

## Narrow band imaging in gastroesophageal reflux disease and Barrett's esophagus

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Narrow Band Imaging (NBI), developed by Olympus Medical Systems (Olympus, Japan), is a new and well-recognized advance in endoscopic imaging. Although conventional white-light endoscopy uses the entire spectrum of visible light (400 nm to 700 nm) to examine tissue, the NBI system uses optic filters to isolate two specific bands of light: 415 nm blue and 540 nm green (1-4). By isolating these two bands of light and taking into account their absorptive and reflective properties on the mucosal surface, an image that enhances visualization of superficial mucosal and vascular structures is created. The highlight of NBI endoscopy is the proposed ability to predict pathology in real-time based on the mucosal and vascular changes detected. NBI has been investigated for use as a diagnostic modality in a variety of lesions in the gastrointestinal, respiratory and genitourinary tract (4-6). Conveniently, the NBI mode on an endoscope can be activated with the depression of a switch similar to taking a picture.

NBI, often referred to as 'digital chromoendoscopy', was developed as an alternative method of obtaining visual enhancement of tissue similar to that seen in chromoendoscopy – a procedure that uses the absorptive properties of various dyes, such as indigo carmine, rather than optical filters (1-4). Although much research concerning the use of chromoendoscopy has been conducted, its widespread use has not been adopted for various reasons including the increased time involved with the procedure and the lack of training (ie, many training centres do not use it regularly).

In the January 2009 issue of *The Canadian Journal of Gastroenterology*, we discussed the role of NBI for the detection of neoplastic lesions of the lower gastrointestinal tract; specifically its utility in the diagnosis of adenomatous polyps and dysplasia in ulcerative colitis, hereditary nonpolyposis colorectal cancer and screening colonoscopy. The purpose of the present paper is to review the use of NBI endoscopy as a diagnostic modality for lesions of the upper gastrointestinal tract with particular emphasis on Barrett's esophagus (BE).

### NBI ENDOSCOPY IN GASTROESOPHAGEAL REFLUX DISEASE

Presently, few studies in the literature have investigated the use of NBI for the diagnosis or management of gastroesophageal reflux disease (GERD). Based on clinical history and upper endoscopy findings, patients with GERD are typically classified into the following groups: nonerosive reflux disease

(NERD), erosive esophagitis and BE (7). Upper endoscopy is considered by many to be a relatively insensitive test for GERD because the disorder often yields normal endoscopic findings. Studies (8) have found that fewer than 40% of patients with GERD have positive upper endoscopy findings. As a result, it has been hypothesized that the use of NBI endoscopy may help in improving diagnostic accuracy over standard endoscopy in patients with GERD. Most studies investigating the use of NBI endoscopy in GERD have focused on determining the correlation of observed mucosal and vascular patterns with histology from biopsies. Sharma et al (9) found that a significantly higher proportion of patients with GERD had changes in the number (OR 12.6;  $P<0.0001$ ), dilation (OR 20;  $P<0.0001$ ) and tortuosity (OR 6.9;  $P<0.0001$ ) of intrapapillary capillary loops. In addition, the presence of microerosions ( $P<0.0001$ ) and an increase in vascularity (OR 9.3;  $P=0.001$ ) at the squamocolumnar junction was noted in patients with GERD compared with controls. A recent study (10) also found that patients with GERD and NERD had changes at the squamocolumnar junction such as the presence of microerosions (GERD 100%, NERD 52.8%, controls 23.3%) and an increase in vascularity (GERD 95.1%, NERD 91.7%, controls 36.7%).

To date, the research performed concerning the use of NBI endoscopy in GERD is relatively new, and there is still a need for prospective randomized controlled trials to validate the mucosal and vascular patterns seen in the above studies. Furthermore, additional research is needed to fully assess the clinical utility of NBI, not only in the diagnosis of GERD compared with conventional endoscopy, but also how it will possibly change the management of patients if they are diagnosed with mild erosive disease.

### NBI ENDOSCOPY IN BE

BE is defined histologically by the replacement of the normal squamous epithelium of the esophagus with columnar-lined epithelium (CLE) and specialized intestinal metaplasia (SIM) (11,12). GERD is a major risk factor for the development of BE because it is believed that chronic acid reflux causes injury to the squamous epithelium of the esophagus, leading to the mucosal changes associated with BE (13). BE is of clinical importance because it is considered to be a premalignant lesion of esophageal adenocarcinoma (14,15). In patients with BE, current protocols recommend upper endoscopy surveillance with four-quadrant random biopsies at 2 cm intervals of



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Barrett's epithelium and targeted biopsies of abnormal mucosa to detect neoplastic changes (16-19). The incidence of esophageal adenocarcinoma is at least 30-fold higher in patients with BE compared with the general population (11,20). Despite the increasing incidence of esophageal adenocarcinoma in Europe and North America, it is often difficult to detect the subtle, early dysplastic appearing lesions in BE (21,22). As a result, a number of new technologies have been proposed for use in the diagnosis and surveillance of patients with BE including high-resolution white-light endoscopy, autofluorescence imaging, chromoendoscopy and NBI to improve detection rates (11,23-28) of dysplasia. NBI also has the benefit of allowing the endoscopist to make an in vivo diagnosis, without the need for random biopsies, which can theoretically be costly, time consuming and can occasionally lead to sampling errors (29,30). It is hoped that with improvements in the diagnosis of BE and its complications, early intervention can be undertaken to improve patient outcomes. Early intervention is available at many centres with the development of endoscopic mucosal resections and several ablative techniques; it is possible that more aggressive therapy of earlier lesions will be advocated.

#### Characterization of lesions seen in BE with NBI endoscopy

A number of studies (31-35) have described the spectrum of changes from CLE to dysplasia, seen with NBI endoscopy in BE. Kara et al (31) used a classification scheme for BE which focused on three criteria: the mucosal pattern (flat, villous/gyrus, other, irregular/disrupted), the vascular pattern (regular, irregular, normal-appearing long-branched) and the presence of abnormal blood vessels. SIM was characterized by villous/gyrus mucosal patterns (80% of cases) and flat mucosa with normal-appearing long-branched vessels (20% of cases). High-grade intraepithelial neoplasia was characterized by three patterns: irregular/disrupted mucosal patterns, irregular vascular patterns and abnormal blood vessels. A study by Sharma et al (32) in 2006 classified NBI images according to mucosal (ridge/villous, circular, irregular) and vascular (normal and abnormal) patterns. The NBI images, correlated with histology, found that the ridge/villous

pattern had a sensitivity, specificity and positive predictive value (PPV) of 93.5%, 85.7% and 94.7%, respectively, for the diagnosis of SIM. The irregular/distorted vascular pattern had a sensitivity, specificity and PPV of 100%, 98.7%, and 95.3%, respectively, for high-grade dysplasia. Goda et al (33) classified the mucosal (1 round/oval, 2 long straight, 3 villous, 4 cerebriform and 5 irregular) and vascular (I honeycomb-like, II vine-like, III coiled, IV ivy-like and V irregular) patterns seen with magnifying endoscopy under NBI for the detection of SIM and superficial Barrett's adenocarcinoma. The most characteristic endoscopic patterns to suggest Barrett's epithelium were the cerebriform mucosal pattern (sensitivity 56%, specificity 79%, OR 4.78) and the ivy-like capillary pattern (sensitivity 77%, specificity 94%, OR 51.6). A study in 2007 (34) investigated the endoscopic features seen in BE under magnified endoscopy with NBI, using a classification scheme consisting of microstructural (regular, irregular, absent) and microvascular (regular and irregular) patterns. The finding of regular microstructural pattern with tubular/linear/villous pattern and regular microvascular pattern with absent microstructural pattern had a diagnostic yield of 90.6% and 98.9% respectively, for SIM. The irregular microvascular/microstructural pattern had a sensitivity and specificity of 90% and 100%, respectively, for the prediction of high-grade dysplasia. Recently, Singh et al (35) proposed a classification scheme using four common patterns found with NBI endoscopic examination in patients with BE: pattern A (round pits with regular microvasculature), pattern B (villous/ridge pits with regular microvasculature), pattern C (absent pits with regular microvasculature) and pattern D (distorted pits with irregular microvasculature). Pattern A had a PPV and negative predictive value (NPV) of 100% and 97%, respectively, for columnar mucosa without intestinal metaplasia. Patterns B and C had a PPV and NPV of 88% and 91%, respectively, for specialized intestinal metaplasia. Pattern D had a PPV and NPV of 81% and 99%, respectively, for high-grade dysplasia.

Although the available results from the studies describing the changes seen under NBI endoscopy for BE appear promising, it is important to note that most groups developed their own classification

system for the mucosal and vascular changes observed. As a result, the lack of a sufficiently validated and standardized classification scheme is one of the main limitations in the use of NBI for BE. With the results of studies characterizing the lesions seen under NBI, the next step in investigating this modality is to validate the classification schemes described above, and to determine its clinical utility by comparing it with conventional white-light endoscopy and other modalities such as chromoendoscopy. We will discuss these studies in the next section.

### NBI ENDOSCOPY VERSUS CONVENTIONAL ENDOSCOPY IN BE

A number of studies have investigated measures such as sensitivity, specificity, diagnostic accuracy and image quality of the NBI system compared with conventional white-light endoscopy in BE. A study in 2004 by Hamamoto et al (11) investigated conventional white-light magnifying endoscopy versus NBI endoscopy in 11 patients with BE. Images taken during the procedure were reviewed with a scoring system (0 to 4, with 4 being optimal) to assess the quality of images of the esophago-gastric junction, capillary vessels and CLE. The squamocolumnar junction was visualized with a score of 3 or greater in 57% and 17% ( $P=0.0002$ ) of images under NBI and conventional endoscopy, respectively, while net-like blood vessels were visualized with a score of 3 or greater in 68% and 42% ( $P=0.1919$ ) of images for NBI and conventional endoscopy, respectively. The CLE was visualized with a score of 3 or greater in 100% and 80% ( $P=0.11$ ) of lesions for NBI and conventional endoscopy, respectively. Although there are limitations in assessing images for subjective factors such as image quality, this paper showed that NBI improves the visualization of important structures seen in BE over conventional endoscopy.

Curvers et al (23) compared high-resolution white-light endoscopy with NBI and determined that the yield of early neoplasia was 81%, 72% and 83% in the white-light endoscopy, NBI, and combination (white-light endoscopy and NBI) groups, respectively. Interestingly, the image quality was significantly better in the NBI group over the white-light endoscopy group (11.3 versus 10.9 on a visual analogue scale;  $P=0.01$ ) but was not found to improve the diagnostic yield of neoplasia. Another study by Singh et al (24) compared the use of high-resolution magnified NBI with conventional white-light endoscopy with magnification in 21 patients with BE and found that the sensitivity, specificity, and accuracy of NBI with magnification was 88.9%, 94.8% and 91.3%, respectively, compared with 71.9%, 90.5% and 84.8% for conventional white-light endoscopy for the prediction of histology. When both modalities were combined, a sensitivity, specificity and accuracy of 90.2%, 95% and 91.7% respectively, was achieved. Furthermore, in this study supporting the use of NBI there was a significant difference between NBI and conventional endoscopy for the detection of high-grade dysplasia (95% versus 62.5%;  $P<0.006$ ).

Wolfsen et al (25) investigated whether NBI targeted biopsies could detect advanced dysplasia using fewer biopsy samples

compared with conventional endoscopy using the four-quadrant biopsy method with a prospective, blinded, controlled tandem study. The study revealed that NBI detected dysplasia in 57% of patients compared with 43% in the conventional endoscopy with four-quadrant biopsy group, with higher grades of dysplasia detected in the NBI group ( $P<0.001$ ). In addition, more biopsies were taken in the four-quadrant biopsy group compared with narrow-band targeted biopsies (mean 8.5 versus 4.7;  $P<0.001$ ). Consequently, the use of 'targeted' biopsy techniques have potential time and cost savings.

Studies have also investigated the use of NBI compared with chromoendoscopy in BE. Curvers et al (26) recently investigated chromoendoscopy, NBI and high-resolution magnification endoscopy in patients with BE. They found that high-resolution endoscopy alone had an 86% yield of identifying high-grade dysplasia, while the combinations of white-light endoscopy with NBI, indigo carmine chromoendoscopy and acetic acid chromoendoscopy had 84%, 70% and 83% yields, respectively. A study by Kara et al (27) in 2005 investigated chromoendoscopy versus NBI, both in combination with high-resolution endoscopy, in a prospective, randomized crossover study with 14 patients. The sensitivity of chromoendoscopy and NBI was 93% and 86%, respectively, compared with 79% for four-quadrant biopsies with conventional endoscopy in the diagnosis of high-grade dysplasia or early cancer in patients with BE.

Although the results of studies comparing the use of NBI endoscopy with other modalities appear favourable, further randomized controlled studies comparing NBI with conventional endoscopy with the four-quadrant protocol for surveillance are required before further recommendations can be made regarding the use of NBI in routine practice. Presently, NBI is typically used as an adjunct to conventional white-light endoscopy to investigate areas appearing suspicious after initial screening.

### CONCLUSION

We have reviewed the current literature regarding the utility of NBI in the upper gastrointestinal tract, with particular emphasis on BE. Although other areas of the upper gastrointestinal tract (ie, stomach in the setting of intestinal metaplasia) may have lesions at increased risk and benefit from NBI, most studies have been performed in the setting of BE. Although there are limited numbers of studies regarding the use of NBI in the upper gastrointestinal tract, the available research appears promising. Presently, NBI is used as an adjunct to conventional white-light endoscopy for targeted investigation of suspicious areas. The main limitations of the NBI system include the learning curve associated with the new technology, the lack of sufficiently validated and standardized classification schemes for the NBI patterns observed in various conditions, and the limited number of randomized controlled trials investigating NBI compared with conventional white-light endoscopy. Further large-scale studies are required to address these limitations before NBI can be recommended as a primary method of screening for lesions of the esophagus in routine practice.

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