ORIGINAL ARTICLE

Diagnosis of histological type of early gastric cancer by magnifying narrow-band imaging: A multicenter prospective study

Takashi Kanesaka1 | Noriya Uedo1 | Hisashi Doyama2 | Naohiro Yoshida2 | Takashi Nagahama3 | Kensei Ohtsu3 | Kunihisa Uchita4 | Koji Kojima4 | Tetsuya Ueo5 | Haruhiko Takahashi5 | Hiroya Ueyama6 | Yoichi Akazawa6 | Toshio Shimokawa7 | Kenshi Yao3

1 Department of Gastrointestinal Oncology, Osaka International Cancer Institute, Osaka, Japan
2 Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Ishikawa, Japan
3 Department of Endoscopy, Fukuoka University Chikushi Hospital, Fukuoka, Japan
4 Department of Gastroenterology, Kochi Red Cross Hospital, Kochi, Japan
5 Department of Gastroenterology, Oita Red Cross Hospital, Oita, Japan
6 Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan
7 Clinical Study Support Center, Wakayama Medical University Hospital, Wakayama, Japan

Correspondence
Takashi Kanesaka, Department of Gastrointestinal Oncology, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka 541-8567, Japan.
Email: takashikanesaka@gmail.com

Funding information
The Yasuda Medical Foundation

Abstract

Objectives: Distinguishing undifferentiated-type from differentiated-type early gastric cancers (EGC) is crucial for determining the indication of endoscopic resection. We aimed to investigate the diagnostic performance of white-light endoscopy (WLE) and magnifying narrow-band imaging (M-NBI) for the histological type of EGC.

Methods: In this multicenter prospective study, patients with histologically proven cT1 EGC, macroscopically depressed or flat type, size ≥5 mm, and without erosion/ulcer, were recruited. The diagnostic criterion of WLE for undifferentiated-type EGC was pale color. The M-NBI algorithm was created based on microsurface and microvascular patterns, and lesions with absent microsurface pattern and opened-loop microvascular patterns were diagnosed as undifferentiated-type. The center of the lesion was defined as the evaluation point and was initially evaluated by WLE, then by M-NBI, and a biopsy specimen was taken as a reference standard. The primary and key secondary endpoints were overall diagnostic accuracy and specificity, respectively.

Results: In total, 167 lesions (122 differentiated-type and 45 undifferentiated-type EGCs) in 167 patients were analyzed. The overall accuracy, sensitivity, specificity, and positive likelihood ratio of WLE for undifferentiated-type EGC was 80%, 69%, 84%, and 4.4, respectively, and those of M-NBI were 82%, 53%, 93%, and 7.2, respectively. There was no significant difference in overall accuracy (p = 0.755), but specificity was significantly higher in M-NBI (p = 0.041).

Conclusions: The use of M-NBI did not improve the accuracy of WLE for the diagnosis of depressed/flat undifferentiated-type EGCs but improved the specificity. It may reduce surgical overtreatment by preventing misdiagnosis of differentiated-type EGC as undifferentiated-type.

KEYWORDS
diagnosis, endoscopy, gastric cancer, prospective study

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. DEN Open published by John Wiley & Sons Australia, Ltd on behalf of Japan Gastroenterological Endoscopy Society
INTRODUCTION

The histological type of gastric cancer is classified into differentiated and undifferentiated types according to Nakamura’s classification, corresponding to the intestinal and diffuse types according to Lauren’s classification, respectively. The indications for endoscopic resection (ER) are more restricted for the undifferentiated type than for the differentiated type. Therefore, unlike other gastrointestinal cancers, distinguishing these histological types is crucial for determining the indication of ER. Forceps biopsy is currently used for diagnosis of cancer and histological type in clinical practice when a suspicious lesion is detected by gastroscopy. Because favorable long-term outcomes relevant to gastric endoscopic submucosal dissection for each histological type have been published, the opportunities of ER for both histological types are increasing.

Recently, the utility of magnifying narrow-band imaging (M-NBI) for the diagnosis of early gastric cancer (EGC) was demonstrated. NBI is an image-enhancing technology that can be combined with magnifying endoscopy to allow for clear visualization of the microsurface structure and microvascular architecture of the gastric mucosa. The superiority of M-NBI over white-light endoscopy (WLE) for the differential diagnosis of small depressed EGC from benign small depression has been verified in a multicenter randomized controlled trial, which demonstrated an increase in accuracy from 64.8% to 90.4% (p < 0.001). However, with regard to the endoscopic diagnosis of EGC histological types, the diagnostic abilities of WLE and M-NBI to distinguish undifferentiated type from differentiated type have not been fully analyzed. Therefore, we aimed to investigate the diagnostic performance of WLE and M-NBI for the histological type of EGC.

METHODS

Study design and ethical statements

This multicenter prospective study was conducted according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Osaka International Cancer Institute on December 22, 2017 (No. 1712226191) and each participating institution. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000032151). All participants provided written informed consent for study participation. The manuscript was described following the Standards for Reporting Diagnostic Accuracy (STARD) statement.

Patients

Patients who planned to undergo ER or gastrectomy to treat cT1 (intramucosal or submucosal) gastric cancer at the participating institutions were assessed eligibility. When eligibility criteria were confirmed, the patient agreed to participate in this trial, and written informed consent was provided, the preoperative endoscopic examination was undertaken according to the trial protocol.

Inclusion criteria were histologically proven common-type EGC, and patients aged ≥20 years. Exclusion criteria were high risk of bleeding after biopsy (e.g., coagulation abnormality and platelet dysfunction), history of gastrectomy, the lesion of macroscopically elevated type, <5 mm in size, and evidence of erosion or an ulcer in the center of the lesion. The elevated-type lesions were excluded because our previous study indicated that elevated-type lesions were mostly differentiated-type with a high positive likelihood ratio. Lesions <5 mm in size were excluded because they were smaller than the opened width of the biopsy forceps. Lesions with erosion/ulcer in the center were also excluded because endoscopic findings were unevaluable. If a patient had multiple lesions, only the largest lesion was chosen for evaluation.

Status of Helicobacter pylori infection was defined as follows: current infection, anti-Helicobacter pylori IgG antibody was ≥10 and history of successful eradication therapy was absent; non-infected, anti-Helicobacter pylori IgG antibody was <3 and history of eradication therapy was absent; past infection, others. Tumor characteristics were described according to the Japanese Classification of Gastric Carcinoma.

Diagnostic methods

Endoscopists who were board-certified fellows of the Japan Gastroenterological Endoscopy Society or had equivalent qualifications participated in this study as examiners. The endoscopists were blinded to the previous endoscopy report of histological findings. The target lesion was evaluated in WLE, and then in M-NBI according to the algorithms described below. To eliminate selection bias, the center of the lesion was defined as the evaluation point. After completion of all diagnostic procedures, at least one biopsy specimen was obtained from the evaluation point.

Evaluation with WLE

The diagnostic algorithm of WLE used to differentiate undifferentiated-type from differentiated-type EGC was
based on the color of the lesions (Figure 1). A lesion paler than the surrounding mucosa was diagnosed as an undifferentiated type.

**Evaluation with M-NBI**

The diagnostic algorithm of M-NBI used to distinguish undifferentiated-type from differentiated-type EGC was based on previous reports (Figure 2). Lesions with absent microsurface pattern and opened-loop microvascular pattern, i.e., undifferentiated-type pattern, were diagnosed as undifferentiated-type.

**Histopathological diagnosis**

All biopsy and resected specimens were histologically evaluated using hematoxylin and eosin staining. The pathologists were blinded to the endoscopic diagnosis for histological type. The histological diagnosis of EGC was made in accordance with the revised Vienna Classification. In this trial, categories 4 (noninvasive, high-grade neoplasia) and 5 (invasive neoplasia) were classified as cancer, while categories 1 (negative for neoplasia), 2 (indefinite for neoplasia), and 3 (noninvasive, low-grade neoplasia) were classified as non-cancer. The histological type of EGC was diagnosed in accordance with the Japanese Classification of Gastric Carcinoma. Well- and moderately-differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as differentiated type, and poorly differentiated adenocarcinoma and signet-ring cell carcinoma were classified as undifferentiated type. Mucinous adenocarcinoma was classified as differentiated or undifferentiated type in each case based on the degree of glandular differentiation. Mixed type histology of differentiated and undifferentiated types in a biopsy specimen was regarded as undifferentiated type.

**Outcomes**

The primary and key secondary endpoints were on-site diagnostic accuracy and specificity to distinguish undifferentiated-type from differentiated-type EGC, respectively. The reason for defining specificity as a key secondary endpoint was because avoidance of misdiagnosis of differentiated-type as undifferentiated-type may reduce over-surgery for lesions ≥2 cm or lesions with an ulcer scar. The sensitivity, positive likelihood ratio, and negative likelihood ratio for distinguishing undifferentiated-type from differentiated-type EGC were secondary endpoints. In order to achieve a one-to-one correspondence between endoscopic and histological findings, the histological diagnosis of a biopsy specimen obtained from the center of the lesion was used for the reference standard in the main analysis. As a subset analysis, the diagnostic performance of M-NBI for undifferentiated-type EGC, according to the lesion color, was evaluated. In addition, diagnostic performance based on the dominant subtypes of resected specimens, which is also clinically relevant, was calculated as a sensitivity analysis. All adverse events were
Statistical analysis

Sample sizes were calculated to compare primary and key secondary endpoints between WLE and M-NBI. In a pilot study using the aforementioned algorithms, 7.1% (4/56) of EGCs were misdiagnosed by M-NBI, despite being correctly diagnosed by WLE, and 21.4% (12/56) were misdiagnosed by WLE, despite being correctly diagnosed by M-NBI. Using McNemar’s test with a two-sided $\alpha$ of 0.05 and power of 0.8, 117 lesions were required to compare accuracy (for the primary endpoint). It was found that 9.8% (4/41) of differentiated-type EGCs were misdiagnosed by M-NBI, despite being correctly diagnosed by WLE, and 24.4% (10/41) were misdiagnosed by WLE, despite being correctly diagnosed by M-NBI. Using McNemar’s test with a two-sided $\alpha$ of 0.05 and power of 0.8, 132 differentiated-type EGCs were required to compare accuracy. Assuming that the proportion of the differentiated type among EGCs was similar to that in a recent multicenter clinical trial (80.8%, 277/343), 163 lesions were required to compare specificity for the undifferentiated type (for the key secondary endpoint). To assess not only the primary endpoint but also the key secondary endpoint, 163 lesions were required. Finally, the total sample size was set to 207 cases, considering 10% of excluded cases and 16.2% of the false-positive rate of biopsy diagnosis for cancer.

Baseline characteristics were summarized as a median and range for continuous variables and as a proportion for categorical variables. The diagnostic performances of WLE and M-NBI were assessed by accuracy, sensitivity, specificity, and likelihood ratio, and they were described with a 95% confidence interval. McNemar’s test was used to compare the diagnostic performance. A $p$-value < 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/).
RESULTS

Patient enrollment and background

Between September 2018 and September 2019, 208 patients were enrolled from six tertiary care institutions in Japan. The consent forms of five patients were not stored, and one patient withdrew consent after enrollment. Among 202 patients who underwent protocol endoscopic examination, the diagnostic procedure and biopsy were completed in 192 patients by 41 participating endoscopists. The median number of biopsy specimens was 1 (range, 1–2 specimens) per lesion. In 25 patients, histological diagnosis of the biopsy specimen was made as non-cancer. Finally, 167 lesions (122 differentiated-type and 45 undifferentiated-type EGCs) were included in the main analysis (Figure 3). Patient characteristics are shown in Table 1.

Diagnostic performance to distinguish the histological types of gastric cancer

The accuracy, sensitivity, and specificity for undifferentiated-type EGC were 80% (73%–86%), 69% (53%–82%), and 84% (77%–90%) with WLE, and 82% (75%–88%), 53% (38%–68%), and 93% (87%–97%) with M-NBI, respectively (Table 2). Specificity was significantly higher with M-NBI than with WLE ($p = 0.041$), but there was no significant difference in accuracy and sensitivity between WLE and M-NBI ($p = 0.755$ and 0.190, respectively). Diagnostic performance of M-NBI for undifferentiated-type gastric cancer according to the lesion color is presented in Table 3.

Of the 192 patients who completed the protocol endoscopic examination, 145 patients received ER and 40 underwent surgery. After exclusion of two special-type EGCs and three non-cancerous lesions, finally, 180 lesions were diagnosed as common-type cancer (135 differentiated-type and 45 undifferentiated-type) in the resected specimens. The accuracy, sensitivity, and specificity for undifferentiated-type EGC in reference to the dominant subtypes of resected specimens were 81% (75%–87%), 71% (56%–84%), and 84% (77%–90%) in WLE, and 84% (78%–89%), 56% (40%–70%), and 94% (89%–97%) in M-NBI, respectively (Table 4). Specificity was significantly higher with M-NBI than with WLE ($p = 0.019$), but there was no significant difference in accuracy and specificity between WLE and M-NBI ($p = 0.451$ and 0.146, respectively).
TABLE 1 Demographics of the study subjects

| Clinicopathological characteristic | n = 167 |
|------------------------------------|---------|
| Median age (years, range)           | 69 (34–93) |
| Sex                                 |         |
| Male                                | 115 (69) |
| Female                              | 52 (31)  |
| *Helicobacter pylori* status        |         |
| Current infection                   | 63 (38)  |
| Past infection                      | 93 (56)  |
| Non-infection                       | 11 (7)   |
| Endoscopy                           |         |
| GIF-Q240Z                           | 5 (3)    |
| GIF-H260Z                           | 27 (16)  |
| GIF-FQ260Z                          | 4 (2)    |
| GIF-H290Z                           | 131 (78) |
| Lesion location                     |         |
| Upper third                         | 33 (20)  |
| Middle third                        | 69 (41)  |
| Lower third                         | 65 (39)  |
| Macroscopic type                    |         |
| Depressed (0-IIC/0-IIIc + III)      | 137 (82) |
| Flat (0-Ilb)                        | 12 (7)   |
| Mixed (others)                      | 18 (10)  |
| Endoscopic diameter (mm)            | 20 (5–100) |
| Histological type                   |         |
| Differentiated-type                 | 122 (73) |
| Undifferentiated-type               | 45 (27)  |

Data are presented as median (range) or n (%).

**Adverse events**

No ≥Grade 2 adverse event occurred in any of the 202 patients.

**DISCUSSION**

In this multicenter prospective study, we did not find a difference in the overall accuracy between M-NBI and WLE for diagnosis of histological type of EGC. Currently, the Japanese guideline for endoscopic diagnosis of EGC states that diagnosis of histological type of EGC should be made comprehensively by endoscopic finding and histological finding of biopsy specimens. However, the level of evidence for the statement is very weak. This study result must increase evidence level in this aspect.

M-NBI showed higher specificity but lower sensitivity for the diagnosis of undifferentiated-type EGCs. Most undifferentiated-type EGCs appeared pale in WLE, showing 69% of sensitivity for undifferentiated-type EGC, and a part of differentiated-type EGC appeared pale (specificity of 84%, Figure 4). Moreover, the undifferentiated-type pattern in M-NBI decreased the false-positive rate of WLE for diagnosis of the undifferentiated-type EGC, but it also decreased the true-positive rate (sensitivity). In subset analysis based on the lesion color, M-NBI showed 79% specificity for undifferentiated-type EGC for the pale lesions in WLE. If a differentiated-type EGC is misdiagnosed as an undifferentiated-type, gastrectomy may be indicated for the lesion and the patient loses the opportunity for treatment via ER. Using M-NBI in addition to WLE enables a more accurate diagnosis and avoidance of over-surgery in such cases. In contrast, if an undifferentiated-type EGC is misdiagnosed as a differentiated type, ER may be indicated for the lesion. However, such cases can be treated by additional surgery after a histological diagnosis of the resected specimens. We did the sub-analyses in addition to the lesion color, but we could not find any trends for each subset (Table S1).

We speculated two reasons for the low sensitivity of M-NBI in this study. First, in our preliminary study, M-NBI diagnosis by an expert endoscopist improved both sensitivity and specificity for the histological type of gastric cancers. When the expert endoscopist reviewed endoscopic images, the opened-loop microvascular pattern was underdiagnosed in several cases. Evaluation of microvessels in M-NBI needs certain experiences, therefore we suspect that further training of endoscopists or use of computer-aided diagnosis may improve sensitivity. Second, undifferentiated-type EGC often exists subepithelially underneath the non-neoplastic foveolar epithelium, therefore, such lesions were misdiagnosed as differentiated-type EGC because of the presence of microsurface pattern of covering non-neoplastic epithelium.

The principle to discriminate undifferentiated-type from differentiated-type EGC in WLE and NBI is different. An undifferentiated-type EGC looks pale in WLE because of a reduction in hemoglobin content. Distinguishing the histological type of EGC by M-NBI is based on differences in microsurface structure and microvascular architecture. A key histological feature of differentiated-type EGC is ductal formation. For differentiated-type EGC, marginal crypt epithelium (microsurface structure) of the cancerous duct is visible in M-NBI. Otherwise, in case the cancerous ducts are too narrow or shallow, the marginal crypt epithelium is invisible (absent), and only network-shaped microvessels (polygonal/closed-loop microvessels) that surround cancerous ducts are seen. On the other hand, for undifferentiated-type EGC, the marginal crypt epithelium is absent and non-network shaped microvessels (opened-loop microvessels) are seen, owing to the absence of the ductal formation.

Among 31 published articles for histological type diagnosis of EGC by M-NBI, there were three prospective studies. Two single-center studies evaluated...
TABLE 2  Diagnostic performance of white-light endoscopy (WLE) and magnifying narrow-band imaging (M-NBI) for undifferentiated-type gastric cancer

| Method | Accuracy, % (95% CI) | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PLR (95% CI) | NLR (95% CI) |
|--------|----------------------|-------------------------|-------------------------|--------------|--------------|
| WLE    | 80(73–86)            | 69(53–82)               | 84(77–90)               | 4.4(2.8–7.0) | 0.37(0.24–0.57) |
| M-NBI  | 82(75–88)            | 53(38–68)               | 93(87–97)               | 7.2(3.6–14.4) | 0.50(0.36–0.69) |
| \(p\)-value | 0.755                     | 0.190                   | 0.041                   |              |              |

Abbreviations: CI, confidence interval; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

TABLE 3  Diagnostic performance of magnifying narrow-band imaging (M-NBI) for undifferentiated-type gastric cancer according to the lesion color

| Lesion color          | Accuracy, % (95% CI) | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|-----------------------|----------------------|-------------------------|-------------------------|
| Reddish or isochromatic \(n = 117\) | 90(83–95) | 50(23–77) | 95(89–98) |
| Pale \(n = 50\)       | 64(49–77)            | 55(36–73)               | 79(54–94)               |

Abbreviation: CI, confidence interval.

the characteristic findings of the histological type of EGC using M-NBI, but there were no comparative data by WLE.\textsuperscript{19,21} A multicenter comparative study showed no significant difference between WLE and M-NBI for diagnosis of histological type of EGCs: the accuracies 96.4% and 96.8%, and the sensitivity for the differentiated-type, which correspond to specificities for the undifferentiated-type, were 99.0% and 99.5%.\textsuperscript{32} However, the proportion of the undifferentiated-type EGC among the study subjects was quite low (7%) and most lesions were small and had no ulceration because only cases of ER were included in that study. We suspect that such selection bias in the study subjects might increase the diagnostic performance of both WLE and M-NBI in that study. Diagnosis of histological type is important for all EGCs to determine the indication of ER. A strength of our study is that patients undergoing both ER and/or surgery were included.

Our study had limitations. First, we did not design this study as a randomized controlled trial. Although the endoscopic finding of each method was evaluated independently, the diagnostic value of M-NBI

TABLE 4  Diagnostic performance for undifferentiated-type dominant gastric cancer in the resected specimen

| Modality | Accuracy, % (95% CI) | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PLR (95% CI) | NLR (95% CI) |
|----------|----------------------|-------------------------|-------------------------|--------------|--------------|
| WLE      | 81(75–87)            | 71(56–84)               | 84(77–90)               | 4.6(3.0–7.1) | 0.34(0.22–0.54) |
| M-NBI    | 84(78–89)            | 56(40–70)               | 94(89–97)               | 9.4(4.6–19.3) | 0.47(0.34–0.66) |
| \(p\)-value | 0.451                     | 0.146                   | 0.019                   |              |              |

Abbreviations: CI, confidence interval; M-NBI, magnifying narrow-band imaging; NLR, negative likelihood ratio; PLR, positive likelihood ratio; WLE, white-light endoscopy.

FIGURE 4  True-positive and false-positive rates in each examination. FP, false-positive; M-NBI, magnifying narrow-band imaging; Sn, sensitivity; Sp, specificity; TP, true-positive; WLE, white-light endoscopy
contained carrying over effect from WLE diagnosis and the comparison between WLE and M-NBI diagnoses was indirect. In clinical practice, M-NBI diagnosis is always performed subsequently to WLE, therefore we considered that making a study arm using only M-NBI diagnosis without WLE was impractical. The prospectively obtained data in this study reflected the diagnostic performance of both methods in real clinical settings. Second, only patients with EGC were recruited, therefore the usefulness of M-NBI for advanced gastric cancers was unknown. However, diagnosis of histological type is the most important in EGC among cancers in all T-stages because it is related to the indication of ER. Third, we defined biopsy diagnosis as a reference standard instead of the diagnosis of the resected specimen in this study. As a result, 25 patients were excluded from the main analysis because the biopsy specimen taken in the protocol examination was diagnosed as non-cancer. When we reviewed these misdiagnosed specimens, most lesions were underdiagnosed because of low-grade atypia of the neoplastic glands. Otherwise, there was no neoplastic gland suggesting sampling error by forceps biopsy. Thus, biopsy diagnosis for EGC has a risk of misdiagnosis. However, we considered biopsy to the exact endoscopic observation point was the most feasible method to achieve a one-to-one correspondence between an endoscopic finding and histology. When the histopathological examination of the resected specimen was used as a reference standard, a precise corresponding evaluation was difficult, especially for surgical specimens. We also evaluated the diagnostic performance of M-NBI for the dominant histological type of resected specimens, and the results were similar (Tables 2 and 4). Fourth, the only color was included in the diagnostic algorithm of WLE, because the color had been demonstrated as the most useful predictor for the histological type of depressed or flat-type EGCs in previous studies. Moreover, although H. pylori eradication is reported to alter the color of the background mucosa, we did not find a significant difference in the diagnostic accuracy of WLE based on the H. pylori status (Table S1), thus its influence may be small.

In conclusion, this prospective study demonstrated that additional use of M-NBI did not improve the overall accuracy of WLE for diagnosis of non-ulcerated flat or depressed type undifferentiated EGCs. However, it improved the specificity of WLE and may reduce surgical over-treatment by preventing misdiagnosis of differentiated-type EGC as undifferentiated-type.

**ACKNOWLEDGMENTS**

We would like to thank the following individuals and organizations. Implementing medical institutions: Ryu Ishihara, Shuntaro Inoue, Takahiro Inoue, Hiroyoshi Iwagami, Taro Iwatsubo, Masayasu Ohmori, Mitsuhiro Kono, Satoki Shichijo, Yusaku Shimamoto, Ayaka Shoji, Yoji Takeuchi, Kentaro Nakagawa, Hiroko Nakahira, Koji Higashino, Hiromu Fukuda, Kenshi Matsuno, Noriko Matsuura, Akira Maekawa, Kotaro Waki, Saori Miyajima, Shigetsugu Tsuji, Takashi Nakashima, Hiroyoshi Nakanishi, Shigenori Wakita, Satoshi Ishikawa, Kentaro Ima-mura, Yoichiro Ono, Takao Kanemitsu, Masahiro Kishi, Masaki Miyaoaka, Junichi Muraiishi, Tatsuhisa Yasaka, and Shigeyoshi Yasukawa. Datacenter: Keiko Shindo. Effectiveness and safety evaluation committee: Hideki Ishikawa and Manabu Muto. Monitoring committee: Yasushi Yamasaki. English language editing: Editage (www.editage.com).

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

**FUNDING INFORMATION**

This study was funded by The Yasuda Medical Foundation.

**ORCID**

Takashi Kanesaka https://orcid.org/0000-0002-8197-2295
Haruhiko Takahashi https://orcid.org/0000-0001-6352-1741
Yoichi Akazawa https://orcid.org/0000-0001-9343-5262

**REFERENCES**

1. Nakamura H, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: Its histogenesis and histological appearances. *Gan* 1968; 59: 251–8.
2. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver.4). *Gastric Cancer* 2017; 20: 1–19.
3. Lauren P. The two histological main types of gastric carcinoma. *Acta Pathol Microbiol Scand* 1965; 64: 31–49.
4. Gotoda T, Yanagisawa A, Sasaki M et al. Incidence of lymph node metastasis from early gastric cancer: Estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; 3: 219–25.
5. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2015; 47: 829–54.
6. Ono H, Yao K, Fujishiro M et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016; 28: 3–15.
7. Hasuika N, Ono H, Boku N et al. A non-randomized confirmatory trial of an expanded indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a). The Japan Clinical Oncology Group study (JCOG0607). *Gastrectomy* 2018; 21: 114–23.
8. Takizawa K, Ono H, Hasuika N et al. A nonrandomized, single-arm confirmatory trial of expanded endoscopic submucosal dissection indication for undifferentiated early gastric cancer. *Dig Endosc* 2018; 30: 1510–1515.
9. Yao K, Anagnostopoulos GK, Raganath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. *Endoscopy* 2009; 41: 462–7.
10. Ezoe Y, Muto M, Uedo N et al. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. *Gastroenterology* 2011; 141: 2017–25.
KANESAKA ET AL.

11. Yao K, Doyama H, Gotoda T et al. Diagnostic performance and limitations of magnifying narrow-band imaging in screening endoscopy of early gastric cancer: A prospective multicenter feasibility study. *Gastric Cancer* 2014; 17: 669–79.

12. Muto M, Yao K, Kaise M et al. Magnifying endoscopy simple diagnostic algorithm for early gastric cancer (MESA-G). *Dig Endosc* 2016; 28: 379–93.

13. Bossuyt PM, Reitsma JB, Bruns DE et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015; 351:h5527.

14. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 3rd English edition. *Gastric Cancer* 2011; 14: 101–12.

15. Kanesaka T, Nagahama T, Uedo N et al. Clinical predictors of histologic type of gastric cancer. *Gastroint Endosc* 2018; 87: 1014–22.

16. Honmyo U, Misumi A, Murakami A et al. Mechanisms producing color change in flat early gastric cancers. *Endoscopy* 1997; 29: 366–71.

17. Yao K, Yao T, Matsui T, Iwashita A, Oishi T. Hemoglobin content in intramucosal gastric carcinoma as a marker of histologic differentiation: A clinical application of quantitative electronic endoscopy. *Gastroint Endosc* 2000; 52: 241–5.

18. Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: Correlation of vascular pattern with histopathology (including video). *Endoscopy* 2004; 36: 1080–94.

19. Li HY, Dai J, Xue HB et al. Application of magnifying endoscopy with narrow-band imaging in diagnosing gastric lesions: A prospective study. *Gastroint Endosc* 2012; 76: 1124–32.

20. Kanesaka T, Sekikawa A, Tsumura T et al. Absent microsurface pattern is characteristic of early gastric cancer of undifferentiated type: Magnifying endoscopy with narrow-band imaging. *Gastroint Endosc* 2014; 80: 1194–8.

21. Ok KS, Kim GH, Park do Y et al. Magnifying endoscopy with narrow band imaging of early gastric cancer: Correlation with histopathology and mucin phenotype. *Gut Liver* 2016; 10: 532–41.

22. Schlemper RJ, Riddell RH, Kato Y et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; 47: 251–5.

23. Kanesaka T, Yao K, Doyama H et al. Proposal of a diagnostic algorithm in magnifying narrow-band imaging to distinguish the histologic types of gastric cancer. *Gastroint Endosc* 2018; 87: ab183.

24. Nagahama T, Yao K, Uedo N et al. Delineation of the extent of early gastric cancer by magnifying narrow-band imaging and chromoendoscopy: A multicenter randomized controlled trial. *Endoscop* 2018; 50: 566–76.

25. Nishitani M, Yoshida N, Tsuji S et al. Optimal number of endoscopic biopsies for diagnosis of early gastric cancer. *Endosc Int Open* 2019; 7: E1683–90.

26. Yao K, Uedo N, Kamada T, et al. Guidelines for endoscopic diagnosis of early gastric cancer. *Dig Endosc* 2020; 32: 663–98.

27. Nakanishi H, Doyama H, Ishikawa H, et al. Evaluation of an e-learning system for diagnosis of gastric lesions using magnifying narrow-band imaging: A multicenter randomized controlled study. *Endoscop* 2017; 49: 957–67.

28. Kanesaka T, Lee TC, Uedo N, et al. Computer-aided diagnosis for identifying and delineating early gastric cancers in magnifying narrow-band imaging. *Gastroint Endosc* 2018; 87: 1339–44.

29. Okada K, Fujisaki J, Kasuga A, et al. Diagnosis of undifferentiated type early gastric cancers by magnification endoscopy with narrow-band imaging. *J Gastroenterol Hepatol* 2011; 26: 1262–9.

30. Yao K. Zoom gastroscopy: Magnifying endoscopy in the stomach. 2014th ed. Tokyo: Springer; 2013.

31. Yagi K, Nozawa Y, Endou S, Nakamura A. Diagnosis of early gastric cancer by magnifying endoscopy with NBI from viewpoint of histological imaging: Mucosal patterning in terms of white zone visibility and its relationship to histology. *Diagn Ther Endosc* 2012; 7: 954809.

32. Kishino T, Oyama T, Funakawa K et al. Multicenter prospective study on the histological diagnosis of gastric cancer by narrow band imaging-magnified endoscopy with and without acetic acid. *Endosc Int Open* 2019; 7: E155–63.

33. Toyoshima O, Nishizawa T, Sakitani K, et al. Helicobacter pylori eradication improved the Kyoto classification score on endoscopy. *JGH Open* 2020; 4: 909–14.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

Supplementary Table. Subset analyses of diagnostic performance of WLE and M-NBI for undifferentiated-type gastric cancer.