Narrow-band imaging versus white light versus mapping biopsy for gastric intestinal metaplasia: a prospective blinded trial

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Background and Aims: Gastric intestinal metaplasia (GIM) is a gastric cancer precursor. Narrow-band imaging (NBI) may improve detection of GIM. We compared detection of GIM with high-definition white-light (HD-WL) endoscopy, NBI, and mapping biopsies in a population with increased gastric cancer risk.

Methods: Patients undergoing upper endoscopy had HD-WL examination by 1 endoscopist, followed by an NBI examination by a second endoscopist blinded to HD-WL findings. The location of abnormalities detected by HD-WL and NBI were recorded by a research coordinator, and targeted biopsies of abnormal areas were performed after NBI. Subsequently, 5 mapping biopsies were performed per patient. Biopsy specimens were read by a pathologist blinded to mode of acquisition. The primary outcome was the proportion of patients with GIM.

Results: We enrolled 112 patients: 107 (96%) were Hispanic or Asian, and 34 (30%) had GIM. Higher proportions of patients with GIM were detected by NBI (22/34 [65%]) and mapping (26/34 [76%]) versus HD-WL (10/34 [29%]) ($P < .005$ for both comparisons). GIM was detected by NBI in only 6 patients and only by mapping biopsy in 10 patients; no patient had GIM detected solely by HD-WL. Higher proportions of sites with GIM also were detected with NBI (30/57 [53%]) and mapping biopsies (38/57 [67%]) than HD-WL (16/57 [28%]) ($P < .005$ for both comparisons). The median number of biopsies per patient with mapping biopsies (5) was significantly higher than with NBI (2) or HD-WL (1).

Conclusions: HD-WL endoscopy is insufficient for detection of GIM in patients at increased risk for gastric cancer. NBI-targeted biopsies plus mapping biopsies should be used. (Clinical trial registration number: NCT02197351.) (Gastrointest Endosc 2017;86:857-65.)

Gastric cancer results in 723,000 deaths annually worldwide.[1] It often presents with vague symptoms of dyspepsia, and is frequently diagnosed at advanced stages. Gastric cancer develops as a series of steps beginning with *Helicobacter pylori*-associated, non-atrophic, chronic gastritis and progresses to atrophic

Abbreviations: GIM, gastric intestinal metaplasia; HD-WL, high-definition white light; NBI, narrow-band imaging.

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gastritis, intestinal metaplasia, dysplasia, and carcinoma.[2-5] Patients with gastric intestinal metaplasia (GIM) are more likely to develop gastric cancer than the general population, and those with high-grade dysplasia have a 25% chance of developing gastric cancer within 1 year.[3,6] The significant risk of stepwise progression is the basis for screening at-risk populations and surveying those with GIM.[7-9]

However, patients with *H pylori* infection, GIM, or dysplasia often have no lesions visible on white light endoscopy.[10] Experts recommend mapping biopsies that are not targeted to specific lesions, from the antrum, angularis, and body to identify gastric preneoplastic histologic findings, although this approach may miss 50% of those with GIM.[11-12] A number of image-enhancement techniques, including narrow-band imaging (NBI), have been proposed to improve the identification of preneoplastic gastric findings. NBI is a noninvasive technique in which illumination from the endoscope is filtered to favor 2 narrow bands of light, 415 nm and 540 nm, which correspond to the hemoglobin absorption wavelength in the capillaries and submucosal vessels, respectively. NBI may enhance evaluation of mucosal surface patterns and vascular irregularities. It improves detection of dysplasia in Barrett's esophagus and characterization of colon polyps.[13-14]

Recently, a simplified classification by using NBI endoscopy was proposed for gastric mucosal examination.[15] As part of a 5-center consortium, we demonstrated in a multicenter, although uncontrolled, cohort study that NBI has favorable accuracy in the detection of GIM and dysplasia.[16] The aim of this study was to determine in a blinded, controlled manner whether targeted biopsies of abnormal mucosa identified with NBI improves the detection of GIM as compared with high-definition white light (HD-WL) and the Sydney mapping protocol.

METHODS

Patients

Patients were enrolled at the Los Angeles County University of Southern California Medical Center from September 2014 to May 2016, and the study was registered at Clinicaltrials.gov (NCT02197351). Written informed consent and Health Insurance Portability and Accountability Act authorization were obtained from all patients before enrollment. All authors had access to the study data and approved the final submission.

Patients undergoing upper endoscopy for standard clinical care for the following indications were eligible: abdominal pain, dyspepsia, iron deficiency anemia, weight loss, abnormal imaging, and gastric ulcer. At time of enrollment we identified the most clinically important indication for the procedure (eg, iron deficiency rather than dyspepsia) as the primary indication. Our institution has a high gastric cancer risk because of the following factors: most patients are Hispanic or Asian, the vast majority were born in regions in which *H pylori* is endemic, and most patients are of lower socioeconomic status.[17] The endoscopists were not blinded to clinical information, including procedure indication and patient demographics.

Those undergoing endoscopy to treat active GI bleeding or to eradicate varices were excluded. Patients at increased risk of bleeding adverse events were excluded: use of clopidogrel, ticlopidine, warfarin, heparin, enoxaparin, or a direct oral anticoagulant or with an international normalized ratio >1.5, (normal range, 0.9-1.1) platelet count $<75 \times 10^9$/L, (normal range, 160-360) or known bleeding dyscrasias.

NBI classification

The endoscopists in this trial used the NBI algorithm described and validated by Pimentel-Nunes et al.[15] Features suggestive of GIM included a well-delineated tubulovillous or ridge glandular pattern (Fig. 1A) and/or a light blue crest sign (Fig. 1B). The latter is a slightly raised bluish-white region. All endoscopists routinely used NBI in clinical practice. However, to standardize interpretation according to the simplified classification system,[15] they completed a validated Web-based training program of 20 tests each made up of 10 randomly ordered gastric NBI videos as described by Dias-Silva et al[18] before initiation of enrollment. The 4 endoscopists each had a mean accuracy of >80% on the final 4 NBI training tests.

Intervention

A prospective repeated measures design was used in which HD-WL and NBI examination of each patient was performed by 2 endoscopists, blinded to each other's findings. After informed consent, HD-WL endoscopy was performed with moderate sedation by using a GIF-H180 endoscope illuminated by the Evis Exera II processor (Olympus America, Center Valley, Pa). Moderate sedation was provided under direction of the attending endoscopist by sequential administration of intravenous fentanyl, midazolam, and in some cases diphenhydramine. The aim was to provide comfort while patients maintained spontaneous ventilation and appropriate responses to tactile and verbal stimulation.[19] Mucolytic agents were not used during any component of the examination. The exact locations of all mucosal findings in the stomach potentially representing GIM, including nodularity and discoloration, were noted by the HD-WL endoscopist and recorded by the research coordinator. Biopsy was not performed until after the NBI examination so that tissue injury and blood would not distort or bias the NBI assessment. At the conclusion of the HD-WL examination, while the endoscope was positioned in the stomach, the HD-WL endoscopist pushed the program button on the head of the endoscope to transition to NBI mode.

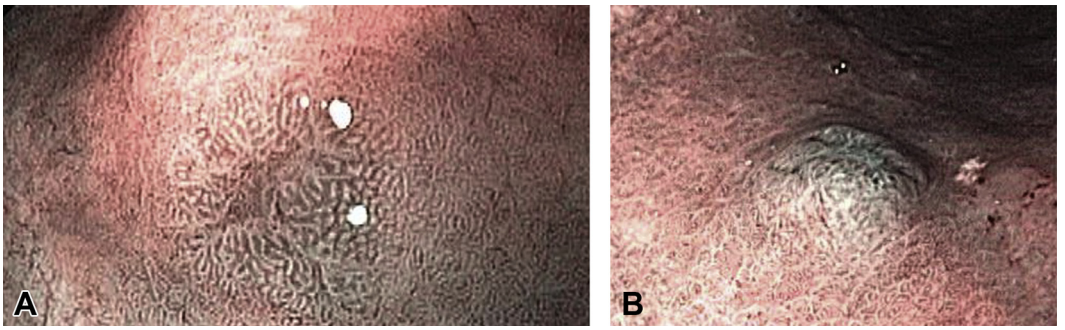

Figure 1. Narrow-band imaging features consistent with gastric intestinal metaplasia. **A,** Tubulovillous or ridge glandular pattern. **B,** The light blue crest sign.

The NBI endoscopist then entered the procedure room, and the HD-WL endoscopist left the room. Endoscopic examination of the stomach by using NBI was performed, the type and location of NBI abnormalities suggestive of GIM were recorded by the research coordinator, and biopsies were obtained from these sites. At the end of this examination, the NBI endoscopist transitioned the view back to white-light mode. The HD-WL endoscopist returned to the room and took a biopsy specimen from the sites identified and recorded during the initial HD-WL examination, if they had not already been sampled by the NBI endoscopist. The research coordinator, who was present for the entire procedure, verified that the HD-WL endoscopist took a biopsy specimen from the specific sites designated before the NBI endoscopist's examination and not from additional sites. Subsequently, mapping protocol biopsies were performed of the following locations according to the updated Sydney protocol[11]: antrum lesser curvature, antrum greater curvature, body lesser curvature, body greater curvature, and angularis.

The biopsies guided by HD-WL, NBI, and mapping were coded and submitted to an expert GI pathologist blinded to the mode of acquisition. The pathologist determined the presence of intestinal metaplasia, dysplasia, cancer, or other findings. If GIM was confirmed in at least 2 sites in the same patient it was defined as extensive.[4]

Endpoints

The primary endpoint of the study was the proportion of patients with a histologic diagnosis of GIM who had this diagnosis identified by HD-WL targeted biopsies, NBI targeted biopsies, or mapping protocol biopsies. An additional endpoint was the yield of HD-WL, NBI, and mapping biopsies on a per-site basis, based on the total number of regions or sites in the stomach with biopsy-confirmed GIM. Each abnormal area that was identified by HD-WL or NBI and from which a biopsy specimen was taken was considered a site, and each mapping protocol–defined biopsy site was considered a separate site. If exactly the same site was targeted by HD-WL and NBI, a single biopsy specimen was obtained and categorized as identified by both modalities. The total number of patients and sites with GIM used to calculate the yield of each method was determined by the combination of all patients and sites with GIM detected by the 3 methods.

Additional endpoints included total and median number of biopsies per patient guided by the 3 modalities and the number of patients found to have dysplasia or gastric cancer.

Statistical analysis

Baseline features and outcomes were described by using means for normally distributed and medians for nonnormally distributed continuous variables and proportions for categorical variables. Given the repeated measures design, the Cochran Q test was used to assess for overall differences in per-person and per-site yield of GIM among the 3 methods. The McNemar test with Bonferroni correction was then used to compare per-patient yield for individual pairs of tests (eg, odds ratio for HD-WL vs NBI). Differences in the median number of biopsies per patient performed by using HD-WL and NBI compared with mapping protocol biopsies (predefined at 5 biopsies) was performed by using the 1-sample Wilcoxon rank sum test. The impact of procedure time on metaplasia detection was performed by using logistic regression.

We performed a sensitivity analysis by using conditional (fixed effects) logistic regression with the patient study number as the matched group variable. We stratified by demographic features of interest including sex, age, indication, ethnicity, proton pump inhibitor and/or histamine blocker use, and comorbidities. We also stratified our analysis by procedure time (<23 vs ≥ 23 minutes) and whether the patient was enrolled in the early (first 56 procedures) or late (last 56 procedures) phase of the study.

Based on an expected 15% difference in detection of gastric metaplasia for HD-WL versus NBI and anticipated prevalence of intestinal metaplasia of 20% (from pilot data), using G*power ($\alpha = .05$, $\beta = .20$) we estimated that a sample size of 200 patients would be sufficient to demonstrate a significant difference. Statistical analysis was performed by using SAS 9.4 (SAS Institute, Cary, NC) and SPSS 22 (IBM, Armonk, NY).

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Patients

Given the transition of our endoscopy unit from the Evis Exera II 180 series upper endoscopes to a newer system with different NBI capabilities, the study was halted after 112 patients were enrolled. The mean age was 51.9 ± 10.6 years, and 63% were female (Table 1). One hundred patients (89%) were Hispanic, 7 (6%) were Asian, and 5 (5%) were black or white. Eight patients were born in the United States (7%); the remainder originated from Mexico (63%), Central America (24%), and Asia (6%). One quarter had previously been treated for *H pylori,* and another 28 patients (25%) had *H pylori* infection identified by biopsy specimens obtained as part of the study. The primary indications for endoscopy included abdominal pain (34%), anemia (34.2%), and dyspepsia (36%). Although 11 patients (9.8%) had previously undergone upper endoscopy, including 6 who had gastric biopsy, none of the patients had a known history of GIM, atrophy, or dysplasia. Among the cohort, 12 patients (10.7%) were smokers, and 5 (4.5%) had a first-degree family member with gastric cancer. None of the patients had a known history of pernicious anemia or Epstein-Barr virus infection.

TABLE 1. Selected characteristics of study cohort

Variable	Patients (N = 112)
Age, mean ± SD, y	51.9 ± 10.6
Female, no. (%)	71 (63.4%)
Race/ethnicity, no. (%)	
Hispanic white	100 (89.3%)
Non-Hispanic white	3 (2.7%)
Asian	7 (6.3%)
Black	2 (1.8%)
Born outside of the United States	97 (88.2%)
Indication for endoscopy, no. (%)	
Dyspepsia	40 (35.7%)
Abdominal pain	38 (34.2%)
Iron deficiency	19 (17.0%)
Other	15 (13.1%)
Prior *H pylori* therapy, no. (%)	27 (24.1%)
Histamine$_2$-receptor antagonist use, no. (%)	12 (10.7%)
Proton pump inhibitor use, no. (%)	64 (57.2%)
Tobacco use, no. (%)	12 (10.7%)
Comorbidities, no. (%)	36 (32.1%)

SD, Standard deviation; *H pylori,* Helicobacter pylori.

Per-patient yield

Overall, 34 patients (30%) had GIM. It was found in the proximal stomach in 17 (50%), extensive in 15 (44%), and either extensive or proximal in 23 (68%). The per-patient yields of the 3 methods to detect metaplasia were significantly different: GIM was detected by HD-WL in 10 patients with GIM (29%), by NBI in 22 (65%), and by mapping biopsies in 26 (76%) (Fig. 2) (P = .001). NBI was more likely to detect patients with metaplasia than HD-WL (odds ratio [OR] 7.0; 95% confidence interval [CI], 1.6-30.8) as were mapping biopsies (OR 9.0; 95% CI, 2.1-38.8). There was no significant different in per-patient yield of NBI versus mapping biopsies (OR 1.5; 95% CI, 0.6-3.7).

Among the 19 patients with GIM at a single site (56%), GIM was in the antrum in 14, angle in 4, and body in 1. Among the 15 with extensive GIM (44%), GIM was present in 3 sites in 8 (23%) and 2 sites in 7 (21%). For those with multiple sites of involvement, the patterns were as follows: antrum and angle in 4; body and angle in 3; body, angle, and antrum in 5; and 2 sites in the antrum at least 3 cm apart in 2.

Mapping protocol biopsies identified 10 patients with GIM in whom GIM was not detected by the other methods. NBI identified 6 patients with GIM not detected by the other methods, whereas HD-WL detected no patients with GIM not detected by NBI or mapping biopsies. In 6 patients GIM was detected by all 3 methods, and in 10 it was detected by 2 of the methods. The highest yield combination of 2 methods was mapping biopsy combined with NBI, which detected all patients with GIM and 95% of sites with GIM (Table 2). The per-patient rate of NBI-guided GIM detection did not differ among the study endoscopists; it ranged from 0.263 to 0.330 (P = .77).

Two of the 112 patients were found to have gastric cancer, both with diffuse-type infiltrating adenocarcinoma. In 1 case, the lesion was detected by HD-WL and NBI but not by mapping biopsies, whereas in the other it was detected by all 3 methods. No patients were found to have dysplasia.

Per-site yield

Fifty-seven individual sites of GIM were identified among the 34 patients with GIM. Per-site metaplasia detection differed significantly among the groups: HD-WL targeted biopsies detected 16 (28%), NBI targeted biopsies 30 (53%), and mapping protocol biopsies 38 (67%) (Fig. 3) (P = .001). NBI was significantly more likely than HD-WL to detect sites of GIM (OR 4.5; 95% CI, 1.5-13.3). Mapping biopsies were also more likely to detect GIM than HD-WL (OR 4.2; 95% CI, 1.8-9.5). There was no significant difference in per-site detection of GIM between mapping biopsies and NBI (OR 1.5; 95% CI, 0.8-2.8). Among the 57 sites, 23 were detected only by mapping biopsies, 12 only by NBI, and 3 only by HD-WL. Eight sites were detected by all 3 methods and 11 by 2 of the methods. NBI-targeted biopsies detected more sites in

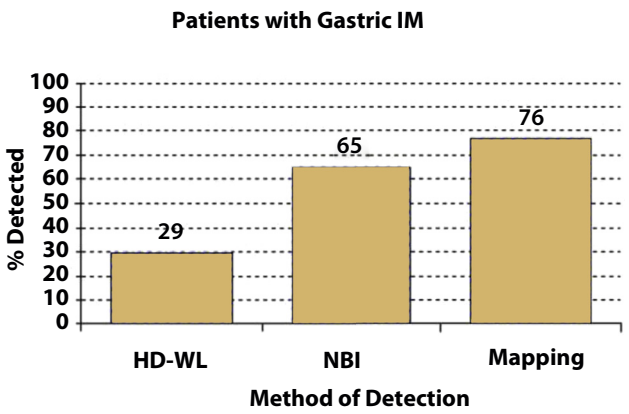

Figure 2. The proportions of the 34 patients with gastric intestinal metaplasia identified by high-definition white-light targeted biopsies, narrow-band imaging targeted biopsies, or mapping protocol biopsies. *IM,* intestinal metaplasia; *HD-WL,* high-definition white light; *NBI,* narrow-band imaging.

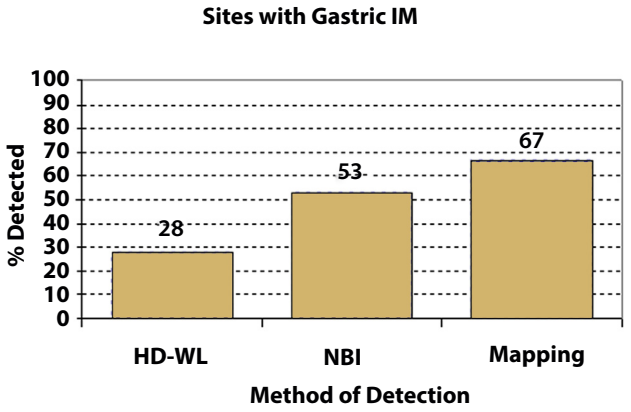

Figure 3. The proportions of 57 sites with gastric intestinal metaplasia identified by high-definition white-light targeted biopsies, narrow-band imaging targeted biopsies, or mapping protocol biopsies. *IM,* intestinal metaplasia; *HD-WL,* high-definition white light; *NBI,* narrow-band imaging.

TABLE 2. Yield of gastric intestinal metaplasia detection by combinations of modalities

	NBI + mapping	NBI + HD-WL	Mapping + HD-WL
Per-patient yield	100% (34/34)	70.6% (24/34)	82.4% (28/34)
Per-site yield	94.7% (54/57)	59.6% (34/57)	75.4% (43/57)

NBI, Narrow-band imaging; *HD-WL,* high-definition white light.

TABLE 3. Locations of gastric intestinal metaplasia sites detected by NBI, HD-WL, and mapping protocols

	Antrum, no. (%)	Angle, no. (%)	Body, no. (%)
NBI (N = 30)	25 (83.3)	4 (13.3)	1 (3.3)
HD-WL (N = 16)	14 (87.4)	1 (6.3)	1 (6.3)
Mapping protocol (N = 38)	16 (42.1)	14 (36.8)	8 (21.1)

NBI, Narrow-band imaging; *HD-WL,* high-definition white light.

the antrum and mapping protocol more sites in the body and angle (Table 3).

Biopsies

Overall, 147 HD-WL, 253 NBI, and 560 mapping protocol guided biopsies were performed (Table 4). The median number of biopsies per patient guided by NBI and HD-WL were significantly fewer than the 5 biopsies mandated by the mapping protocol. The average number of biopsies guided by each method per patient detected with GIM by that method was 11.5 for NBI, 14.7 for HD-WL, and 21.5 for the mapping protocol. The primary HD-WL finding for each of the patients and histologic correlates are reported in Table 5. No single HD-WL finding was correlated with GIM in more than one third of patients, and 22.6% of those with a normal HD-WL examination were found to have metaplasia by NBI or mapping biopsy. We found that among the abnormal regions targeted by NBI in which targeted biopsies did not demonstrate GIM, 52% had chronic gastritis, with *H pylori* organisms identified in 50% of these specimens.

Endoscopic procedures

The mean procedure time was 24.2 (± 7.8) minutes, and the median procedure time was 23 minutes, with the interquartile range of 19 to 28 minutes. When modeled as a continuous variable procedure, time was not associated with detection of metaplasia (OR 0.99; 95% CI, 0.94-1.04); $P = .667$. When modeled as the categorical variable of greater than or equal to the median procedure time of 23 minutes, time also was not correlated with metaplasia detection (OR 1.23; 95% CI, 0.54-2.80); $P = .618$. Moderate sedation directed by the attending endoscopist was used successfully for all procedures; fentanyl and midazolam were used in every procedure with supplemental diphenhydramine (25-50 mg) in 17 patients (15.2%).

Sensitivity analysis

Risk factors for metaplasia. We observed consistent trends when the methods were compared among groups stratified by potential risk factors for GIM including age, sex, and ethnicity and the presence of comorbidities. NBI and mapping protocol guided biopsies detected more patients with GIM than did HD-WL (Table 6). NBI also performed better than HD-WL among those who had been diagnosed previously with *H pylori* infection. There were too few patients with tobacco use or family history of gastric cancer to enable statistical comparison among the groups.

TABLE 4. Biopsies guided by NBI, HD-WL, and mapping protocols

	Total biopsies	Biopsies per patient (% by method)			Median (IQR)	*P* value for comparison with mapping
		0-1	2-4	≥5		
NBI	253	36.3	52.2	10.8	2 (2)	< .001
HD-WL	147	63.7	28.3	7.1	1 (2)	< .001
Mapping protocol	560	0	0	100	5 (0)*	–

NBI, Narrow-band imaging; *HD-WL,* high-definition white light; *IQR,* interquartile range.
*Value defined by protocol (n = 5 for all 112 patients).

Comparison of methods stratified by procedure time. Among those whose total procedure time was less than the median of 23 minutes, NBI and the mapping protocol (OR 4.5; 95% CI, 2.3-9.7 for both) enabled greater GIM detection compared with HD-WL. Among those whose procedures were ≥23 minutes, NBI (OR 4.2; 95% CI, 2.3-8.2) and the mapping protocol (OR 4.9; 95% CI, 2.5-10.8) also improved metaplasia detection relative to HD-WL.

Comparison of methods stratified by early versus late enrollment in the study. Among the first 56 patients enrolled in the study, NBI (OR 3.8; 95% CI, 2.0-7.6) and the mapping biopsy (OR 3.5; 95% CI, 1.9-6.9) were more likely to detect metaplasia than HD-WL during the first half of the study. Among the 56 patients enrolled in the latter part of the study, NBI (OR 4.1; 95% CI, 2.2-8.2) and mapping biopsy (OR 6.6; 95% CI, 3.1-16.1) were more likely to detect metaplasia during the second half of the study.

DISCUSSION

In this prospective blinded trial, we demonstrated that targeted biopsies guided by NBI or mapping biopsies had a per-patient yield more than 2-fold greater than that of targeted biopsies guided by HD-WL. Because NBI-guided biopsies and updated Sydney mapping protocol biopsies identified different patients and sites, our data suggest that these methods are best used in combination in the evaluation of patients at increased risk for gastric cancer because of country of origin and ethnicity.

Prior studies that used mapping protocol biopsies as the criterion standard have shown that white-light endoscopy has a relatively poor sensitivity (32%-56%) for detection of histologic gastritis and gastric cancer precursors.[10,20-21] Although mapping biopsies appear adequate to identify gastric precursors in some cohorts, others have shown that both the original and revised Sydney biopsy protocols may miss numerous sites with GIM.[11-12,22] In order to improve detection of GIM, a number of approaches including chromoendoscopy with methylene blue and electronic image enhancement techniques such as NBI have been studied. The advantage of the latter approach is that it does not require the additional time, cost, and burden of obtaining, preparing, and applying dye solutions.

Prior observational studies suggest that NBI improves the sensitivity for GIM as compared with HD-WL. Uedo et al[23] demonstrated that the magnification-NBI finding of the light blue crest sign had a per-site 89% sensitivity and 93% specificity for GIM in a small study of 34 patients. However, magnification (×80) gastroscopes are not available in Western countries. Additionally, Japanese gastric NBI algorithms are complex, with classification systems that vary by region of the stomach.[24-26] Simplified gastric NBI approaches that primarily recognize the tubulovillous or ridge patterns of GIM have shown promising preliminary results.[27-28] The Porto[15] group has developed the most widely used simplified gastric NBI system, which does not require high magnification endoscopy. In their validation study, the approach had an accuracy of 84% for the diagnosis of GIM and high reproducibility, with a kappa of 0.62. We participated in a recent multicenter cohort study, which demonstrated that NBI increased the sensitivity for GIM detection from 53% with HD-WL alone to 87% with NBI combined with HD-WL.[16]

The strength of the current study is that it prospectively compares NBI with the standard modalities of white-light endoscopy and of mapping protocol biopsies, and the design more rigorously reduces bias in the comparison of NBI with these other methods. In prior studies, NBI and biopsies were performed by the same endoscopists who performed the white-light examination of the stomach. To minimize the risk that the white-light examination would bias NBI assessment and vice versa, in our study these assessments were performed in tandem by 2 different endoscopists blinded to one another's findings. A research coordinator with 25 years of experience conducting upper endoscopic trials verified that the sites that biopsy specimens were obtained from by the HD-WL endoscopist corresponded to the specific locations in the stomach identified before the NBI assessment. We also further decreased potential bias by holding off on performing biopsies until after both NBI and HD-WL examinations were completed.

Correa et al[4] recommend that, in patients at increased risk of gastric cancer, sampling of all abnormal mucosa

TABLE 5. Primary white light findings with histologic correlate

Primary white light finding per-patient (N = 112)	Cancer, no. (%)	Intestinal metaplasia, no. (%)	Chronic gastritis, no. (%)	Reactive gastropathy, no. (%)	Fundic gland polyp, no. (%)	Normal, no. (%)
Erosions (N = 11)	–	2 (18.2)	3 (27.3)	4 (36.4)	0	2 (18.2)
Pale mucosa (N = 6)	–	2 (33.3)	1 (16.6)	–	–	3 (50)
Erythema (N = 15)	–	4 (26.7)	6 (40)	2 (13.3)	1 (6.7)	2 (13.3)
Nodule (N = 11)	–	2 (18.2)	4 (3.4)	4 (36.4)	–	1 (9.1)
Polyp (N = 7)	–	–	1 (14)	–	3 (42.9)	3 (42.0)
Ulcer (N = 6)	1 (16.7)	1 (16.7)	3 (50)	1 (16.7)	–	–
Thickened fold (N = 2)	–	–	–	2 (100)	–	–
Mass (N = 1)	1	–	–	–	–	–
Normal, no biopsies (N = 53)	–	12 (22.6)	25 (47.2)	6 (11.3)	–	10 (18.8)

TABLE 6. Stratified comparison of per-patient metaplasia detection

	NBI vs HD-WL OR (95% CI)	Mapping vs HD-WL OR (95% CI)	Mapping vs NBI OR (95% CI)
Age >53, y	6.6 (1.6-26.9)	5.6 (1.4-22.2)	0.8 (0.3-2.7)
Male	11.9 (1.3-108.0)	11.9 (1.3-108.0)	1.0 (0.2-4.2)
Hispanic ethnicity	4.3 (1.2-14.6)	5.7 (1.6-20.0)	1.3 (0.5-3.9)
Higher risk indication*	14.7 (1.8-120.8)	19.9 (2.4-165.3)	1.4 (0.5-4.0)
History of *H pylori* infection	15.7 (1.1-235.8)	3.3 (0.3-35.0)	0.2 (0-2.1)
Comorbidities	11.1 (1.2-107.2)	8.1 (0.9-76.0)	0.7 (0.2-3.5)
Proton pump inhibitor and/or histamine blocker use	6.3 (1.5-26.7)	5.1 (1.2-21.1)	0.8 (0.2-2.9)

NBI, Narrow-band imaging; *HD-WL,* high-definition white light; *OR,* odds ratio; *CI,* confidence interval.
*High risk indications included abdominal pain and iron deficiency anemia.

seen on white-light endoscopy plus mapping biopsies that use the updated Sydney protocol be used. Our findings suggest that NBI examination should be performed to optimize yield. The recent uncontrolled multicenter cohort trial suggests that NBI might obviate the need for mapping protocol biopsies.[16] Our findings in this controlled trial, however, indicate that although NBI was more efficient than mapping biopsies (nearly twice as many biopsy specimens were taken with the mapping protocol compared with NBI [21.5 vs 11.5] for each patient diagnosed with GIM), if mapping biopsies had not been performed, GIM would have been missed in 29% of patients. Nevertheless, if NBI had not been performed, 18% of cases of GIM would not have been identified. This blinded, tandem study suggests that the NBI and mapping biopsies are complementary, and both should be performed even though the latter approach requires relatively more biopsies.

Prior studies primarily included patients with a personal history of early gastric cancer or dysplasia or intestinal metaplasia.[15,27,29] Although our study population was at increased risk for gastric cancer, given origin and ethnicity, none of our patients had a history of gastric cancer or precursor lesions. Thus, our findings support the use of NBI in the evaluation of symptomatic patients with demographic risk factors for gastric neoplasia but no personal history of gastric pathology, in order to identify gastric cancer precursor lesions such as GIM.

This study has several limitations. The most important is potential variability in NBI interpretation among endoscopists. To standardize interpretation, all study endoscopists had to complete a rigorous training and assessment course that has been validated and reported.[18] By completion of this training, the study endoscopists demonstrated high accuracy. Furthermore, the rate of GIM detection by NBI did not differ among the study endoscopists; it ranged from 0.26 to 0.33. A limitation is that specific endoscopists were not assigned to perform NBI during designated periods of the study, and thus there is a risk that endoscopists later in the study may have had more NBI experience. A design that randomly assigned specific endoscopists to perform NBI versus HD-WL examinations throughout the study would have addressed the potential effect of experience on GIM detection. Nevertheless, a

sensitivity analysis comparing GIM detection during the first and latter portions of the study showed a similar performance of NBI relative to HD-WL.

Another consideration was that the endoscopists were not blinded to clinical variables associated with detection of gastric pre-neoplasia including prior *H pylori* positivity, older age, and Hispanic ethnicity. Nevertheless, our repeated measures design in which all patients receive all treatments in a blinded manner controlled for these factors. Furthermore, our findings remained consistent in a sensitivity analysis in which we analyzed stratified subsets of our cohort to address these important clinical variables.

Teh et al[30] recently demonstrated that longer upper endoscopies are more likely to detect gastric cancer and precursor lesions including GIM. Although we did not directly compare study procedures to typical upper endoscopy without NBI and mapping biopsies, our procedure duration was likely longer than upper endoscopy without these procedures. Our median procedure time was 23 minutes, and the shortest procedure was 11 minutes, both longer than the mean time, 8.6 minutes, for slow endoscopists in the study of Teh et al. The fact that all of our procedures were relatively long is likely the reason we did not see major differences in overall yield with respect to study time. The sensitivity analysis did show that regardless of procedure duration, NBI and mapping biopsy protocol improved the diagnostic yield. Our results, in concert with those of Teh et al, suggest that both the increased duration of the examination and the additional use of NBI and mapping improve the yield of upper endoscopy for detection of gastric cancer precursors.

Our planned sample size was 200 patients. However, after enrollment of 112 patients, our endoscopy unit transitioned from 180 series to 190 series gastroscopes, which use a different processor. The newer system supports a different NBI image and may have disparate performance characteristics.[31-32] We felt that inclusion of patients analyzed by using the new system would introduce inconsistency in the study, and enrollment was therefore halted. Nevertheless, even with the smaller than planned sample size, we demonstrated that NBI markedly increased the proportion of patients who were diagnosed with GIM as compared with HD-WL endoscopy. Our results remain clinically meaningful because 180 systems remain among the most commonly used upper endoscopy platforms. The encouraging results of this study also provide a basis for initiating controlled studies by using the 190 system. An additional consideration is that the criterion standard for GIM was based on detection of GIM with any of the 3 biopsy methods being evaluated in the study. Ideally, the criterion standard for a diagnostic test does not include results of the tests being evaluated. Nevertheless, short of total gastrectomy, no independent standard exists to definitively determine whether GIM is present in a patient.

An ongoing controversy is whether GIM is of clinical significance when detected in North American and European centers. In the largest Western study assessing the risks associated with GIM, de Vries et al[3] reported on a cohort of 61,707 patients with GIM. They found that 875 patients with GIM developed gastric cancer, yielding an annual incidence of 0.25%. Li et al[33] used the Kaiser Permanente Northern California database to assess 4146 patients with GIM and found a relative risk for gastric adenocarcinoma of 2.6 compared with the overall Kaiser Permanente population; the annual incidence of progression from GIM to gastric adenocarcinoma was only 0.07%. However, the relative risk for gastric adenocarcinoma among Hispanic patients with GIM was 6.1 as compared with the Kaiser Permanente member population.[33]

Current American Society for Gastrointestinal Endoscopy guidelines suggest surveillance endoscopy for patients with GIM who are at increased risk of gastric cancer because of ethnic background or family history.[9] In addition, guidelines from a multi-society European consortium, including the European Society of Gastrointestinal Endoscopy, recommend surveillance for patients with extensive GIM (GIM in the body and antrum) at 3-year intervals.[7] Almost all of our patients were Hispanic or Asian, and extensive metaplasia was present in nearly half of those with GIM. Thus, even by Western guidelines, patients identified with GIM in our trial require surveillance for progression.

In summary, this blinded, tandem study demonstrates that both NBI and mapping biopsies are superior to HD-WL endoscopy in identifying patients with GIM. Given that NBI and mapping biopsies identified different patients, they appear to be optimally used in combination to identify precursor lesions in patients at increased risk of gastric cancer.

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