Role of Endoscopy and Novel Imaging in GERD

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Introduction

Gastro esophageal reflux disease (GERD) is a condition which develops due to reflux of gastric contents into the esophagus causing symptoms, complications, or both.

GERD-related symptoms are common, affecting 25–30% of the general population in the west. Recent studies suggest a worldwide increase in prevalence of at least 4% per year [1].

GERD is less prevalent in the Asia Pacific region but appears to be on a rapidly rising phase [2]. Needless to say, it causes a significant decrease in quality of life and is a huge economic burden [3, 4].

Upper gastrointestinal endoscopy and examination of the esophagus has been the most widely used modality for the diagnosis and grading of severity of erosive reflux disease and its complications. It also allows tissue sampling and application of therapeutic procedures like dilatation and endoscopic mucosal resection [5]. Quite expectedly, with the increasing prevalence of GERD, the usage of upper GI endoscopy is on the rise.

Standard endoscopy using white light endoscopy has been the norm. However, more than 60% of patients with reflux symptoms suffer from nonerosive reflux disease (NERD) and show no visible changes on white light endoscopy (WLE).

Novel imaging technologies are now evolving which enable better visualization of mucosal details. These technological advances, such as digital chromoendoscopy, help circumvent the limitations of WLE in reflux disease by (a) improved detection of subtle irregularities and (b) characterization of anomalies and possible optical biopsies, providing real-time diagnosis.

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This chapter aims to discuss the role and appropriate utilization of endoscopy and novel imaging technology in patients with GERD.

Indications for Endoscopy in GERD

High-definition, high-resolution endoscopy is now widely available and accepted as standard endoscopic care for GERD across the globe. It enables direct visualization of the esophageal and gastric mucosa and allows tissue sampling for histology. GERD is the most common indication for endoscopy.

It is important to clarify here that the diagnosis of GERD can usually be made on the basis of clinical symptoms alone. Additionally, as mentioned earlier, 50–85% of patients with GERD have nonerosive reflux disease with a normal endoscopy. The sensitivity of endoscopy for GERD is low, but it has high specificity at 90–95%. Empiric medical therapy with once-daily proton pump inhibitors is therefore an appropriate initial step for uncomplicated disease, and a routine endoscopy is not warranted. Endoscopy is indicated only if 4–8 weeks of twice-daily PPI fails to resolve the symptoms [6].

It has been debated whether a screening endoscopy should be done in patients with well-controlled symptoms for detection of complications like Barrett's esophagus (BE) or esophageal adenocarcinoma. However, an endoscopy in every patient with GERD would be a low-yield, high-cost procedure and would still not detect BE in asymptomatic individuals. Also, numerous studies have now shown that the absolute risk of adenocarcinoma in women even with symptoms is low. Similarly, the incidence is low in patients <50 years of age and the non-Caucasian population. Recent guidelines by the British Society of Gastroenterology have clearly stated that screening endoscopy in an unselected population with reflux symptoms is not feasible [7]. A reasonable and plausible approach would be to individualize to patients with chronic symptoms with multiple risk factors (at least three of: age 50 years or older, white race, male sex, obesity). A family history of adenocarcinoma would also warrant an early examination.

Endoscopy at presentation is indicated only in certain specific situations, listed below. These include the presence of alarm symptoms of weight loss, dysphagia, anemia, bleeding, or recurrent vomiting, or the presence of extra-esophageal symptoms like hoarseness of voice and cough. The probability of lesion detection is much higher in the presence of alarm symptoms. In a recent retrospective analysis of 30,337 patients with dysphagia as an alarm symptom, more than 50% had significant findings, primarily stricture formation.

Indications for Endoscopy in Patients with GERD

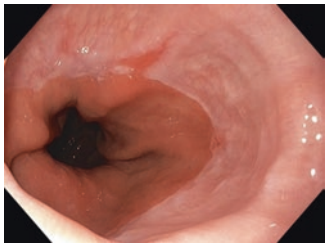
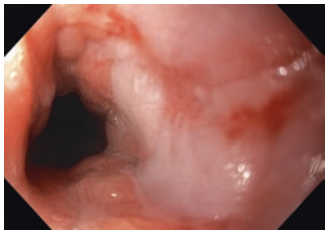
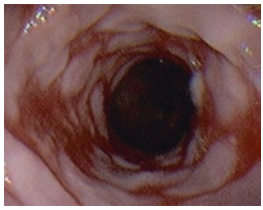
1. GERD symptoms that are persistent or progressive despite appropriate medical therapy
2. Dysphagia or odynophagia
3. Involuntary weight loss O5%

4. Evidence of GI bleeding or anemia
5. Finding of a mass, stricture, or ulcer on imaging studies
6. Evaluation of patients with suspected extra-esophageal manifestations of GERD
7. Screening for BE in selected patients (as clinically indicated)
8. Persistent vomiting
9. Evaluation of patients with recurrent symptoms after endoscopic or surgical anti-reflux procedures

Follow-up endoscopy is advocated in patients with a documented severe esophagitis (Los Angeles classification: Grade B and above; Table 6.1) after 8 weeks of PPI therapy. This helps ensure complete healing and duration of PPI usage. Additionally, it can detect Barrett's esophagus in previously denuded esophageal epithelium. Generally, no further endoscopy is needed if the follow-up endoscopy is normal.

Repeated endoscopies are often needed in cases of esophageal strictures because recurrence is common, requiring repeated dilatations. The timing of these endoscopies can usually be guided by the presence and severity of symptoms. In asymptomatic patients with a history of a peptic stricture a repeat endoscopy is not required.

Table 6.1 The modified Los Angeles classification of esophagitis

Grades		Image
Grade A	One (or more) mucosal breaks no longer than 5 mm that do not extend between the tops of two mucosal folds	
Grade B	One (or more) mucosal break more than 5 mm long that do not extend between the tops of two mucosal folds	
Grade C	One (or more) mucosal breaks that are continuous between the tops of two or more mucosal folds but which involve less than 75% of the circumference	
Grade D	One (or more) mucosal breaks which involve at least 75% of the esophageal circumference	

Surveillance endoscopy has been advocated for the early detection of dysplasia and/or malignancy in BE by many guidelines. These have been based primarily on observational data studies that indicate that surveillance correlates with earlier stage and improved survival from cancer. There are no randomized controlled trials. Accordingly, upper endoscopy with multiple four-quadrant biopsies every 3 to 5 years is considered adequate. More frequent examinations may be required in patients with dysplasia due to the enhanced risk of progression. Serial endoscopy for the detection of BE in patients with chronic GERD symptoms is not recommended.

Endoscopy for Diagnosis and Grading of Severity of GERD

Upper endoscopy is the standard for documenting the presence and extent of esophagitis and excluding other etiologies for the patient's symptoms.

Edema and erythema are the earliest endoscopic signs of acid reflux, but these findings are nonspecific and dependent on the quality of endoscopic images. Other signs are friability, granularity, and red streaks as a direct consequence of gastric acid injury. Mucosal friability is due to enlarged capillaries near the mucosal surface. Red streaks develop upward along the ridges of the esophageal folds. Progressive acid injury causes shallow breaks or erosions in the mucosa surrounded by erythema.

Erosions start at the gastroesophageal junction, occurring along the tops of esophageal mucosal folds where acid injury is most prone. Finally, ulcers develop, indicating more severe form of esophageal damage involving mucosa or submucosa [8, 9].

Endoscopy also allows for biopsies in patients with irregular or deep ulceration and any mass lesion or obvious nodularity and to rule out Barrett's esophagus.

Numerous studies have shown a specificity of more than 95% for the diagnosis of GERD. However, it is important to remember here that more than 50% of patients with GERD symptoms have a normal endoscopy. Also, there is often no correlation between the severity of symptoms and the endoscopic findings. Empirical treatment with proton pump inhibitors resolves the symptoms in many cases, further supporting the recommendation that endoscopy is not warranted in all cases of GERD.

There are several classification systems for the grading of endoscopic severity of GERD. The Los Angeles (LA) classification has been the most widely used (see Table 6.1). The severity of endoscopic findings on LA classification has correlated well with the pH-metry data. This system has demonstrated good intra- and interobserver agreement [10].

Role of Newer Imaging Technologies in GERD and Complications

There are two primary limitations of conventional white light endoscopy (WLE) in the GERD spectrum:

Nonerosive Reflux Disease More than 60% of patients suffering from reflux symptoms show no visible changes on WLE [11]. Consequently, NERD has remained a heterogeneous disease with reflux symptoms and an unpredictable response to antireflux therapy. It appears possible that minute mucosal changes and minimal change esophagitis are not adequately visualized by conventional WLE [12, 13].

Barrett's Esophagus (BE) and Surveillance Amidst the increasing worldwide prevalence of GERD is the rising incidence of complications, including BE and esophageal adenocarcinoma [14]. Here again early neoplastic lesions are difficult to diagnose with WLE. Four-quadrant biopsies every 2 cm length is time consuming and has been associated with high sampling error. Moreover, the low incidence (0.5% per year) reduces the cost-effectiveness of this laborious surveillance measure (Fig. 6.1a and b) [14–16].

Endoscopic imaging today has evolved beyond the confines of white light endoscopy to advanced optical imaging with a precise and real-time endoscopic diagnosis [17]. It has also helped in the early diagnosis of complications with targeted biopsies (Fig. 6.2a and b).

These technological advances have helped circumvent the limitation of WLE in reflux disease by (a) improved detection of subtle irregularities, and (b) characterization of anomalies and possible optical biopsies, providing real-time diagnosis.

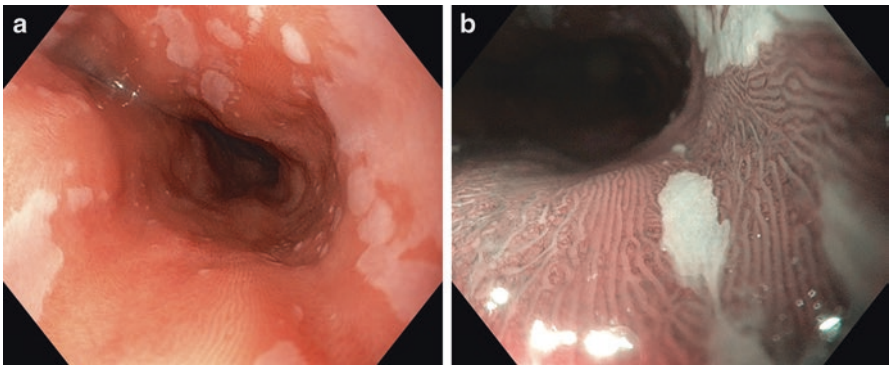


Fig. 6.1 (**a**) Barrett's esophagus on WLE; (**b**) on NBI a ridged pit pattern with regular vascular pattern clearly identified

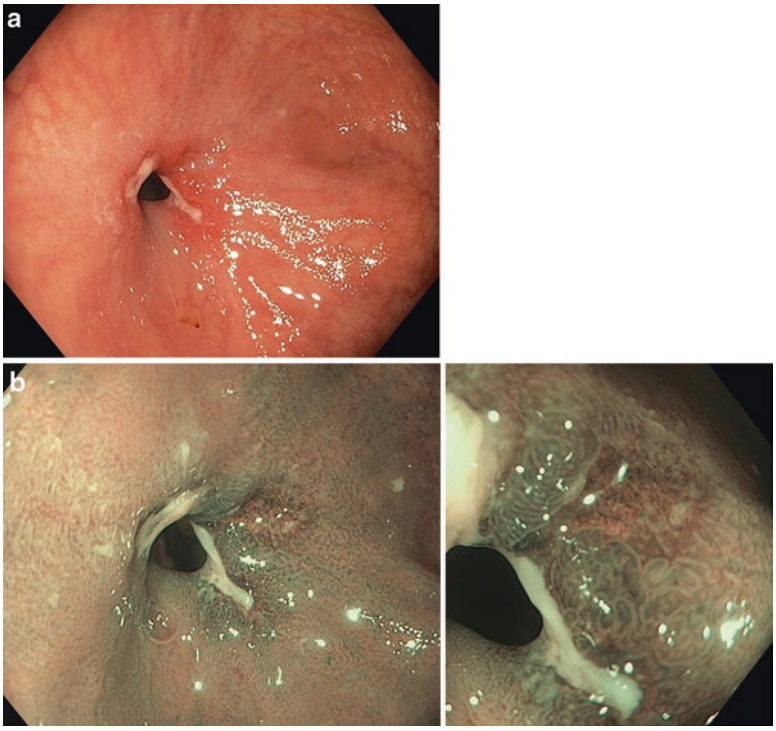


Fig. 6.2 NBI in the detection of complications. (**a**) Long-term peptic stricture with proximal ulceration on WLE. (**b**) Area of irregular microvessel pattern noted on NBI with magnification (inset). Carcinoma in situ detected on targeted biopsy

Newer imaging technologies used in GERD can be categorized into:

1. *Image-enhanced endoscopy or field enhancement* technologies. This involves contrast enhancement using dye (chromoendoscopy) or digital techniques including:
   (a) HRME
   (b) NBI, i-scan, FICE
   (c) Autofluorescence endoscopy
2. *Virtual histology or point enhancement* for in vivo histological examination during endoscopy:
   (a) Confocal laser endomicroscopy
   (b) Endocytoscopy

High-Resolution Magnification Endoscopy (HRME)

High-resolution magnification endoscopy (HRME) involves the use of high-resolution endoscopes of around 850 K pixel density with a movable lens and optical zooming facility of up to ×200 magnification. This results in a higher-resolution magnified image with the ability to detect and discriminate minute lesions [18].

HRME has been able to identify subtle changes such as punctuate erythema, pinpoint vessels, and triangular indentations above the Z line (GE junction) in subjects with otherwise normal WLE [12].

A few studies have evaluated these changes as markers of minimal change esophagitis in NERD. Kiesslich et al. demonstrated endoscopic signs of minimal change esophagitis for the prediction of NERD in 39 patients before and after treatment with esomeprazole [19]. In a small pilot study of 18 patients, we found subtle vascular pattern changes including the comma-shaped intrapapillary capillary loops in subjects with nonerosive reflux disease, which resolved after PPI therapy [20].

HRME was described for detection of BE by Guelrud in 2001 [21] and a Japanese group in 2002 [22]. Subsequently HRME alone for the characterization of BE has not been much reported. However, increased detection rates of intestinal dysplasia and high-grade dysplasia have been reported when HRME is used in conjunction with indigo carmine dye spraying or NBI [23].

The primary limitation of magnification endoscopy has been a substantial inter- and intraobserver variability with unacceptable kappa levels. The advent of newer generation endoscopes including narrow-band imaging with greater contrast enhancement has better defined and categorized the changes of both minimal change esophagitis and BE.

Chromoendoscopy

Chromoendoscopy involves the topical application of dyes for image enhancement during endoscopy. Vital stains which actively stain the cells and contrast stains, which are not absorbed but pool in the crevasses of the mucosa, are used. Of these, Lugol's iodine, methylene blue, and indigo carmine are most commonly used for the esophagus [18].

Lugol's iodine has been used to identify minimal mucosal breaks and can identify minimal change esophagitis in a subset of patients with NERD and normal WLE. Iodine is absorbed by the glycogen-containing nonkeratinized squamous epithelium of the normal esophagus. Inflammatory or dysplastic squamous epitheliums do not stain and appear as unstained streaks [24].

Methylene blue and indigo carmine spraying has primarily been used to characterize BE [25, 26]. Five distinct patterns of columnar-appearing mucosa have been identified including small/round, straight, long oval, tubular, and villous. Metaplastic tissue has been associated with the tubular and villous patterns in reported series. The results of chromoendoscopy for the diagnosis of dysplasia in BE have been quite inconsistent. However, there has been a consistent and significant reduction in the number of biopsies required for diagnosis [18, 26].

Overall chromoendoscopy has limited usage in GERD in view of inconsistent results, possible DNA effects of the vital dyes, inability to detect superficial vascular patterns, and of course the time-consuming and messy procedure. The advent of the no-dye "switch of the button" digital chromoendoscopy is set to replace chromoendoscopy [27–29].

Digital Chromoendoscopy (NBI/i-scan/FICE)

Digital chromoendoscopy has been developed as an alternative method of visual enhancement similar to chromoendoscopy. These novel optical technologies include narrow-band imaging (NBI), i-scan, and FICE, which can demonstrate and distinguish the alteration in the pit pattern and vasculature between inflammatory and neoplastic lesions [30].

Narrow-band imaging developed by Olympus Medical Systems (Olympus, Japan) is the most well-recognized advance in endoscopic imaging. This involves the placement of narrow-band pass filters to obtain tissue illumination at selected narrow wavelength bands, enhancing visualization and assisting in tissue characterization, differentiation, and diagnosis.

i-scan from Pentax (Montvale, NJ) and Fuji Intelligent Chromo Endoscopy (FICE) (Fujinon, Wayne, NJ) on the other hand involve spectral estimation technology and are based on post-imaging processing. There is no optical filter involved in contrast to NBI. Only a limited number of studies have been reported with i-scan/FICE.

NBI of the Normal Esophagus

On NBI, the stratified squamous epithelium of the esophagus appears featureless and has no pit pattern. There is a regular palisading capillary network. The intrapapillary capillary loop (IPCL) pattern, which is barely visible on WLE, is clearly outlined on NBI and plays an important role in the diagnosis of GERD and related complications [30]. The normal IPCL is a smooth-running, small-diameter capillary vessel positioned upright from a branching vessel about 10 μm in size. The branching vessels appear green, while the IPCLs are observed as dark brown loops/dots on NBI [31].

IPCLs have shown characteristic changes including dilatation, prolongation, meandering, and irregularity in form and caliber, according to the extent of tissue atypism from inflammation to dysplasia and cancer. Many of these publications are in Japanese. Inoue et al. have actually classified IPCLs from Type I (normal), Type II (inflammation), Type III (borderline), Type IV (carcinoma in situ), to Type V (invasive CA) (Fig. 6.3) [31, 32].

NBI Endoscopy in GERD

Conventional WLE has often been considered to be a relatively insensitive test for GERD because it is able to identify lesions in only 40% of cases with symptoms. [33] The ability of NBI to depict subtle mucosal lesions has improved the diagnostic accuracy in GERD.

Various subtle changes not seen regularly on WLE have been noted on NBI. These have included: (a) increased Type II IPCLs (elongated and arranged in linear orientation) above the Z line; (b) punctate erythema proximal to the Z line; (c) increased vascular markings distal to the Z line; (d) triangular indentations of columnar mucosa at the SC junction; and (e) islands of squamous epithelium distal to the Z line.

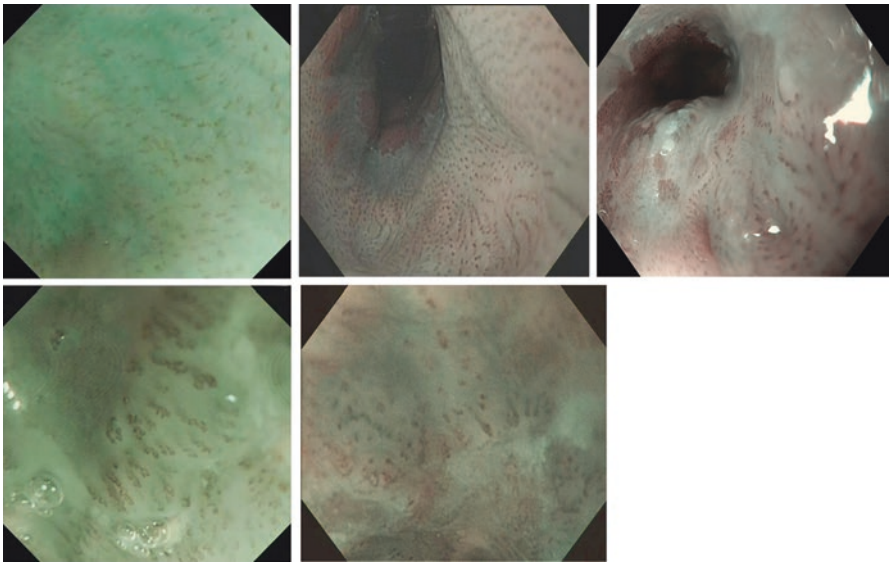


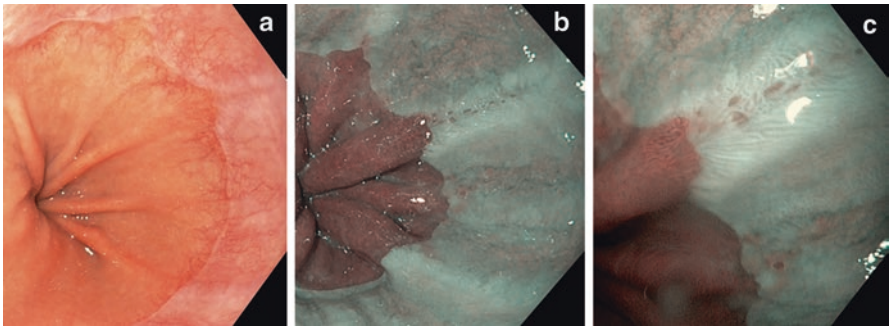
Fig. 6.3 The IPCLs: Type I to Type V. Note the gradual dilatation, tortuosity, and change in caliber from normal to esophageal malignancy

Some of these changes have been found to be reversible on PPI therapy and may represent the true endoscopic markers of minimal change esophagitis.

Sharma et al. in the landmark study of 80 patients with GERD reported an increased number and dilatation of IPCLs as the best predictors of GERD on multivariate analysis. The maximum, minimum, and average number of IPCLs per field was significantly greater in GERD. Also, a significantly higher proportion of patients with GERD had changes in the number (OR 12.6; $p > 0.00001$), dilatation (OR 20; $p > 0.0001$), and tortuosity (OR6.9; $p > 0.001$) of IPCLs [34].

Similarly, we evaluated 60 patients with NERD on WLE by NBI. Minimal changes were detected in 21 patients. Increased and dilated IPCLs were noted most frequently in 19/21 (90.4%) patients. Increased vascular markings with hyperemia and punctate erythema proximal to the Z line was detected in 15/21 (71.4%). Interestingly, these resolved in 95% cases on PPI (pantoprazole) therapy [35].

Fock et al. in a recent study of 107 subjects used simpler criteria to identify minimal change disease. Micro-erosions, increased vascularity, and pit pattern at the GE junction not seen on WLE were identified on NBI. Micro-erosions were present in 100%, 92.8%, and 23.3% of GERD, NERD, and controls, respectively. An increase in vascularity was noted in 95.1% GERD, 91.7% NERD, and 36.7% of controls. The increase in vascularity with the absence of round pit pattern was helpful to differentiate NERD from controls, with a sensitivity of 86.1% and specificity of 83.3%, respectively. In addition, there was good interobserver agreement for the presence of micro-erosions (kappa 0.89), increased vascularity at SCJ (kappa 0.95), and round pit pattern (kappa 0.80) [36].



Figs 6.4 (**a**) Normal-appearing GE junction on WLE; (**b**) fine linear erosion clearly visible on NBI; (**c**) typical appearance of minimal change esophagitis with dilated IPCLs arranged in a linear fashion (inverted fir tree)

A recent study found subjects with minimal changes on NBI (normal on WLE) responded better to PPI. Accordingly, NBI could be used for prediction of therapeutic response to PPI in NERD. [37].

The ability of NBI to depict small erosive foci could also increase consistency in the grading of erosive disease (GERD). On NBI, the limit between the squamous and columnar epithelium is clearly demarcated. Inflamed mucosal breaks appear dark brown, corresponding to the crowding of capillaries. This provides a sharp contrast to the greenish featureless epithelium. We find a classical appearance of minimal change esophagitis on NBI in a subset of patients with normal WLE (Fig. 6.4a–c). This includes a central fine ridge above the Z line, with plenty of dilated intrapapillary capillary loops (IPCLs) arranged in a linear fashion giving an inverted fir tree appearance, which resolves on PPI therapy [38]. In a recent comparative study of endoscopic images of 230 patients by WLE and NBI, both intra- and interobserver reproducibilities in grading esophagitis were improved with NBI (kappa 0.62 vs. 0.45) [39].

It appears reasonable to infer that a subset of patients with NERD would have minimal change esophagitis, which would respond therefore to PPI therapy. NBI endoscopy would thereby substantially improve our ability to predict therapeutic response in patients with reflux disease and optimize therapy.

There are still some limitations on the routine use of these endoscopic criteria in clinical practice. The assessment of dilated and tortuous IPCLs could be subjective, and objective manual counting of IPCLs is time consuming and complicated, as only a small area can be seen at one time.

Feasibility of FICE/I-Scan for the Diagnosis of GERD

These post-processing systems have been recently evaluated for the detection of mucosal breaks in GERD. Publications are limited.

In a study of 50 patients with reflux symptoms, the detection rates of mucosal rates improved with i-scan. The degree of esophagitis could be upgraded in 10% of

cases [40]. A similar small study with FICE has shown higher sensitivity, NPV, and accuracy than WLE. However, the interobserver agreement was poor [41].

NBI Endoscopy in Barrett's Esophagus

Barrett's esophagus (BE) is a known premalignant lesion and has been attributed to the increasing incidence of esophageal adenocarcinoma, especially in the western world. Accordingly, regular surveillance of BE with random four-quadrant biopsies every 1–2 cm has been the standard practice. However, the distribution of dysplasia within BE is patchy and not clearly visible with WLE. The random biopsy technique is thus suboptimal and subject to sampling error.

The role of NBI in detection of BE and early cancer has been evaluated in quite a number of studies. A spectrum of changes from columnar epithelium (CLE) to high-grade dysplasia (HGD) and malignancy has been described.

Kara et al. classified Barrett's according to the mucosal pattern (flat, villous/gyrus, irregular), vascular pattern (regular, irregular, long branched), and the presence of abnormal blood vessels. Intestinal metaplasia was associated with the villous/gyrus patterns in 80% of cases and a flat mucosa in 20% of cases. On the other hand, high-grade dysplasia was characterized by irregular/disrupted mucosal and vascular patterns with abnormal blood vessels [42].

Sharma et al. used a simplified version with mucosal (ridged/villous, regular, irregular) and vascular (normal and abnormal) patterns. Here the ridged/villous pattern had a sensitivity, specificity, and PPV of 93.5%, 85%, and 94.7%, respectively, for the diagnosis of SIM. The distorted vascular pattern had a sensitivity and specificity of 100% and 98.7% [43].

Goda et al. used a more elaborate classification of the mucosal patterns into round/oval, long, straight, villous, cerebriform, and irregular and vasculature into honeycomb, vine-like, coiled, ivy-like, and irregular [44].

Singh et al. have recently proposed a combined classification based on both the mucosal and vascular patterns: (1) Pattern A, round pits and regular vasculature; (2) Pattern B, villous/ridged pits and regular vasculature; (3) Pattern C, absent pits but regular microvasculature; and (4) Pattern D, distorted pits with irregular microvasculature. Pattern A had a high PPV (100%) and NPV (97%) for CLE without SIM. Patterns B and C were indicative of SIM. Pattern D had a PPV and NPV of 81% and 99%, respectively, for high-grade dysplasia [45].

A recent meta-analysis assessed the accuracy of NBI for the characterization of dysplasia in BE with histopathology, in which 446 patients with 2194 lesions were assessed. It revealed a high diagnostic precision for HGD with a pooled sensitivity, specificity, diagnostic accuracy, and AUC revealed of 0.95 (95%CI 0.87–1.0), 0.65 (95% CI 0.52–0.78), 37.53 (95% CI 6.50–217.62), and 0.88 (SE 0.08), respectively. NBI was also able to characterize SIM with high sensitivity, but the specificity was poor [46].

Although these studies have shown promising results for NBI in detection of intestinal metaplasia and HGD, all were performed by experts in single centers and/or involved relatively small numbers of patients. By contrast, a study comparing NBI, indigo carmine chromoendoscopy, and acetic acid chromoendoscopy found no

benefit from the enhanced imaging methods in identifying early neoplasia in Barrett's esophagus [47].

NBI vs. WLE in BE

Head-to-head comparison of NBI and conventional WLE in BE has been done in terms of sensitivity, specificity, diagnostic accuracy, and image quality.

Hamamoto et al. reported improved visualization of important structures with NBI. They used a scoring system of 0–4 to grade the quality of images. The squamocolumnar junction was visualized with a score of >3 in 57% of NBI compared to 17% with WLE ($p = 0.0002$). The blood vessel and CLE observation was also higher with NBI (100% vs. 80%) [48]. Curvers et al. also reported significantly better image quality with NBI compared to WLE (11.3 vs. 10.9 on visual analog scale; $p = 0.01$). Interestingly however, the diagnostic yield of neoplasia did not improve (81% vs. 83%) [49]. Singh et al. in a recent study found a significant difference between NBI and WLE in the detection of high-grade dysplasia (95% vs. 62.5% $p < 0.006$). In this study, a combination of WLE with NBI and magnification achieved a sensitivity, specificity, and accuracy of 90.2, 95, and 91.7% [50].

We find that a majority of studies comparing NBI with WLE and other modalities appear favorable for NBI. However, some interobserver studies have questioned the additional value of NBI for detection of high-grade dysplasia. NBI does appear to be operator experience dependent, and a recent study found NBI to be of limited value in BE with endoscopists in general practice [51].

In conclusion, the primary advantage of NBI is the detection of advanced dysplasia using fewer biopsy samples compared to surveillance WLE and four-quadrant biopsy. Wolfsen et al. reported 57% detection of dysplasia compared with 43% with conventional WLE and random biopsies. Additionally, the number of biopsy specimens in the four-quadrant group was much higher than targeted with NBI (mean 8.5 vs. 4.7) [52].

Autofluorescence Imaging

Autofluorescence imaging (AFI) is based on the detection of the relative concentration of endogenous fluorophores and fluorescence emission between healthy and neoplastic tissue**.** The use of AFI in GERD is primarily as a wide area functional imaging of Barrett's mucosa for identification of dysplastic areas [53].

Two in vivo autofluorescence-based endoscopic techniques have been investigated for detecting early neoplasia in BE:

1. Light-induced fluorescence spectroscopy (LIFS)

Autofluorescence Endoscopy

LIFS

LIFS can accurately distinguish BE with high-grade intraepithelial neoplasia (HGIN) from nondysplastic BE. An important drawback is that it only samples a small area of mucosa, making it impractical as a surveillance tool [54].

A few studies have shown improved detection of high-grade dysplasia and detection of additional cases on AFL compared to WLE with four-quadrant biopsies. The sensitivity and PPV, however, are poor, with unacceptably high false positives [55].

However, studies suggest that by combining AFI with another imaging technique (e.g., narrow-band imaging), false-positive rate can be reduced to 10–26% [56, 57].

As such, the role of AFI as a stand-alone technique for BE appears remote.

Endoscopic Trimodal Imaging (ETMI)

The ETMI system (XGIF-Q240/GIF-FQ260FZ; Olympus, Tokyo) incorporates high-resolution WLE together with AFI and NBI modalities which can be used in tandem. The improved sensitivity and specificity of the combined technique are primarily attributable to reduction of the false positivity of AFI [53].

This has been the primary intention of the studies of trimodal imaging in BE. Kara et al. first reported a significant reduction of false-positive AFI with trimodal imaging [56]. In a similar multicenter trial, Curvers et al. found that AFI could identify all cases with HGD, and false positivity was reduced by NBI from 81 to 26% [58]. The same group has recently reported improved detection of early neoplasia with ETMI compared to WLE. Here again, NBI reduced the false positivity of AFI but did misclassify 17% of cases [59].

Very interestingly, the results were not repeated when the procedures were performed by general endoscopists in the community setting, and the detection of dysplasia did not improve with ETMI [57].

Optical Biopsy (Confocal Endomicroscopy)

Confocal endomicroscopy (CLE) and endocytoscopy allow subsurface analysis of the gastrointestinal mucosa using the principle of optical sectioning. This enables real-time in vivo histology during ongoing endoscopy. Endomicroscopy and endocytoscopy dramatically expand the imaging capabilities of flexible endoscopy by their ability to obtain "optical biopsies" of nearly any accessible endoluminal surface. The current CLE incorporates a confocal laser microscope into the tip of a flexible endoscope (Pentax EC 3830FK, Tokyo, Japan). A probe-based confocal endomicroscope (Cellvizio, Mauna Kea Technologies, France) is also available.

There is limited full-length publications on the use of CLE in BE, but numerous abstracts are being presented at the GI conferences [60].

The main difference between CLE and endocytoscopy is that endocytoscopy is based solely on high-level magnification using optical lenses. Therefore, because there is no confocal plane, only the very superficial layer of the mucosa can be imaged. In addition, the lens must come into direct contact with the tissue being examined [61].

Becker et al. reported significantly higher microvessel density in neoplastic BE compared to nonneoplastic (23.6% vs. 14.2%; $p > 0.001$) on CLE [62].

Kiesslich and colleagues in a study of 63 patients with BE demonstrated good correlation between in vivo histology and conventional histology in normal squamous vis-a-vis gastric and Barrett's epithelium. A confocal classification system to predict the histopathology of the distal esophagus was also proposed.

Nondysplastic BE was characterized by regular villous-like epithelium with dark goblet cells. An increase in the number of dark cells with an irregular border was consistent with BE-associated neoplasia. The loss of regular basement membrane integrity and disruption of the villous epithelial structure suggested HGD/CA [63].

As with new technologies, CLE will need time to move from the research arena into routine clinical practice [64]. However, initial results for the prediction of dysplasia in Barrett's real time are promising [65].

Newer Imaging Advancements [66, 67]

Spectroscopic techniques such as light-scattering spectroscopy and Raman spectroscopy carry diagnostic information on the microstructural and molecular composition of tissues, which enables early detection of dysplasia. Similarly, peptides have been used as molecular probes that can be fluorescence tagged and can identify cell surface targets/molecular markers of neoplasia in BE. The results are promising. These technological advances have helped circumvent the limitation of WLE in reflux disease by (a) improved detection of subtle irregularities, (b) characterization of anomalies, and (c) possible optical biopsies providing real-time diagnosis [68]. However, these novel technologies are very much in the experimental stage and beyond the scope of this review.

Endoscopic Therapies for GERD

The endoluminal treatment of GERD is evolving and may have the potential to decrease the need for long-term antisecretory medications in selected patients.

The aim of endoscopic treatment is to create an antireflux barrier and reduce esophageal exposure to refluxate. This can be achieved by:

1. Improving the gastroesophageal flap valve that serves as a mechanical barrier to reflux
2. Reducing lower esophageal sphincter relaxation
3. Remodeling the smooth muscle at the gastroesophageal junction
4. Increasing lower esophageal sphincter length [69]

Indication for Endoscopic Therapy

Patients who may be candidates for endoscopic GERD therapy include:

1. Patients with refractory GERD, which is defined as persistent heartburn despite escalating doses of proton pump inhibitors, or residual regurgitation without heartburn symptoms while on PPIs. Esophageal pH monitoring while on PPIs to confirm increased esophageal acid exposure is mandatory in such patients.
2. Patients with bile acid reflux or non-acid reflux that has been confirmed by impedance testing.
3. Patients who are intolerant of PPIs or wish to stop drug therapy due to concerns about long-term side effects.
4. Patients who are concerned about potential side effects of antireflux surgery, such as dysphagia or gas/bloat.
5. Patients with symptomatic documented GERD following fundoplication.

In contrast, the following groups of patients are not candidates for any from endoscopic therapy for GERD:

- Patients who do not respond to PPI therapy, who have negative esophageal pH studies, and whose symptoms do not temporally correlate with acid events seen on pH monitoring probably do not have GERD and should **not** be offered endoscopic or surgical therapy for GERD.
- Patients with large, fixed hiatal hernias and esophageal foreshortening are not good candidates for endoscopic therapy, due to a high risk of technical failure.

Endoscopic Devices for Treatment of GERD

Various types of devices have been developed for the endoscopic treatment of gastroesophageal reflux disease (GERD), using approaches such as sewing, transmural fasteners, endoscopic staplers, and thermal treatment (Table 6.2).

EndoCinch The Bard EndoCinch was the first endoscopic sewing device approved by the US Food and Drug Administration (FDA) in April 2000. It has the best safety profile among the endoscopic sewing and full-thickness plication devices. Prospective observational studies in adults and children have shown mixed results, with symptomatic success rates ranging from 20 to 82% after at least 1 year of follow-up [70–73].

Adverse events noted in studies of EndoCinch included pharyngitis, vomiting, abdominal pain, mucosal tears, microperforation, bleeding, dysphagia, bronchospasm, and adverse reactions to sedation [74].

EsophyX The EndoGastric Solutions EsophyX EndoLuminal Fundoplication System is based on the principle to restore angle of His at the gastroesophageal

Table 6.2 Endoscopic devices for treatment of GERD

Devices that are currently commercially available	EndoCinch
	EsophyX
	Stretta procedure (radiofrequency treatment for GERD)
Devices that are being studied for the treatment of GERD	SRS endoscopic stapling system
Devices that are no longer or never became commercially available	Endoscopic suturing device
	NDO Plicator
	Syntheon AntiReflux device
	His-wiz device
	Enteryx procedure
	Gatekeeper reflux repair system
	Durasphere GR

junction. It affixes tissue from the GEJ to the fundus to create a neogastroesophageal valve. Efficacy of EsophyX was tested in the largest multicenter prospective study with a one-year follow-up and included 86 patients, 84 of whom successfully underwent the procedure. Objective parameters that were examined included esophageal acid exposure, which improved in 61% of patients, and mean lower esophageal sphincter pressure, which increased significantly from 12 mmHg pre-procedure to 18 mmHg post-procedure [75].

Radio Frequency Energy (Stretta Procedure) In this procedure radio frequency (RF) energy is delivered via endoscopic needles placed in the tissues surrounding the lower esophageal sphincter with constant tissue temperature monitoring to a prefixed target temperature. The putative mechanisms for efficacy include increased thickness of the LES muscle, decreased distensibility of the LES without fibrosis, and decreased frequency of TLESRs.

Many studies have demonstrated efficacy of radio frequency treatment for gastroesophageal reflux disease. Overall, 50–80% of patients have reported satisfactory symptom control or cessation of proton pump inhibitor (PPI) therapy in studies with average follow-up periods of 1–3 years [76–79].

An Italian study reported 48 months follow-up data for 56 out of 69 patients undergoing Stretta procedure. RF treatment significantly improved heartburn scores, GERD-specific quality-of-life scores, and general quality-of-life scores at 24 and 48 months in 52 out of 56 patients (92.8%); 72.3% were completely off PPIs [80].

We have recently demonstrated that the application of electrical stimulation therapy (EST) using a pacemaker significantly and consistently increases the lower esophageal sphincter (LES) pressure [81]. However, no endoscopic therapy has been completely effective in normalizing acid exposure, healing esophagitis, controlling reflux symptoms, or allowing patients to be off of all of their antisecretory medications.

Studies evaluating various endoscopic techniques for the treatment of GERD have significant limitations. More data from prospective, randomized,

sham-controlled studies with adequate numbers of subjects is required. Effect of the various endoluminal treatments on esophageal tissue and the durability of response are major factors that are areas for further improvement and are important in achieving better clinical outcomes. If endoscopic treatments are to prove beneficial for patients with GERD, then devices and techniques need to be optimized and evaluated in well-designed clinical trials.

Thus, the endoscope definitely is a tool to not only diagnose and assess the patient with GERD but could also become the mode of therapy for the future. Needless to say, well-designed, independent comparative clinical trials with long-term follow-up are required before endoluminal therapy comes to clinical practice.

Conclusion

High-definition, high-resolution endoscopy enables direct visualization of the esophageal and gastric mucosa and allows tissue sampling for histology. GERD is the most common indication for endoscopy. Improved detection of GERD and surveillance of BE have now become essential in the background of rising incidence worldwide.

Standard white light endoscopy does have some limitations. Novel-enhanced imaging technology attempts to circumvent these limitations, and the results appear promising. NBI has been evaluated extensively and appears to be a useful adjunct to WLE for identification of minimal change esophagitis and for the targeted investigation of suspicious areas in BE. There is considerable evidence that NBI would help target endoscopic biopsies and delineate resection margins during endotherapy of dysplastic areas. We would recommend routine usage for detection of high-grade dysplasia in Barrett's esophagus. The days of random four-quadrant biopsies may well be over.

The primary limitation as with all new technologies is the lack of sufficiently validated and standardized classification systems and the limited number of randomized controlled trials. Additionally, most of these are conducted at tertiary care specialized centers. Routine clinical practice and cost-effectiveness remain to be tested or achieved.

References

1. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro−oesophageal reflux disease: a systematic review. Gut. 2005;54:710–7.
2. Fock KM, Talley NJ, Fass R, Goh KL, Katelaris P, Hunt R, et al. Asia-Pacific consensus on the management of gastroesophageal reflux disease: update. J Gastroenterol Hepatol. 2008;23(1):8–22.
3. Bruley Des Varannes S, Marek L, Humeau B, Lecasble M, Colin R. Gastroesophageal reflux disease in primary care: prevalence, epidemiology and quality of life of patients. Gastroenterol Clin Biol. 2006;30:364–70.

4. Wahlqvist P, Karlsson M, Johnson D, Carlsson J, Bolge SC, Wallander MA. Relationship between symptom load of gastro-oesophageal reflux disease and health-related quality of life, work productivity, resource utilization and concomitant diseases: survey of a US cohort. Aliment Pharmacol Ther. 2008;27(10):960–70.
5. An evidence-based appraisal of reflux disease management: the Genval workshop report [no authors listed]. Gut. 1999; 44 (Suppl 2):S1–16.
6. Kahrilas PJ, Shaheen NJ, Vaezi M. AGAI medical position panel on GERD management. AGAI medical position statement: management of gastroesophageal reflux disease. Gastroenterology. 2008;135:1383–91.
7. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
8. Richter JE. Severe reflux esophagitis. Gastrointest Endosc Clin North Am. 1994;4:677–98.
9. Nayer DW, Vaezi MF. Classification of esophagitis: who needs it? Gastrointest Endosc. 2004;60:253.
10. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172–80.
11. Falk GW, Fennerty BF, Rothstein RI. AGA institute technical review on the use of endoscopic therapy for gastroesophageal reflux disease. Gastroenterology. 2006;131:1315–36.
12. Wani S, Sharma P. Changing the "contrast" in GERD. Gastrointest Endosc. 2007;66(2):237–9.
13. Nakamura T, Shirakawa K, Masuyama H, Sugaya H, Terano A. Minimal change oesophagitis: a disease with characteristic differences to erosive esophagitis. Aliment Pharmacol Ther. 2005;21(Suppl 2):19–26.
14. Spechler SJ. Clinical practice. Barrett's esophagus N Engl J Med. 2002;346:836–42.
15. Falk GW, Rice TW, Goldblum JR, Richter JE. Jumbo biopsy forceps protocol still misses unsuspected cancer in Barrett's esophagus with high grade dysplasia. Gastrointest Endosc. 1999;49:170–6.
16. Kim SL, Waring JP, Spechler SJ, Sampliner RE, Doos WG, Krol WF, et al. Diagnostic inconsistencies in Barrett's esophagus. Department of Veterans Affairs Gastroesophageal Reflux Study Group. Gastroenterology. 1994;107:945–9.
17. Bergman JJ, Tytgat GN. New developments in the endoscopic surveillance of Barrett's oesophagus. Gut. 2005;(Suppl I):54, 138–142.
18. Reddymasu SC, Sharma P. Advances in endoscopic imaging of the oesophagus. Gastroenterol Clin N Am. 2008;37:763–74.
19. Kiesslich R, Kanzler S, Vieth M, Moehler M, Neidig J, Thanka Nadar BJ, et al. Minimal change esophagitis: prospective comparison of endoscopic and histological markers between patients with non-erosive reflux disease and normal controls using magnifying endoscopy. Dig Dis. 2004;22:221–7.
20. Banerjee R, Reddy DN. Minimal-change esophagitis on narrow-band imaging. Clin Gastroenterol Hepatol. 2008;6(8):A26.
21. Guelrud M, Herrera I, Essenfeld H, Castro J. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. Gastrointest Endosc. 2001;53:559–65.
22. Endo T, Awakawa T, Takahashi H, Arimura Y, Itoh F, Yamashita K, et al. Classification of Barrett's epithelium by magnifying endoscopy. Gastrointest Endosc. 2002;55:641–7.
23. Sharma P, Weston AP, Topalovski M, Cherian R, Bhattacharyya A, Sampliner RE. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. Gut. 2003;52:24–7.
24. Yoshikawa I, Yamasaki M, Yamasaki T, Kume K, Otsuki M. Lugol chromoendoscopy as a diagnostic tool in so−called endoscopy−negative GERD. Gastrointest Endosc. 2005;62:698–703.
25. Canto MI, Setrakian S, Willis J, Chak A, Petras R, Powe NR, et al. Methylene blue-directed biopsies improve detection of intestinal metaplasia and dysplasia in Barrett's esophagus. Gastrointest Endosc. 2000;51:560–8.

26. Horwhat JD, Maydonovitch CL, Ramos F, Colina R, Gaertner E, Lee H, et al. A randomized comparison of methylene blue-directed biopsy versus conventional four-quadrant biopsy for the detection of intestinal metaplasia and dysplasia in patients with long-segment Barrett's esophagus. Am J Gastroenterol. 2008;103:546–54.
27. Olliver JR, Wild CP, Sahay P, Dexter S, Hardie LJ. Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. Lancet. 2003;362:373–4.
28. Curvers W, Baak L, Kiesslich R, Van Oijen A, Rabenstein T, Ragunath K, et al. Chromoendoscopy and narrow-band imaging compared with high-resolution magnification endoscopy in Barrett's esophagus. Gastroenterology. 2008;134:670–9.
29. Kara MA, Peters FP, Rosmolen WD, Krishnadath KK, ten Kate FJ, Fockens P, et al. High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in Barrett's esophagus: a prospective randomized crossover study. Endoscopy. 2005;37:929–36.
30. Banerjee R, Reddy DN. Advanced gastrointestinal endoscopy: a primer on narrow band imaging. Hyderabad: Paras Medical Publisher; 2009. p. 5–26.
31. Kumagai Y, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. Endoscopy. 2002;34:369–75.
32. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc. 2004 Feb;59(2):288–95.
33. Dent J, Armstrong D, Delaney B, Moayyedi P, Talley NJ, Vakil N. Symptom evaluation in reflux disease: workshop background, processes, terminology, recommendations and discussion outputs. Gut. 2004;53(Suppl 4):1–24.
34. Sharma P, Wani S, Bansal A, Hall S, Puli S, Mathur S, et al. A feasibility trial of narrow band imaging endoscopy in patients with gasdtroesophageal reflux disease. Gastroenterology. 2007;133:454–64.
35. Banerjee PN, Ramchandani M, Tandan M, Guduru V. Narrow band imaging (NBI) can detect minimal changes in non erosive reflux disease (NERD) which resolve with PPI therapy. Gastrointest Endosc. 69(5):AB356.
36. Fock KM, Teo EK, Ang T, Tan JY, Law NM. The utility of narrow band imaging in improving the endoscopic diagnosis of gastroesophageal disease. Clin Gastroenterol Hepatol. 2009;7(1):54–9.
37. Tseng PH, Chen CC, Chiu HM, Liao WC, Wu MS, Lin JT, et al. Performance of narrow band imaging and magnification endoscopy in the prediction of therapeutic response in patients with gastroesophageal reflux disease. J Clin Gastroenterol. 2010.; [Epub ahead of print]
38. Lee YC, Lin JT, Chiu HM, Liao WC, Chen CC, Tu CH, et al. Intraobserver and interobserver consistency for grading esophagitis with narrow-band imaging. Gastrointest Endosc. 2007;66(2):230–6.
39. Banerjee R, Reddy DN. Minimal-change esophagitis on narrow band imaging. Clin Gastroenterol Hepatol. 2008;6(8):A26.
40. Hoffman A, Basting N, Goetz M, Tresch A, Mudter J, Biesterfeld S, et al. High definition endoscopy with i-scan and Lugol's solution for more precise detection of mucosal breaks in patients with reflux symptoms. Endoscopy. 2009;41:107–12.
41. Chaiteerakij R, Geratikornsupuk N, Tangmankongworakoon N, et al. Efficacy of intelligent chromo endoscopy for detection of minimal mucosal breaks in patients with typical reflux symptoms of gastroesophageal reflux disease. Gastrointest Endosc. 2008;67:AB86.
42. Kara MA, Ennahachi M, Fockens P, ten Kate FJ, Bergman JJ. Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging. Gastrointest Endosc. 2006;64(2):155–66.
43. Sharma P, Bansal A, Mathur S, Wani S, Cherian R, McGregor D, et al. The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. Gastrointest Endosc. 2006;64(2):167–75.
44. Goda K, Tajiri H, Ikegami M, Urashima M, Nakayoshi T, Kaise M. Usefulness of magnifying endoscopy with narrow band imaging for the detection of specialized intestinal

metaplasia in columnar-lined esophagus and Barrett's adenocarcinoma. Gastrointest Endosc. 2007;65(1):36–46.
45. Singh R, Anagnostopoulos GK, Yao K, Karageorgiou H, Fortun PJ, Shonde A, et al. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. Endoscopy. 2008;40(6):457–63.
46. Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of HGD and SIM in Barrett's esophagus: a meta-analysis. Endoscopy. 2010;42:351–9.
47. Curvers W, Baak L, Kiesslich R, Van Oijen A, Rabenstein T, Ragunath K, et al. Chromoendoscopy and narrow-band imaging compared with high-resolution magnification endoscopy in Barrett's esophagus. Gastroenterology. 2008;134:670–9.
48. Hamamoto Y, Endo T, Nosho K, Arimura Y, Sato M, Imai K. Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. J Gastroenterol. 2004;39(1):14–20.
49. Curvers WL, Bohmer CJ, Mallant-Hent RC, Naber AH, Ponsioen CI, Ragunath K, et al. Mucosal morphology in Barrett's esophagus: interobserver agreement and role of narrow band imaging. Endoscopy. 2008;40(10):799–805.
50. Singh R, Karageorgiou H, Owen V, Garsed K, Fortun PJ, Fogden E, et al. Comparison of high-resolution magnification narrow-band imaging and white-light endoscopy in the prediction of histology in Barrett's oesophagus. Scand J Gastroenterol. 2009;44(1):85–92.
51. Silva FB, Dinis-Ribeiro M, Vieth M, Rabenstein T, Goda K, Kiesslich R, et al. Endoscopic assessment and grading of Barrett's esophagus using magnification endoscopy and narrow-band imaging: accuracy and interobserver agreement of different classification systems (with videos). Gastrointest Endosc. 2011;73(1):7–14.
52. Wolfsen HC, Crook JE, Krishna M, Achem SR, Devault KR, Bouras EP, et al. Prospective, controlled tandem endoscopy study of narrow band imaging for dysplasia detection in Barrett's Esophagus. Gastroenterology. 2008 Jul;135(1):24–31.
53. Falk GW. Autofluorescence endoscopy. Gastrointest Endosc Clin N Am. 2009 Apr;19(2):209–20.
54. Georgakoudi I, Jacobson BC, Van Dam J, Backman V, Wallace MB, Müller MG, et al. Fluorescence, reflectance, and light-scattering spectroscopy for evaluating dysplasia in patients with Barrett's esophagus. Gastroenterology. 2001;120(7):1620–9.
55. Kara MA, Peters FP, Ten Kate FJ, Van Deventer SJ, Fockens P, Bergman JJ. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointest Endosc. 2005;61(6):679–85.
56. Kara MA, Peters FP, Fockens P, Kate FJ, Bergman JJ. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. Gastrointest Endosc. 2006;64(2):176–85.
57. Curvers WL, Van Vilsteren FG, Baak LC, Böhmer C, Mallant-Hent RC, Naber AH, et al. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicenter, randomized, crossover study in general practice. Gastrointest Endosc. 2011;73(2):195–203.
58. Curvers WL, Singh R, Song LM, Wolfsen HC, Ragunath K, Wang K, et al. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut. 2008;57(2):167–72.
59. Curvers WL, Herrero LA, Wallace MB, Wong Kee Song LM, Ragunath K, Wolfsen HC, et al. Endoscopic tri-modal imaging is more effective than standard endoscopy in identifying early-stage neoplasia in Barrett's esophagus. Gastroenterology. 2010;139(4):1106–14.
60. Nguyen NQ, Leong RW. Current application of confocal endomicroscopy in gastrointestinal disorders. J Gastroenterol Hepatol. 2008;23(10):1483–91.
61. Tomizawa Y, Iyer PG, Wongkeesong LM, Buttar NS, Lutzke LS, Wu TT, Wang KK. Assessment of the diagnostic performance and interobserver variability of endocytoscopy in Barrett's esophagus: a pilot ex-vivo study. World J Gastroenterol. 2013;19(46):8652–8.

62. Becker V, Vieth M, Bajbouj M, Schmid RM, Meining A. Confocal laser scanning fluorescence microscopy for in vivo determination of microvessel density in Barrett's esophagus. Endoscopy. 2008;40(11):888–91.
63. Kiesslich R, Gossner L, Goetz M, Dahlmann A, Vieth M, Stolte M, et al. In vivo histology of Barrett's esophagus and associated neoplasia by confocal laser endomicroscopy. Clin Gastroenterol Hepatol. 2006;4(8):979–87.
64. Bajbouj M, Vieth M, Rösch T, Miehlke S, Becker V, Anders M, et al. Probe-based confocal laser endomicroscopy compared with standard four-quadrant biopsy for evaluation of neoplasia in Barrett's esophagus. Endoscopy. 2010;42(6):435–40.
65. Canto MI. Endomicroscopy of Barrett's Esophagus. Gastroenterol Clin N Am. 2010;39(4):759–69.
66. Wallace MB, Wax A, Roberts DN, Graf RN. Reflectance spectroscopy. Gastrointest Endosc Clin N Am. 2009 Apr;19(2):233–42.
67. Li M, Anastassiades CP, Joshi B, Komarck CM, Piraka C, Elmunzer BJ, et al. Affinity peptide for targeted detection of dysplasia in Barrett's esophagus. Gastroenterology. 2010;139(5):1472–80.
68. Banerjee R, Reddy DN. Enhanced endoscopic imaging and gastroesophageal reflux disease. Indian J Gastroenterol. 2011;30(5):193–200.
69. Jafri SM, Arora G, Triadafilopoulos G. What is left of the endoscopic antireflux devices? Curr Opin Gastroenterol. 2009;25(4):352–7.
70. Schiefke I, Zabel-Langhennig A, Neumann S, Feisthammel J, Moessner J, Caca K. Long term failure of endoscopic gastroplication (EndoCinch). Gut. 2005;54(6):752–8.
71. Chen YK, Raijman I, Ben-Menachem T, Starpoli AA, Liu J, Pazwash H, et al. Long-term outcomes of endoluminal gastroplication: a U.S. multicenter trial. Gastrointest Endosc. 2005;61(6):659–67.
72. Arts J, Lerut T, Rutgeerts P, Sifrim D, Janssens J, Tack J. A one-year follow-up study of endoluminal gastroplication (Endocinch) in GERD patients refractory to proton pump inhibitor therapy. Dig Dis Sci. 2005;50(2):351–6.
73. Schwartz MP, Wellink H, Gooszen HG, Conchillo JM, Samsom M, Smout AJ. Endoscopic gastroplication for the treatment of gastro-oesophageal reflux disease: a randomised, sham-controlled trial. Gut. 2007;56(1):20–8.
74. Montgomery M, Håkanson B, Ljungqvist O, Ahlman B, Thorell A. Twelve months' follow-up after treatment with the EndoCinch endoscopic technique for gastro-oesophageal reflux disease: a randomized, placebo-controlled study. Scand J Gastroenterol. 2006;41(12):1382–9.
75. Cadière GB, Buset M, Muls V, Rajan A, Rösch T, Eckardt AJ, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. World J Surg. 2008;32(8):1676–88.
76. Wolfsen HC, Richards WO. The Stretta procedure for the treatment of GERD: a registry of 558 patients. J Laparoendosc Adv Surg Tech A. 2002;12(6):395–402.
77. Torquati A, Houston HL, Kaiser J, Holzman MD, Richards WO. Long-term follow-up study of the Stretta procedure for the treatment of gastroesophageal reflux disease. Surg Endosc. 2004;18(10):1475–9.
78. White B, Jeansonne LO, Cook M, Chavarriaga LF, Goldenberg EA, Davis SS, et al. Use of endoluminal antireflux therapies for obese patients with GERD. Obes Surg. 2009;19(6):783–7.
79. Corley DA, Katz P, Wo JM, Stefan A, Patti M, Rothstein R, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology. 2003;125(3):668–76.
80. Dughera L, Navino M, Cassolino P, De Cento M, Cacciotella L, Cisarò F, et al. Long-term results of radiofrequency energy delivery for the treatment of GERD: results of a prospective 48-month study. Diagn Ther Endosc. 2011;2011:507157.
81. Banerjee R, Pratap N, Kalpala R, Reddy DN. Effect of electrical stimulation of the lower esophageal sphincter using endoscopically implanted temporary stimulation leads in patients with reflux disease. Surg Endosc. 2014 Mar;28(3):1003–9.