MUCOSAL PATTERN OF THE UPPER GASTROINTESTINAL TRACT VIEWED BY MAGNIFICATION ENDOSCOPY IN COMBINATION WITH NARROW-BAND IMAGING

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ABSTRACT

The introduction of white light endoscopy has improved dramatically the management of gastrointestinal tract disorders. Tissue sampling, however, is mandatory for accurate diagnosis, especially if dysplasia, cancer or *H. pylori* infection is suspected. It is also associated with high missing rates due to the uneven distribution of the mentioned pathology. Chromoendoscopy has proven to be superior to standard white light for detecting of lesions but requires different dyes and a long learning curve. On the other hand, narrow band imaging in combination with magnification endoscopy shortens the procedure time, allows close observation of the mucosal surface gaining excellent real-time images, and guides the endoscopist for target biopsies of suspected areas. This review will briefly cover the current knowledge of high quality endoscopy of the upper gastrointestinal tract.

Keywords: *squamous cell cancer, Barrett's esophagus, dysplasia, early gastric cancer, coeliac disease, narrow band imaging, magnification endoscopy*

INTRODUCTION

NBI is an optical image enhancement technology that improves visualization of the gastrointestinal (GI) mucosa by enhancing vessels and patterns of the surface by employing the characteristics of light spectrum. Historically, the development of NBI goes back to 1994, when a project for early diagnosis of cancer was initiated in Japan. In December 2005, the NBI system became commercially available

from Olympus, and has now expanded worldwide. At present, two different systems are available: the 200 LUCERA series using a rotating red-green-blue (RGB) filter and the 100 EXERA series, which uses a charge-coupled device (CCD) chip. Each system has its advantages, with the former producing crisper higher resolution images and the latter – better quality of video motion. The concept of the NBI system is placement of a double-band light filter after a white-light source, which leads to split of the light into two bands: blue – 415 and green – 540 nm. The blue light corresponds to mean peak absorption of hemoglobin that highlights capillaries in the superficial mucosa, whereas the green light provides deeper penetration focusing on deeper mucosal vessels. Most of the current endoscopes are supplied with high definition imaging which allows resolution enhancement, and zoom (either optical or digital) for close observation of the mucosal surface (1,2). The purpose of this

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review is to present a brief summary of the current knowledge in the field of modern endoscopy focusing on the upper GI tract.

Esophagus

The stratified squamous epithelium in the esophagus has no pit pattern which is routinely observed in the stomach and colon. It is the intra-epithelial papillary capillary loop (IPCL) observed by magnification endoscopy and NBI that is considered the main micro-vascular structure. In *normal epithelium*, IPCL is observed as a brownish smooth running small-diameter capillary vessel (IPCL Type I) located superficially, while the branching vessel, from which the IPCL emerges, looks green and more deeply situated (3).

Gastroesophageal reflux disease has been divided into erosive disease with typical endoscopic features classified according to the LA classification and non-erosive reflux disease (NERD) with absence of macroscopic abnormalities (4). For the classical erosive esophagitis the macroscopic changes are easily seen on standard white light endoscopy, so additional switch to NBI-magnification regime is not supposed to enhance diagnosis. Nevertheless, type II IPCL (enlarged but linear and regular vessels), which is equivalent to regeneration or inflammation have been seen in typical erosive esophagitis (3). Non-erosive esophagitis represents an important issue since it may progress to erosive esophagitis with subsequent development of strictures and Barrett's esophagus. Recent data from Malfertheiner et al have proven that progression of NERD to mild esophagitis can be as high as 40% (5). Therefore, early detection of NERD is essential. It has been shown that NBI magnification endoscopy can detect microvascular abnormalities such as micro-erosions, increased vascularity and abnormal ICPL in patients with NERD. The best predictors are presence of micro-erosions, increased number and dilatation of IPCL (6). The same changes – micro-erosions and increased vascularity are also proven at the squamo-columnar junction of patients with both NERD and erosive esophagitis compared to controls (7). Also, significant improvement of these NBI features was present after initiation of therapy with proton pump inhibitors (8), showing that they are reliable markers for reflux disease.

Barrett's esophagus is defined as a replacement of the distal squamous epithelium with metaplastic columnar and is associated with adenocarcinoma. The best tissue biomarker for the assessment of cancer risk is dysplasia confirmed by two expert GI pathologists. The standard protocol includes quadrantic, 2 cm biopsies in addition to sampling any visible lesion for confirming presence of dysplasia or early cancer (9). This protocol is labor intensive, requires addition procedure time and may have false-negative results since lesions harboring dysplasia are subtle and difficult to detect with the standard endoscopic equipment. By introducing magnification NBI endoscopy it became evident that presence of regular villous/gyrus-forming mucosal pattern and long-branching normal-appearing vessels were associated with non-dysplastic intestinal metaplasia and irregular/disrupted mucosal pattern and abnormal blood vessels were more often found in highly dysplastic mucosa (10). These data prove that magnifying endoscopy with NBI reliably detects areas harboring intestinal metaplasia and high grade dysplasia. More recent data show that this combined method cannot differentiate between intestinal metaplasia and low grade dysplasia (11) but requires fewer biopsies per patient compared to white light endoscopy (12).

Diagnosis of advanced *squamous cell carcinoma* has a detrimental consequence on the prognosis of patients. Therefore, early detection of premalignant lesions of the esophagus, which is possible by NBI magnification endoscopy, is crucial to prevent incurable cases. The first diagnostic step is careful observation of the esophageal mucosa for presence of a suspicious lesion that usually looks brownish compared to the surrounding mucosa by NBI without magnification. If such lesion is discovered the next step is to evaluate the IPCL pattern (3). If type III IPCL (minimal proliferation or meandering in a brownish area) is visualized this is considered a borderline or low grade intra-epithelial neoplasia. A follow-up endoscopy is generally recommended for these patients. If a well-demarcated brownish area along with elevated margins, loss of visible branching vessels and IPCN type IV or V is present, this corresponds to early squamous cell carcinoma (11). Inoue originally described intraepithelial papillary capillary loops into 4 distinct entities: dilation, meandering, caliber changes and difference in shapes (13). Type IV IPCL

shows 2 or 3 of the four patterns, whilst Type V IPCL demonstrates all 4 characteristic changes. Therefore, type IV and V IPCL are equal to early squamous cell carcinoma (11).

Stomach

Magnified NBI endoscopic findings of normal gastric mucosa differ according to the part of the stomach, e.g. gastric body or antrum. The normal gastric body shows a honeycomb-like subepithelial capillary network pattern with collecting venules. More precisely, a polygonal loop of subepithelial capillary surrounds each gastric pit and these loops form a honeycomb-like network beneath the epithelium and converge onto a collecting venule. By magnification with NBI, the pits demonstrate a round or oval shape. In contrast, the gastric antrum demonstrates a completely different structure. Its subepithelial capillary network is coil-shaped, collecting venules are rarely seen since they are located deeply in the lamina propria, and pits show a linear or reticular pattern (14).

The leading course of *chronic gastritis* is *H. pylori* infection. The latter has been recognized as the most consistent risk factor for gastric cancer. This is a multi-step process characterized by formation of gastric atrophy, intestinal metaplasia and dysplasia (15). On magnification NBI endoscopy HP infection causes regression of the honey-comb pattern and loss of collecting venules with sensitivity of 100% and specificity of 92%. Gastric atrophy has been described as complete loss of pit pattern and subepithelial capillary network with sensitivity and specificity exceeding 90% (16, 17). These features, however, have been described only the gastric corpus and typical NBI endoscopic characteristics for gastritis and atrophy in the gastric antrum to our knowledge are lacking.

The extent and severity of the gastritis together with atrophy and especially *intestinal metaplasia (IM)* is positively associated with intestinal type of cancer (Maastricht iv). Therefore, early detection of this precancerous lesion is important for patient follow-up. Conventional white light endoscopy detects subtle changes such as areas with flat mucosa (17). However, Uedo et al reported that a distinctive finding called "light blue crest" (LBC) which is a fine, blue-white line on the crests of the epithelial surface

or gyri visualized by magnification and NBI, is an indicator of IM. It is probably caused by reflection of short and narrow wavelength light (400-430 nm) at the surface of ciliated tissues such as the brush border of the gastric intestinal metaplasia and duodenum (18). Furthermore, An et al observed a more subtle finding, called marginal turbid band (MTB) which is defined as a white band on the epithelial surface or gyri. The latter, together with LBC are associated with atrophy and IM. MTB represents an early sign of IM while LBC is related to progression to severe IM (19). The ability of the current endoscopes to view the mucosal surface microstructure by pressing only 2 buttons – one for NBI and one for zoom is fascinating. The only drawback is that MTB is best visualized by LUCERA 200 system and videoendoscopes from 260 series which are not widely available in Europe.

Early gastric cancer differs in its structure on magnification NBI endoscopy depending on its histology. Differentiated carcinoma shows loss of subepithelial capillary network and microvessels, which are irregular in shape and arrangement. There is a clear demarcation line between the cancerous and non-cancerous tissue, the latter preserving the shape and arrangement of its subepithelial capillary network. These features are very useful in clinical practice since they could differentiate between carcinoma and focal gastritis (14) or other benign small depressed lesions with sensitivity and specificity above 95% (20). Also, they could clearly distinguish the tumor margins from the surrounding mucosa which can have therapeutic consequences, for example aiding endoscopic submucosal dissection. Irregular subepithelial capillary network is not uniform. Nakayoshi et al observed 3 types of irregular vascular pattern on magnification NBI endoscopy: fine network, corkscrew and unclassified. Fine network pattern was associated with differentiated early gastric cancer and corkscrew pattern- with undifferentiated one. Approximately 10% was unclassified (21). NBI is, however, unable to assess the depth of tumor invasion since narrow band of light penetrates to only 200-250 µm into the superficial mucosa (22). Another feature of differentiated early gastric cancer is the presence of white opaque substance that obscures the neoplastic subepithelial capillary network (23). This is due to subepithelial accumulation of lipid droplets which can be absorbed from the neoplastic mucosa

from intestinal type. Adenomas express regular distribution of white opaque substance while in early carcinoma it is irregular (24).

Approximately 40% of early gastric carcinoma is of undifferentiated type (25). Its only endoscopic feature on NBI with magnification is reduced density of the subepithelial capillary network (14). This could be explained by the fact that it extends subepithelially and can be covered by normal mucosa. Therefore, a clear demarcation line between cancerous and surrounding non-cancerous tissue is not seen.

Duodenum

On magnification NBI endoscopy the normal duodenal mucosa exhibits finger- or leaf-like villi with light blue crests at their edge and fine intravillous capillary loop network (14).

The villous atrophy seen in coeliac disease by standard white-light endoscopy is often patchy and therefore unreliable. With the help of high-resolution endoscopy the endoscopist can visualize these mosaic fields, perform target biopsies and even assess the degree of villous atrophy. A scoring system (Z score) was proposed for grading the appearance of villous atrophy: "Z1" for normal mucosa, "Z2" for blunted villi, "Z3" for markedly blunted villi (with ridges and pits) and "Z4" for flat mucosa (26). This scoring system seemed to be well correlated with histological assessment of villous atrophy.

CONCLUSION

With the advent of new imaging modalities such as NBI and magnification endoscopy it has become clear that GI tract mucosa hides more secrets and challenges than previously apprehended. In the hands of an experienced endoscopist this method could provide exact diagnosis and even be cost-saving by avoiding unnecessary tissue sampling. Appropriate training of unexperienced performers is of paramount importance. Although a good amount of data has been accumulated still standardization and selection of validated endoscopic classifications is needed.

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