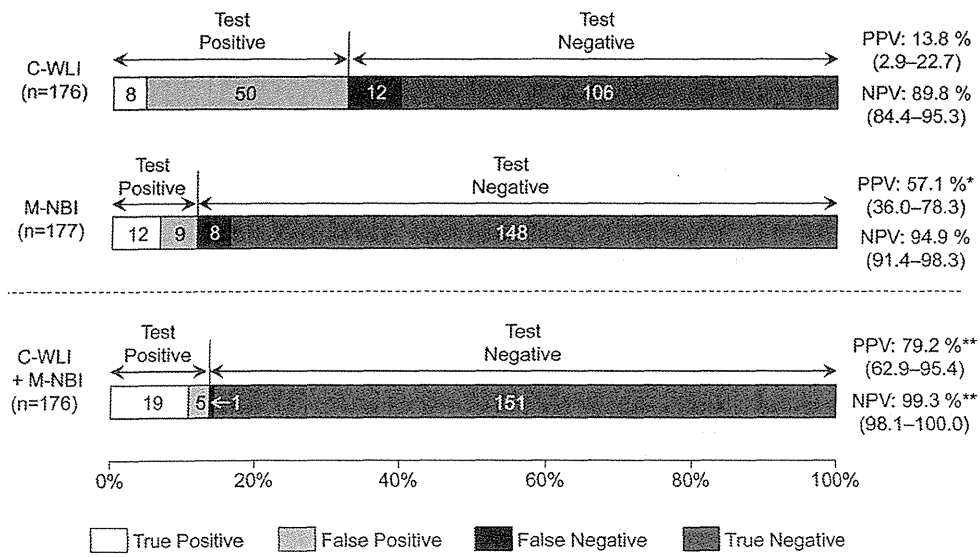

Figure 3. PPV and NPV in each examination. *The PPV for M-NBI was significantly higher than for C-WLI ($P = .001$). The NPV in M-NBI was higher than that of C-WLI; however, the difference was not significant ($P = .16$). **Both PPV and NPV were significantly enhanced by additional examination using M-NBI compared with C-WLI alone ($P < .001$).

Table 4. Clinical Course and Pathologic Diagnosis of Patients With Gastric Cancers

No. of patients	40
Treatment	
Endoscopic mucosal resection/endoscopic submucosal dissection	2/30
Surgery	5
No treatment	3
Histologic type	
Adenocarcinoma	40
Intestinal type	39
Diffuse type	1
Other diagnosis	0
Pathologic depth	
Mucosa	35
Submucosa	2
Muscularis propria	0
Unknown	3

submucosal dissection. In this study, all of the newly diagnosed small gastric cancers were good candidates for these procedures. Among the 37 cancers removed, 35 (95%) were mucosal. Early diagnosis using M-NBI and minimally invasive treatment is ideal for patients with gastric cancers, because it will improve their survival and quality of life. Although eradication of *Helicobacter pylori* is effective in reducing the incidence of gastric cancer,[17,28] endoscopic examination using M-NBI in conjunction with C-WLI should be indicated for high-incidence areas such as East Asia, South America, Eastern European countries, and Russia.[29]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.08.007.

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Conflicts of interest

The authors disclose no conflicts.

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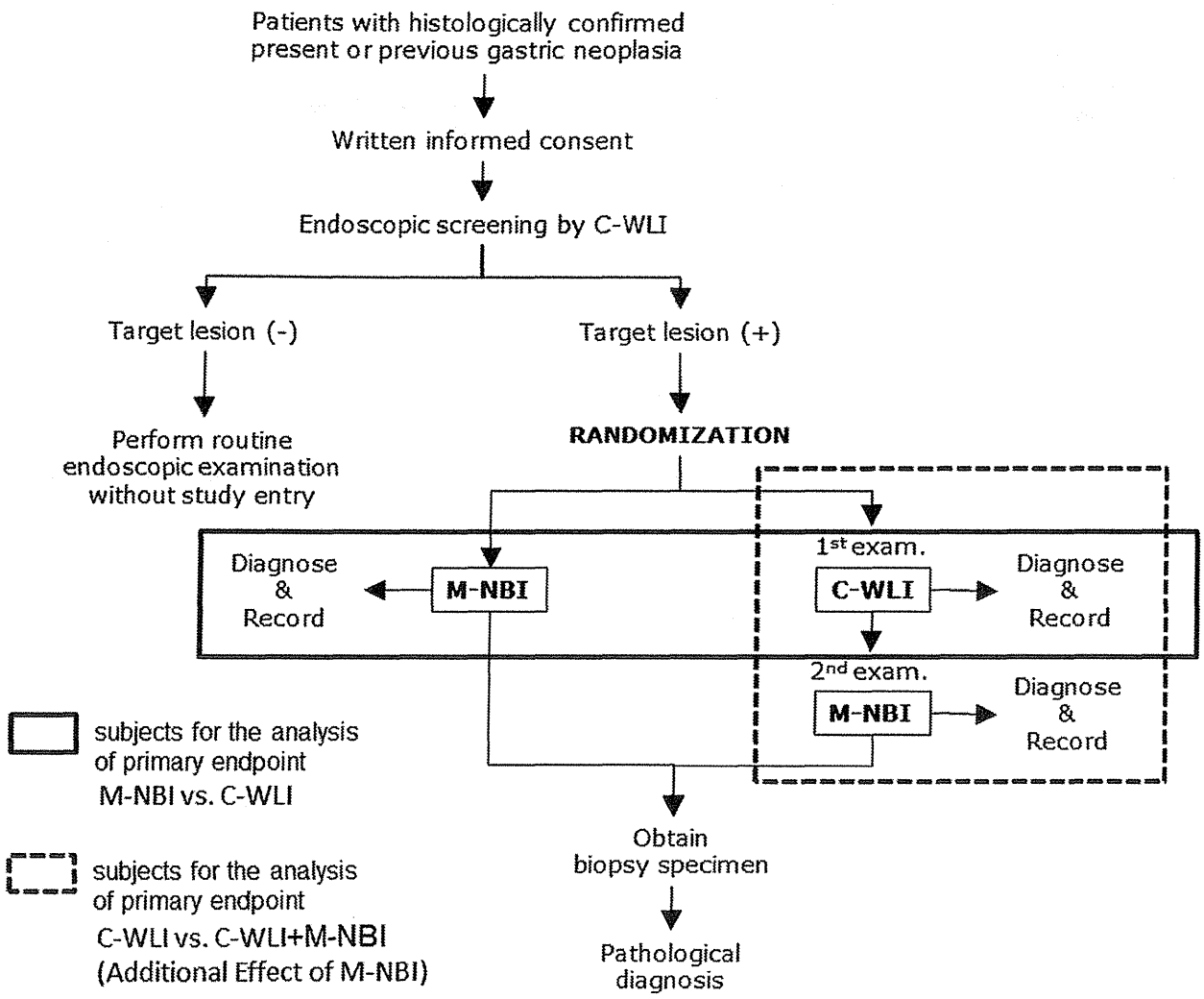
Supplementary Materials and Methods

Study Flow

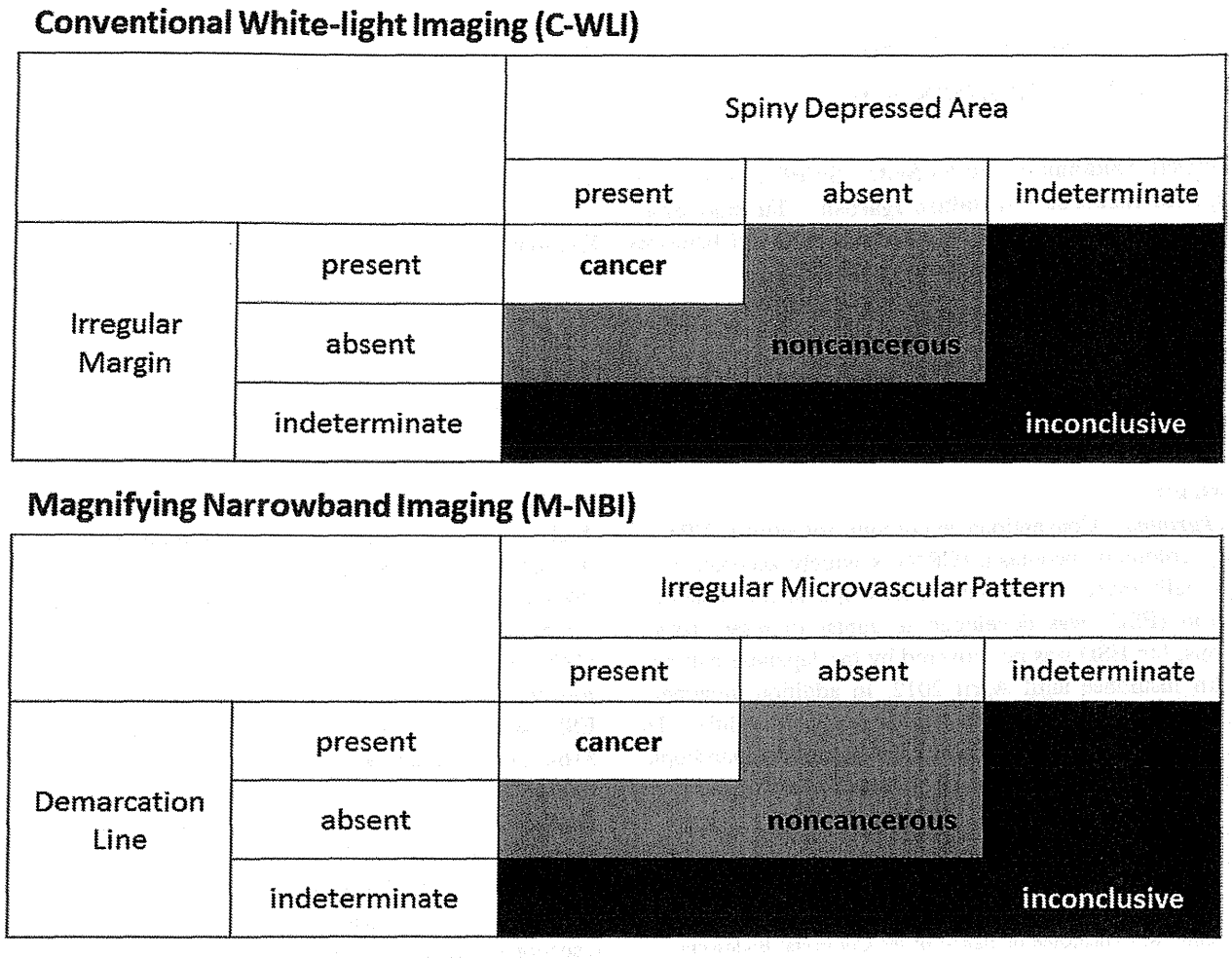
Written informed consent was obtained from all eligible patients. To detect a target lesion, endoscopic screening was performed using C-WLI. If no target lesion was detected, routine endoscopic examination was performed without study entry. When a target lesion was detected, patients were immediately assigned randomly to undergo detailed examination using C-WLI or M-NBI. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI. After all diagnoses were compiled, at least one biopsy specimen was obtained from the target lesion. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities: C-WLI and M-NBI (*solid line box*). The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI (*dashed line box*).

Diagnostic Method Based on Endoscopic Findings

Endoscopic diagnoses were made according to the combination of the endoscopic findings. In the case of C-WLI, an irregular margin and a spiny depressed area were used for the diagnostic findings. In the case of M-NBI, a demarcation line between the depressed cancerous lesion and the surrounding noncancerous area and an irregular microvascular pattern inside the lesion were used for the diagnosis. If both findings were present in each examination, the diagnosis of "cancer" was made. If either finding was indeterminate, the diagnosis was "inconclusive." If either or both findings were absent, the diagnosis was "noncancerous."



Supplementary Figure 1. Study flow.



Supplementary Figure 2. Diagnostic method based on endoscopic findings.

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Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan

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Abstract
Background Conventional endoscopic resection (CER) for early colorectal neoplasia (CRN) is widely accepted as a minimally invasive treatment. Endoscopic submucosal dissection (ESD) was developed in Japan to resect larger lesions, but ESD was not covered by the Japanese national health insurance until April 2012. In addition, treatment strategies vary considerably among medical facilities. To evaluate the current situation in Japan regarding endoscopic treatment of CRNs measuring ≥20 mm, we conducted a prospective multicenter study at 18 medium-volume and high-volume specialized facilities in cooperation with the Japan Society for Cancer of the Colon and Rectum (JSCCR).
Methods The JSCCR conducted a multicenter, observational study of all patients treated by CER and ESD of CRNs measuring ≥20 mm.
Results From October 2007 to December 2010, CERs and ESDs were performed on 1,845 CRNs (CERs 1,029; ESDs 816). Lesions diagnosed as protruded, flat, and depressed totaled 541, 1224, and 48, respectively. En bloc resection rates and mean procedure times for CER/ESD were 56.9 %/94.5 % ($P < 0.01$) and 18 ± 23 min/96 ± 69 min, respectively. The average ESD procedure time was 129 ± 83 min in the ≥40-mm group. As lesion size increased, the CER en bloc resection rate decreased significantly (trend $P < 0.01$), but the ESD en bloc resection rate remained over 93 %. Perforation and delayed bleeding rates of CER/ESD were 0.8 %/1.6 % ($P < 0.05$) and 2 %/2.2 % ($P = 0.3$), respectively.

This study was reported at the United European Gastroenterology Week held at Stockholm, Sweden, October 24, 2011.

This study was conducted on behalf of the Colorectal Endoscopic Resection Standardization Implementation Working Group, Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan. The working group that participated in this study are listed in "Appendix".

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Conclusions The en bloc resection rate for ESD was significantly higher than for CER, although complication rates were fairly low. Despite a longer procedure time, safety of colorectal ESD has improved in various facilities in Japan. However, ESD for lesions measuring ≥40 mm must be performed by experienced endoscopists due to the longer procedure time.

Keywords Endoscopic mucosal resection · Endoscopic submucosal dissection · Colorectal cancer · Colorectal neoplasia

The number of endoscopic submucosal dissections (ESDs) for colorectal neoplasms has been increasing in Japan, and the effectiveness of colorectal ESD has been reported not only in Japan but also in western countries. However, colorectal ESD still has a higher risk of perforation because the colonic wall is thinner and endoscope stabilization is more difficult than in gastric and esophageal ESD. Consequently, treatment strategies for CRN vary considerably among facilities even in Japan.

Colorectal cancer is a major cause of morbidity and mortality in the world [1]. According to the adenoma–carcinoma sequence theory, early detection and resection of colorectal neoplasm (CRN) is essential for improving cancer mortality [2, 3]. CRNs without risk of lymph node metastasis, including adenomas, are good candidates for endoscopic resection (ER) [4]. Conventional endoscopic resection (CER), including polypectomy and endoscopic mucosal resection (EMR), was developed as a minimally invasive treatment for CRN [5, 6] and is widely accepted. However, CER for lesions exceeding 20 mm in diameter sometimes results in piecemeal resection, decreasing the accuracy of pathological diagnosis and resulting in local recurrences [7–9].

ESD is an established therapeutic technique for the treatment of gastrointestinal neoplasms. Because it is typically completed as en bloc resection, this technique provides a complete specimen for precise histopathological evaluation [10–12]. Following widespread use in treatment of gastric ESDs, the number of medical facilities performing colorectal ESDs has been increasing not only in Japan, but also in western countries [13–21]. However, In the guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), CRN diagnosed as clinical mucosal cancer or superficial submucosal cancer (invasion depth of <1,000 μm), a size of ≥20 mm was initially recommended for surgical resection [22] because of the greater technical difficulty involved and the risk of perforation and resultant peritonitis [19, 23, 24].

Consequently, treatment strategies (and payment arrangements) for CRN vary considerably among facilities. To evaluate the current situation in Japan regarding endoscopic treatment of CRNs measuring ≥20 mm, we conducted a cross-sectional multicenter study in cooperation with JSCCR. We seek to convey the effectiveness and safety of both CER and ESD treatments to the world.

Materials and methods

From October 2007 to December 2010, patients were prospectively and consecutively enrolled at the 18 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group of JSCCR, and all obtained data were sent to a data center. JSCCR has proposed Japanese guidelines and this working group has a responsibility in ER section of the guideline [19, 20]. The study was conducted with the approval of each institution's ethical review board, and informed written consent was obtained from all patients for each specific colonoscopic treatment. The clinical trial number of this study is UMIN000001642.

We analyzed the following clinicopathological factors: ER method, patient age at the initial ER, sex, tumor size, location, macroscopic type, histological margin, histological grade, depth of submucosal invasion, and lymphatic/venous involvement, determined based on the Japanese classification of cancer of the colon and rectum (JCCCR) [22].

All procedures were performed by experienced colonoscopists, or under their supervision, with a standard videoendoscopic system (EVIS LUCERA system, Olympus Optical, Tokyo, Japan; or Advancia HD/Advancia, Fujifilm, Tokyo, Japan).

Inclusion criteria

ER is indicated to treat intramucosal CRNs and lesions with submucosal invasion limited to less than 1,000 μm, because the risk of lymph node metastasis is very low [4, 25]. Before treatment, only depth of invasion could be estimated endoscopically in combination with conventional endoscopic findings and, if possible, pit pattern analysis with magnifying chromoendoscopy (CF-H260AZI, CF-Q260AZI, or PCF-Q240ZI, Olympus, Tokyo, Japan; and EC590Z series, Fujifilm, Tokyo, Japan) [26–32]. We have indicated the use or nonuse of magnification.

The Colorectal ESD Standardization Implementation Working Group has attempted to standardize colorectal ESD, and guidelines have been proposed by this group

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[19, 20]. Based on extensive clinicopathological analyses, the indications for colorectal ESD in this study are the same as those recommended in the guidelines: a tumor for which the use of a snare EMR for en bloc resection is difficult, such as a laterally spreading tumor of the nongranular type (LST-NG) [7, 20, 33, 34], especially the pseudo-depressed type, a tumor with a type V_I pit pattern, a shallow infiltrating submucosal carcinoma, a large depressed tumor, and large elevated, probably malignant lesions (tall nodule-aggregating lesions such as a granular-type LST; LST-G), because these lesions have a high submucosal invasion rate and are difficult to treat even by piecemeal EMR [19, 33, 35]. Other lesions, such as intramucosal tumors accompanied by submucosal fibrosis, which are induced by a biopsy or peristalsis of the lesion, sporadic localized tumors in chronic inflammation, including ulcerative colitis, and local residual early carcinomas after EMR, also are indications for colorectal ESD [19].

Exclusion criteria for ER

Exclusion criteria included findings of submucosal cancer such as V_N pit pattern, an invasive pattern as determined by magnification chromoendoscopy [27, 29, 36], and presence of other invasive cancers and circumferential tumors that require surgical treatment because of the increased technical difficulty involved and the anticipated risk of stenosis.

Clinicopathological characteristics

The location of tumors was based on the Japanese classification of cancer of the colon and rectum [22, 37] and included the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

For macroscopic typing, we divided the lesions into five macroscopic groups according to the Paris classification and LST features as follows: (1) protruded type, which is 0-Is(p); (2) flat type, which is 0-IIa and 0-IIc with LST features; (3) mixed type, 0-Is(p) + IIa, most of which have LST character; (4) depressed type, 0-IIc or IIa + IIc in Paris classification without LST features; and (5) recurrent cases.

CER procedures

In this study, CER was defined as snare technique, EMR, or snare polypectomy; endoscopists, including gastroenterologists and digestive surgeons, chose treatment methods according to the size and endoscopic features of the CRN. In EMR, after successful fluid injection of normal saline and/or glycerol [38] and/or 0.4 % hyaluronic acid solution into the submucosal layer, the endoscopist performed resection using the snare [6]. After resection, additional snare resection or coagulation using hot biopsy forceps also was performed if there was a suspicion of small residual tumors in the resection plane.

ESD procedures

Procedures were primarily performed using one or two ESD knives, including a bipolar needle knife (Xeon Medical Co, Tokyo, Japan) [9, 15, 39], flex knife [40], hook knife (Olympus Co, Tokyo, Japan) [41], flush knife (Fujinon Co, Tokyo, Japan) [42], and insulation-tipped knife (Olympus) [10, 13]. Hemostatic forceps (Coagrasper; Olympus) and Hemostat Y (PENTAX Co., Tokyo, Japan) were used for hemostasis. Lesion margins were delineated before ESD using 0.4 % indigo-carmine spray dye. Following injection of Glycerol and/or sodium hyaluronate into the submucosal layer, a circumferential incision was made using the ESD knife [14]. Both partial circumferential incision and subsequent submucosal dissection were performed alternately using ESD knives.

Definition of ESD and CER

Some lesions were treated by a combined CER/ESD technique, using a special ESD knife and resected by snaring. We defined those cases of resection by snaring with only circumferential incision [43] as CER and cases in which the physician performed any submucosal dissection after marginal resection as ESD.

Definition of complication

Perforation during an ESD procedure was defined as immediate, and delayed perforation was defined as any perforation occurring after completion of the procedure. Immediate perforation was defined as a full-thickness defect in the colonic wall. Closure with endoscopic clips was performed or surgical treatment was pursued. Postoperative bleeding was defined as bleeding that required repeat colonoscopy for hemostasis therapy, blood transfusion, or decreased level of hemoglobin >2 g/dl.

Histological assessment

All specimens were fixed in 10 % formalin, cut into 2-mm sections, and examined microscopically for histological type, depth of invasion, and lateral and vertical resection margins. Resections were considered tumor-free when the lateral and vertical margins of a specimen were both negative for tumor cells, independent of histological features. The submucosal depth was defined as the distance determined by microscopic observation of specimens using an optical micrometer [4]. A curative resection was achieved when both the lateral and vertical margins of the specimen were free of cancer, with none of the following features: submucosal invasion deeper than 1,000 μm, lymphatic invasion, vascular involvement, or poorly differentiated

components [4]. An adenoma with an unknown lateral margin also was considered to be resected curatively when the neoplasm met all other criteria. Lesions resected in a piecemeal fashion were reconstructed faithfully on the basis of the mirror endoscopic images obtained before treatment and fixed in formalin. Histological diagnoses were based on the Japanese classification of cancer of the colon and rectum [37] and the Vienna classification [44]. The former is a standard pathological classification in Japan, and these results were converted to the latter form for standardization with global classifications.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL). Data are presented as mean ± standard deviation, medians, ranges, and percentages. For analysis of clinicopathological characteristics, we used Student's t test and χ^2 and Fisher's exact tests, as appropriate. All tests were two-tailed, and $P < 0.05$ was considered significant.

Results

Patient and lesion characteristics

A total of 1,845 CRNs that were ≥20 mm in size were examined in this study. CER was used in 1,029 cases and ESD in 816. Mean lesion sizes in CER and ESD cases were 26.4 ± 8.6 (range 20–120) mm and 39.4 ± 18.2 (range 20–174) mm, respectively. Patient characteristics and distributions of lesions are detailed in Tables 1 and 2. Tumor distribution between the two groups was different ($P < 0.01$). The frequency of cecum and sigmoid colon lesions were higher in the CER group than in the ESD group. On the other hand, lesions of the rectum were less frequent in the CER group. Submucosal cancer, including both superficial submucosal cancer and deep submucosal invasion cancer, was more common in the ESD group. Thus, the distribution of tumor characteristics differed between CER and ESD. The frequency of use of magnification colonoscopy also differed in the two groups (71.9 % in CER vs. 85.7 % in ESD, $P < 0.01$).

Table 1 Patients and tumor location

	CER	ESD	Total	*P* value
No. of lesions	1,029	816	1,845	
Age, mean ± SD (range)	65.2 ± 11.7 (20–89)	66.6 ± 9.9 (23–91)	65.8 ± 10.9	<0.01
Sex, male/female (ratio)	637/392 (1.6)	468/348 (1.3)	1105/740 (1.5)	<0.05
Use of magnification (%)	740 (71.9)	700 (85.7)	1440 (78)	<0.01
Distribution				
Cecum (%)	137 (13.3)	71 (8.7)	208 (11.3)	
Ascending colon (%)	231 (22.4)	152 (18.6)	383 (20.8)	
Transverse colon (%)	161 (15.6)	144 (17.6)	305 (16.5)	
Descending colon (%)	38 (3.7)	32 (3.9)	70 (3.8)	
Sigmoid colon (%)	300 (29.2)	121 (14.8)	421 (22.8)	
Rectum (%)	162 (15.7)	296 (36.3)	458 (24.8)	<0.001
Total (%)	1,029 (100)	816 (100)	1,845 (100)	

Table 2 Pathological results, by procedure type and lesion size

Range of lesion sizes (mm)	20–29 CER/ ESD	30–39 CER/ ESD	≥40 CER/ ESD	Total CER/ ESD	Total
Pathological results					
Adenoma	380/72	86/95	36/95	502/262	764
(%)	(84/16)	(48/52)	(27/73)	(66/34)	
Intramucosal cancer	283/95	85/109	65/194	433/398	831
(%)	(75/25)	(44/56)	(25/75)	(52/48)	
Submucosal cancer	48/52	17/51	5/47	70/150	220
(%)	(48/52)	(25/75)	(10/90)	(32/68)	
<1,000 μm	18/34	8/31	3/23	29/88	117
(%)	(35/65)	(21/79)	(12/88)	(25/75)	
≥1,000 μm	30/18	9/20	2/24	41/62	103
(%)	(63/38)	(31/69)	(8/92)	(40/60)	
Unknown	0/0	0/1	0/2	0/3	3
(%)	(0/0)	(0/100)	(0/100)	(0/100)	
Others	18/0	6/2	0/1	24/3	27
(%)	(100/0)	(75/25)	(0/100)	(89/11)	
Total	729/219	194/258	106/339	1029/816	

Differences in endoscopic treatment choice according to tumor size and macroscopic type

We divided the cases into three groups according to lesion size: 20–29, 30–39, and ≥40 mm. Associations between tumor size, macroscopic type, and treatment choice are detailed in Table 3. In the 20–29-mm group, 77 % (729/948) of the lesions were treated by CER. In contrast, as the lesion size increased, lesions were more likely to be treated by ESD. Macroscopic type also influenced treatment choice. In the 20–29-mm group, 93.8 % of the protruded lesions were treated by CER, whereas 37 % of the flat lesions were treated by ESD. In the 30–39-mm group, approximately 70 % of mixed and flat lesions were treated by ESD. In the ≥40-mm group, approximately 80 % of mixed and flat lesions were treated by ESD. All five cases of recurrence were treated by ESD, regardless of lesion size.

Treatment results: comparison of CER and ESD

The treatment results for CER and ESD are detailed in Table 4. Operation time for ESD was much longer than for CER, although the en bloc resection rate was significantly higher in the ESD group. We found that procedure time and tumor size were associated, especially in ESD cases. Compared with the CER cases, as lesion size increased, the ESD procedure time increased.

Even in the 20–29-mm group, the en bloc resection rate for CER was only 66.5 %, which is significantly lower than that of the ESD group. As lesion size increased, the en bloc resection rate for CER decreased; the en bloc resection rate in the ≥40-mm group was only 12.3 %. In contrast, the en bloc resection rate for ESD was maintained at >93 %, even in the ≥40-mm group.

Complication rate

The number of delayed bleeding cases was 18 (1.7 %) in the CER group and 18 (2.2 %) in ESD ($P = 0.3$). The number of perforation cases in these groups was 8 (0.8 %) and 16 (2 %; $P < 0.05$), respectively. The ESD perforation rate was higher than the CER rate, but most ESD and CER perforation cases were successfully treated endoscopically; only three cases (1 CER, 2 ESD) required emergency surgery.

Table 3 Macroscopic type of lesion, by procedure type and lesion size

Range of lesion sizes (mm)	20–29 CER/ESD	30–39 CER/ESD	≥40 CER/ESD	Subtotal CER/ESD	Total
Lesion number	729/219	194/258	106/339	1,029/816	1,845
(%)	(23)	(57)	(76)	(44)	
Macroscopic type					
Protruded	363/24	87/27	25/17	475/68	543
(%)	(6)	(24)	(40)	(13)	
Mixed	88/28	39/86	56/220	183/334	517
(%)	(24)	(69)	(80)	(65)	
Flat	275/164	68/144	25/101	368/409	777
(%)	(37)	(68)	(80)	(53)	
Depressed	3/0	–/–	–/–	3/0	3
(%)	(0)			(0)	
Recurrence	0/3	0/1	0/1	0/5	5
(%)	(100)	(100)	(100)	(100)	

Table 4 Treatment results by procedure type and lesion size

Range of lesion sizes (mm)	CER			ESD			CER	ESD	Total
	20–29	30–39	≥40	20–29	30–39	≥40	Sub total		
Lesion number	729	194	106	219	258	339	1029	816	1,845
Procedure time (min, mean ± SD)	13 ± 13	43 ± 23	42 ± 46	66 ± 45	79 ± 42	129 ± 83	18 ± 23	96 ± 69	53 ± 63
Complication									
Delayed bleeding	12	4	2	3	7	8	18	18	36
(%)	(1.6)	(2.1)	(1.9)	(1.4)	(2.7)	(2.4)	(1.7)	(2.2)	(2)
Perforation	5	3	0	4	7	5	8	16	24
(%)	(0.7)	(1.5)	(0)	(1.8)	(2.7)	(1.5)	(0.8)	(2.0)	(1.3)
Emergency surgical operation	–	1	–	–	–	2	1	2	3
(%)		(0.5)				(0.6)	(0.1)	(0.2)	(0.2)
En bloc resection rate	485	88	13	206	248	317	586	771	1,357
(%)	(66.5)	(45.4)	(12.3)	(94.1)	(96.1)	(93.5)	(56.9)	(94.5)	(73.6)
Non-curative resection	33	9	2	23	24	31	44	77	122
(%)	(4.5)	(4.6)	(1.9)	(10.5)	(9.3)	(9.1)	(4.3)	(9.4)	(6.6)
Additional surgery	29	9	3	17	22	23	41	62	103
(%)	(4.0)	(4.6)	(2.8)	(7.8)	(8.5)	(6.8)	(4.0)	(7.6)	(5.6)

Pathological results and additional surgery

Histopathological assessment led to the diagnosis of 44 (4.3 %) CER cases and 77 (9.4 %) ESD cases as noncurative resections. Furthermore, 41 CER patients (4 %) and 62 ESD patients (7.6 %) underwent additional surgery.

Discussion

Key findings

In this prospective, multicenter study in Japan, we surveyed the current status of endoscopic treatment for relatively large CRNs (≥20 mm). As size increased, Japanese endoscopists were more likely to select ESD, especially for the treatment of flat- and mixed-type CRNs. As a result, the en bloc resection rate for ESD was significantly higher than for CER, although complication rates were very low in both groups. Despite longer procedure time, ESD is becoming safe and is considered a standard procedure in Japan for the treatment of large, superficial CRNs.

Before this study, Saito et al. reported the results of an initial, prospective, multicenter cohort study of ESD [18]. They analyzed the results of all colorectal ESD cases from the time of introduction of the procedure, performed at ten specialized facilities ($n = 1{,}111$). By contrast, the present study was planned after approval of ESD with advanced medical care systems, with a strict treatment indication; therefore, both highly advanced medical facilities and general facilities participated, enrolling the cases in a limited research registration period. In our study, the overall perforation rate was only 1.3 % ($n = 24$), and the rate of emergency surgery was extremely low (0.3 %, $n = 3$) compared with the previous study [18], suggesting improved safety of colorectal ESD in various facilities.

Japanese guidelines for ER for colorectal cancer and ESD indication

According to the guidelines of the JSCCR, CRNs diagnosed as clinical mucosal cancer or superficial submucosal cancer (<1,000 μm) are indicated for ER. However, 20 mm is the largest size of a tumor that can be easily resected en bloc by polypectomy or snare EMR. If the preoperative diagnosis is adenoma or carcinoma in adenoma, piecemeal resection can be performed. It should be noted, however, that piecemeal resection is associated with a high incomplete resection rate and a high local recurrence rate. Therefore, such lesions were a relative indication for surgical resection [22]. After introduction of the ESD technique for CRN treatment, it became possible to perform en bloc resections for lesions measuring > 20 mm. Our study shows that Japanese endoscopists selected ESD rather than CER, as tumor size increased, especially for mixed- and flat-type CRNs. Endoscopists make this choice, because they know the pathological character of large CRNs, which incur the risk of noncurative resection contrary to pre-ESD expectations and because they know the indication of colorectal ESD.

Treatment selection and outcome as related to tumor size

In this study, we performed endoscopic treatment according to the guidelines of JSCCR and indication of ESD. As size increased, selection of ESD became more common, perhaps because Japanese endoscopists understand the difficulty of performing en bloc resection for larger CRNs by CER.

However, ESD has a big limitation. As tumor size increased, procedure time increased, compared with CER. Our data showed that the average procedure time for colorectal ESD for lesions measuring ≥40 mm was more than 2 h. It should be noted that such lesions were treated by surgery before ESD became widespread; therefore, it may be more informative to compare ESD procedure time with that of surgical cases instead of EMR cases. ESD for CRNs measuring ≥40 mm is thought to be a difficult and time-consuming treatment, so we recommend that ESD for lesions <40 mm be considered a general procedure but that lesions measuring ≥40 mm should be treated in medical facilities with more experienced staff.

Treatment selection as related to tumor macroscopic type

In the 20–29-mm group, protruded-type CRNs were likely to be treated by CER. However, the proportion of CER for mixed and flat lesions was less than that for protruded type. As the lesion size increased, mixed and flat lesions were more likely to be treated by ESD. As the proportion of the flat component in the CRN groups increased, the proportion of ESD increased.

En bloc resection rate and complication rate

We found that the en bloc resection rate for ESD was significantly higher than for CER, although complication rates in both groups were quite low in these representative Japanese facilities. The ESD technique enabled complete resection even for the large-sized tumors. This may indicate that recent improvements in endoscopic devices and instruments have reduced complications (such as perforation) in ESD. Most perforation cases were managed