Center for Cancer and Cardiovascular Diseases, Osaka; Masafumi Ikeda, National Cancer Center Hospital East, Kashiwa; Shinichi Ohkawa, Kanagawa Cancer Center, Yokohama; Hiroaki Yanagimoto, Kansai Medical University, Hirakata; Narikazu Boku and Akira Fukutomi, Shizuoka Cancer Center, Sunto-gun; Kazuya Sugimori, Yokohama City University Medical Center, Yokohama; Hideo Baba, Kumamoto University, Kumamoto; Kenji Yamao, Aichi Cancer Center Hospital, Nagoya; Tomotaka Shimamura, Saitama Cancer Center, Saitama; Masayuki Sho, Nara Medical University, Kashihara; Masayuki Kitano, Kinki University, Osakasayama; Kazuhiro Mizumoto and Masao Tanaka, Kyushu University; Akihiro Funakoshi, Fukuoka Sanno Hospital, Fukuoka; Taketo Yamaguchi, Chiba Cancer Center, Chiba; Shinichi Egawa, Tohoku University, Sendai, Japan; Ann-Lii Cheng, National Taiwan University Hospital, Taipei; and Jen-Shi Chen, Linkou Chang Gung Memorial Hospital and Chang Gung University, Tao-Yuan, Taiwan.

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Appendix

Members of the Gemcitabine and S-1 Trial Group

Steering committee. T. Okusaka, S. Egawa, J. Furuse, T. Yamaguchi, H. Ueno, T. Hatori, S. Ohkawa, N. Boku, K. Yamao, T. Ioka, A. Funakoshi, K. Mizumoto, M. Tanaka.

Independent data and safety monitoring committee. A. Nakao, I. Hyodo, S. Morita; Medical Advisor: A. Sato; Statistical Analyst: Y. Ohashi.

Principal investigators. National Cancer Center Hospital: T. Okusaka; Osaka Medical Center for Cancer and Cardiovascular Diseases: T. Ioka; National Cancer Center Hospital East: M. Ikeda, K. Nakachi; Kanagawa Cancer Center: S. Ohkawa; Kansai Medical University: H. Yanagimoto; Yokohama City University Medical Center: K. Sugimori; Shizuoka Cancer Center: A. Fukutomi; Kumamoto University: H. Baba; Saitama Cancer Center: T. Shimamura, H. Hara; Aichi Cancer Center Hospital: K. Yamao; Nara Medical University: M. Sho; Kinki University, Department of Gastroenterology and Hepatology: M. Kitano; Sapporo-Kosei General Hospital: H. Miyagawa; Kyushu University, First Department of Surgery: K. Mizumoto; Jichi Medical University Hospital: H. Fujii; National Hospital Organization Osaka National Hospital: S. Nakamori; Kinki University, Department of Medical Oncology: T. Satoh, S. Ueda; Tochigi Cancer Center: Y. Hamamoto, E. Warita; Kyushu University, Department of Hepatology and Pancreatology: T. Ito; Teine-Keijinkai Hospital: H. Maguchi; Kyorin University: J. Furuse; Kyoto University Hospital: S. Matsumoto; Saitama Medical University International Medical Center: Y. Sasaki; Hokkaido University Hospital: Y. Komatsu; Tokyo Women's Medical University: M. Yamamoto; Saku Central Hospital: T. Hisa; Osaka City Juso Hospital: T. Yamazaki, O. Kurai; Kochi Health Sciences Center: A. Tsuji; National Kyushu Cancer Center: A. Funakoshi, M. Furukawa; Niigata Cancer Center Hospital: Y. Tsuchiya; Chiba Cancer Center: T. Yamaguchi; Osaka Red Cross Hospital: Y. Okabe; Tohoku University, Division of Gastroenterology: K. Sato; Tohoku University, Division of Gastroenterological Surgery: F. Motoi; Matsusaka Chuo General Hospital: H. Naota; Kyoto Second Red Cross Hospital: K. Yasuda; Hyogo College of Medicine: J. Fujimoto; Toyama University Hospital: A. Hosokawa; Fukuoka University Chikushi Hospital: T. Ueki; Hokkaido Social Insurance Hospital: K. Furuya; Kameda Medical Center: Y. Oyama; Nagoya Medical Center: H. Iwase; Shinshu University Hospital: N. Arakura; Yodogawa Christian Hospital: A. Watanabe; Osaka Medical College Hospital: H. Takiuchi; Kitano Hospital: S. Yazumi; Sakai Municipal Hospital: H. Ohzato; Kawasaki Medical School Hospital: K. Yoshida; Onomichi General Hospital: K. Hanada; Kagawa University Hospital: F. Goda; Shikoku Cancer Center: H. Iguchi; Keio University Hospital: T. Hibi; Osaka City General Hospital: H. Nebiki; Chiba University Hospital: T. Ishihara; Nippon Medical School Hospital: E. Uchida; Tokai University Hospital: T. Imaizumi; Nagoya City University Hospital: H. Ohara; Aichi Cancer Center Aichi Hospital: H. Kojima; Osaka City University Hospital: N. Yamada; Wakayama Medical University Hospital: H. Yamaue; Tokyo Medical University Hospital: F. Moriyasu; Showa University Northern Yokohama Hospital: K. Shimada; Shizuoka General Hospital: K. Matsumura; Hyogo Cancer Center: H. Nishisaki; Kanazawa University Hospital: S. Yano; Hiroshima Prefectural Hospital: K. Shinozaki; University of Miyazaki Hospital: H. Inatsu; Linkou Chang Gung Memorial Hospital and Chang Gung University: Jen-Shi Chen; National Taiwan University Hospital: Chiun Hsu; Taipei Veterans General Hospital: Jin-Hwang Liu; Chang Gung Medical Foundation, Kaohsiung: Kun-Ming Rau; Chung-Ho Memorial Hospital, Kaohsiung Medical University: Sheng-Fung Lin; China Medical University Hospital: Chang-Fang Chiu; Mackay Memorial Hospital, Taipei: Ruey-Kuen Hsieh; Changhua Christian Hospital: Cheng-Shyong Chang; Chi Mei Medical Center, Yong Kang: Wei-Shou Huang; Chi Mei Medical Center, Liou Ying: Wen-Tsun Huang; National Cheng Kung University Hospital: Wu-Chou Su.

Details of Adequate Organ Functions in Enrollment Criteria and Main Exclusion Criteria

Adequate organ functions were defined as follows: leukocyte count $\geq$ 3,500/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, hemoglobin level $\geq$ 9.0 g/dL, serum creatinine level $\leq$ 1.2 mg/dL, creatinine clearance $\geq$ 50 mL/min, serum AST and ALT levels $\leq$ 150 U/L, and serum total bilirubin level $\leq$ 2.0 mg/dL or $\leq$ 3.0 mg/dL if biliary drainage was performed.

Main exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; and serious complications such as heart failure, peptic ulcer bleeding, or poorly controlled diabetes. Pancreatic cancers other than adenocarcinoma or adenosquamous carcinoma (eg, anaplastic carcinoma) were excluded from the study.

Dosage Adjustment Guideline for Toxicities

All treatment cycles were repeated until disease progression, unacceptable toxicity, or patient refusal. If patients had a leukocyte count of less than 2,000/μL, a neutrophil count of less than 1,000/μL, a platelet count of less than $70 \times 10^3/\mu$L, or grade 3 or worse rash, the administration of anticancer agents was postponed. S-1 was temporarily halted both in S-1 and in GS groups if patients had a creatinine level of 1.5 mg/dL or higher or grade 2 or worse diarrhea or stomatitis. Treatment was discontinued if these events did not resolve within 4 weeks after treatment suspension. In patients who experienced febrile neutropenia, grade 4 leukopenia, neutropenia, or thrombocytopenia or grade 3 or worse rash, the dose of gemcitabine was reduced by 200 mg/m^2. In patients with febrile neutropenia; grade 4

leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

Gemcitabine in Patients With Intraductal Papillary Mucinous Neoplasm With an Associated Invasive Carcinoma of the Pancreas

Taiga Otsuka, MD, Chigusa Morizane, MD,* Satoshi Nara, MD,† Hideki Ueno, MD,* Shunsuke Kondo, MD,* Kazuaki Shimada, MD,† Tomoo Kosuge, MD,† Masafumi Ikeda, MD,‡ Nobuyoshi Hiraoka, MD,§ and Takuji Okusaka, MD**

Objectives: The standard chemotherapy for invasive ductal carcinoma of the pancreas (IDC) is gemcitabine; however, the efficacy of gemcitabine in invasive intraductal papillary mucinous neoplasm with an associated invasive carcinoma of the pancreas (IPMN-IC) is still unknown.

Methods: Because it is difficult to distinguish between IPMN-IC and IDC based only on radiological findings in advanced unresectable cases, recurrent cases after surgical resection were analyzed to identify the efficacy of gemcitabine monotherapy for IPMN-IC.

Results: Between 1992 and 2010, 128 patients with IPMN-IC and 548 patients with IDC underwent pancreatic resection at the National Cancer Center Hospital. Twelve patients with IPMN-IC and 73 patients with IDC had recurred after surgery and subsequently underwent gemcitabine at the standard dosage. The disease-control rates were comparable between the IPMN-IC and IDC patients (58.3% vs 59.4%). The median progression-free survival was 2.8 and 4.1 months in the IPMN-IC and IDC patients, respectively ($P = 0.46$). Also, no statistically significant difference in the median survival times was observed between the 2 groups (9.3 vs 8.8 months, respectively; $P = 0.09$).

Conclusions: Among patients who had IPMN-IC and IDC with recurrent disease after resection, there was no significant difference in treatment outcomes after gemcitabine.

Key Words: chemotherapy, pancreatic cancer, IPMN, invasive ductal carcinoma of the pancreas, intraductal papillary mucinous carcinoma, IPMC

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Intraductal papillary mucinous neoplasm of the pancreas (IPMN) was first reported in Japan. The patients were described as having a dilated pancreatic duct with mucus hypersecretion, and a dilated orifice of ampulla.[1] The true incidence of IPMNs is unknown because they are usually asymptomatic and small; however, IPMNs have a pronounced malignant potential. The 10-year actuarial risk of developing invasive cancer was reported as being 29% in patients with highly probable or histologically proven IPMNs.[2] Moreover, there is a report that around 40% of patients have invasive malignancy at the time of diagnosis.[3] IPMNs with a component of invasive carcinoma led to the designation "IPMN with an associated invasive carcinoma (IPMN-IC)."[4] Although there are several reports of surgically resected IPMN cases, clinical outcomes and sensitivity to chemotherapy in patients with unresectable or recurrent IPMN-IC are still unknown. The aim of the present study was to identify the efficacy of chemotherapy for IPMN-IC. The chemotherapeutic regimen was limited to gemcitabine monotherapy, which is one of the standard regimens for invasive ductal carcinoma of the pancreas (IDC), and the treatment outcome was compared between IPMN-IC and IDC as reference. Because it is difficult to distinguish between IPMN-IC and IDC based only on radiological findings in advanced unresectable cases, we limited the target population of our study to recurrent cases of IPMN-IC and IDC patients whose definitive diagnosis was confirmed by pathological findings of the resected specimen.

MATERIALS AND METHODS

Patients

We reviewed the records of patients treated at the National Cancer Center Hospital between August 1992 and March 2010. One hundred twenty-eight consecutive patients with IPMN and 548 consecutive patients with IDC of the pancreas underwent pancreatic resection. In our hospital, patients were followed up for at least 5 years. The clinical data for patients who experienced a recurrence before July 2010 were then retrieved, and the treatments after recurrence were surveyed. Recurrences after surgery were diagnosed using computed tomography or magnetic resonance imaging. All patients provided written informed consent for chemotherapy before the initiation of treatment. The institutional review board of our center approved this retrospective study.

Classifications of IPMN

All the surgical specimens of the target population had been examined pathologically and a diagnosis of IPMN or IDC had been confirmed. The classification of IPMN was based on the World Health Organization classification[4] and International Consensus Guideline.[5] IPMNs were classified into 3 macroscopic types, namely, main duct type, branch duct type, and mixed type.[5] We diagnosed the macroscopic types by macroscopic examinations of resected samples. Furthermore, IPMNs were classified into the following 4 subtypes using histopathological and immunohistochemical findings: gastric type, intestinal type, pancreatobiliary type, and oncocytic type. The morphological types were diagnosed according to criteria described previously that were based on the predominant architectural and cell differentiation pattern.[4,6–8] We performed immunohistochemistry using antibodies against mucin 1 (MUC1) (Ma552), mucin 2 (MUC2) (Ccp58), mucin 5AC (MUC5AC) (CLH2), mucin 6 (MUC6) (CLH5), and CDX-2 (AMT28). These were all

From the *Hepatobiliary and Pancreatic Oncology Division; †Hepatobiliary and Pancreatic Surgery Division, National Cancer Center Hospital, Chuo-ku, Tokyo; ‡Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital East, Kashiwa; and §Pathology Division, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan.

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Reprints: Chigusa Morizane, MD, Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: cmorizan@ncc.go.jp).

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purchased from Novocastra Laboratories Ltd (Newcastle-upon-Tyne, UK). IPMNs were further categorized into 2 types with regard to invasion, namely, noninvasive IPMN (IPMN with low-grade, intermediate-grade, or high-grade dysplasia) or IPMN-IC.[4] Noninvasive IPMN was restricted to the pancreatic duct wall. IPMN-IC had a definite invasion into the pancreatic parenchyma. With respect to the staging of the invasion, the T1 category in the American Joint Committee on Cancer/TNM (invasive carcinoma of <2 cm) was divided into the following 3 subcategories: T1a, T1b, and T1c.[5,9] The T1a subcategory was formerly referred to as "minimally invasive" and was defined as invasive carcinoma measuring less than or equal to 5 mm.[5,10–14]

Statistical Analysis

Distributions of variables between 2 groups were compared using the χ^2 test for categorical data and the Mann-Whitney *U* test for continuous data. Objective response rate was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.0.[15] Survival times were estimated using the Kaplan-Meier method, and compared using the log-rank test. Recurrence-free survival was defined as the interval between surgical resection and recurrence. Progression-free survival was calculated from the date of the initiation of gemcitabine monotherapy until documented disease progression, or death due to any cause (whichever occurred first). Overall survival was defined as the time from initiation of gemcitabine monotherapy to the date of death or the last follow-up. Differences with values of $P < 0.05$ were considered as being statistically significant.

TABLE 1. Demographic and Tumor Characteristics

	IPMN-IC	IDC	
	n = 12	n = 73	*P*
At the time of pancreatic resection			
Age, median (range), y	70 (53–79)	63 (39–80)	0.04
Sex, n (%)			
Male	6 (50)	45 (62)	0.45
Female	6 (50)	28 (38)	
AJCC stage, n (%)			
I	3 (25)	0	0.01
IIa	2 (17)	9 (12)	
IIb	5 (41)	57(78)	
III/IV	2 (17)	7 (10)	
CEA median (range), ng/mL	9.6 (1.2–434.0)	5.9 (0.7–213.0)	0.48
CA19-9, median (range), U/mL	48 (2–6510)	596 (1–25270)	0.08
At the time of recurrence			
Age, median (range), y	73 (54–80)	64 (40–81)	0.03
Recurrent free survival, mo	14.4	7.5	0.04
Recurrent site, n (%)			
Liver	6 (50)	20 (40)	0.93
Local	2 (17)	21 (29)	
Lung	1 (8)	11 (15)	
Lymph	3 (25)	9 (12)	
Others	0	11 (15)	

AJCC indicates American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

TABLE 2. Summary of Efficacy Measures

	IPMN-IC	IDC	
	n = 12	n = 73	*P*
Level of response, n			
Complete	0	0	
Partial	0	2	
Stable disease	7	42	
Response rate, %	0	2.7	0.56
Disease-control rate, %	58.3	60.3	0.90
Progression-free survival, median, mo	2.8	4.1	0.46
Overall survival, median, mo	9.3	8.8	0.09

Statistical analysis was performed using R version 2.12.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We selected 12 patients with IPMN-IC and 73 patients with IDC who received gemcitabine monotherapy after recurrence and were followed up in our center. The clinical findings involving recurrent IPMN and IDC patients are shown in Table 1. All of the recurrent IPMN patients were classified using pathological findings from resected specimens as having IPMN-IC, including 3 patients with T1a carcinoma. The median recurrence-free survival time after surgery for the IPMN-IC patients was longer than that for the IDC patients (14.4 vs 7.5 months, respectively; $P = 0.04$). Patients with IPMN-IC were diagnosed at an earlier stage at the time of resection.

In all patients, gemcitabine monotherapy was initiated at the standard dosage after recurrence. The antitumor effects and prognosis are summarized in Table 2. The disease-control rates were comparable between the IPMN-IC and IDC patients (58.3% vs 60.3%, respectively). The median progression-free survival was 2.8 and 4.1 months in the IPMN-IC and IDC patients, respectively ($P = 0.46$). At the time of disease progression, second-line chemotherapy was administered in 58% of the IPMN-IC patients and in 33% of the IDC patients ($P = 0.09$). No statistically significant difference in overall survival times was observed between the IPMN-IC and IDC groups (median, 9.3 vs 8.8 months, respectively; $P = 0.09$) (Fig. 1).

Among the IPMN-IC patients, the macroscopic classifications of the IPMN at the time of resection were main duct

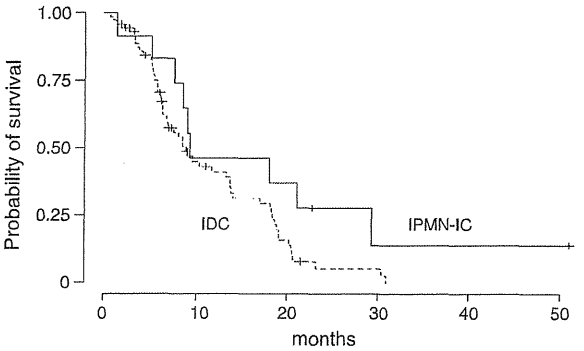

FIGURE 1. Kaplan-Meier analysis of overall survival after initiation of gemcitabine. The median survival time was 9.3 and 8.8 months in the IPMN-IC and IDC patients, respectively ($P = 0.09$).

TABLE 3. Classifications of IPMN at the Time of Resection

	Macroscopic Type		
	Main Duct	Branch Duct	Mixed
	n = 6	n = 2	n = 4
Histopathological subtype, n (%)			
Pancreatobiliary	5 (83)	1 (50)	2 (50)
Intestinal	1 (17)	1 (50)	1 (25)
Oncocytic	0	0	1 (25)
Invasion, n (%)			
T1a (minimally)	1 (17)	1 (50)	1 (25)
Colloid	1 (17)	0	0
Tubular	4 (66)	1 (50)	3 (75)

type in 6 patients, mixed type in 4, and branch duct type in 2. Regarding the subtypes of the IPMN, 8 were the pancreatobiliary type, 3 were the intestinal type, and 1 was the oncocytic type (Table 3). In comparing the main duct and mixed type with the branch duct type, the median survival times from initiation of gemcitabine were 18.0 and 8.1 months, respectively ($P = 0.08$). Between the pancreatobiliary type and others, the median survival times from initiation of gemcitabine were 21.1 and 8.5 months, respectively ($P = 0.09$). Survival times after initiation of gemcitabine in 3 patients with T1a carcinoma were 1.5, 7.6, and 18.0 months. Survival times after pancreatic resection in these patients were 15.3, 61.7, and 37.0 months, respectively. The subtype of all of the patients with minimally invasive carcinoma was the intestinal type.

DISCUSSION

Since the first report was described in Japan,[1] IPMNs of the pancreas have been discovered with increasing frequency because of the improvement in diagnostic imaging techniques. IPMNs express a latent or overt malignant potential. Although resected IPMN-IC has a favorable prognosis as compared with IDC,[16–21] the prognosis for advanced IPMN-IC is reported to be as poor as advanced IDC.[18] In clinical practice, one of the standard regimens of first-line chemotherapy for advanced pancreatic cancer remains gemcitabine monotherapy. To our knowledge, there have been no reports on the efficacy of chemotherapy for advanced or recurrent IPMN-IC. Our study evaluated the efficacy of gemcitabine for IPMN-IC, which is a standard regimen for IDC, and showed that IPMN-IC and IDC exhibited no significant difference in treatment outcomes from the start of gemcitabine monotherapy for the recurrent disease.

In advanced pancreatic cancer, the proportion of IPMN-IC has been reported to be less than 5%.[22–24] The carcinogenic pathway involved in the conversion of noninvasive IPMN to IPMN-IC is often compared with that involved in the conversion of pancreatic intraepithelial neoplasia (PanIN) to the invasive ductal carcinoma sequence.[25] Some disparities between IPMN and PanIN exist. In contrast to PanIN and ductal adenocarcinoma, *DPC4* loss or mutation in *p16* is uncommon in IPMNs.[26–32] Thus, the carcinogenesis of IPMNs may differ from those of PanINs and conventional ductal adenocarcinomas. Our study did not show a significant difference in clinical behavior such as chemosensitivities or outcomes between IPMN-IC and IDC. Because the results of our study were based on a small number of patients, further studies are needed to evaluate whether the difference in carcinogenesis may affect treatment effects.

The main duct type IPMNs including the mixed type show a more aggressive clinical course than the branch duct type IPMNs. The prevalence of invasive carcinoma at diagnosis has been reported to be higher in patients with main duct type than in patients with branch duct type.[5] Moreover, patients with main duct type and mixed type have a poorer prognosis than patients with branch type in surgical resected cases.[33] IPMN-IC is typically divided into of the following 2 histologic types: tubular type (conventional ductal adenocarcinoma) and colloid type (mucinous adenocarcinoma).[8] With respect to the histopathological classification of IPMNs, invasive cancer arising from the pancreatobiliary type is usually the tubular type carcinoma that is morphologically indistinguishable from IDC and has a poorer prognosis than other types.[33] The subgroup analysis of IPMN-IC in our study showed that the patients with the main duct type or the pancreatobiliary type had favorable prognoses, albeit that it was not statistically significant. Although the reason why these results seemed paradoxical when compared with previous reports could not be adequately explained, it may be partially due to an insufficient sample size. Additionally, the pancreatobiliary type is reported to be a less common disease entity than other types.[8,33] However, the most common subtype of IPMNs in our study was the pancreatobiliary type. This discrepancy may be due to the bias of patient selection in our study because we limited the target population to patients with recurrent status; this in itself indicated the clinically aggressive nature of the cancer. Regarding the type of invasion, the recurrence rate and prognosis for T1a carcinoma (formerly "minimally invasive carcinoma") is better than that for invasive carcinoma as reported previously.[10,11,14] However, our study showed that once recurrence had occurred, prognosis was poor even for T1a carcinoma. One patient with T1a carcinoma had an extremely aggressive clinical course with a survival time after initiation of gemcitabine that was only 1.5 months, and a survival time after pancreatic resection was 15.3 months.

In conclusion, there was no significant difference in the treatment outcomes after gemcitabine monotherapy between IPMN-IC and IDC in patients with recurrent disease after surgical resection. When we take into account the lack of other promising treatment regimens, our results do not deny the appropriateness of gemcitabine use in clinical practice of IPMN-IC. The number of patients in this study was limited and further studies are needed to define the role of gemcitabine in this disease.

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DISEASES OF THE ESOPHAGUS

Case report

Multimodal endoscopic treatment for delayed severe esophageal stricture caused by incomplete stent removal

T. Setoyma,[1] S. Miyamoto,[1] T. Horimatsu,[1] S. Morita,[1] Y. Ezoe,[2] M. Muto,[1] G. Watanabe,[3] E. Tanaka,[3] T. Chiba[1]

Departments of [1]Gastroenterology and Hepatology and [2]Multidisciplinary Cancer Treatment, and [3]Division of Gastrointestinal Surgery, Department of Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

SUMMARY. **The usefulness of a covered self-expandable metallic stent for benign esophageal stricture and perforation was well established. In case of benign disease, early stent removal was recommended within 6–8 weeks after placement. A case with severe esophageal stricture caused by incomplete stent removal 7 years after stent placement for spontaneous esophageal rupture was reported. Residual stent fragments could be removed by step-by-step multimodal endoscopic treatment, producing satisfactory luminal diameter of the esophagus. In particular, stent trimming with argon plasma coagulation was safe and effective strategy. The endoscopic stent removal is minimally invasive and should be attempted before surgical intervention; however, it is most important to ensure early stent removal before tissue ingrowth or overgrowth can develop.**

INTRODUCTION

Although rare, spontaneous rupture of the esophagus, or Boerhaave's syndrome, is a potentially fatal condition. Surgical treatment has long been considered the 'gold standard' response. However, if the diagnosis is delayed, a surgical procedure can cause morbidity and mortality.[1,2] Over the past few years, various invasive endoscopic treatment options have emerged. It has recently been reported that the temporary placement of a covered self-expandable metallic stent is an effective treatment for sealing a benign esophageal rupture and perforation.[3–9] However, stent-related complications, such as stent migration and tissue ingrowth or overgrowth, have been reported.[4,5,8–10] Reactive benign tissue ingrowth or overgrowth can cause stricture, especially when stents remain in place for long periods.[4,8–10] Endoscopic stent removal in cases of severe stent embedding may cause esophageal perforation,[4,9,11] and the embedded stent must be removed by force after it is cut into pieces during a surgical intervention. Incomplete stent removal can lead to further esophageal stricture. We report a patient with severe esophageal stricture induced by residual stent fragments after surgical stent removal, and its multimodal endoscopic treatment.

CASE REPORT

A 56-year-old man suffered spontaneous rupture of his esophagus. We placed a covered self-expandable metallic stent over the fistula just above the esophagogastric junction. After this treatment, the patient's condition improved dramatically. We attempted to remove the stent endoscopically 3 months after its placement, but it was too firmly fixed to the esophageal wall to allow it to be extracted through the patient's mouth (Fig. 1). The stent was removed surgically, piece by piece, via the gastric wall after it had been cut into pieces with scissors, but some stent fragments remained in the esophagus (Fig. 2). Our colleagues have reported the clinical course of the acute stages of this case.[12] During 7 years of observation since the laparotomy, the patient showed worsening dysphagia because granulation tissue developed around the residual stent fragments (Fig. 3). The protruding granulation tissue was removed using a

Address correspondence to: Dr Shin'ichi Miyamoto, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Shogoin-kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
Email: shmiyamo@kuhp.kyoto-u.ac.jp

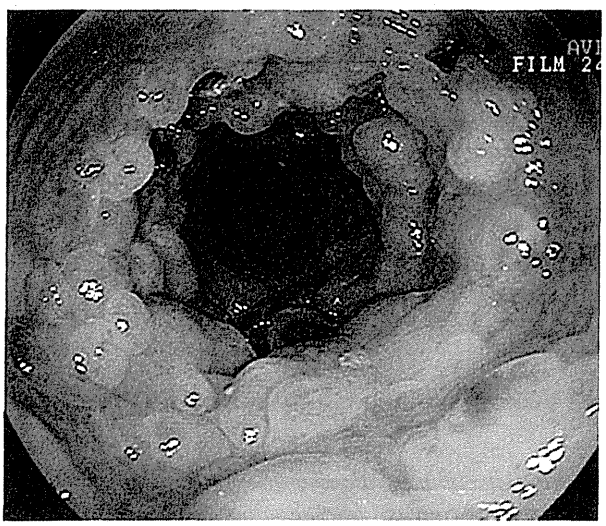

Fig. 1 The stent was firmly fixed to the esophageal wall because of tissue ingrowth.

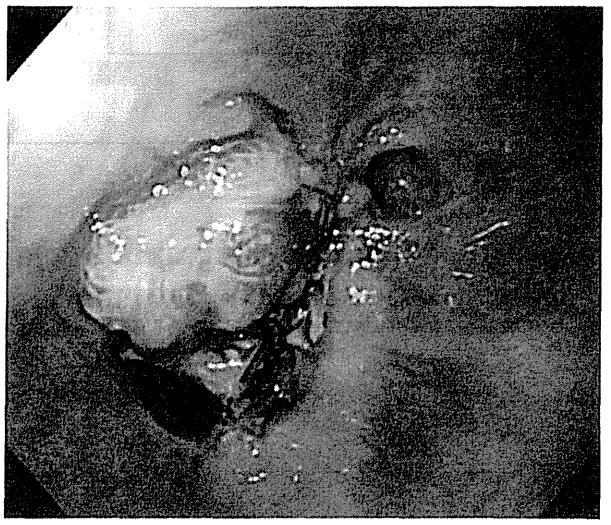

Fig. 3 Step 1: Esophageal lumen was occupied by protruding granulation tissue around the residual stent fragments. Large polypoid lesion was removed using a snare.

snare (step 1), but the patient's symptoms remained unchanged. One and a half years later after step 1, an exposed stent fragment was trimmed using argon plasma coagulation (APC) (Figs 4,5; step 2). The power setting was 30–40 W, and the argon gas flow was set at a rate of 1.0–1.2 L/min using an argon plasma electrosurgical generator (VIO 300D/APC2, Erbe, Tübingen, Germany). Three days later after step 2, several stent fragments were removed with grasping forceps via the patient's mouth after balloon dilatation of the esophagus (Fig. 6; step 3). After almost all the stent fragments had been removed, 5 months later after step 3, the residual granulation tissue formed 'bridges' across the esophageal lumen (Fig. 7), which were severed with a diathermic knife and a snare, producing a satisfactory luminal diameter of the esophagus (Fig. 8; step 4). The patient is currently asymptomatic 3 years later after step 4 without further treatment.

DISCUSSION

The rate of successful clinical sealing after temporary endoscopic stent placement for a benign esophageal rupture and perforation has been reported to be about 80%, with low morbidity and mortality.[6–9] The major reported complications of endoscopic stent placement are stent migration and tissue ingrowth or overgrowth.[4,5,8–10,13] Fibrosis and the proliferation of granulation tissue around the stent result from the

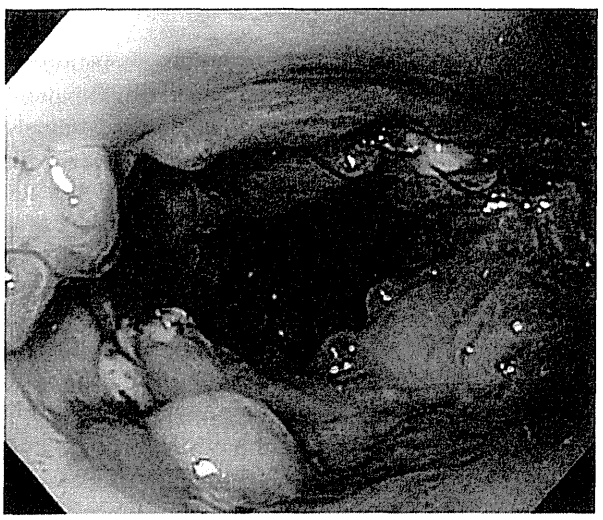

Fig. 2 Some stent fragments remained in the esophageal wall after removing the stent surgically, piece by piece via the gastric wall.

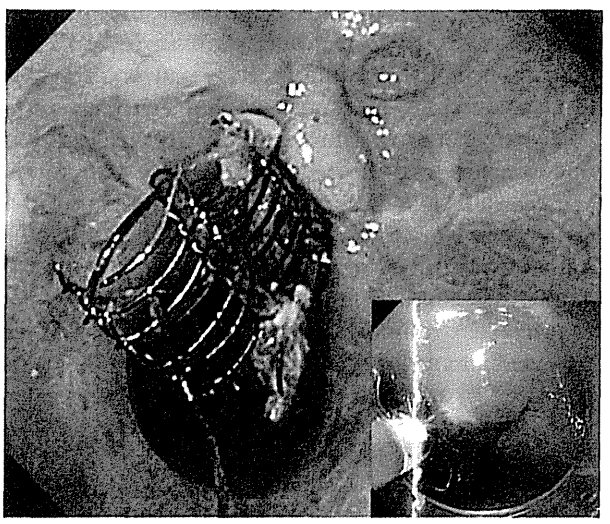

Fig. 4 Stent fragment exposed to the esophageal lumen after the removal of the protruding granulation tissue. We tried to trim the stent fragment with argon plasma coagulation (inset).

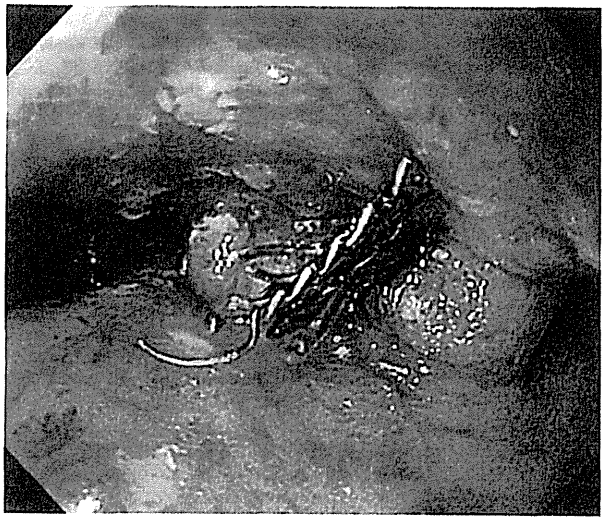

Fig. 5 Step 2: Part of a stent fragment exposed to the esophageal lumen could be trimmed with argon plasma coagulation (one and a half years later after step 1).

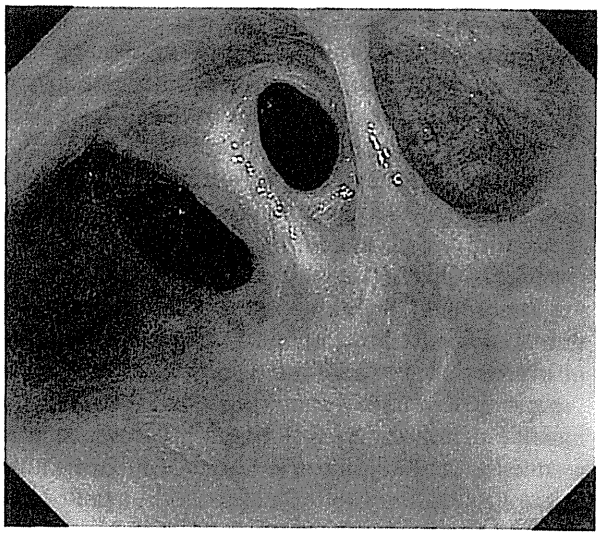

Fig. 7 Residual granulation tissue forming several 'bridges' across the esophageal lumen.

foreign body reaction to the stent,[14] and tissue ingrowth or overgrowth may occur in 5–8% of patients.[8,9] The stent can become firmly embedded in the esophageal wall, especially with long-term placement, and its removal may entail complications such as bleeding, tearing off the mucosa, and perforation.[4,9,11,13] In some of these patients, subsequent surgical intervention may be required to forcibly remove the embedded stent in a piecemeal fashion. However, it is sometimes difficult to ensure that all the fragments of the stent are removed completely.[3,4,12,13] As a result, secondary severe stricture caused by residual stent fragments can develop in the long term.

Over the past few years, three different type of a stent such as a partially (PSEMS) and a fully covered self-expandable metallic stent (FSEMS), and a self-expandable plastic stent (SEPS) has been able to be selected for a benign esophageal rupture and perforation. van Boeckel *et al.* have reported that stent migration occurred most frequently with FSEMS followed by SEPS and PSEMS, while tissue ingrowth or overgrowth was only seen with PSEMS.[9] However, the same group reported in their review that stent migration occurred more often with FSEMS and SEPS, whereas there was no significant difference in tissue ingrowth or overgrowth between them.[8] Moreover, like our case, Jaganmohan and Raju reported their cases in which even FSEMS can be complicated by tissue ingrowth.[15] Even though tissue ingrowth or overgrowth tends to be higher with PSEMS

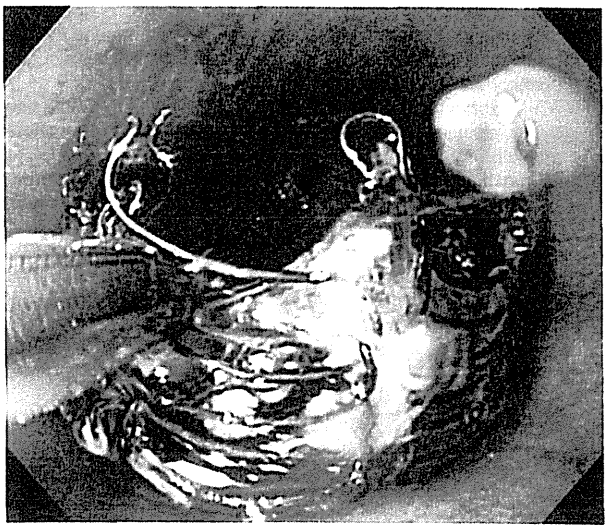

Fig. 6 Step 3: Some stent fragments were removed with grasping forceps after balloon dilatation of the esophagus (3 days later after step 2).

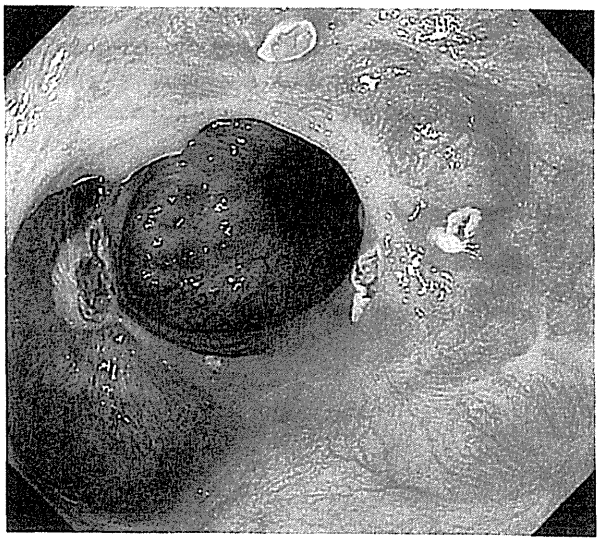

Fig. 8 Step 4: Granulation 'bridges' were severed with a diathermic knife and a snare, producing a satisfactory luminal diameter of the esophagus (5 months later after step 3).

compared with the other two, such complication may occur regardless of the stent type. As efficacy between them was not found to be significantly different, stent choice should depend on the expected risks of complications with a particular stent type.[8,9]

In our patient, step-by-step multimodal endoscopic treatment made it possible to remove the stent fragments through the patient's mouth and to relieve the stricture without surgical reintervention. Recently, the use of APC to trim a metallic stent in the biliary tract, duodenum, colon, or rectum to relieve an obstruction has been reported.[16–18] However, few reports are available about the use of APC to trim a metallic stent in the esophagus.[15,17] We have demonstrated for the first time that residual fragments after the surgical removal of an esophageal metallic stent can be trimmed safely using APC. The endoscopic removal of the stent, including its fragmentation with APC, is minimally invasive and should be attempted before surgical intervention.

However, it is most important to ensure early stent removal because tissue ingrowth or overgrowth is related to the duration of stenting in the esophagus.[8,9,13] van Heel *et al.* reported that the stent had been in place significantly longer in patients who underwent a complicated stent removal than in those with an uncomplicated primary stent removal.[13] Moreover, it has recently been recommended to remove embedded metallic stent that FSEMS of the same diameter should be placed inside embedded stent.[8,9,19] This stent-in-stent technique causes necrosis of the hyperplastic tissue ingrowth or overgrowth. Hirdes *et al.* reported that both these stents could be removed uneventfully after a period of 10–14 days.[19]

In conclusion, thanks to the technological advances and in the hands of skillful endoscopists, endoscopic removal of esophageal stents can avoid surgery. However, we emphasize that temporary stents used for benign disease should be removed before tissue ingrowth or overgrowth can develop (within 6–8 weeks of placement) regardless of the stent type.[9,13]

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ORIGINAL ARTICLE: Clinical Endoscopy

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

Shinya Yamada, MD,[1] Hisashi Doyama, MD, PhD,[1] Kenshi Yao, MD, PhD,[2] Noriya Uedo, MD,[3] Yasumasa Ezoe, MD, PhD,[4] Ichiro Oda, MD,[5] Kazuhiro Kaneko, MD, PhD,[6] Yoshiro Kawahara, MD, PhD,[7] Chizu Yokoi, MD, PhD,[8] Yasushi Sugiura, MD,[9] Hideki Ishikawa, MD, PhD,[10] Yoji Takeuchi, MD,[3] Yutaka Saito, MD, PhD,[5] Manabu Muto, MD, PhD[11]

Ishikawa, Fukuoka, Osaka, Kyoto, Tokyo, Chiba, Okayama, Japan

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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Current affiliations: Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Ishikawa, Japan (1), Department of Endoscopy, Fukuoka University Chikushi Hospital, Fukuoka, Japan (2), Department of Gastrointestinal Oncology, Osaka Medical Cancer for Cancer and Cardiovascular Diseases, Osaka, Japan (3), Department of Multidisciplinary Cancer Treatment, Graduate School of Medicine, Kyoto University, Kyoto, Japan (4), Department of Gastroenterology, National Cancer

(footnotes continued on last page of article)

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

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

Take-home Message

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

METHODS

Study design and endoscopic procedure

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

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

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

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

Endoscopy system and setting

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

TABLE 1. Demographics of the study sample

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

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

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

Endoscopic criteria used to diagnose cancers

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

Outcome measurements

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

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

Statistical analysis

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

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

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

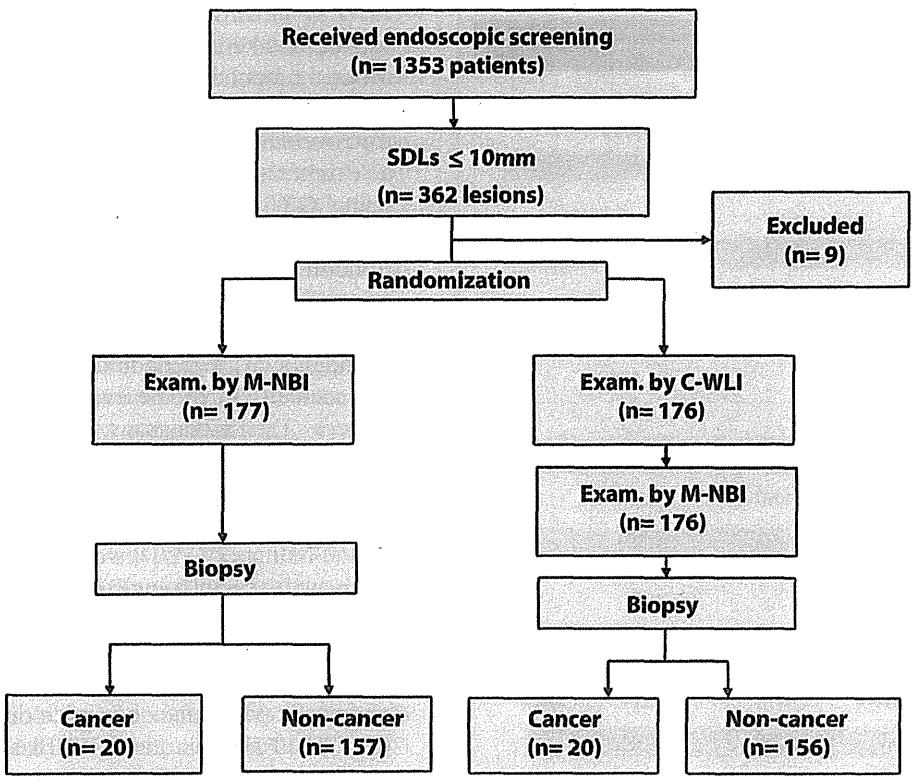

Figure 1. Trial profile, randomization, and examination. In this study, 1353 patients with concomitant gastric cancer or a history of endoscopic resection of early gastric cancer were enrolled and underwent endoscopic screening with C-WLI. Among these patients, 353 previously undiagnosed lesions were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

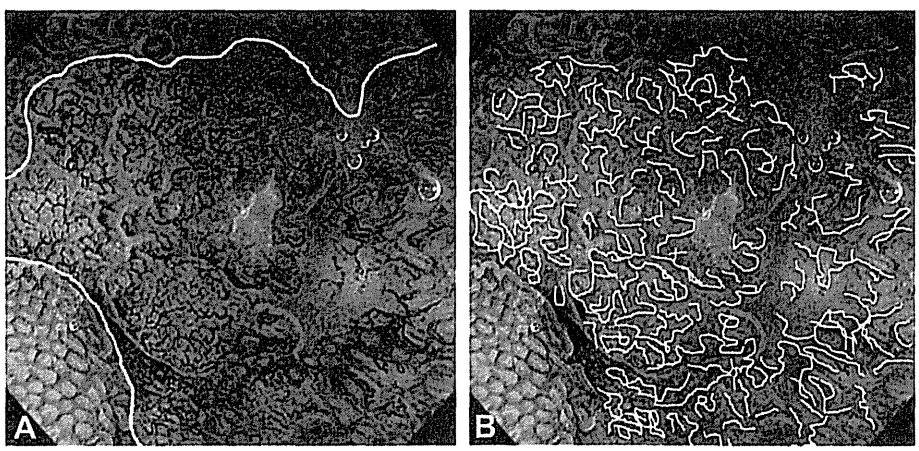

Figure 2. Endoscopic findings from magnifying narrowband imaging (M-NBI), **A,** A demarcation line (DL) is present between a depressed lesion and the surrounding mucosa (*yellow lines*). **B,** An irregular microvascular pattern (IMVP), is diagnosed if the vessels differ in shape or are a closed loop,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

RESULTS

Association between each endoscopic finding and histologic result

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

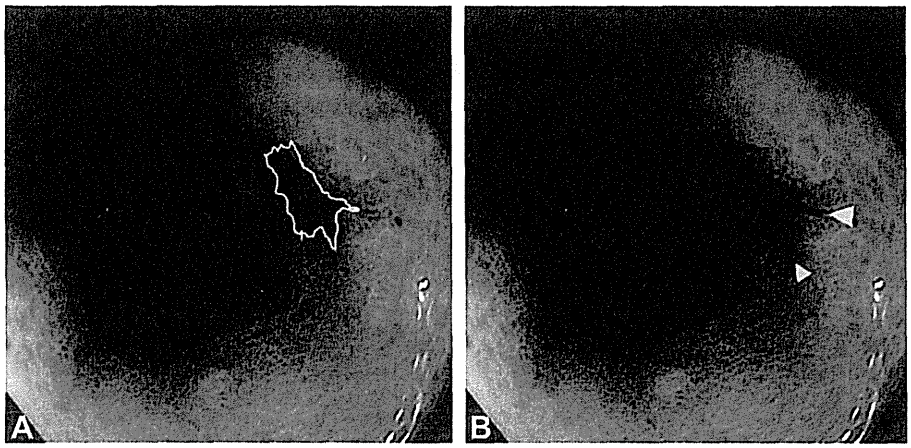

Figure 3. Endoscopic findings from conventional white-light imaging (C-WLI). **A,** An IM indicates the presence of an IM between a small, depressed lesion and the surrounding mucosa (*yellow line*). **B,** A spiny depressed area (SDA) indicates the presence of an SDA at the edge of a small, depressed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

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

Diagnostic performance of each endoscopic finding

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

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

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

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

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

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

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

TABLE 2. Association between each endoscopic finding and cancer

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

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

TABLE 3. Diagnostic performance according to endoscopic findings

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

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

Analysis of lesions incorrectly diagnosed by M-NBI

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

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

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

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

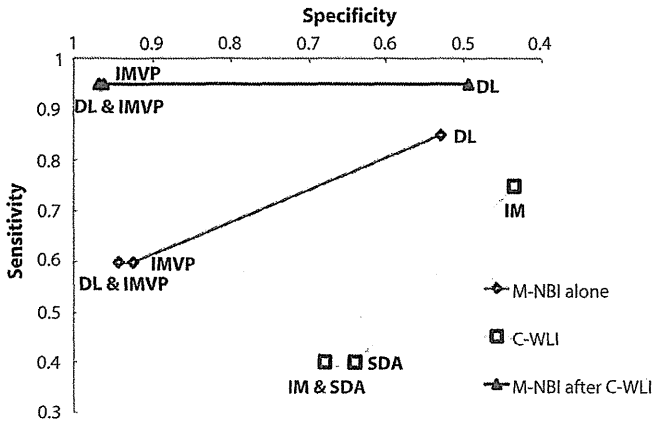

Figure 4. Comparison of the sensitivity and specificity of individual endoscopic findings in magnifying narrow-band imaging (M-NBI) alone, conventional white-light imaging (C-WLI), and M-NBI after C-WLI. Among all endoscopic findings, diagnostic performance improved significantly for C-WLI alone, followed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

DISCUSSION

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

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

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

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

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

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

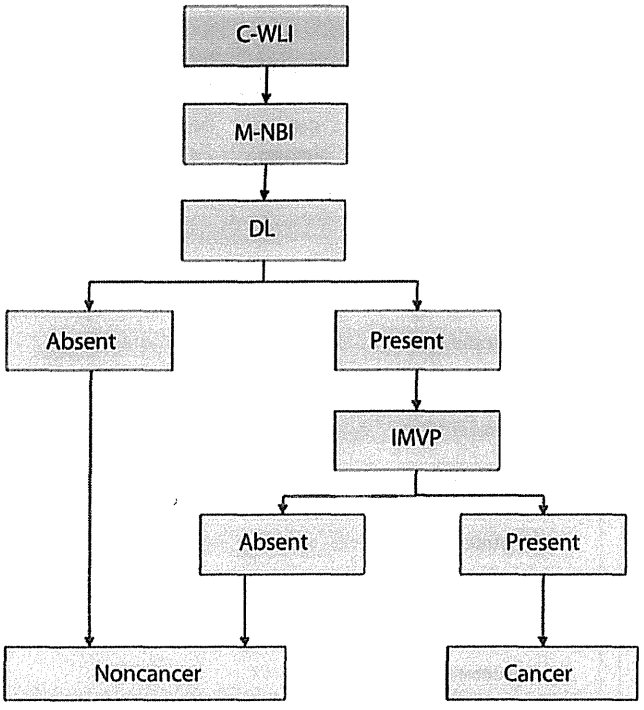

Figure 5. Strategy of using simplified criteria to make an endoscopic diagnosis of small, depressed lesions using magnifying narrowband imaging (M-NBI). When a small, depressed gastric lesion is detected by conventional white-light imaging (C-WLI), the presence or absence of a demarcation line (DL) should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

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

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

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

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Center Hospital, Tokyo, Japan (5), Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan (6), Division of Endoscopy, Okayama University, Okayama, Japan (7), Endoscopy Division, National Center for Global Health and Medicine, Tokyo, Japan (8), Division of Gastroenterology and Hepatology, Kitano Hospital, Osaka, Japan (9), Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan (10), Department of Gastroenterology and Hepatology, Graduate school of Medicine, Kyoto University, Kyoto, Japan (11).

Reprint requests: Shinya Yamada, MD, Ishikawa Prefectural Central Hospital, 2-1 Kuratsukihigashi, Kanazawa, Ishikawa 920-8530, Japan.