

## Narrow band imaging with magnification for the diagnosis of lesions in the upper gastrointestinal tract

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### Abstract

Endoscopy plays an important role in the diagnosis and management of gastrointestinal (GI) tract disorders. Chromoendoscopy has proven to be superior to white light endoscopy for early detection of various GI lesions. This has however been fraught with problems. The use of color stains, time taken to achieve an effect and the learning curve associated with the technique has been some of the pitfalls. Narrow band imaging (NBI) particularly in combination with magnifying endoscopy may allow the endoscopist to accomplish a fairly accurate diagnosis with good histological correlation similar to results achieved with chromoendoscopy. Such enhanced detection of pre-malignant and early neoplastic lesions in the gastrointestinal tract should allow better targeting of biopsies and could ultimately prove to be cost effective. Various studies have been done demonstrating the utility of this novel technology. This article will review the impact of NBI in the diagnosis of upper gastrointestinal tract disorders.

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**Key words:** Narrow band imaging; Magnifying endos-

copy; Upper gastrointestinal tract

**Core tip:** Narrow band imaging with magnifying endoscopy has shown promising results in improving detection and characterization of gastrointestinal lesions. This may allow better targeting of biopsies, improved prediction of histology, appropriate treatment and better patient outcomes. Most studies have been conducted in expert centers and carried out only by one or a few observers. Large-scale prospective multi center randomized trials are needed to duplicate the results achieved in these institutions.

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### INTRODUCTION

Recent advances in endoscopic imaging technologies have enabled endoscopists to improve the capability of detecting and characterizing lesions in gastrointestinal tract (GIT). Amongst some of these novel technologies, narrow band imaging (NBI) appears to be the most promising. Current available data on the utility of NBI with magnification (NBI-ME) has been encouraging for Barrett's esophagus, early Oropharyngeal, esophageal and gastric cancers and to a lesser extent reflux disease and gastritis. It also has a role in aiding endoscopic resection where margin assessment is essential. This review will focus on the role of NBI-ME in the diagnosis of lesions in upper gastrointestinal tract.

### ESOPHAGEAL SQUAMOUS CELL CARCINOMA

NBI enables detailed observation of the microvascu-

lature in the esophageal mucosa, described as intraepithelial papillary capillary loops (IPCL's). The NBI-ME findings of early squamous cell carcinoma (SCC) include a well-demarcated brownish area, elevated margins, loss of visible branching vessels and a type IV or type V intraepithelial papillary capillary loops pattern<sup>[1,2]</sup>. Inoue originally described intraepithelial papillary capillary loops into 4 distinct entities: dilation, meandering, caliber changes and difference in shapes<sup>[3,4]</sup>. Type IV intraepithelial papillary capillary loops shows 2 or 3 of the four patterns, whilst Type V intraepithelial papillary capillary loops demonstrates all 4 characteristic changes. Type III intraepithelial papillary capillary loops (minimal proliferation or meandering in a brownish area) is considered borderline or low grade intra-epithelial neoplasia. Thus, a follow up endoscopy is generally recommended for these patients. However, type II intraepithelial papillary capillary loops (enlarged but linear and regular vessels) indicates regenerative tissue or inflamed mucosa. Type I intraepithelial papillary capillary loops, are generally normal vessels with smooth, slender, regular caliber with a smaller diameter (10 µm).

Muto *et al*<sup>[5]</sup> conducted a multicentre randomised controlled trial on 320 patients with a history of Squamous Cell CA (SCC), comparing white light endoscopy (WLE) with NBI in the detection of Squamous Cell CA in patients with a history of head and neck Squamous Cell CA or previous esophageal Squamous Cell CA. The sensitivity of NBI for a diagnosis of superficial cancer was 100% for the oropharynx and 97.2% for the esophagus. The diagnostic accuracy was 90% when two endoscopic criteria, namely, a well demarcated brownish area and an irregular micro vascular pattern, were used.

Goda *et al*<sup>[6]</sup> conducted a non-randomized comparative study of 101 lesions of esophageal Squamous Cell CA, which gauged the sensitivity and specificity of WLE, NBI and endoscopic ultrasound (EUS) in predicting the depth of superficial esophageal Squamous Cell CA. The authors concluded that all 3 modalities did not differ significantly. Kuraoka *et al*<sup>[7]</sup> conducted a study comparing endoscopy with iodine staining to NBI. Endoscopy assisted with NBI was more useful in the detection of early esophageal Squamous Cell CA than that obtained with iodine. Another study assessed the efficacy of 1204 high-resolution esophagoscopies with NBI using a novel "Endo View" Program. Color segmentation of narrow band images apparently increased the chances of diagnosing even the smallest abnormality in the esophagus. NBI endoscopy also allowed specifying premalignant lesions in esophageal mucosa in both low grade and high-grade dysplasia (HGD)<sup>[8]</sup>.

A consensus of expert endoscopists from the Asia-Pacific region put all of this together and reported a strong agreement on importance of interpretation of both vascular architecture and surface structure of the superficial mucosa in the esophagus. NBI was useful for detection of esophageal Squamous Cell CA (100% consensus achieved), distinguishing neoplastic from non-neoplastic lesions (89% consensus), determining the ex-

tent of the neoplasia (78% consensus) and depth of the tumor (100% consensus). However, the panel of experts agreed that chromo endoscopy is still superior to delineate the extent of the tumor<sup>[9]</sup>. They also agreed that there was no significant difference in terms of sensitivity and specificity for the assessment of the depth of tumor invasion by NBI when compared to EUS.

## BARRETT'S ESOPHAGUS

Singh *et al*<sup>[10]</sup> conducted a study on 109 patients with more than 1000 corresponding biopsies, which not only validated a simplified classification of the various morphologic patterns visualized in Barrett's Esophagus (BE) and corresponding histology with high predictive values, but also confirmed its reproducibility and repeatability when the grading system was used by both endoscopists experienced in the use of NBI and those unfamiliar with it. On the basis of the 1021 areas visualized, NBI-ME allowed correct prediction of 99% of the areas harboring intestinal metaplasia (IM) and 96% of the areas demonstrating high grade dysplasia (HGD). However intestinal metaplasia was not clearly differentiated from low grade dysplastic lesions. Mannath *et al*<sup>[11]</sup> in a large meta analysis found a very high sensitivity and specificity of NBI in diagnosing in high grade dysplasia patients with Barrett's Esophagus.

## GASTRO-ESOPHAGEAL REFLUX DISEASE AND NON-EROSIVE REFLUX DISEASE

Approximately 60% of patients with gastro-esophageal reflux disease (GERD) have normal standard endoscopy and are labeled as suffering from non-erosive reflux disease (NERD)<sup>[12]</sup>. NBI-ME can detect microvascular changes and also enhance the contrast between esophageal and gastric mucosa<sup>[13]</sup>. Microvascular changes of non-erosive reflux disease on NBI include increased number and dilatation of intraepithelial papillary capillary giving an inverted fir tree appearance, punctate erythema, loss of vascular palisade pattern and triangular indentation of squamo-columnar junction above the Z line<sup>[14]</sup>. Changes below the Z line include islands of squamous epithelium and increased vascular markings<sup>[15,16]</sup>. Some of these features were tested in a study comparing ten control subjects and eleven patients with non-erosive reflux disease confirmed by a validated questionnaire, standard endoscopy and 24-h pH-metry<sup>[17]</sup>. The investigators proposed and explored seven different distal esophageal mucosal appearances that can be observed with a high-resolution endoscope (triangular lesions, apical mucosal breaks, palisade vessels, pin point vessels, branching vessels, villiform mucosa and serrated squamo-columnar junction). However none of these changes proved to be sufficiently sensitive and specific to justify their use as a diagnostic criterion for non-erosive reflux disease. A study conducted by Fock *et al*<sup>[18]</sup> concluded that NBI detected a significantly higher prevalence of

micro-erosions (gastro-esophageal reflux disease 100%, non-erosive reflux disease 52.8% and controls 23%) and increased vascularity (gastro-esophageal reflux disease 95%, non-erosive reflux disease 91.7% and controls 36.7%) but a lower prevalence of round pit patterns (gastro-esophageal reflux disease 4.9%, non-erosive reflux disease 5.6% and controls 70%).

Tseng *et al*<sup>[15]</sup> studied 82 patients where 20 were detected as having gastro-esophageal reflux disease by WLE. Out of the remaining 62 patients declared normal by WLE, NBI detected an additional 44 patients having erosions. They also demonstrated that the changes which visualized on NBI could predict a therapeutic response in patients with gastro-esophageal reflux disease. Sharma *et al*<sup>[14]</sup> compared NBI with WLE in a prospective study of 101 patients. Patients with and without gastro-esophageal reflux disease symptoms were examined by standard WLE followed by NBI. The features seen only by NBI were compared between gastro-esophageal reflux disease patients and controls. A significantly higher proportion of patients with gastro-esophageal reflux disease had increased number (OR = 12.6), dilatation (OR = 20), tortuosity of intraepithelial papillary capillary (OR = 6.9) and increased vascularity at the squamo-columnar junction (OR = 9.3) compared with controls.

## GASTRITIS AND *HELICOBACTER PYLORI*

*Helicobacter pylori* (*H. pylori*) is the commonest cause of chronic gastritis<sup>[19]</sup>. This can lead to intestinal metaplasia and dysplasia; conditions which may progress onto gastric carcinoma<sup>[20]</sup>. On NBI-ME, the normal gastric corpus and fundus have small round pits, sub-epithelial capillaries networks (SECN) in a honeycomb pattern and stellate shaped collecting venules (CV) arranged at regular intervals in deeper mucosa<sup>[21,22]</sup>. These patterns have a 100% predictive value for normal corporal mucosa<sup>[23]</sup>. The normal gastric antrum has a reticular pattern of circular pits and coiled elongated sub-epithelial capillaries networks. The collecting venules are situated too deep to be visible<sup>[21,24]</sup>. *H. pylori* gastritis visualized by NBI shows a loss of collecting venules due to associated inflammation and this pattern has 100% sensitivity, 92% specificity and a positive predictive value (PPV) of 100% for *H. pylori* gastritis. *H. pylori* related atrophic gastritis is patchy starting from Incisura and progressively involves the Antrum, body and corpus. NBI findings suggestive of atrophy are loss of pits and sub-epithelial capillaries networks. The sensitivity and specificity of these findings for atrophic gastritis have been suggested to be up to 90% or above<sup>[23]</sup>.

Dalal *et al*<sup>[25]</sup> conducted a pilot study in the stomach that concluded that when compared to WLE, abnormal findings on NBI had a sensitivity of 100% and a specificity of 90.6%; whereas WLE has a sensitivity of only 42.9% and specificity of 75%. Negative predictive value (NPV) of NBI was 100%, whereas WLE has Negative predictive value of 85.7%. However, with a small-sized

study of 25 patients, further refinement and validation of the NBI grading criteria was suggested. Banerjee and colleagues also compared NBI with WLE on 74 patients and showed that high resolution endoscopy with NBI could be a potential tool for the instantaneous real time diagnosis of *H. pylori* infection. The sensitivity, specificity, positive predictive value and negative predictive value for absence of infection were 85%, 93%, 96% and 77% respectively<sup>[26]</sup>.

## SUPERFICIAL GASTRIC CANCER

As with all cancers, an early diagnosis is crucial for a good prognosis in gastric carcinoma, which is the second leading cause of cancer related deaths worldwide<sup>[27-31]</sup>. Atrophy, metaplasia, dysplasia followed by neoplasia are the usual sequence of events<sup>[32,33]</sup> in some of these patients. NBI may assist in identifying premalignant lesions and hence enable appropriate therapy. Amorphous pit pattern, irregular size and/or arrangement of pits or complete loss of pits along with abnormal micro-vascular pattern are associated with neoplastic lesions. Regular, round, slit or villous like pits indicate non-neoplastic lesions<sup>[34-36]</sup>. These changes are however not always straightforward as findings can be altered by many conditions such as chronic inflammation, ulceration, atrophy or metaplasia and *H. pylori* infection<sup>[37-39]</sup>. Superficial but elevated lesions make the visibility of micro-vascular pattern difficult<sup>[35,40,41]</sup>.

A consensus of expert endoscopists in the Asia-Pacific region agreed that NBI is not useful for detection of gastric carcinoma at an early stage. They however concurred that NBI increases sensitivity and accuracy of differential diagnosis of early gastric carcinoma (EGC) in elevated, flat and depressed lesions. NBI may also distinguish tumor margins from the surrounding normal mucosa. They also agreed that NBI has no significant role in detecting tumor depths as the narrow band of light is speculated to penetrate to only 200-250  $\mu\text{m}$  into the superficial mucosa<sup>[9]</sup>. Approximately 40% of early gastric carcinoma are of the undifferentiated type according to Japanese literature<sup>[42,43]</sup>. This type of early gastric carcinoma can extend subepithelially and may be covered by non-neoplastic foveolar epithelium. In undifferentiated early gastric carcinoma, it is recommended that biopsies are obtained from the surrounding mucosa to diagnose the undetectable tumor extent<sup>[44]</sup>.

Light blue crest (LBC) is a fine, blue-white line on the crest of the epithelial surface/gyri. An JK conducted a study on 42 patients and concluded that the Light blue crest sign (LBC) observed in the gastric mucosa with magnifying NBI endoscopy are highly accurate indicators of the presence of Intestinal Metaplasia (IM) and Light blue crest also correlates with progression to severe Intestinal Metaplasia. For the diagnosis of Intestinal Metaplasia, Light blue crest had a sensitivity, specificity, and accuracy of 72.1%, 96.0%, and 84.9%<sup>[45]</sup>. Uedo *et al*<sup>[46]</sup> tested NBI-ME on 34 patients with atrophic gastritis and demonstrated that the appearance of Light blue crest correlated

with histological evidence of Intestinal Metaplasia, with a sensitivity of 89% (95%CI: 83-96), a specificity of 93% (95%CI: 88-97), a positive predictive value of 91% (95%CI: 85-96), a negative predictive value of 92% (95%CI: 87-97) and an accuracy of 91% (95%CI: 88-95). Yao *et al.*<sup>[47]</sup> reported that the hallmark of a white opaque substance (WOS) is the presence of lipid droplets (LDs) that accumulate in the superficial part of the epithelial neoplasia within the stomach. The authors also reported that the white opaque substance in adenomas was regular and homogeneous, whereas the white opaque substance in adenocarcinomas was irregular and speckled. Ueyama *et al.*<sup>[48]</sup> suggested that the white opaque substance-positive epithelium corresponded to the dysplasia in this lesion. The presence of a white opaque substance in a gastric hyperplasia may be considered an endoscopic finding that is predictive of the neoplastic transformation of a gastric hyperplasia. Therefore, in gastric hyperplasia, white opaque substance positivity may be considered an endoscopic finding that indicates endoscopic resection<sup>[48]</sup>.

## CELIAC DISEASE

Normal duodenal mucosa exhibits regularly arranged finger like villi and a regular network of capillaries on high resolution magnifying WLE<sup>[49]</sup>. Reduced duodenal folds, scalloping of fold margins, mosaic pattern of mucosa and grooves in the mucosa are usual conventional endoscopic signs for celiac disease<sup>[50-54]</sup>. However these findings are not reliable in patchy<sup>[55,56]</sup> or milder cases of subtotal atrophy<sup>[57]</sup>. Overall, the sensitivity, specificity, positive predictive value and negative predictive value for villous atrophy on NBI are 100%, 91%, 83% and 100% respectively<sup>[58]</sup>.

Banerjee *et al.*<sup>[59]</sup> mentioned earlier in 2008 that NBI may be a useful yet simple adjunctive tool for the direct visualization of villous architecture and guide to tissue sampling. This may improve the diagnostic yield as well as reduce the number of biopsy specimens that need to be taken. Singh *et al.*<sup>[60]</sup> conducted a study using NBI-ME to detect villous atrophy in patients presenting with suspected celiac disease using forty-one videos obtained from 21 patients (3 celiac disease, 18 normal). The overall sensitivity and specificity in correctly distinguishing the presence or absence of villi were 93% and 98% respectively, with inter-observer and intra-observer agreement ( $\kappa$ ) at 0.82 and 0.86 respectively. The sensitivity and specificity in differentiating partial from total villous atrophy were 83.3% and 100% respectively, with  $\kappa$  at 0.73 and 0.68 respectively.

## CONCLUSION

Narrow band imaging is a promising endoscopic technology which may improve the diagnostic accuracy of detecting and characterizing premalignant and neoplastic lesions in the upper gastrointestinal tract. Most studies have been conducted in expert centers and carried out by one or a few observers. Large-scale prospective

multicenter randomized trials are needed to duplicate the results achieved in these institutions. Standardization of endoscopic criteria and amalgamation of the various classifications cannot be overemphasized. Once this is achieved, teaching and learning modules for more widespread dissemination to the community will be crucial.

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