Journal of Gastroenterology and Hepatology

WILEY

JGHF Journal of Gastroenterology and Hepatology Foundation

ORIGINAL ARTICLE - GASTROENTEROLOGY (CLINICAL) OPEN ACCESS

The West Catching Up With the East: High-Magnification NBI Is Accurate for the Diagnosis of Gastric Neoplasia in a Western Population

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Received: 5 October 2024 | **Revised:** 20 January 2025 | **Accepted:** 2 February 2025

ABSTRACT

Background and Aim: Accurate endoscopic prediction of histology is key to recognition of early gastric neoplasia and selection of appropriate resection techniques. Narrow-band imaging with magnification (M-NBI) has proven to be highly accurate for gastric lesions in eastern countries; however, we sought to examine whether it can be effectively utilized in the west where evidence is scarce.

Methods: This is an analysis of a prospective database of gastric lesions at a single Australian center from 2009 to 2023. All lesions were assessed endoscopically using M-NBI and a determination made whether the lesion was neoplastic or non-neoplastic, as well as prediction of histological subtype. This was then correlated with final histology.

Results: A total of 232 lesions in 183 patients were included: 135 non-neoplastic and 97 neoplastic lesions. Thirty-five were adenomas, 29 early gastric cancers, and 6 advanced adenocarcinomas. For differentiating neoplastic versus non-neoplastic lesions, M-NBI had a sensitivity of 97.9% (CI 92.6%–99.7%) and specificity of 97.1% (CI 92.7%–99.2%). M-NBI was also highly accurate (97.0%, CI 93.9%–98.8%) for identifying lesions suitable for endoscopic resection. The observed agreement between the M-NBI predicted histology and the final pathology was 91.8% with a derived kappa statistic of 0.87, indicating excellent agreement. Comparatively, prior biopsies had an observed agreement of 40.4% with final histology, with a derived kappa statistic of 0.27.

Conclusions: M-NBI can be used with a high degree of accuracy in a western population. M-NBI can effectively differentiate neoplastic from non-neoplastic gastric lesions and delineate histological subtypes with superior accuracy to previous biopsies.

1 | Introduction

Gastric cancer remains a leading cause of cancer-related morbidity and mortality worldwide, ranking fifth in incidence among all malignant tumors [1]. Despite advances in treatment including endoscopic resection techniques for early gastric cancers, the overall prognosis remains poor. In western regions such as the United States, the United Kingdom, and Europe, the estimated 5-year survival ranges from 10% to 30% [2, 3]. Comparatively, high-incidence countries in the east have a far superior prognosis, with Korea now reporting 5-year survival as high as 77% [4]. This is in large part due to the success of population-wide gastric cancer screening programs with an associated 40% relative risk reduction in gastric cancer mortality [5]. As such, the importance of endoscopic detection of premalignant gastric lesions and early gastric cancer cannot be overstated, providing a direct method of identifying lesions that would otherwise remain asymptomatic until they have progressed beyond potential curability.

With the evolution of endoscopic resection techniques, guidelines now clearly define lesions that are suitable for endoscopic resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [6]. These guidelines rely on the accurate identification

of premalignant lesions and early gastric cancers, as well as prediction of invasion depth in order to recognize lesions beyond the remits of endoscopic resection. Fortunately, recent advances in endoscopic imaging have made this possible, including narrow-band imaging with magnification (M-NBI). Narrow-band imaging (NBI) involves spectral bandwidth filters in a red-green-blue sequential illumination system in order to augment the visualization of mucosal and vascular patterns and enhance the endoscopic assessment of neoplastic lesions [7]. Modern magnification systems are capable of up to 125× magnification allowing intricate assessment of the mucosal and vascular patterns seen under NBI [8]. In high-incidence populations, M-NBI has been shown to outperform white light imaging (WLI) for differentiation of gastric adenomas and gastric cancers [9–11]. A 2015 meta-analysis of 14 studies from China and Japan assessing early gastric cancer detection demonstrated a pooled sensitivity and specificity of M-NBI of 86% and 96%, respectively, with an area under ROC curve of 0.96 [11]. Additionally, M-NBI has been shown in a Japanese population to enhance the prediction of invasion depth, even differentiating SM2 ($\geq 500\,\mu m$ of submucosal invasion) from SM1 ($< 500\,\mu m$) early gastric cancers with diagnostic accuracy as high as 89%, allowing delineation of lesions with submucosal invasion that would be suitable for ESD [12].

To date, western countries have not endorsed population gastric cancer screening programs. Nevertheless, associations including the British Society of Gastroenterology have published clear guidelines on endoscopic screening and surveillance in those at higher risk of gastric cancer [13]. These guidelines similarly rely on accurate endoscopic identification of superficial and advanced gastric lesions. While the efficacy of M-NBI has been proven when used by expert endoscopists in eastern countries with a wealth of experience in identifying early gastric cancers, evidence remains lacking on the accuracy of endoscopic histology prediction using M-NBI in the west. The reduced uptake of M-NBI in the west is likely multifactorial, due to the absence of nationwide gastric cancer screening, less extensive training in M-NBI interpretation, and less standardization of gastroscopic examination compared with the expected systematic mapping protocols employed in the east [14]. As a result, the vast majority of published data originates from higher-incidence countries and it therefore remains unclear whether these data can be reliably extrapolated to the western setting. We sought to assess the accuracy of M-NBI for endoscopic histology prediction in a western population.

2 | Methods

This was a retrospective analysis of a prospectively collected database including all patients with gastric lesions that were assessed or resected by an interventional endoscopist at a single Australian tertiary center between 2009 and 2023. We included only lesions that were either biopsied or resected to enable histological confirmation. In cases where lesions were initially biopsied and then resected either endoscopically or surgically, the final histology was based on the resection specimen rather than initial biopsies given the risk of sampling error.

As these data were collected over a 15-year period, there was a considerable advancement in endoscopic technology during the study; however, all endoscopes used had NBI and magnification capability. Initially, Olympus GIF-Q160Z endoscopes were used, followed by GIF-HQ190 and finally GIF-EZ1500. All procedures were performed by a single interventional endoscopist with dedicated training in advanced mucosal imaging including M-NBI. Endoscopies were performed under a procedural sedation unless the anesthetist determined that general anesthesia was required. A transparent cap attachment was used in all cases. In addition, all patients were given oral simethicone immediately prior to the procedure to aid visualization.

After initial assessment using WLI, a targeted assessment of each lesion using M-NBI was performed. An assessment was then made at the time of endoscopy whether the lesion was neoplastic or non-neoplastic, as well as whether the lesion was adenomatous, early gastric cancer, or advanced adenocarcinoma that would not be suitable for endoscopic resection. 'Other neoplastic lesions' included either neuroendocrine tumors or lymphoma. Early gastric cancer included all gastric cancers that would have been considered eCuraA or eCuraB according to the Japanese Gastric Cancer Treatment Guidelines (6th Edition) 2021 (Table 1) [6]. Final histology results were then collected for

TABLE 1 | eCura Classification as described in the Japanese Gastric Cancer Treatment Guidelines (6th Edition) 2021 [6].

eCura Classification	Definition	
eCuraA	No ulceration	En bloc resection Any tumor size if differentiated-type dominant ≤ 2 cm if undifferentiated-type dominant pT1a (intramucosal) Clear horizontal and vertical margins No lymphovascular infiltration
	Ulceration	En bloc resection Differentiated-type dominant pT1a (intramucosal) Tumor size ≤ 3 cm Negative horizontal and vertical margins No lymphovascular invasion
eCuraB		pT1b (SM1): $< 500\,\mu m$ from the muscularis mucosa Negative horizontal and vertical margins Tumor size ≤ 3 cm Differentiated-type dominant No lymphovascular invasion

all lesions. Demographic variables were recorded as well as lesion characteristics including size, shape (according to the Paris classification), location in the stomach and the presence or absence of ulceration [15].

Given the small sample size for lesion subtypes, descriptive statistics were reported. Sensitivity, specificity, negative predictive values, and positive predictive values were derived from contingency tables of the M-NBI prediction and the pathological result using Fisher's exact tests. 95% confidence intervals were obtained based on binomial proportions. A kappa statistic was calculated to assess the agreement between M-NBI prediction and pathological diagnosis, as well as between previous biopsies and final histology. Bootstrapping was performed to calculate confidence intervals for kappa statistics to determine statistical significance. This study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (Reference number: 19213).

3 | Results

A total of 232 lesions from 183 patients (44.8% female) were included in the study, 137 non-neoplastic lesions and 95 neoplastic. Demographic variables have been described for each pathological diagnosis in Table 2. There were 35 adenomas, 29 early gastric cancers (Figure 1), and 6 advanced adenocarcinomas included. Nineteen of 29 early gastric cancers (65.5%) were well differentiated, with 10 (34.5%) being poorly differentiated/signet ring cell adenocarcinoma. Similarly, 4 of 6 (66.7%) advanced adenocarcinomas were well differentiated with two (33.3%) being poorly differentiated. The majority of lesions were located in the gastric antrum (42.7%) and body (44.8%); 41.4% of lesions were sessile (Paris Is), 32.3% were flat (Paris 0-IIa), and 22.4% were ulcerated (Paris 0-IIc). The median lesion size was 20 mm for adenomas, 25 mm for early gastric cancers, and 30 mm for advanced adenocarcinomas.

M-NBI was highly effective for differentiating neoplastic versus non-neoplastic lesions with sensitivity, specificity, NPV, PPV and accuracy of 97.9% (92.6%–99.7%), 97.1% (93%–99.2%), 95.9% (89.8%–98.9%), 98.5% (94.8%–99.8%), and 97.4% (94.5%–99.1%), respectively (Table 3). For histological subtypes, the observed agreement between M-NBI and histology was 91.8% overall, 97.1% for non-neoplastic lesions, 74.3% for adenomas, 82.8% for early gastric cancer, and 83.3% for advanced adenocarcinoma. The derived kappa statistic for agreement between M-NBI and histological subtype was 0.87, indicating an excellent agreement. There was no significant impact of lesion size or shape on the accuracy of M-NBI for differentiation of lesion subtypes.

M-NBI was also highly accurate for stratifying lesion types according to those appropriate for endoscopic resection (adenoma, early gastric cancer, and neuroendocrine tumor) versus those not suitable for endoscopic resection (non-neoplastic, advanced adenocarcinoma, and lymphoma) with a sensitivity, specificity, NPV, PPV, and accuracy of 97.7% (91.9%–99.7%), 96.6% (92.1%–98.9%), 98.6% (95.0%–99.8%), 94.4% (89.5%–98.2%), and 97.0% (93.9%–98.8%), respectively (Table 3). Although low subgroup numbers limit statistical conclusions, for the 35 adenocarcinomas, M-NBI was able to differentiate resectable versus unresectable lesions with sensitivity, specificity, PPV, NPV, and accuracy of 100% (88.3%–100%), 83.3% (43.7%–99.2%), 96.7% (83.3%–99.8%), 100% (56.6%–100%), and 97.1% (85.1%–99.9%) respectively.

The accuracy of M-NBI was compared with previous histology for lesions that had been biopsied prior to assessment. A total of 47 lesions had been biopsied prior to the endoscopic assessment with M-NBI, with observed agreement of 40.4% between previous biopsy and final histology for lesion subtypes. The derived kappa statistic for agreement between prior biopsies and final histology was 0.27. Through bootstrapping for 1000 replicates, the kappa statistic for M-NBI (0.87, 95% CI 0.8–0.92) was confirmed to be superior to that of previous biopsies (0.27, 95% CI 0.09–0.43). Importantly, in 40.4% of cases ($n = 19/47$), the final pathology was further advanced than previous biopsies, with nine early gastric cancers previously identified as non-malignant adenomas on initial biopsy.

4 | Discussion

This study demonstrates M-NBI to be highly accurate as an advanced imaging technique for the diagnosis of neoplastic gastric lesions in the western population. The accuracy of histology prediction in this study was equivocal to that reported in eastern countries, with a similar study in Japan involving superficial gastric lesions demonstrating the sensitivity and specificity of M-NBI to be 92.9% and 94.7%, respectively [16]. While M-NBI would therefore seem likely to improve the accuracy of gastric cancer detection at endoscopy, this was disputed by a 2021 Japanese randomized controlled trial, which found no impact of M-NBI for lesion detection during more than 4500 screening endoscopies [17]. Further to this, the benefit has only been demonstrated to date when used by interventional endoscopists with experience in advanced imaging. Previous studies have highlighted the limitations in the efficacy of NBI when used by proceduralists unfamiliar with this technology [18, 19]. Nevertheless, with appropriate training, non-NBI expert endoscopists are able to achieve a high degree of accuracy using M-NBI in assessment of gastric lesions. Prior studies have demonstrated that performing prospective endoscopy in at least 50 patients in gastric intestinal metaplasia results in comparable accuracy to expert interventionalists, while in a video-based study, it demonstrated similar results after video-based training including 200 gastric lesions [18, 20]. At this stage, in the western context, the greatest benefit of NBI remains in its use by expert interventionalists at referral centers for the careful assessment of gastric lesions in order to determine suitability for endoscopic resection and guide appropriate resection techniques. With appropriate training and exposure, this benefit may eventually be generalizable to all endoscopists.

In our study, lesion morphology according to the Paris classification was not helpful in differentiating between lesion subtypes. This is unsurprising as unlike in colorectal lesions where ulceration and central depression are highly suggestive of malignancy, benign lesions in the stomach are commonly ulcerated in a similar fashion to early and invasive gastric cancers. In addition, previous biopsies were found to be inaccurate and were confirmed to be inferior to M-NBI when correlated with final histology. This likely relates to sampling error, particularly if the

TABLE 2 | Demographic variables by pathological diagnosis.

		Adenoma	Early gastric cancer	Advanced adeno-carcinoma	'Other neoplastic'	Non- neoplastic	Total
Total		15.1% ($n=35$)	12.5% ($n=29$)	2.6% ($n=6$)	10.8% ($n=25$)	59% ($n=137$)	$n=232$
Age Median (Q1, Q3)		76 (71, 79)	74 (67–81)	71 (66–80)	43 (30–77)	66 (52–75)	70 (54–77)
Female		48.6% ($n=17$)	37.9% ($n=11$)	33.3% ($n=2$)	44% ($n=11$)	46% ($n=63$)	44.8% ($n=104$)
Size (mm) Median (Q1, Q3)		20 (13, 30)	25 (20, 30)	30 (25, 40)	10 (10, 12)	10 (5, 10)	10 (5, 20)
Paris Classification	Ip	5.7% ($n=2$)	0	0	0	2.9% ($n=4$)	2.6% ($n=6$)
	Is	51.4% ($n=18$)	31% ($n=9$)	16.7% ($n=1$)	72% ($n=18$)	36.5% ($n=50$)	41.4% ($n=95$)
	0-IIa	34.3% ($n=12$)	55.2% ($n=16$)	0	20% ($n=5$)	30.7% ($n=42$)	32.3% ($n=75$)
	0-IIc	8.6% ($n=3$)	10.3% ($n=3$)	50% ($n=3$)	8% ($n=2$)	29.9% ($n=41$)	22.4% ($n=52$)
	0-IIa + IIc	0	3.5% ($n=1$)	33.3% ($n=2$)	0	0	1.3% ($n=3$)
Location	Pre-pyloric	0	0	0	0	12.4% ($n=17$)	7.3% ($n=17$)
	Antrum	60% ($n=21$)	48.3% ($n=14$)	0	0	46.7% ($n=64$)	42.7% ($n=99$)
	Body	28.6% ($n=10$)	31% ($n=9$)	50% ($n=3$)	84% ($n=21$)	32.8% ($n=45$)	44.8% ($n=88$)
	Cardia	2.9% ($n=1$)	6.9% ($n=2$)	33.3% ($n=2$)	16% ($n=4$)	3.7% ($n=5$)	6% ($n=14$)
	Fundus	2.9% ($n=1$)	0	0	0	0.7% ($n=1$)	0.9% ($n=2$)
	Incisura	5.7% ($n=2$)	13.8% ($n=4$)	16.7% ($n=1$)	0	3.7% ($n=5$)	5.2% ($n=12$)

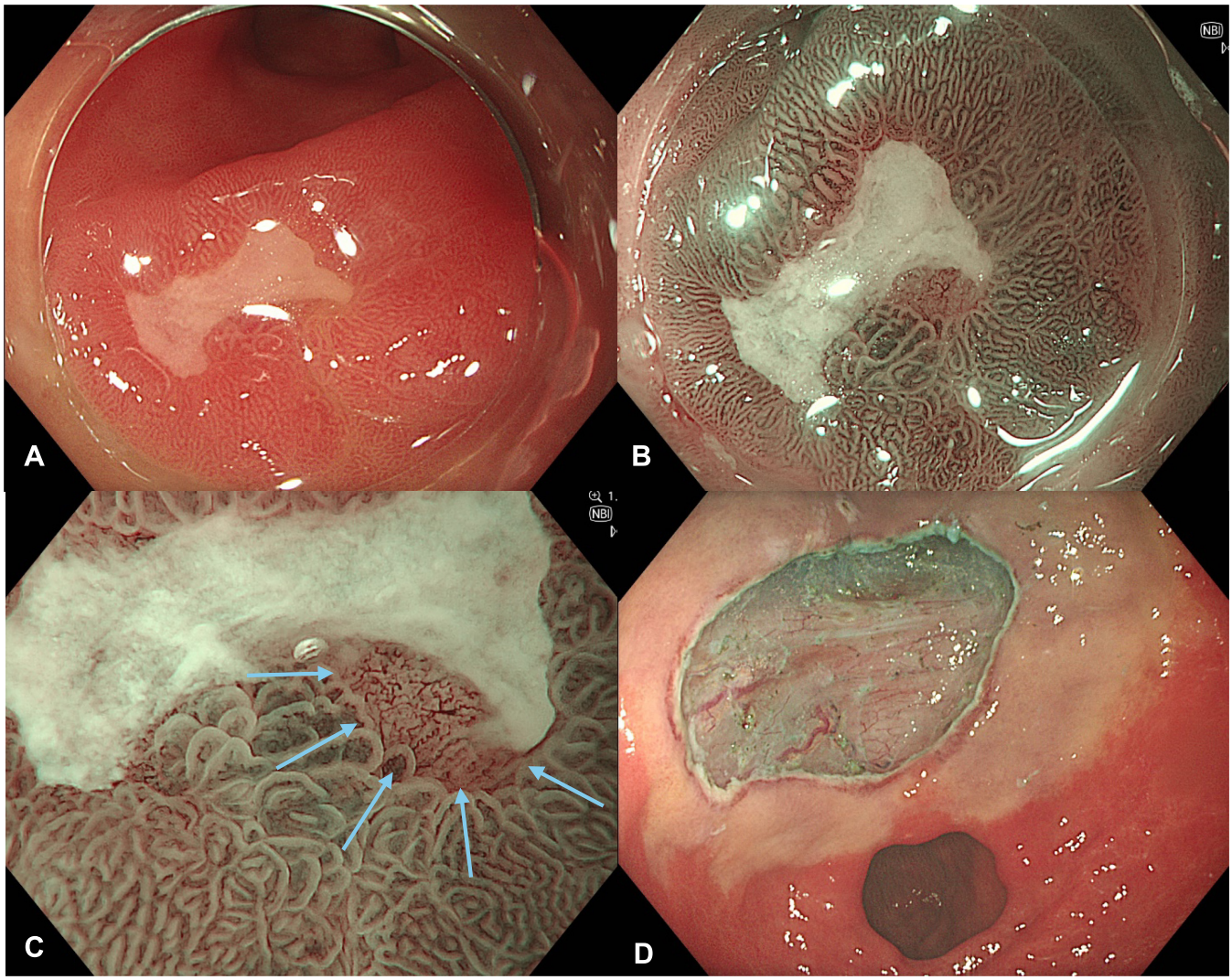

FIGURE 1 | (A) Initial views of a pre-pyloric ulcer on WLI. (B) View of the ulcer under NBI. (C) NBI and high-magnification demonstrating an area of altered vasculature that highlighted the presence of what was histologically proven to be poorly differentiated adenocarcinoma. (D) The base after endoscopic submucosal dissection.

TABLE 3 | Classification statistics for M-NBI histology prediction differentiating neoplastic versus non-neoplastic histology and differentiating lesions suitable for endoscopic resection.

	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Accuracy (95% CI)
Neoplastic versus non-neoplastic	97.9% (92.6, 99.7)	97.1% (92.7, 99.2)	95.9% (89.8, 98.9)	98.5% (94.8, 99.8)	97.4% (94.5, 99.1)
Resectable	97.7% (91.9, 99.7)	96.6% (92.1, 98.9)	98.6% (95.0, 99.8)	94.4% (89.5, 98.2)	97.0% (93.9, 98.8)

most advanced component of the lesion is not targeted for biopsy. In nine cases of early gastric cancer, biopsies had previously shown non-malignant adenoma. Fortunately, after assessment with M-NBI, the decision was made to proceed with en bloc ESD for these lesions as piecemeal resection would have been considered non-curative according to the eCura Classification described above. These results are consistent with previous data, with a 2012 study demonstrating that almost a half of gastric lesions with "indeterminate" histology for either regenerative or neoplastic tissue were confirmed to be adenocarcinoma on endoscopic resection specimens [21]. Accordingly, in the absence of meaningful guidance from lesion morphology or previous biopsies, imaging techniques are of even greater importance in the determination of appropriate resection techniques. Our study has demonstrated accuracy as high as 97.0% when using M-NBI for delineating lesions that are appropriate for endoscopic resection. The accuracy in our study was comparable with the accuracy of 81%–95% for prediction of invasion depth reported in eastern studies with M-NBI [12, 22]. M-NBI should therefore be utilized when planning endoscopic resection rather

than relying on previous histology. M-NBI may also have a role in increasing the yield of biopsies prior to referral if employed by endoscopists to guide locations for biopsy.

To our knowledge, this is the first study published in a western cohort examining the accuracy of NBI for histology prediction in early gastric cancers and advanced adenocarcinoma. From the limited existing data in western populations on pre-malignant gastric lesions, results have been conflicting. A 2010 study from the Netherlands involving 43 patients undergoing surveillance gastroscopy for intestinal metaplasia or prior dysplasia found that NBI was superior for detection of intestinal metaplasia [23]. A larger prospective study from America in 2017 involving 112 patients undergoing screening endoscopy found that while NBI was superior to WLI, it was not superior to routine mapping biopsies [24]. Our study is therefore important in demonstrating the accurate application of M-NBI in a western cohort including for assessment of early gastric cancers.

The study does however have a number of limitations that we acknowledge. This was a retrospective, single-center study, which introduces several potential forms of bias. However, it is important to highlight that histological predictions were made and documented prospectively at the time of reporting, prior to the availability of final histology. Additionally, all lesions assessed by the participating interventionalist using M-NBI over this period were included in the analysis, reducing the risk of selection bias. We also acknowledge the small patient numbers for the malignant lesion types, particularly for advanced adenocarcinomas, which limits the strength of some of the conclusions drawn. Nevertheless, small patient numbers are inevitable in low-incidence countries such as Australia, and therefore, larger multicenter studies are required to confirm our findings. Finally, we did not compare the accuracy of M-NBI to high-definition WLI, and therefore, we are unable to discern the degree to which the high accuracy of endoscopic assessment can be attributed to M-NBI rather than expertise in endoscopic imaging and assessment of mucosal patterns. While our study is also unable to differentiate the influence of the initial WLI assessment on the subsequent M-NBI assessment for factors such as prediction of invasion depth, we feel that this is generalizable and applicable in real-world practice where WLI is almost always used for initial assessment prior to M-NBI.

Narrow-band imaging with magnification (M-NBI) is a highly accurate form of advanced mucosal imaging for differentiation of non-neoplastic from neoplastic gastric lesions in a western population. It also remains accurate for selection of lesions that would be appropriate for endoscopic resection and distinction from lesions harboring advanced malignancy. It is more strongly correlated with final histology than even previous biopsies of the same lesion, likely due to sampling error. The use of M-NBI should therefore be strongly considered in the western context, particularly by interventional endoscopists planning endoscopic resection techniques for gastric neoplasia.

Acknowledgments

Aline Kunnel from the University of Adelaide for the statistical support and analysis. Open access publishing facilitated by The University of Adelaide, as part of the Wiley - The University of Adelaide agreement via the Council of Australian University Librarians.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

These data are not publicly available; however, deidentified information can be shared if an appropriate request is sent to the corresponding author.

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