Advances in imaging and endoscopic therapy in Barrett’s esophagus
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Autofluorescence and Narrow Band Imaging
in Barrett’s esophagus

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Part I: Imaging in Barrett’s esophagus

Synopsis

This review discusses the application of two novel imaging techniques in Barrett’s esophagus: autofluorescence imaging and narrow band imaging (NBI). Autofluorescence as well as NBI may help to direct endoscopic therapy for early neoplasia in Barrett’s esophagus, their value in daily practice, however, appears to be limited and needs further evaluation.
Introduction

Barrett’s esophagus is a premalignant condition with an estimated annual cancer risk of 0.5%. Barrett’s esophagus is a premalignant condition with an estimated annual cancer risk of 0.5%.1 Esophageal adenocarcinoma is known to arise through a multi-step transition sequence, starting with non-neoplastic Barrett’s epithelium, through low-grade intraepithelial neoplasia (LGIN) and high-grade intraepithelial neoplasia (HGIN), finally progressing into invasive early neoplasia (EN).2 Patients with Barrett’s esophagus are offered regular surveillance endoscopies in order to detect neoplasia at an early and curable stage. Current guidelines advise to biopsy Barrett’s epithelium according to the Seattle protocol in which biopsies are obtained from any visible abnormality in addition to four-quadrant random biopsies taken every 2 cm.3, 4 This approach is, however, associated with sampling error since neoplastic lesions are often poorly visible and random biopsies only sample a small part of the Barrett’s esophagus. Furthermore, biopsying in four quadrants every 2 cm is time consuming leading to low protocol adherence by endoscopists in daily practice.5, 6

In recent years, new imaging techniques have been developed in order to improve the detection of (intraepithelial) neoplasia at an early stage, thereby possibly improving Barrett’s surveillance practice. These imaging techniques can mainly be divided into two types: detection techniques and characterization techniques. Detection imaging techniques are developed to serve as a “red flag” technique in order to improve the detection of early neoplasia by drawing the attention to lesions that may harbor early neoplasia. A detection imaging technique is typically used during broad field overview examination in addition to white light endoscopy. Characterization imaging techniques on the other hand, are meant for detailed inspection of detected lesions in order to characterize the lesion, and to differentiate between neoplastic and non-neoplastic lesions. In general, characterization techniques are used on a small area by zooming in on the mucosa to provide more details.

This review will discuss the application of two novel imaging techniques in Barrett’s esophagus: autofluorescence imaging and narrow band imaging (NBI).

Autofluorescence

Principle and technique

Autofluorescence is the phenomenon in which tissue, after exposure to light of a certain wavelength, emits light of a longer wavelength. In tissue, endogenous fluorophores (e.g. collagen, amino acids, flavins, nicotinamide adenine dinucleotide (NADH) and porphyrins) emit fluorescent
light with a longer wavelength (i.e. green and red light) after exposure to the short wavelength light (i.e. ultraviolet or blue light). Besides initiating autofluorescence, short wavelength light can also be reflected, scattered and absorbed by the tissues. Absorption of (fluorescent) light is possible by chromophores. The main chromophore in gastrointestinal tissue in the visible wavelength (400-700 nm) is hemoglobin.

Changes in the composition of the endogenous fluorophores and chromophores as well as stromal changes such as thickening of the mucosa can influence the wavelength and intensity of the emitted autofluorescent light. Because of these changes, neoplastic lesions can exhibit a different autofluorescent pattern than normal tissue. Studies using point spectroscopy techniques with small probes inserted through the accessory channel of the endoscope have shown that the autofluorescence pattern of Barrett's neoplasia is indeed different compared to that of normal Barrett's mucosa. This difference in autofluorescence in Barrett's neoplasia is, however, believed to be mainly caused by stromal changes and hemoglobin concentrations rather than changes in fluorophores composition.

The LIFE system (light induced fluorescence endoscopy, Xillix, Richmond, British Columbia, Canada) was the first endoscopy system that enabled autofluorescence imaging as a broad field technique. This system consisted of a camera mounted on the ocular portion of a fiberoptic endoscope. Switching between the white light mode and the autofluorescence mode was possible by using the switch on the camera. After excitation with blue light, the emitted red and green autofluorescent light passed from two charge coupled devices (CCD) in the camera to the image processor. Based on the ratio of red to green autofluorescence the image processor produced a real time endoscopic image on a monitor using pseudocolors. Concurrently with LIFE, another comparable system from another manufacturer was also available (Storz, Tuttlingen, Germany).

The major problem with these systems was the use of fiberoptic endoscopy, which had a much lower resolution than the current video endoscopy systems. A new autofluorescence imaging system (AFI, Olympus, Tokyo, Japan) was therefore developed, consisting of a sequential Red Green Blue (RGB) light source and a high-resolution video endoscope. Changing between high-resolution white light mode and the AFI mode was made easy by pushing a control button on the endoscope. After excitation with blue light, a real time AFI image was produced based on three light features: total emitted autofluorescence, green reflectance (540-560nm) and red reflectance (600-620nm). This was a more extended algorithm than LIFE, which only used the ratio of red to green autofluorescence.

Finally the endoscopic tri-modal imaging (ETMI, Olympus, Tokyo, Japan) was developed, which is currently commercially available in Asia and the United Kingdom. ETMI is comparable to the AFI system, but has additional features when using the high resolution white light mode during which
Autofluorescence and narrow band imaging

NBI and optical zoom (magnification up to 100x) are possible. Most importantly, the algorithm of the autofluorescence mode was changed. The autofluorescence image is composed of two instead of three light features: total emitted autofluorescence and green reflectance (540-560 nm). Similar to the other systems, these light features are displayed as pseudocolors on the real time endoscopic image on the monitor. In case of ETMI, normal Barrett’s mucosa appears green and (an area suspicious for) neoplasia is displayed as purple on the monitor (Figure 1).

Figure 1 Autofluorescence image of a Barrett’s esophagus with corresponding high resolution white light image. Neoplastic Barrett’s mucosa (A and B) appears purple at the 3 o’clock position with autofluorescence (B).

Clinical application

Detection of neoplasia in Barrett’s mucosa

The first studies with the autofluorescence systems using fiberoptic endoscopy (the LIFE-system) reported a higher detection rate of HGIN/EN with autofluorescence.\textsuperscript{11, 12} Further evaluation with randomized cross-over studies comparing white light video endoscopy with autofluorescence using the LIFE system showed, however, that autofluorescence did not increase the number of patients detected with HGIN/EN.\textsuperscript{13, 14} Possible explanations for the lack of increased detection were the poor image quality of the fiberoptic endoscopy and the algorithm used that did not take distorting effects into account.

Both problems were overcome when autofluorescence was translated to video endoscopy (AFI and ETMI) which had high resolution endoscopy and a new algorithm. Feasibility studies with AFI and ETMI showed that after inspection with high resolution white light, inspection with autofluorescence resulted in additional detection of lesions and patients with HGIN/EN.\textsuperscript{15-17}
The targeted detection of patients with HGIN/EN increased from 43-65% after high resolution white light, up to 90-100% after additional inspection with autofluorescence. Major drawback of autofluorescence was the high false positive rate as 40-81% of the lesions detected with autofluorescence did not contain HGIN/EN.15-17

A recent randomized cross-over study comparing ETMI with standard video endoscopy showed that targeted detection was significantly better with ETMI: 65% versus 44% with standard video endoscopy.18 Overall detection of the patients with HGIN/EN with ETMI (i.e. targeted and random biopsies), however, was not statistically different from standard video endoscopy (84% versus 73%, respectively).18 Furthermore, random biopsies resulted in the detection of additional patients with HGIN/EN (64% with targeted biopsies versus 84% with targeted and random biopsies), which suggests that improved targeted imaging with ETMI is not enough to abandon random biopsy sampling. Finally, a high number of lesions detected with ETMI was false positive (71%), though standard video endoscopy showed a high false positive rate as well (53%). This study was performed by endoscopists with extensive expertise in imaging and endoscopic treatment of Barrett's esophagus and only patients referred for HGIN/EN were included. In other words, the study was performed in a high risk population (with a high pre test likelihood of having HGIN/EN) by endoscopists who were used to see subtle lesions with HGIN/EN.

Hence, although autofluorescence did not lead to the identification of more patients with HGIN/EN in a tertiary referral setting, its use in a community hospital setting might be of additional value. Therefore a randomized cross-over study comparing ETMI with standard video endoscopy was performed in patients with an intermediate risk (i.e. LGIN) by endoscopists without specific expertise in Barrett's esophagus.19 Similar to the tertiary referral setting, the targeted detection of in this case LGIN/HGIN/EN was again significantly increased with ETMI compared to standard video endoscopy (54% and 34% respectively), but overall detection rates of patients with neoplastic changes in their Barrett's esophagus were not significantly different. False positive rate remained high with ETMI (68%) as well as with standard video endoscopy (64%).19

So, autofluorescence appears to increase the targeted detection of HGIN/EN lesions, although it does not result in a better overall detection of patients with HGIN/EN. The increased targeted detection rate might be useful to direct endoscopic therapy, although studies on this subject are lacking. Interobserver agreement on autofluorescent seems also to be reasonable with a kappa of 0.48-0.76.20, 21 Still the false positive rate of autofluorescence remains a drawback.

Attempts to reduce the false positive rate have been made by inspecting autofluorescent positive areas in detail with NBI. The false positive rate was substantially reduced after NBI inspection from 40-81% to 10-48%.16-19 This reduction in false positive rates, however, was achieved at the expense of misclassifying a significant proportion (8-17%) of the autofluorescent true positive areas as non-neoplastic.16-19
The endoscopic features associated with true positive autofluorescent areas (i.e. autofluorescent positive areas containing HGIN/EN) were therefore studied in order to reduce the false positive rate of autofluorescence. Opaque autofluorescent intensity, a different appearance of the area after re-inspection with white light and no close proximity to gastric folds (>1cm) were found to be associated with true positive autofluorescent lesions. Although further evaluation is needed, these endoscopic features may be helpful in improving the accuracy of autofluorescence.

In summary, autofluorescence increases the targeted detection of lesions with HGIN/EN and may therefore be useful in a tertiary center setting to direct endoscopic therapy. Autofluorescence, however, does not result in a better overall detection of patients with HGIN/EN. Furthermore, the false positive rate of autofluorescence remains a major drawback.

**NBI**

**Principle and technique**

Narrow Band Imaging (NBI, Olympus, Tokyo, Japan) is a technique that uses optical filters to visualize the mucosal morphology by enhancing mucosal as well vascular patterns. NBI is based on the fact that the depth of light penetration into tissues depends on the wavelength of the light. Longer wavelength light (red) penetrates deeper into tissue than short wavelength light (blue). Consequently, red light provides more information on the deeper layers of the mucosa, while blue light, which has a more superficial penetration, provides more information on the morphology of the mucosal surface. In addition, blue light reveals also the superficial vasculature as it is absorbed by hemoglobin. With NBI the relative intensity of the blue light is increased, while other wavelengths are reduced or eliminated by using a filter with narrow bandpass ranges.

Other techniques that enhance the mucosal morphology during real time endoscopy such as Fuji Intelligent Color Enhancement (FICE, Fujinon Inc., Saitama, Japan) and I-scan (Pentax, Tokyo, Japan) have also become available. The difference with NBI is that these are postprocessing techniques. These techniques do not use actual filters, but change the white light endoscopic image from the video processor by arithmetically processing it into a virtual image for different wavelength settings. Studies using these techniques for Barrett’s esophagus are rare (FICE) or lacking (I-scan). Consequently, most data is known from studies that have been performed with NBI.

NBI is easy to use during endoscopy. Changing between the white light mode and the NBI mode on the endoscope is achieved by using a switch on the endoscope that deploys the NBI filter. NBI can be used during overview examination as a detection technique, or for detailed inspection of mucosal and vascular patterns as a characterization modality.
Clinical applications

Detection of neoplasia in Barrett’s mucosa

The value of NBI for the detection of HGIN/EN is unclear. Two studies have reported on the use of NBI for the detection of (intraepithelial) neoplasia in Barrett’s esophagus. Kara et al. evaluated the additional value of NBI and indigo carmine chromoendoscopy (ICC) to high resolution white light endoscopy performed by endoscopists with specific expertise in Barrett’s esophagus in patients referred with endoscopically inconspicuous HGIN/EN. A total of 28 patients underwent two endoscopies with an interval of 6-8 weeks, one with high resolution white light endoscopy followed by NBI, the other endoscopy with high resolution white light endoscopy followed by ICC. NBI, as well as ICC, did not result in additional detection of patients with HGIN/EN. Nevertheless NBI, as well as ICC, resulted in the detection of a limited number of additional lesions with HGIN/EN in patients in whom high resolution white light endoscopy already detected neoplasia.

Wolfsen et al. evaluated the detection rate of (intraepithelial) neoplasia with NBI compared to standard resolution white light in 65 patients referred for evaluation of (intraepithelial) neoplasia or enrolled in Barrett’s surveillance. Patients underwent one endoscopy, first inspected with standard resolution white light endoscopy by one endoscopist followed by high resolution white light endoscopy and NBI performed by a second endoscopist. NBI detected significantly more patients with higher grades of (intraepithelial) neoplasia compared to standard resolution white light endoscopy.

Some limitations may, however, have biased the results. First, the standard resolution white light endoscopy was performed by a group of endoscopists, while the NBI endoscopy was restricted to two endoscopists with experience in advanced endoscopy. Most important, the NBI endoscopy included inspection with high resolution white light endoscopy which may be at least as important as NBI alone for the detection of neoplasia. In addition, NBI endoscopy inspection time was twice as long as inspection with standard endoscopy because the Barrett’s esophagus was inspected twice: once with high resolution white light endoscopy and once with NBI. Clearly, further studies are needed to determine if NBI is useful during overview examination for the detection of (intraepithelial) neoplasia in Barrett’s esophagus.

Characterization of Barrett’s neoplasia

When using NBI with zoom, detailed inspection of mucosal and vascular patterns can be performed. Mucosal morphology has been described and classified by several study groups in order to differentiate (intraepithelial) neoplasia from non-neoplastic tissue. Generally, regular/normal patterns are considered to be associated with non-neoplastic Barrett’s mucosa while irregular/abnormal patterns are considered to be associated with neoplasia (Table 1 and Figure 2).
Table 1 Classifications on mucosal morphology to differentiate (intraepithelial) neoplasia from non-neoplastic tissue in Barrett's esophagus. Regular/normal patterns are considered to be associated with non-neoplastic mucosa; irregular/abnormal patterns are considered to be associated with neoplasia.

<table>
<thead>
<tr>
<th>Mucosal pattern</th>
<th>Mucosal pattern</th>
<th>Mucosal pattern</th>
<th>Microstructural pattern</th>
<th>Microstructural/ microvascular pattern</th>
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</thead>
<tbody>
<tr>
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<td>Regular</td>
<td>Round</td>
<td>Round pits &amp; regular mv (A)</td>
<td></td>
</tr>
<tr>
<td>Ridge/villous</td>
<td>Regular</td>
<td>Linear/tubular/villous</td>
<td>Villous/ridge pits &amp; regular mv (B)</td>
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</tr>
<tr>
<td>-</td>
<td>Flat</td>
<td>Flat</td>
<td>Nonstructural</td>
<td>Absent pits &amp; regular mv (C)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular pattern</th>
<th>Vascular pattern</th>
<th>Vascular pattern</th>
<th>Microvascular pattern</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Regular</td>
<td>Regular</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Irregular</td>
<td>Irregular</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal blood vessels</td>
<td>Absent</td>
<td>-</td>
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<tr>
<td></td>
<td>Present</td>
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</table>

*mv microvasculature*
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Figure 2 Narrow band imaging of mucosa in the cardia with round pits (A), Barrett’s mucosa with a more complicated branching pattern (B) and irregular/abnormal appearing Barrett’s mucosa containing neoplasia (C).

Most of the studies have been performed by blinded image evaluation: endoscopists scoring the NBI zoom images were blinded for the endoscopic overview information. Other studies have been performed real time, by freezing an NBI zoom image of a suspected area found during (autofluorescence) endoscopy. The sensitivity to differentiate HGIN/EN from LGIN/non-neoplastic tissue has been reported to be 71-100%, with a specificity of 33-99%. The sensitivity to differentiate LGIN/HGIN/EN from non-neoplastic tissue has been reported to be 59-89%, with a specificity of 36-72%. Although initial studies were promising, subsequent studies showed a rather moderate sensitivity. Possibly, NBI zoom provides too much detail without apparent clinically relevant information, which might confuse the endoscopist more than providing him with valuable information.

The ability to differentiate neoplastic from non-neoplastic lesions by NBI zoom was not influenced by the endoscopist’s expertise as no clear differences were found between endoscopists with extensive experience in Barrett’s imaging and endoscopists without special interest in Barrett’s.

Another important aspect in this respect is the agreement between endoscopists on the mucosal morphology with NBI. Interobserver agreement (i.e. agreement between different endoscopists) has been reported to be fair to moderate according to Landis and Koch (κ 0.39-0.59). Intraobserver agreement (i.e. agreement between the same endoscopist) has been reported to be slightly higher with κ-value between 0.60 and 0.62, which is moderate to substantial. Surprisingly, interobserver and intraobserver agreement did not differ between endoscopists without extensive experience in Barrett’s esophagus compared to expert endoscopists from tertiary referral centers. Characterization of Barrett’s lesions with NBI is thus disappointing, with a relative low sensitivity and moderate agreement between endoscopists with and without extensive experience in Barrett’s esophagus. Additionally, all studies used still images that were obtained by experienced endoscopists and images of inferior quality were excluded by most studies. In daily practice, less experienced endoscopists may encounter difficulties when trying to
take a high quality still zoom image for evaluation with NBI. Biopsying areas that are suspected to have neoplasia may therefore not only result in a more accurate diagnosis, but is probably also faster and more practical than obtaining a good quality NBI image of the area of interest.

Characterization of intestinal metaplasia
Different mucosal patterns have been described and classified in order to differentiate intestinal metaplasia from gastric mucosa. Generally, round and circular patterns are believed to be associated with gastric mucosa, while more complicated branching patterns are believed to be associated with intestinal metaplasia (Figure 2). The sensitivity for identifying intestinal metaplasia has been reported to be 56-100%, with specificities varying between 77-95%. Despite assessments have been performed by expert endoscopists, accuracy is not optimal. Analogous to characterization of neoplasia, characterization of intestinal metaplasia is best achieved by retrieving biopsies for histological assessment instead of inspection with NBI.

Other clinical applications
A different application of NBI in Barrett’s esophagus is its use for the detection of minute (1-5 mm) islands of columnar epithelium that might remain after ablation therapy such as radiofrequency ablation (RFA). Detection of such islands may be difficult with high resolution white light endoscopy, while NBI may reveal the islands more easily (Figure 3). Detecting such islands might help to direct adequately further ablative therapy. Finally, NBI may help to better delineate early neoplastic lesions before endoscopic resection.

Figure 3 Barrett’s esophagus after radiofrequency ablation seen with high resolution white light (A & C) and with narrow band imaging (B & D), in which the reaming islands of columnar epithelium are seen more clearly.
Summary and future prospective

Autofluorescence does increase the targeted detection of lesions containing HGIN/EN and may therefore be useful in tertiary centers, in order to locate neoplastic lesions adequately for further endoscopic treatment. Compared to the current Seattle biopsy protocol, however, autofluorescence does not result in the detection of more patients with HGIN/EN, and autofluorescence in its current form will not replace random biopsies. Whether NBI detects more patients with HGIN/EN compared to the Seattle protocol needs further evaluation as to date only two studies with conflicting results have investigated NBI for this purpose. NBI appears, however, not to be useful in the characterization of Barrett’s neoplasia given the relative low sensitivity, even in expert hands. Biopsying areas that are suspected to harbor neoplasia is more practical and will result in a more accurate diagnosis. Although autofluorescence as well as NBI may help to direct endoscopic therapy for early neoplasia in Barrett’s esophagus, their current value in daily practice appears to be limited.

Nevertheless there is room to improve both techniques. In the case of autofluorescence imaging, new algorithms as well as combination with fluorescent markers may improve the detection rate of neoplasia and reduce the false positivity. In the case of NBI, studies have too much focused on characterization of lesions by evaluating still images. This is an artificial setting, quite different from real time video assessment. In addition, histology of the biopsies was used as gold standard, which may be suboptimal: studies have shown that endoscopic resection (i.e. a larger sample) leads to upgrading of the histological diagnosis in 34% of cases when early neoplasia is evaluated. Most important, however, is the possibility that too much focus may be directed on high magnification inspection by the evaluation of the mucosal and vascular patterns in detailed zoom. There may be other NBI features that are helpful in overview, such as for example surface relief which might reveal neoplastic lesions more clearly in the Barrett’s esophagus (Figure 4).

In summary, autofluorescence as well as NBI may be useful in directing endoscopic therapy for early neoplasia in Barrett’s esophagus. Further research may reveal additional value for daily practice.
Figure 4 Neoplastic lesions in Barrett’s esophagus shown with high resolution white light (A, B and C) and their corresponding images with narrow band imaging (E, F and G). Surface relief is better appreciated with narrow band imaging which might aid in detecting more subtle lesions (E and F) or delineating them for endoscopic resection (D).
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References


Autofluorescence and narrow band imaging


