REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Narrow band imaging endoscopy for detection of precancerous lesions of upper gastrointestinal tract

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Abstract

Gastric cancer (GC) is an important health problem despite the advances in surgery and chemotherapy and although the incidence is decreasing, GC is still considered the second most common cause of deceases produced by cancer. Survival rates in gastric cancer are low, mainly because most patients are often diagnosed in late stages. The current interest in the diagnostic of GC is the detection of early gastric cancer. Advances in high-resolution endoscopic techniques such as narrow band imaging (NBI) allow the detection of early precancerous lesions like polyps or metaplastic mucosa. Performing only white light imaging endoscopy in order to detect gastric cancer can lead to omission or misdiagnose of a considerable number of early gastric cancers. NBI endoscopy associated with other high-resolution examinations is viable in detecting early gastric cancer, though few studies also indicate that the endoscopist's expertise plays an important factor as well.

Keywords: narrow band imaging, gastric cancer, precancerous lesions.

Introduction

Gastric cancer (GC) remains a major health burden despite the advances in surgery and chemotherapy [1]. Even though the incidence of gastric cancer is decreasing, it is still considered the second most common cause of deceases produced by cancer [2]. Currently, literature supports a multifactorial model in gastric carcinogenesis where environmental factors, diet and genetic susceptibility interact in producing the host's disease. Because most patients are often diagnosed in late stages of gastric cancer, the survival rate is extremely diminished and recent UK studies estimate survival rates of less than 5% after 5 years of the diagnostic for patients with stage IV stomach cancer [3].

Gastric cancer is a malignant disease that develops silently and most of the times without any symptoms until end stages. For this matter, countries with high incidence of gastric cancer like Japan have introduced screening programs that resulted in increasing the five-year survival rate of patients up to 90%, mainly due to early detection. In Western Europe, as well as in our country, there is no screening program implemented and usually there is a big diagnostic delay for patients with no symptoms that has proven to be catastrophic for the outcome and long term prognosis of these patients [4]. Gastric cancer has a higher incidence in patients over 65 years in age, but as of recent, many cases are diagnosed in early 30s or 40s, mostly with non-specific symptoms prior to diagnosis [5]. The question arisen is what can be done in order to improve the diagnosis of early gastric cancer [6]. One solution could be represented by performing routine white light upper endoscopies for patients with dyspepsia regardless of age and even without alarm symptoms. Other solutions are represented by performing high-resolution endoscopic techniques such as narrow band imaging.

Narrow band imaging (NBI) technique

As of recent interest, the introduction of new endoscopic technologies such as narrow band imaging in association with high definition scopes has increased the rate of detection for small polyps, flat lesions or early cancers.

Narrow band imaging (NBI) is a high-resolution endoscopic technique that uses a spectral narrow band filter, which enhances the visualization of microvascular and mucosal patterns [7, 8]. The mechanism of narrow band imaging includes the usage of only two bands of light: 390–445 nm for blue light and 530–550 nm for green light [9]. The resulted light is reflected by the mucosa and absorbed by the vessels which provide an image that succeeds to enlighten a contrast between the vessels and the surrounding mucosa. The shorter NBI light wavelength has proven to be useful in the detection of highly vascularized tumors due to its absorption in the superficial vessels. The green NBI light penetrates deeper under mucosal vessels and provides the layout of deeper vascular lesions.

NBI for upper gastrointestinal organic disorders

NBI has already been proven handy for the detection of various upper gastrointestinal organic disorders [10]. Sharma *et al.* published a study in 2013 performed on 123 patients that compared the biopsies yielded using high definition white light endoscopy with biopsies taken with narrow band imaging for the detection of esophageal intestinal metaplasia and neoplastic tissue Barrett's esophagus. The authors concluded that NBI can improve the efficiency and cost of Barrett's esophagus surveillance due to the fewer biopsies needed for the detection of dysplasia and intestinal metaplasia [11]. In the same matter

that the NBI technique enables better visualization of mucosal and vascular patterns in patients with Barrett's esophagus, hence allowing the improvement of the sensitiveness and specificity in the diagnosis of Barrett's esophagus. By identifying with great accuracy the affected areas, the NBI technique directs the physician to more precise biopsies that require to be further characterized by the histological examination (Figure 1, A and B). It enhances a strong correlation between the histological staging and the NBI score obtained after examination [12].

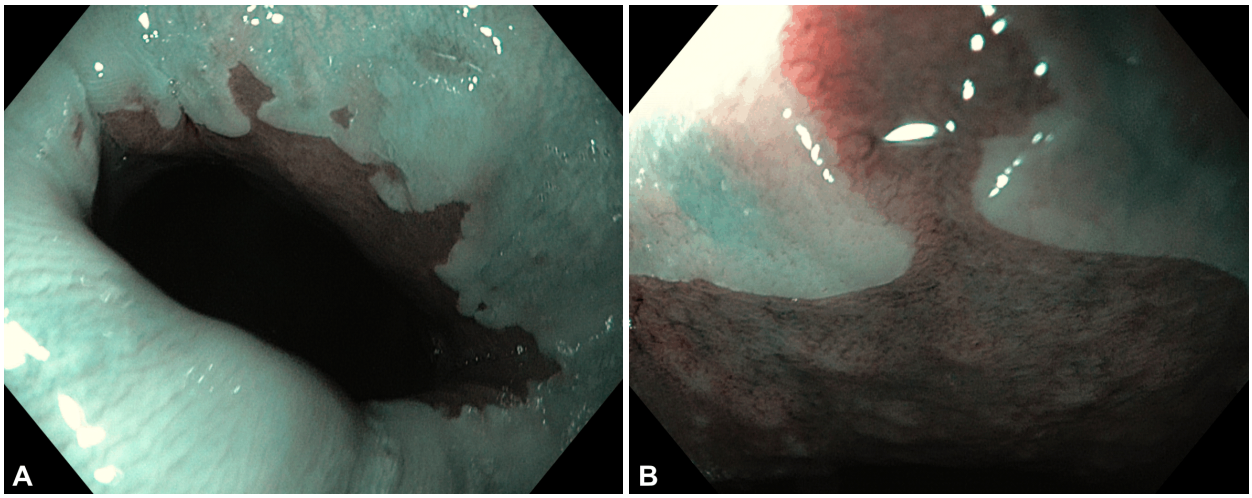

Figure 1 – ***Barrett's esophagus in NBI mode view A (panoramic) and B (detail).***

Another study performed by Muto *et al.* on 320 patients compared real-time detection rates of esophagus squamous cell carcinoma using white light imaging and NBI. The patients were randomly divided into two groups that were examined back to back. The first group was primarily assessed by white light imaging and then by narrow band imaging, whether the second group was first examined with NBI and then with white light endoscopy (WLE). The results were highly promising because white light imaging examination was able to detect 55% of the lesions in the esophagus compared to NBI examination, which was able to detect 97% of the lesions if performed after the initial white light endoscopy. The authors concluded that NBI could become a standard examination for early detection of esophageal superficial cancers [13].

NBI and detection of early gastric cancer

In 2016, the same authors published a guideline for the detection of early gastric cancer using magnifying narrow band imaging endoscopy technique. The review focused on the detection of early gastric cancer lesions, which were defined as carcinomas affecting the gastric mucosa and submucosa. The macroscopic classification of early gastric cancer using the *Japanese Classification of Gastric Carcinoma* enhances a superficial-type tumor (type 0) as a typical morphological tumor of early gastric cancer. Type 0 is further divided into type 0-I, type 0-IIa, type 0-IIb, type 0-IIc, type 0-III, corresponding to protruding, superficial elevated, superficial flat, superficial depressed and excavated lesions [14]. The authors stated that in order to perform a proper diagnosis of early gastric cancer, the physician has to assess any suspicious lesion as possible malignant. To further detect such a lesion, the authors indicate following any morphological changes on the surface of the gastric mucosa such as elevation, depression or flatness as well as color changes from white to red. The next step should be distinguishing a demarcation line between the lesion and the normal mucosa. In case of the absence of the demarcation line, the diagnosis of benign lesion is possible (Figure 2). If the demarcation line is present, then by using magnifying NBI the physician can assess subsequent presence of irregular microvascular and microsurface patterns [15].

Therefore, by using NBI technique on early gastric cancers (Figure 3), the physician can describe mucosal and vascular patterns such as: absence of fine mucosal structure with microvascular dilation, irregular V pattern or complete loss of architectural and mucosal pattern with much higher diagnostic accuracy then conventional white light endoscopy [16–18]. At the same time, NBI with or without magnification allows the endoscopist to discern various patterns in differentiated-type early gastric cancers (D-EGC) *versus* undifferentiated-type early gastric cancers (UD-EGC). D-EGC is characterized by relatively regular fine network pattern or grid network pattern with hypervascularity compared to irregular, twisting or corkscrew patterns with hypovascularity in UD-EGC [19, 20].

NBI for precancerous lesions

Recent studies show that gastric precancerous lesions such as *Helicobacter pylori*-associated chronic gastritis or metaplastic mucosa can be better assessed with magnifying endoscopy (ME) with narrow-band imaging. In the case of *H. pylori*-associated chronic gastritis by using ME-NBI, the physician performing the endoscopy can better distinguish the abnormal form and arrangement of the crypt openings with changes in color represented by the presence of whitish elliptical shape patterns [21]. In the same matter, a previous study published in 2010 by Kawamura *et al.* assessed gastric micromucosal patterns with ME-NBI on 95 patients of which 24 had duodenal ulcers, 24 had diffuse-type early gastric cancer and further 47 more patients suffered from intestinal-type early gastric cancer. The authors observed a total of 190 areas using ME-NBI and histological grading. The areas were significantly differentiated among the established micromucosal patterns. The authors concluded that the NBI examination can better reveal enhanced micromorphological disparities

corresponding to endoscopic and histological assessments in patients with various *H. pylori*-related pathologies [22].

A special attention is likely required on monitoring gastric polyps, which are classified based on histological aspects into two groups: neoplastic and non-neoplastic polyps [23]. Of the two groups, gastric polyps are more often non-neoplastic compared to colorectal ones, which encounter a higher prevalence of neoplastic polyps. NBI international colorectal endoscopic classification (NICE) describes colorectal polyps as hyperplastic, adenoma and deep submucosal invasive cancer based on color, vessels and surface patterns. On the other hand, gastric polyps have similar endoscopic appearances and another classification arises from the histological alcove from which they emerge (epithelial, mesenchymal and hamartomatous) [24]. The types of gastric polyps [Figures 4 (A and B) and 5 (A and B)], which have been described in literature based on histological and endoscopic features are: fundic gland polyps (FGPs), hyperplastic polyps (HPPs), adenomatous polyps, inflammatory fibroid polyps, gastric neuroendocrine tumors, leiomyomas, granular cell tumors, ectopic pancreatic tumors and gastrointestinal stromal tumors (GISTs). Until recent, it was considered that the most common gastric polyps were HPPs but lately, many studies on very large cohorts in Asia and America have expressed an increase in prevalence of FGPs. At the same time, the gastric location of the polyps has changed throughout the studies reported in the past decade since reports indicate a decrease in prevalence of antrum polyps compared to polyps located in the antrum [23, 25, 26]. Even though not every polypoid elevated lesion is a polyp until histological confirmation, ME-NBI has proven useful on foreseeing histological aspects on gastric polypoid lesions hence the advanced endoscopic technique can describe mucosal and microvascular patterns. The mucosal patterns were classified into: small round, prolonged, villous or ridge and unclear. Furthermore, the micro vascular patterns were likewise classified into: honey comb, dense vascular, fine network, core vascular and unclear. According to Omori *et al.*, the honeycomb microvascular pattern had high sensitivity and specificity (94.7% and 97%) for anticipating fundic gland polyps and hyperplastic polyps, as well as the dense vascular pattern with similar sensitivity and specificity (93.6% and 91.6%). On the other hand, the other three microvascular patterns had very high specificity in anticipating gastric adenocarcinoma (97% for fine network pattern, 100% for core vascular and unclear patterns) [27].

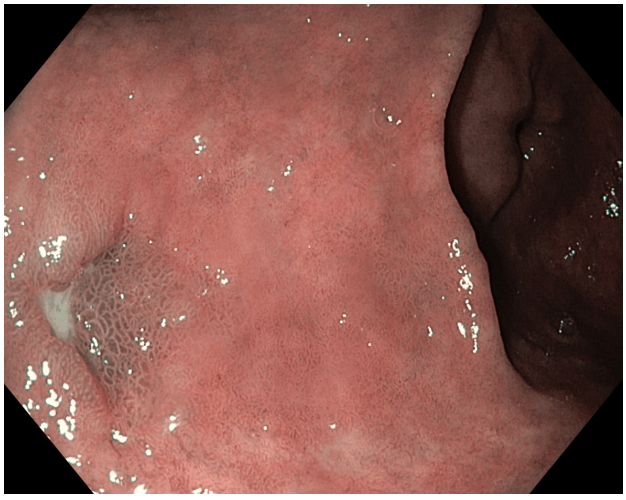

Figure 2 – ***Benign gastric ulcer in NBI mode view (regular aspect of vascularization of the lesion).***

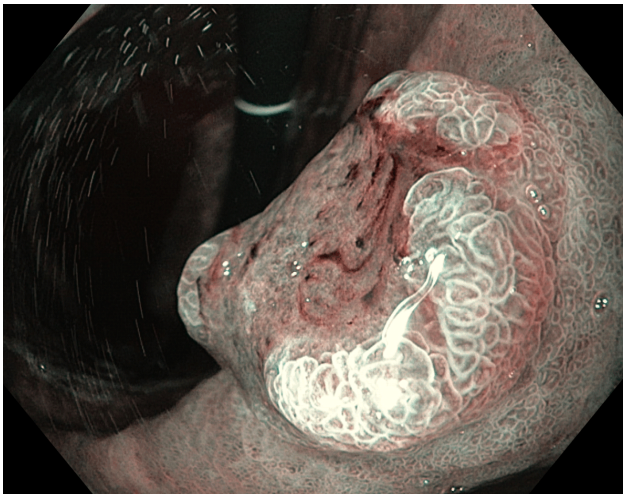

Figure 3 – ***Malignant lesion at the level of gastric angle in NBI mode view (absence of fine mucosal structure, complete loss of architectural and mucosal pattern in the center of the lesion).***

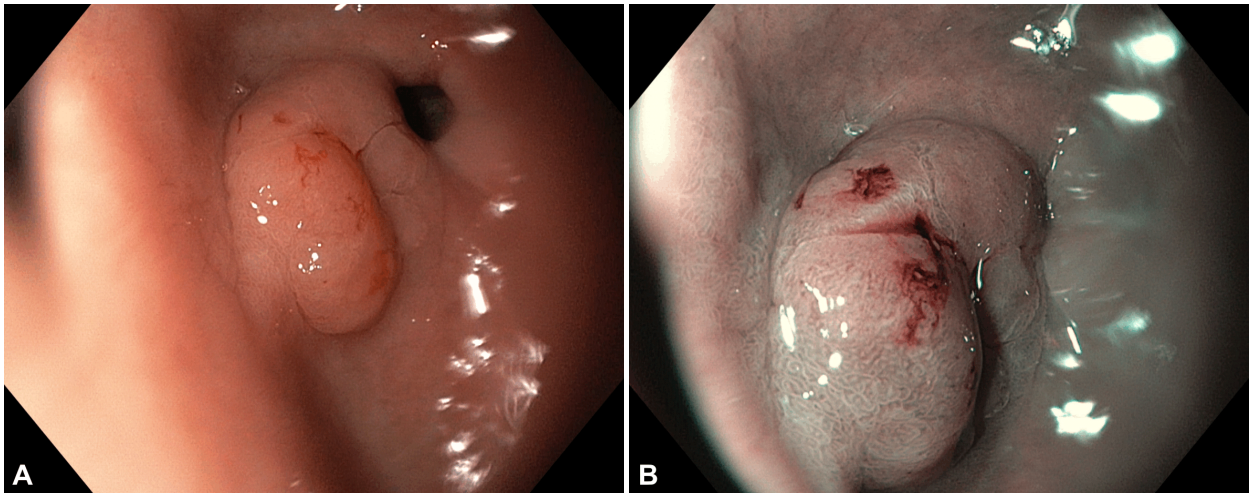

Figure 4 – ***Adenomatous gastric polyp near the pylor in white light view (A) and NBI view (B).***

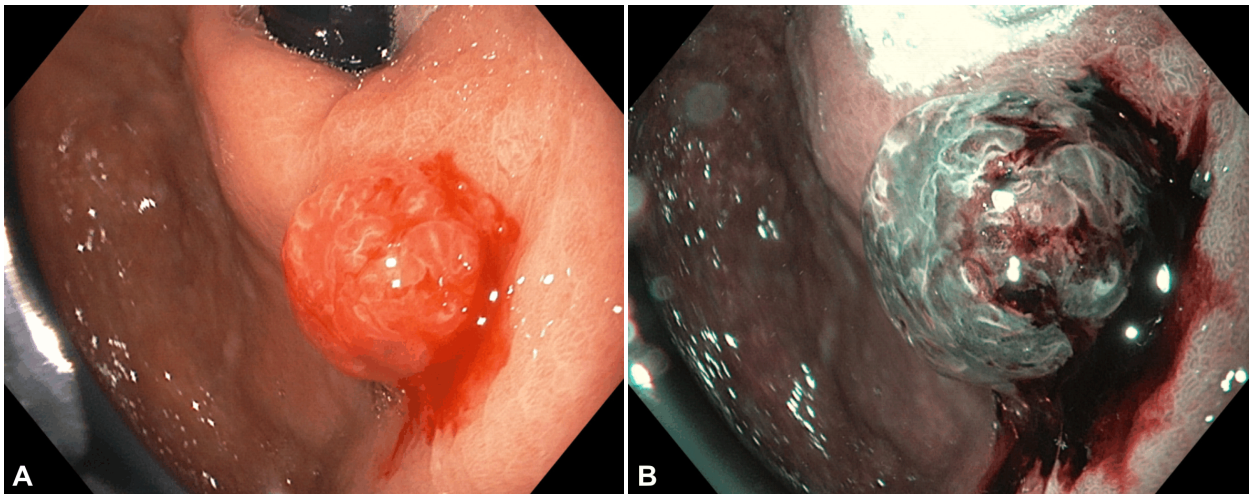

Figure 5 – ***Hyperplastic gastric polyp near the pylor in whit light view (A) and NBI view (B).***

ME-NBI visual markers and immunohistochemistry for early gastric cancer

A Korean study published in 2012, which enrolled 47 patients who were diagnosed with early gastric cancer or were simply assessed for dyspeptic symptoms. The authors examined the patients using ME-NBI, visualizing the lesser curvature of the gastric midbody and the greater curvature of the upper gastric body. An *et al.* used two visual indicators (MTB – marginal turbid band and LBC – light blue crest) in order to yield biopsies from the evaluated areas. The results were spectacular since MTB had good values of sensitivity, specificity and accuracy ranging from 100%, 66% and 81.7% indicating that marginal turbid band can be highly accurate in terms of intestinal metaplasia early diagnosis. Furthermore, the light blue crest indicator seemed to be highly accurate for progression to severe intestinal metaplasia [28].

Later, in 2015, Doyama *et al.* tried to assess a potential new ME-NBI marker called "white globe appearance" (WGA) for a proper diagnosis of early gastric cancer. The "white globe appearance" was described as a small white lesion with globular shape situated beneath the cancerous epithelium. The authors retrospectively analyzed the ME-NBI images from a total of 111 gastric lesions in order to determine the prevalence of WGA in early gastric cancer and in low grade adenoma. Out of the 111 gastric lesions, 93 were cancers with the WGA being observed in 20 cases. The rest of 18 gastric lesions were low-grade adenomas in which WGA was not observed at all. Although the results indicated 100% specificity and positive predictive value, the percentages for sensitivity and negative predictive value were as low as 20%. The authors conclude that WGA can prove to be a new ME-NBI endoscopic marker used to distinguish low-grade adenoma with early gastric cancer, however further studies are needed to fully validate this marker [29].

Ok *et al.* examined 160 lesions of early gastric cancer using ME-NBI before undergoing surgical or endoscopic resection. The authors classified the early gastric cancers as differentiated or undifferentiated, as well as mucosal or submucosal lesions. They also assessed mucin phenotypes of the tumors *via* immunohistochemistry. The results were promising since the ME-NBI examination displayed distinct characteristics during the visualization of the microvascular and microsurface patterns. Furthermore, the mucin phenotypes were correlated with the observed patterns. Thus, the authors were able to state that ME-NBI can be used to foresee the histopathological and mucin phenotype in early gastric cancers [30].

NBI and autofluorescence imaging (AFI) for early gastric cancer detection

More Asian studies, where the incidence of gastric cancer is the highest, are reporting more accurate diagnosis of early gastric cancer using endoscopic examinations that combine autofluorescence imaging (AFI) with narrow band imaging. The percentages outlined in the detection of intestinal metaplasia show values of sensitivity and specificity up to 88.89 and 91.58% for the AFI-NBI combination. Same reports admit sensitivity and specificity percentages of 83.33 and 98.51% for the diagnosis of dysplasia with even higher percentages for the detection of early gastric cancer (90.91 and 99.22%). The results suggest that the combination between the methods could increase the rate of diagnosis for early gastric cancer or precancerous lesions [31]. The results stated are similar to other published studies that indicate magnifying NBI endoscopy is superior to the white light endoscopy in detecting early gastric cancer [32–34].

The European incidence of gastric cancer is lower than in Asian areas but the studies published on European patients solidify the importance of NBI endoscopic examination for early gastric cancer detection.

Limitations of NBI examination

A European study published in April 2016, which included 60 patients divided into two groups, outlined the limitations of NBI endoscopic examination based on the experience level of the physician performing the endoscopy. The assessment of the patients was complex since the first group was examined by six endoscopists with two levels of expertise, who had to evaluate the grade of gastric intestinal metaplasia based on endoscopic images obtained with white light endoscopy, narrow band imaging and magnifying endoscopy. The second group was assessed by a group of experts with higher experience who examined real-time images in a similar way and

compared their diagnosis with the histological diagnosis. The results showed diagnosis accuracy of 60% in the first group during white light endoscopy examination, with a small percentage variation between non-expert 59% and expert 63%. During ME-NBI examination, the accuracy further increased to 73% with much higher percentage variation between non-expert 63% and expert 83%. The diagnosis stated by the endoscopists was identical to the histology diagnosis in 83% of the cases and in the real-time assessment group, the experts managed to correctly establish the diagnosis of extensive intestinal metaplasia in 91% of the cases. By summing up, the authors raise the question of the necessity of biopsies when up to 90% of the patients at risk can be diagnosed with high-resolution endoscopy with NBI without the need for further biopsies [35].

The limitations of ME-NBI in the endoscopic screening of early gastric cancer were enhanced by a Japanese study in 2014 performed on 1097 subjects. A number of 371 lesions were detected of which 20 were cancers and 351 were non-malignant. The sensitivity, specificity and diagnosis accuracy of ME-NBI was diminished by the presence of pale mucosal lesions, which contributed to a false negative case in which a pale mucosal lesion was histological diagnosed as signet-ring cell carcinoma. The overall diagnosis performance of ME-NBI was very good with the authors considering that a filtered strategy of excluding pale mucosal lesions can lead to performing "optical biopsies" during gastric cancer endoscopic screening [36].

Conclusions

Gastric cancer is a malignant disease which often develops silently with few unspecific symptoms that can be ignored by either the patients or the physician. Due to this matter, gastric cancer is rarely diagnosed in an early stage where the prognostic can be favorable for the patient. Performing only white light imaging endoscopy in order to detect gastric cancer can lead to omission or misdiagnose of a considerable number of early gastric cancers. Narrow band imaging endoscopy associated with other high resolution examinations are viable in detecting early gastric cancer, though few studies also indicate that the endoscopist's expertise plays an important factor as well.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

This work was supported from a research grant funded by the National Research Council (CNCS), Romania, entitled *Study of minimally invasive endoscopic IMaging methods for the evaluation of neoANGiogenesis in gastrointestinal cancers (IM-ANG)*, contract number PN-II-RU-TE-2014-4-2289.

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Received: March 3, 2016

Accepted: November 5, 2016