Original research

Early gastric cancer detection in high-risk patients: a multicentre randomised controlled trial on the effect of second-generation narrow band imaging

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ABSTRACT
Objective Early detection of gastric cancer has been the topic of major efforts in high prevalence areas. Whether advanced imaging methods, such as second-generation narrow band imaging (2G-NBI) can improve early detection, is unknown.

Design This open-label, randomised, controlled tandem trial was conducted in 13 hospitals. Patients at increased risk for gastric cancer were randomly assigned to primary white light imaging (WLI) followed by secondary 2G-NBI (WLI group: n=2258) and primary 2G-NBI followed by secondary WLI (2G-NBI group: n=2265) performed by the same examiner. Suspected early gastric cancer (EGC) lesions in both groups were biopsied. Primary endpoint was the rate of EGC patients in the primary examination. The secondary endpoint was the positive predictive value (PPV) for EGC in suspicious lesions detected (primary examination).

Results EGCs were found in 44 (1.9%) and 53 (2.3%; p=0.412) patients in the WLI and 2G-NBI groups, respectively, during primary EGD. In a post hoc analysis, the overall rate of lesions detected at the second examination was 25% (n=361/1455), with no significant differences between groups. PPV for EGC in suspicious lesions was 13.5% and 20.9% in the WLI (50/371 target lesions) and 2G-NBI groups (59/282 target lesions), respectively (p=0.015).

Conclusion The overall sensitivity of primary endoscopy for the detection of EGC in high-risk patients was only 75% and should be improved. 2G-NBI did not increase EGC detection rate over conventional WLI. The impact of a slightly better PPV of 2G-NBI has to be evaluated further.

Trial registration number UMIN000014503.

INTRODUCTION
Gastric cancer is relatively common worldwide, with over 1 000 000 new cases reported in 2018 and an estimated 783 000 deaths.1 The prognosis for gastric cancer is generally poor, but detection at an early stage substantially improves the 5-year disease-specific survival rate (99.3% for mucosal cancer and 97.2% for submucosal cancer).2 Hence, early detection is an ideal strategy for maximising gastric cancer survival rates. However, valid screening procedures for early gastric cancer (EGC) are lacking, even in high-incidence areas (Asia, Russia and South America). While the current standard practice for detecting gastric cancer is endoscopy using white light imaging (WLI),3–6 the sensitivity of WLI for detecting EGC is not satisfactory.7 Narrow band imaging (NBI) endoscopy is an innovative optical image-enhanced technology that better visualises surface structures and blood vessels than does WLI.8 For example, first-generation NBI (1G-NBI) improved the detection rate of superficial head and neck and oesophageal cancers relative to that of WLI.9 However, 1G-NBI images are often too dark in the stomach area, making them unsuitable for EGC screening. Second-generation NBI...
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(2G-NBI) images are significantly brighter, with higher resolution. Thus, we hypothesised that 2G-NBI could be an effective screening method for detecting EGC.

The primary objective of this study was to investigate whether 2G-NBI detects significantly more EGCs than does WLI in patients at high risk for gastric cancer.

METHODS

Study design

This randomised, open-label, two-arm-parallel trial was conducted at 13 hospitals in Japan in accordance with the Declaration of Helsinki. The required sample size was amended 1 year after registration initiation (see below). The manuscript was prepared in accordance with the Consolidated Standards of Reporting Trials statement. All authors had access to the study data and have reviewed and approved the final manuscript.

Participants

We recruited patients at high risk for gastric cancer to maximise the number of lesions detected, allowing for a suitable evaluation of the efficacy of EGC screening. The reported incidence of synchronous or metachronous multiple gastric cancer is 6.7%–14.5% in patients with gastric neoplasms and 5.4%–7.7% in patients with oesophageal cancer. These incidence rates are higher than those of the general population. Therefore, we enrolled patients aged 20–85 years with either of the following: (1) a history of endoscopic resection for an oesophageal cancer or gastric neoplasm, (2) a current oesophageal cancer or gastric neoplasm or (3) a history of chemotherapy and/or radiation therapy for oesophageal cancer. The exclusion criteria were as follows: (1) previous gastrectomy or gastric tube reconstruction, (2) emergency endoscopy, (3) current use of antithrombogenic therapy for oesophageal cancer. The exclusion criteria were as follows: (1) previous gastrectomy or gastric tube reconstruction, (2) emergency endoscopy, (3) current use of antithrombogenic therapy for oesophageal cancer, (4) a serious underlying disease and (5) participation in this study within the last 8 months. Written informed consent was obtained from all study participants.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to the WLI group (primary WLI followed by secondary 2G-NBI) or the 2G-NBI group (primary 2G-NBI followed by secondary WLI). A centralised randomisation process was conducted using a computerised minimisation procedure on the Medical Research Support Web site (Kyoto, Japan). A minimisation method with a random component was used to balance the groups with respect to institution, age (<70 and ≥70 years) and indication of endoscopy (oesophageal cancer and gastric neoplasm). Masking of the study group allocations was not attempted for either the endoscopists or the patients.

Endoscopy and the NBI system

A 2G-NBI endoscopic system (EVIS LUCERA ELITE; Olympus Corporation, Tokyo, Japan) consisting of a light source (CLV-290SL/CLV-290), video processor (CV-290) and gastrointestinal videoscope (GIF-HQ290) was used for both WLI and 2G-NBI. The video processor settings for structure enhancement were type B, level 4 or 6 for WLI, and type B, level 8 for 2G-NBI. The GIF-HQ290 gastroscope has a dual focus function that allows endoscopists to switch between a normal-focus mode and a near-focus mode (45 times maximum) by pressing a button on the gastroscope.

The NBI system has a dedicated built-in narrow-bandwidth filter in its light source, with central wavelengths of 415 and 540 nm and a bandwidth of 30 nm. Since haemoglobin absorbs this narrow-band light, the microvascular architecture of the mucosal surface can be easily visualised. 2G-NBI produces higher quality images than does 1G-NBI owing to the following features: a rotary NBI filter for double exposure; a dedicated xenon lamp to improve brightness; a signal processing system to reduce noise; and improved colour contrast (online supplementary figure S1). Users can switch between WLI and 2G-NBI by simply pushing a button on the gastroscope (online supplementary figure S2).

Endoscopic diagnosis criteria

An EGC is classified as a tumour confined to the mucosa or submucosa, regardless of lymph node metastasis. Newly detected suspicious lesions for EGC, identified by non-magnifying observation, were defined as ‘target lesions’. Target lesions had at least one of the following endoscopic characteristics: (1) an area with an irregular margin; (2) an area with irregular discoloration; or (3) an area with an irregular surface (figure 1). Lesions with findings typical of advanced gastric cancer (eg, hardness and poor extensibility) were excluded as target lesions, as were pre-existing lesions. The criteria for a target lesion applied to both the WLI and 2G-NBI examinations.

Examination protocol

The examination protocol consisted of non-magnifying observation (primary WLI and secondary 2G-NBI, or primary 2G-NBI and secondary WLI), near-focus NBI observation and biopsy of the target lesion (online supplementary figure S3). Non-magnifying observation using the allocated procedure was initially performed to detect target lesions. After completing the primary examination of the entire stomach, a secondary examination was immediately performed by the same endoscopist for the detection of any missed target lesions. Both primary and secondary examinations were conducted to observe the whole stomach according to the systematic screening protocol for the stomach. There was no restriction on observation time in both WLI and 2G-NBI. If a target lesion was detected, a detailed near-focus NBI examination was immediately performed to differentiate between gastric cancer and non-cancer. All detected target lesions were ultimately biopsied, regardless of the diagnosis by near-focus NBI.

To maintain endoscopic quality control, all endoscopists in this study were Board-certified fellows of the Japan Gastroenterological Endoscopy Society or had equivalent qualifications. To minimise diagnostic variability, all participating endoscopists were trained using WLI and 2G-NBI endoscopic images of gastric lesions before the study began.

Pathological evaluation

Pathological diagnoses were made on biopsied tissue or resected specimens obtained during endoscopic resection or surgical removal. If biopsied tissues and resected specimens were both available, the latter was used for the final diagnosis. A lesion was diagnosed as a focal gastric cancer if the biopsy-based diagnosis was gastric cancer and the resected specimen-based diagnosis was non-cancer. Differentiation between gastric cancer and non-cancer was based on the revised Vienna classification: category 4 (mucosal high-grade neoplasia) and category 5 (submucosal invasion by carcinoma) tumours were diagnosed as gastric cancers, whereas category 1–3 tumours were diagnosed as non-cancers.

Outcomes

The primary endpoint was the detection rate of EGC, which was defined as the proportion of patients with newly detected...
EGC in the primary examination. The secondary endpoints were positive predictive value (PPV), observation time, characteristics of missed EGCs and adverse events. Observation time was measured from the passing of the endoscope through the gastro-oesophageal junction until the completion of the primary examination, including the time required to remove the gastric mucus. A missed EGC was defined as an EGC that was detected in the secondary but not primary examination. Each cancer was classified according to the Japanese Classification of Gastric Carcinoma, including tumour location and macroscopic and histological subtype.

Sample size
Our previous study showed that the detection rate of small depressed gastric cancers by WLI was 3.0%. In the present study, most participants were supposed to be similar to those in the previous study, and there were no limitations on size or macroscopic types for target EGC lesions. Therefore, we predicted the detection rate of EGC by WLI to increase to 5%. Since no data have been published previously regarding the detection rate of EGC by NBI, we expected that 2G-NBI would increase the detection rate by at least 3% compared with the detection rate by WLI, resulting in a prediction of 8%. As such, the necessary sample size was initially calculated as 2200 patients, with 1100 patients per group, to achieve 80% power with a two-sided alpha of 5%.

In October 2015, 1 year after the beginning of enrolment, the data centre added up the number of EGC from the data that masked the assignment results, according to the predefined study monitoring/review process. This process revealed that the overall detection rate was 2.1% among 1097 patients enrolled at that time. Since the overall detection rate was about one-third
of the initial estimation, the detection rate of each group was reduced by one-third of the initial estimation to 1.5% in the WLI group and 2.7% in the 2G-NBI group (2.1% overall). Although the detection rate became small, we still considered this difference to be valuable because a number of patients would be affected by the results of this study. That is to say, over 1 million new gastric cancer cases were recorded in 2018,1 and majority of them were estimated to belong to the gastric cancer high-risk group, which corresponded to the analysis target of this study. The revised sample size requirement was 4520 patients, with 2260 patients per group. This sample size was sufficient to achieve the predetermined 80% power with a two-sided alpha of 5%. This adjustment, intended to maintain a balance between clinical significance and study feasibility, was approved by the Institutional Review Boards of all participating institutions.

Statistical analysis
The EGC detection rate and the secondary endpoints (with the exception of observation time) were analysed in the intent-to-treat population, defined as all randomised patients who agreed to participate in this study. Cases excluded after randomisation were counted as not having any target lesion. Differences in proportions between groups were evaluated using Fisher’s exact test. Comparisons of continuous data were performed using the t-test. All p values were two-sided, with an alpha of 5% as the significance level. Continuous variables are expressed as means and SD. All statistical analyses were performed using JMP V.14.

RESULTS

Group characteristics
Between September 2014 and September 2017, 4,575 patients were assessed for study eligibility (figure 2). Fifty-two patients refused to participate (46 patients before randomisation, six patients after randomisation). The remaining 4523 patients were randomly assigned to the WLI group (2258 patients, primary WLI followed by secondary 2G-NBI) or the 2G-NBI group (2265 patients, primary 2G-NBI followed by secondary WLI). After randomisation, 51 patients were excluded: 21 patients who had inadequate preparation; 15 patients who violated the study protocol; 4 patients who had intragastric haemorrhage; 4 patients who had oesophageal stenosis; and 7 patients who had other reasons. A total of 2234 and 2238 patients underwent examination in the WLI group and 2G-NBI group, respectively. The baseline characteristics of the two groups were well balanced, as summarised in table 1. In both groups, approximately 80% of patients underwent endoscopic examination for surveillance after endoscopic resection for a gastric neoplasm.

Outcomes
Table 2 shows the details of the target lesions found in the primary and secondary examinations. New EGCs were detected in 97 patients (2.1%) during the primary examination. The EGC detection rate by primary WLI and 2G-NBI was 1.9% (44/2258 patients) and 2.3% (53/2265 patients), respectively (p=0.412). Two synchronous EGCs were detected in four patients via primary WLI and six patients via primary 2G-NBI. Three synchronous EGCs were detected in one patient via primary WLI.

Primary WLI detected 371 target lesions, and primary 2G-NBI detected 282 target lesions, 50 and 59 of which were EGCs, respectively. Accordingly, the PPV for diagnosing EGC was significantly greater for 2G-NBI than for WLI (20.9% and
Among all patients who completed the primary examination, the mean observation times for primary WLI and primary 2G-NBI were 233±92 – 254±104 seconds, respectively (p<0.001). Among patients without target lesions, the mean observation times for primary WLI and primary 2G-NBI were 0.8% and 0.5% (p=0.686), respectively. In the gastric neoplasm group, the EGC detection rates of primary WLI and 2G-NBI were 0.8% and 0.5% (p=0.686), respectively. In the gastric neoplasm group, the EGC detection rates of primary WLI and 2G-NBI were 2.2% and 2.7% (p=0.342), respectively (online supplementary table S1).

**DISCUSSION**

Endoscopic screening has been reported to reduce gastric cancer mortality in high-risk countries. Furthermore, an earlier detection is crucial, because most patients with EGC can be cured by endoscopic resection, with positive impacts on their quality of life and on the medical economy. However, conventional WLI has limited ability to detect EGC, with a sensitivity of 65.7%, as reported in an Asian screening programme. The characteristics of the missed EGCs were similar, with no significant differences between the groups.

The only adverse event observed in this study was bleeding from a target lesion after biopsy in the 2G-NBI group, which required haemostatic therapy.

An additional subanalysis of indication of endoscopy (oesophageal cancer and gastric neoplasm) was also conducted. In the oesophageal cancer group, the EGC detection rates of primary WLI and 2G-NBI were 0.8% and 0.5% (p=0.686), respectively. In the gastric neoplasm group, the EGC detection rates of primary WLI and 2G-NBI were 2.2% and 2.7% (p=0.342), respectively (online supplementary table S1).

### Table 2 Diagnoses of the target lesions and observation times in each group

| Outcome                  | Primary WLI (n=2258) | Secondary 2G-NBI | Primary 2G-NBI (n=2265) | Secondary WLI | P value (primary WLI vs primary 2G-NBI) |
|--------------------------|----------------------|------------------|-------------------------|---------------|----------------------------------------|
| Patients with EGC, n (%) | 44 (1.9)             | 19 (0.8)         | 53 (2.3)                | 17 (0.8)      | 0.412                                  |
| Patients with a target lesion, n (%) | 308 (13.8) | 114 (5.0) | 251 (11.2) | 124 (5.5) |                                      |
| Target lesion, n (%)     | 371                  | 118              | 282                     | 132           |                                        |
| EGC*, n (%)              | 50 (13.5)            | 19 (16.1)        | 59 (20.9)               | 17 (12.9)     |                                        |
| Others*, n (%)           |                      |                  |                         |               |                                        |
| Low-grade adenoma        | 17 (4.6)             | 7 (5.9)          | 20 (7.1)                | 2 (1.6)       |                                        |
| Advanced gastric cancer  | 0 (0)                | 0 (0)            | 1 (0.4)                 | 0 (0)         |                                        |
| Negative for neoplasia   | 287 (77.4)           | 90 (76.3)        | 195 (69.1)              | 107 (81.1)    |                                        |
| Indefinite for neoplasia | 1 (0.3)              | 0 (0)            | 1 (0.4)                 | 1 (0.8)       |                                        |
| Not biopsied             | 16 (4.3)             | 2 (1.7)          | 6 (2.1)                 | 5 (3.8)       |                                        |
| Positive predictive value, % | 13.5                | 16.1             | 20.9                    | 12.9          | 0.015                                  |
| Observation time, seconds | 233±92               | 254±104          | –                       | –             | <0.001                                 |

*The common denominator of this set of values is the number of target lesions.

**Note:** Observation time was measured in the patients who completed the primary examination: 2234 in the WLI group and 2238 in the 2G-NBI group. Values are expressed as means±SD. An en dash represents no data collected.

WLI, white light imaging; 2G-NBI, second-generation narrow band imaging; EGC, early gastric cancer.

13.5%, respectively; p=0.015). Some of the remaining lesions were neoplastic; primary WLI detected 17 low-grade adenomas, while primary 2G-NBI detected 20 low-grade adenomas plus one advanced gastric cancer. Other detected lesions were non-neoplastic: primary WLI detected 246 focal gastritis, 27 intestinal metaplasia, 5 gastric ulcers, 5 hyperplastic polyps and 4 fundic gland polyps, while primary 2G-NBI detected 167 focal gastritis, 26 intestinal metaplasia, 1 fundic gland polyp and 1 xanthoma. There was one lesion in each primary examination whose final pathological diagnosis was undetermined despite re-examination. EGC diagnostic performance by non-magnified examination for patients was as follows: sensitivity and specificity were 80.0% and 88.0%, respectively, in WLI, and 76.8% and 91.0%, respectively, in 2G-NBI.

Among all patients who completed the primary examination, the mean observation times for primary WLI and primary 2G-NBI were 233 (range: 34–715) and 254 (range: 37–902) seconds, respectively (p<0.001). Among patients without target lesions, they were 223 (range, 34–613) and 244 (range, 37–902) seconds, respectively (p<0.001). Among all non-magnifying examinations (primary WLI, primary 2G-NBI, secondary WLI and secondary 2G-NBI) 145 EGCs were detected. The characteristics of these tumours are summarised in table 3. The 109 EGCs detected in the primary examination did not differ significantly between the WLI and 2G-NBI groups with respect to tumour location, macroscopic type or histological classification. Among the EGCs in the WLI group, 65 were endoscopically resected, 1 was surgically resected and 3 were untreated. Among the EGCs in the 2G-NBI group, the corresponding numbers were 65 (including three focal gastric cancers), 2 and 6. There were no significant differences in tumour size or tumour depth, as defined by pathological findings, between the groups. Primary WLI failed to detect 19 (27.5%) EGCs, and 2G-NBI failed to detect 17 (22.4%). The characteristics of the missed EGCs were similar, with no significant differences between the groups.

The only adverse event observed in this study was bleeding from a target lesion after biopsy in the 2G-NBI group, which required haemostatic therapy.

An additional subanalysis of indication of endoscopy (oesophageal cancer and gastric neoplasm) was also conducted. In the oesophageal cancer group, the EGC detection rates of primary WLI and 2G-NBI were 0.8% and 0.5% (p=0.686), respectively. In the gastric neoplasm group, the EGC detection rates of primary WLI and 2G-NBI were 2.2% and 2.7% (p=0.342), respectively (online supplementary table S1).
| Characteristic of the detected EGC | WLI group | 2G-NBI group | P value (primary WLI vs primary 2G-NBI) | P value (secondary WLI vs secondary 2G-NBI) |
|-----------------------------------|-----------|-------------|---------------------------------------|----------------------------------------|
|                                   | Detected by primary WLI (n=50) | Detected by secondary 2G-NBI (n=19) | Detected by primary 2G-NBI (n=59) | Detected by secondary WLI (n=17) |
| Tumour location*, n (%)           |           |             |                                       |                                       |
| Upper third                       | 12 (24.0) | 5 (26.3)    | 15 (25.4)                            | 6 (35.3)                             |
| Anterior wall                     | 3         | 0           | 5                                     | 1                                     |
| Lesser curvature                   | 2         | 0           | 2                                     | 1                                     |
| Posterior wall                    | 5         | 3           | 5                                     | 1                                     |
| Greater curvature                  | 2         | 2           | 3                                     | 3                                     |
| Middle third                      | 23 (46.0)| 8 (42.1)    | 26 (44.1)                            | 7 (41.2)                             |
| Anterior wall                     | 5         | 1           | 6                                     | 1                                     |
| Lesser curvature                   | 9         | 2           | 7                                     | 2                                     |
| Posterior wall                    | 6         | 0           | 7                                     | 1                                     |
| Greater curvature                  | 3         | 5           | 6                                     | 3                                     |
| Lower third                       | 15 (30.0)| 6 (31.6)    | 18 (30.5)                           | 4 (23.5)                             |
| Anterior wall                     | 3         | 2           | 0                                     | 0                                     |
| Lesser curvature                   | 5         | 2           | 6                                     | 1                                     |
| Posterior wall                    | 2         | 1           | 5                                     | 0                                     |
| Greater curvature                  | 5         | 1           | 7                                     | 3                                     |
| Tumour macroscopic type*, n (%)   |           |             |                                       |                                       |
| 0-I                               | 2 (4.0)   | 0 (0)       | 2 (3.4)                               | 0 (0)                                 |
| 0-IIa                             | 10 (20.0)| 5 (26.3)    | 12 (20.3)                             | 2 (11.8)                             |
| 0-IIb                             | 1 (20.0) | 0 (0)       | 1 (1.7)                               | 0 (0)                                 |
| 0-IIc                             | 37 (74.0)| 14 (73.7)   | 44 (74.6)                             | 15 (88.2)                            |
| Tumour histological classification* |         |             |                                       |                                       |
| High-grade adenoma                 | 0 (0)     | 0 (0)       | 5 (8.5)                               | 0 (0)                                 |
| Well-differentiated tubular AC     | 43 (86.0)| 16 (84.2)   | 41 (69.5)                             | 15 (88.2)                            |
| Moderately differentiated AC       | 5 (10.0) | 3 (15.8)    | 4 (6.8)                               | 1 (5.9)                              |
| Poorly differentiated AC, solid type | 0 (0) | 0 (0)       | 1 (1.7)                               | 1 (5.9)                              |
| Poorly differentiated AC, non-solid type | 0 (0) | 0 (0)       | 1 (1.7)                               | 0 (0)                                 |
| Signet-ring cell carcinoma         | 2 (4.0)   | 0 (0)       | 3 (5.1)                               | 0 (0)                                 |
| Others†                           | 0 (0)     | 0 (0)       | 4 (6.8)                               | 0 (0)                                 |
| Resected EGC, n (%)               | 47 (94.0)| 19 (100)    | 51 (86.4)                             | 16 (94.1)                             |
| Tumour size‡, mm                  | 11.9±8.9  | 13.3±8.4    | 14.5±9.8                              | 12.5±7.5                              |
| Tumour depth§, n (%)              | 0.777     | 1           |                                       |                                       |

* P value calculated using the Wilcoxon–Mann–Whitney test. † P value calculated using the Chi-square test. ‡ P value calculated using Student’s t-test. § P value calculated using the Fisher’s exact test.
Although the detection rate of 2G-NBI was slightly higher than that of WLI (2.3% vs 1.9%), we were unable to demonstrate the expected superiority of 2G-NBI. However, this result suggested that 2G-NBI was equivalent to WLI in EGC detection. There are two possible explanations for our inability to show positive results. First, all participating endoscopists had extensive experience and adequate skills for EGC detection using WLI. As a result, they could detect EGC using WLI at a higher rate than initially expected. Second, the period to enrich experience in the use of non-magnified 2G-NBI was probably not enough, even for experts, because the detection rate of EGC by 2G-NBI was lower than initially expected.

2G-NBI had a significantly better PPV than did WLI. PPV is a critical indicator of screening efficiency, and a sufficiently high PPV can reduce unnecessary biopsies and the associated risks of bleeding. Bleeding may especially be of concern to patients undergoing antithrombotic treatment. Although several guidelines regard biopsy as a low-risk procedure for such patients, the number of biopsies should be minimised if antithrombotics are prescribed. Reasons for these positive findings for BLI might be related to the difference in used wavelength. Because the primary endpoint and patient background were different from those in our study, a direct comparison between 2G-NBI and BLI could not be made and may be warranted in the future.

Our study has several limitations. First, the actual EGC detection rate of each modality was lower than the initial assumption, whereas this rate was quite higher than that of the general population. This might have been caused by patient factors, such as widespread implementation of Helicobacter pylori eradication, and that most of the concomitant EGC might have been detected during previous endoscopic resections. These might also cause the high missing rate. The screening for such patients will become the issue to be solved, in the future of the gastric cancer high-risk region. Second, it was open label, as it is impossible to blind the endoscopist to the
endoscopy modality. Therefore, we cannot exclude observer bias. Third, the analysis of the characteristics of missed EGCs was not sufficiently powered owing to the small number of EGCs detected. Finally, it is unclear whether our results can be extended to patients with a low risk for gastric cancer.

Conclusions
Taken together, our analysis indicates that 2G-NBI did not show improved detection of EGC than WLI in patients at high risk for gastric cancer. However, the 2G-NBI showed a better cancer detection potential that needs further investigations. An incomplete sensitivity of current endoscopy in detecting EGC is still an issue that need to be solved.

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NY: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; final approval of the article and study supervision.
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Competing interests
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Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not required.

Provenance and peer review
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Data availability statement
Data are available on reasonable request. The data that support the findings of this study have been deposited in UMIN (https://www. umin.ac.jp/ctr/index.htm), and the data are available from the corresponding author, MM, on reasonable request.

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