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### Advanced endoscopic imaging of esophageal neoplasia; old looks and new visions

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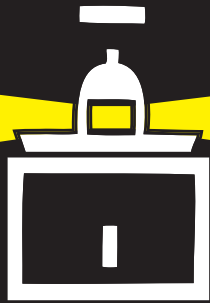
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## THE CLINICAL CONSEQUENCES OF ADVANCED IMAGING TECHNIQUES IN BARRETT'S ESOPHAGUS



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## ABSTRACT

Dye-based chromoendoscopy, optical chromoendoscopy, autofluorescence imaging (AFI) and confocal laser endomicroscopy (CLE) do not significantly increase the number of Barrett's patients diagnosed with early neoplasia compared to high-definition white light endoscopy (HD-WLE) with random biopsies. These techniques have little clinical relevance for standard Barrett's surveillance since the prevalence of early neoplasia is low and the use of HD-WLE and random biopsies will detect the majority of neoplastic cases.

Work-up and treatment of early Barrett's neoplasia should be centralised in tertiary referral centers. In this setting, the prevalence of early neoplasia is much higher and procedures are performed under optimal circumstances by expert endoscopists. Lesions that require resection will virtually always be detected on HD-WLE by the expert team performing the work-up endoscopy. Advanced imaging techniques may detect additional flat lesions, inconspicuous with WLE, but these are clinically of limited significance since they harbor only flat type mucosal neoplasia that will be effectively eradicated by ablation therapy.

No endoscopic imaging technique can reliably assess submucosal or lymphangio invasion. Endoscopic resection of early Barrett's neoplasia is therefore imperative for staging and optimal patient selection. Optical chromoendoscopy plays an important role in delineation prior to endoscopic resection and follow-up after successful ablation therapy.



## INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) in the western world has increased sixfold over the past three decades and has a dismal prognosis when detected at a symptomatic stage<sup>1</sup>. Adenocarcinoma develops through a precursor lesion called Barrett's esophagus (BE) in a sequence of gradually evolving, histologically recognizable steps: intestinal metaplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal carcinoma (IMC) and eventually invasive carcinoma. These intermediate grades of dysplasia offer a window of opportunity for curative therapy.

In the last decade, endoscopic therapy has become the treatment of choice for early Barrett's neoplasia (*i.e.* HGD and IMC), with an excellent prognosis and safety profile compared to surgical resection<sup>2</sup>. A prerequisite for endoscopy therapy is adequate patient selection; only patients with HGD and IMC have a virtual absent risk of lymph node metastasis and are therefore amendable for endoscopic therapy<sup>3</sup>.

In patients with known BE, regular surveillance endoscopy with random biopsies is recommended to detect early neoplastic lesions at a curable stage<sup>4</sup>. However, these lesions are often small, focally distributed and endoscopically poorly visible (*Figure 1*). Random four-quadrant biopsies may easily miss early lesions, since only about 5% of the Barrett's segment is sampled<sup>5</sup>. Moreover, this process is laborious and many endoscopists do not adhere to the protocol<sup>6</sup>.

In recent years, many advanced imaging techniques have been developed to improve the detection of early Barrett's neoplasia. In this review we discuss how these techniques may affect clinical management of BE either by improving the primary detection of early neoplastic lesions, allowing real-time diagnosis and decision making during endoscopy, or guiding the endoscopic work-up and treatment.

## PRIMARY DETECTION OF EARLY NEOPLASIA

For primary detection of early neoplastic lesions in BE, wide-field imaging techniques are required that allow detection of lesions in overview: to "red flag" areas of interest. As stated in current guidelines, advanced imaging techniques should be superimposed on high-resolution white light endoscopy (WLE) using high-definition (HD) systems. The currently available HD-WLE systems have a spatial resolution of less than 10 $\mu$ m and offer high-quality imaging that is the basis for endoscopy in BE<sup>7-9</sup>.

### Chromoendoscopy

In chromoendoscopy, stains are applied on the mucosa to improve the visualisation of neoplastic lesions. In general, two types of dye are available: vital and contrast stains. Vital stains (*e.g.* methylene blue) are actively absorbed by the epithelium. Contrast stains (*e.g.* indigo carmine) accumulate in pits and grooves along the epithelial surface, highlighting the superficial mucosal architecture (*Figure S1*). Early studies on methylene blue chromoendoscopy suggested an increased detection of early neoplasia<sup>10</sup>, yet a recent meta-analysis of 9 studies showed that there is no incremental yield for methylene blue chromoendoscopy over standard WLE<sup>11</sup>. Acetic acid

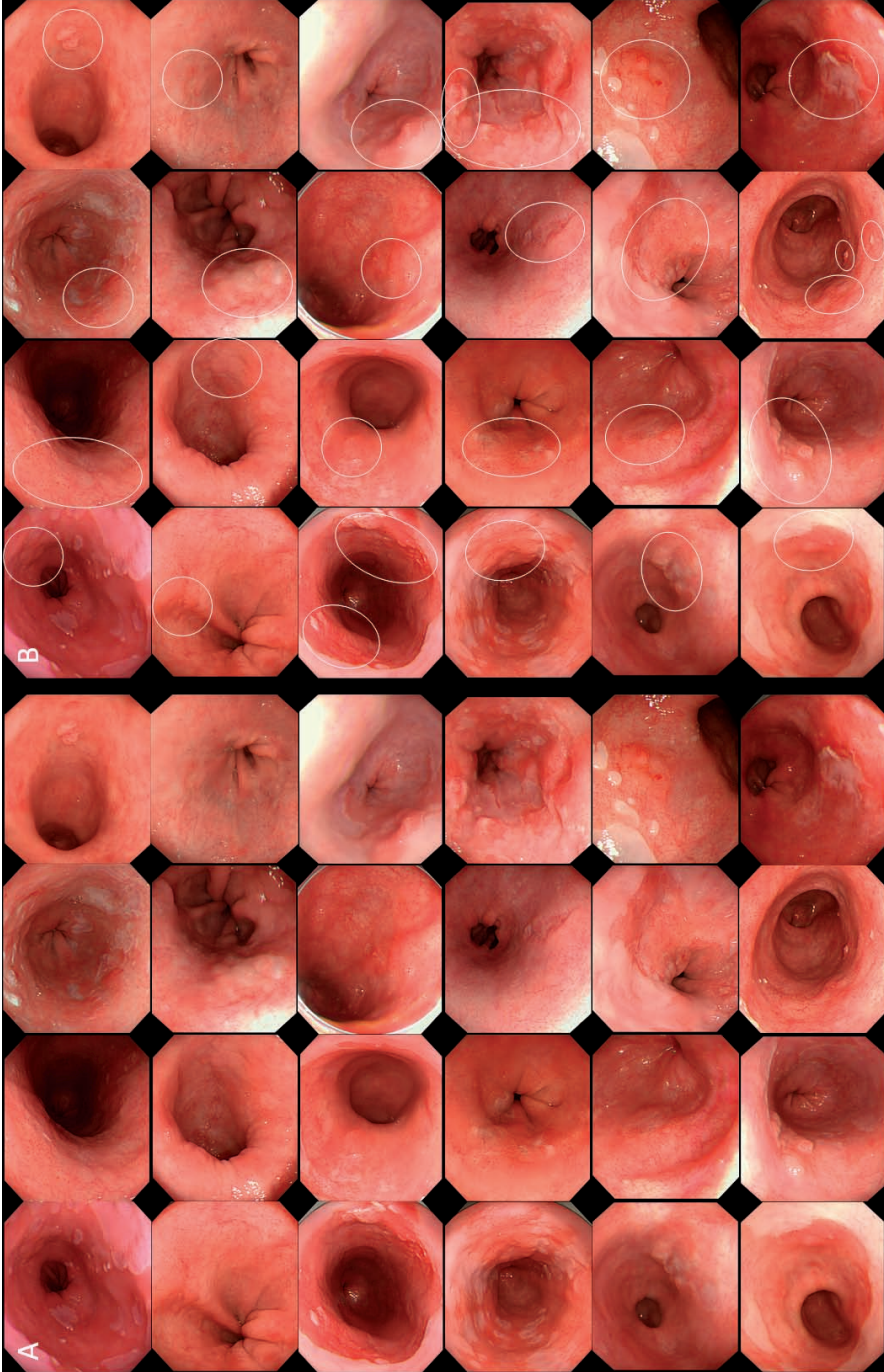


Figure 1. Examples of subtle neoplastic lesions in Barrett's esophagus (a). The neoplastic lesions are encircled (b). Reproduced with permission from [www.endosurgery.eu](http://www.endosurgery.eu)



(AA) is an inexpensive agent that increases the contrast of the mucosal pattern (*Figure S1*). Recent publications have suggested that AA may be beneficial for identification of early neoplasia<sup>12,13</sup>. However, no randomized (cross-over) controlled studies have been performed comparing AA to standard practice and other studies have questioned the additional value of AA over HD-WLE<sup>14</sup>. Chromoendoscopy techniques are not widely used in Barrett's endoscopy: it is questionable if they really increase the detection of early neoplasia over HD-WLE, many endoscopists consider chromoendoscopy a cumbersome procedure, and correct application of dyes and interpretation of the images are operator dependent.

### Optical and digital chromoendoscopy techniques

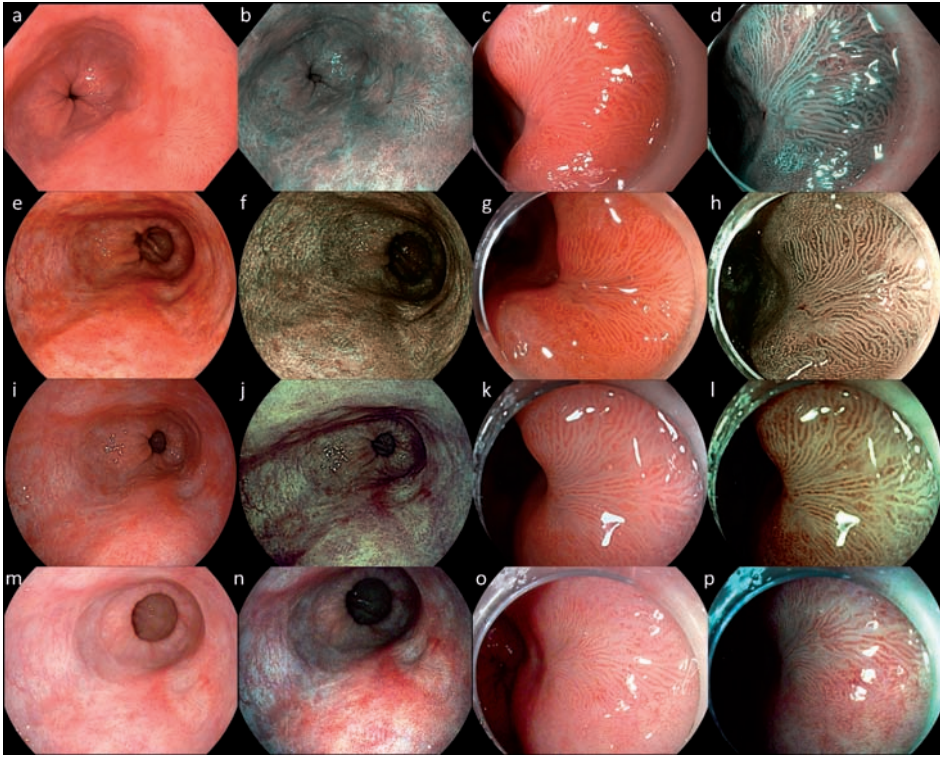
These techniques improve the visualisation of mucosal morphology without the use of dyes. This can be done with *pre-processing* techniques - optical chromoendoscopy – such as narrow band imaging (NBI; Olympus, Tokyo, Japan), or blue laser imaging (BLI; Fujifilm, Tokyo, Japan). The mucosal imaging is enhanced by using blue light, that only penetrates superficially into the tissue and causes less scattering. In addition, blue light encompasses the maximum absorption wavelength of haemoglobin, which results in better visualization of vascular structures<sup>15</sup>.

Digital chromoendoscopy techniques that are based on *post-processing* (Fujifilm intelligent chromo-endoscopy (FICE; Fujifilm, Tokyo, Japan) and i-scan (Pentax, Tokyo Japan)) use normal white light excitation. The reflected image is then reprocessed by a proprietary algorithm. In our opinion, pre-processing techniques have a better signal-to-noise ratio, resulting in images with a higher resolution and brightness compared to post-processing techniques (*Figure 2*).

Most studies on optical chromoendoscopy techniques in Barrett's esophagus have used NBI. Regular mucosal and vascular NBI patterns have been shown to correlate with non-dysplastic BE, while irregular features are associated with early neoplasia<sup>15,16</sup>.

The yield of NBI for the detection of early neoplasia has been investigated in 3 randomized studies. *Kara et al.* compared HD-WLE plus NBI to HD-WLE plus indigo carmine chromoendoscopy in a randomized cross-over design<sup>17</sup>. NBI and indigo carmine both increased the targeted detection of neoplastic lesions, but all patients with neoplasia were already diagnosed with HD-WLE. *Wolfsen et al.* suggested that NBI increases the detection of patients with early neoplasia over standard resolution WLE<sup>18</sup>. The tandem endoscopy design of this study, however, was biased because standard WLE endoscopy was performed by general endoscopists and compared to HD-WLE plus NBI inspection performed by endoscopists with experience in the detection of early Barrett's neoplasia<sup>19</sup>. Finally, a recent randomized cross-over study compared HD-WLE plus random biopsies to NBI with targeted biopsies only<sup>20</sup>. The authors conclude that although both modalities detected a comparable number of patients and lesions with early neoplasia, NBI may reduce the number of biopsies taken during Barrett's surveillance and thus add to its efficacy and (cost-) effectiveness. A drawback of this study was the relative low prevalence of early neoplasia.

Optical chromoendoscopy techniques offer a more detailed inspection of the mucosal morphology than HD-WLE, but whether this translates into clinically relevant information is yet unknown. After the initial enthusiasm, subsequent clinical studies have not provided new insights in detection of neoplasia by NBI<sup>21,22</sup>.

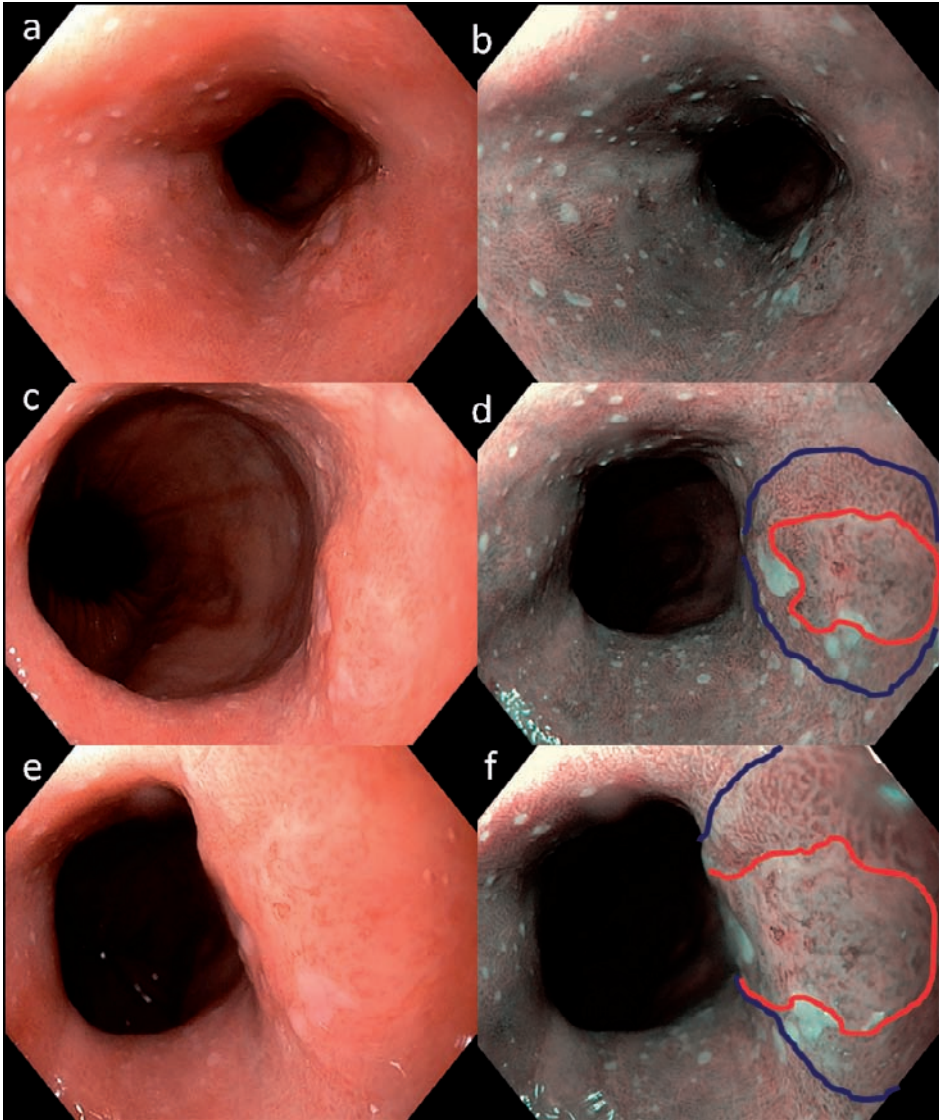


**Figure 2.** Overview and detailed images of a neoplastic lesions in a Barrett's esophagus: Olympus high resolution white light endoscopy (a,c) and narrow band imaging (b, d); Fujinon white light endoscopy (e,g) and blue light imaging (f,h); Fujinon white light endoscopy (i,k) and Fujinon intelligent chromoendoscopy (j,l); Pentax white light endoscopy (m,o) and iSCAN (n,p).

In our opinion, NBI studies may have focussed too much on irregularity of mucosal and vascular patterns as the main features of neoplasia. These studies evaluated *magnified* NBI images obtained after zoom endoscopy. Zoom endoscopy, however, is technically demanding, not generally used in the Western world and evaluation of magnified NBI images is associated with a significant interobserver variability<sup>23-25</sup>. In our opinion, the use of NBI in overview for primary detection was limited by the relative darkness of the image in overview and the loss of resolution of still images due to motion artefacts and interlaced videoprocessing. The latest version NBI systems and the recently introduced BLI system have overcome these technical limitations and may allow their use as a "red-flag technology". Which NBI features are relevant for detection in overview is yet unknown, but our impression is that minute differences in surface appearance ("surface relief") are much better appreciated with these techniques than with HD-WLE (*Figure 3*).

### Autofluorescence imaging

Autofluorescence imaging (AFI) is based on the principle that certain endogenous substances, such as nicotinamide adenine dinucleotide and collagen emit light of longer wavelengths when



**Figure 3.** Overview, detailed and near-focus images of a neoplastic lesion in a Barrett's esophagus with white light endoscopy (WLE; a,c,e) and narrow band imaging (NBI; b,d,f). The red line indicates the border of the vascular and mucosal abnormalities, based on the NBI appearance, the blue line illustrates the extension of the neoplastic lesion based on the mucosal relief, which can be better appreciated with NBI, compared to WLE.

excited with light of short wavelength. Spectroscopy studies have shown that Barrett's neoplasia has a different autofluorescence spectrum compared to non-neoplastic Barrett's mucosa<sup>26,27</sup>. These findings led to the development of wide-field autofluorescence imaging, that was integrated with HD-WLE and NBI into an "endoscopic trimodal imaging" (ETMI) system (figure S2).

In uncontrolled ETMI studies, AFI increased the detection of early neoplasia, while NBI reduced the false positive rate associated with AFI<sup>28</sup>. However, two subsequent randomized crossover trials, comparing ETMI to standard resolution WLE, failed to show superiority of ETMI<sup>29,30</sup>. In these studies, AFI again significantly increased the targeted detection of areas with neoplasia that were inconspicuous with WLE, but the strategy of only obtaining targeted biopsies after ETMI inspection was found to be inferior to standard WLE plus random biopsies.

The finding that AFI improves the targeted detection of neoplasia may be clinically relevant in two ways. First, there is relevance from a *diagnostic* perspective: if the AFI detected lesion is the only neoplastic lesion identified during the endoscopy and all random biopsies are negative, AFI “upstages” the neoplastic status of the patient. Second, there is relevance from a *therapeutic* perspective. In patients with an indication for endoscopic treatment, visible lesions should be resected and not ablated<sup>7,31</sup>. Endoscopic resection allows histological diagnosis of submucosal invasion, which is generally considered an indication for esophagectomy given the associated risk of lymph node metastasis. AFI detected lesions therefore have therapeutic relevance if endoscopic resection of the lesion shows histology that changes the management from an endoscopic to a surgical approach. A recent study found that AFI detected lesions rarely lead to diagnostic upstaging of neoplasia or a change in the therapeutic approach. Neoplastic lesions that direct the choice of therapy are virtually always found with HD-WLE inspection only<sup>32</sup>. This is in line with previous observations in patients who were treated with stepwise endoscopic resection of the whole Barrett’s segment: after endoscopic resection of the most suspicious lesion detected with HD-WLE, subsequent resections of the remaining Barrett’s segment did not lead to histological upstaging of the neoplasia<sup>33,34</sup>. Recently, third generation AFI was introduced with a dual-band autofluorescence algorithm. The hypothesis was that this algorithm specifically targets fluorescent changes in neoplastic cells, yet initial feasibility studies have yielded disappointing results<sup>35</sup>.

## REAL-TIME DIAGNOSIS AND DECISION MAKING

After the detection of suspicious lesions, advanced imaging techniques might be able to confirm the diagnosis of neoplasia without the need for histological evaluation, allowing real-time diagnosis and decision making during endoscopy.

Optical chromoendoscopy enables detailed inspection of mucosal and vascular structures. However, multiple studies with different modalities have shown that this does not allow a reliable distinction between neoplastic and non-neoplastic lesions<sup>14,23,24,29,30</sup>.

Confocal laser endomicroscopy (CLE) has the potential of real-time histology during endoscopy. Probe-based CLE (pCLE) and integrated CLE (iCLE) have been studied in the colon, stomach and esophagus<sup>36</sup>. Both techniques differ significantly in a practical sense: pCLE can be performed in combination with HR-WLE and other red-flag techniques, yet has a lower resolution and frame-rate compared to iCLE. With iCLE, high resolution images can be obtained, while leaving room in the accessory channel for a biopsy forceps. However, the maneuverability of the stiff iCLE scope-tip is limited and the system lacks HD-WLE. CLE has demonstrated good performance in predicting the presence of neoplasia in Barrett’s esophagus<sup>37,38</sup>. Moreover, HR-WLE in



combination with pCLE was shown to increase the detection of early neoplasia, compared to HR-WLE alone<sup>38</sup>. With a sensitivity of 68%, the performance of pCLE is limited. A promising benefit of CLE is the possible reduction of the number of random biopsies taken, by sampling only areas suspicious on CLE<sup>39</sup>. In our opinion, obtaining good quality CLE images is technically challenging. In addition, CLE equipment is expensive and exogenous contrast agents are required. More importantly, the relevance of real-time diagnosis, risk stratification and decision making during Barrett's endoscopies is questionable. In the presence of visible abnormalities on HD-WLE, few endoscopists will withhold taking biopsies based on CLE or another real-time diagnosis technique, such as endocytoscopy: the pre-test likelihood of neoplasia is so high that neoplasia cannot be excluded based on a negative test result<sup>30,40</sup>. Second, immediate decision making based on real-time diagnosis is neither practical nor ethical: patients need to be consented for endoscopic therapy and according to guidelines this should be centralised in high-volume centers, which generally implies referral to a different hospital<sup>4,9</sup>. We therefore question the wide-scale applicability of CLE for this purpose given its cost and endoscopic complexity.

Reducing histological sampling error by probe based techniques may not be relevant in the near future. Molecular markers will predict which patients will develop neoplasia well before morphological changes can be observed with histology or CLE. Barrett's surveillance will then consist of optimal HD-WLE inspection to detect prevalent and visible neoplasia that is subsequently biopsied for histological diagnosis and referral for treatment. In the absence of visible abnormalities, the Barrett's segment will be sampled by biopsies or brush cytology to detect a neoplastic field defect with molecular markers<sup>41,42</sup>.

CLE has been proposed as a valuable tool for follow up after endoscopic resection or radiofrequency ablation, yet controlled studies demonstrating this are lacking<sup>43</sup>.

## ADVANCED IMAGING TECHNIQUES AND SURVEILLANCE ENDOSCOPIES

Most surveillance endoscopies are performed in community hospitals. In this setting, the prevalence of early neoplasia is low (*i.e.* <5%) and therefore endoscopists are generally not familiar with the endoscopic appearance of early Barrett's neoplasia<sup>44,45</sup>.

In surveillance settings, detection of early neoplasia can be significantly improved by the use of HD-WLE and implementation of the following "detection essentials" (*Figure S3*): perform the procedure under sedation; clean the mucosa by using the waterjet channel; carefully inspect by varying insufflation and desufflation to detect subtle surface irregularities; retroflex the endoscope to inspect the distal Barrett's segment in a retrograde view; consider the use of a transparent cap on the tip of the endoscope, to facilitate magnification-endoscopy; obtain biopsies only after adequate inspection has been completed ("look longer, biopsy less"); improve recognition by studying "the face of Barrett's neoplasia" in endoscopy atlases and publications (*Figure 1*); obtain random biopsies for risk stratification<sup>7-9</sup>.

In our opinion, advanced imaging techniques have little clinical relevance for Barrett's surveillance, since the use of HD-WLE and adherence to the "detection essentials" will detect the majority

(>80%) of neoplastic cases. The potential value of advanced imaging techniques is therefore small (<1%) and with such a low pre-test likelihood most techniques will suffer from unacceptably high false-positive rates<sup>17,29,30</sup>. Finally, advanced imaging techniques are costly, not widely available in community hospitals and require endoscopic expertise that may not be uniformly available.

## ADVANCED IMAGING TECHNIQUES AND TREATMENT OF BARRETT'S ESOPHAGUS

Work-up and treatment of early Barrett's neoplasia should be centralised in tertiary referral centers<sup>49</sup>. Here, the prevalence of early neoplasia is much higher (i.e. >25%) and procedures are performed under optimal circumstances by expert endoscopists. The work-up endoscopy serves three purposes: the referral diagnosis and indication for treatment have to be confirmed; visible lesions requiring endoscopic resection (instead of ablation) have to be detected and staged; prior to resection lesions have to be delineated.

To confirm the referral diagnosis and indication for treatment, advanced imaging techniques have limited value: HD-WLE and the "detection essentials" generally suffice. Compared to surveillance settings, work-up endoscopies are performed under better circumstances. The procedures are generally performed on a dedicated endoscopy program by an endoscopy team with experience in detection and treatment of Barrett's neoplasia. More importantly, the team is aware of the neoplastic status of the Barrett's segment, based on the referral information.

Advanced imaging techniques have limited value for detection of lesions that require endoscopic resection. These lesions will virtually always be detected on HD-WLE by the expert team performing the work-up endoscopy. Advanced imaging techniques may indeed detect additional flat lesions, inconspicuous with WLE, but these are clinically of limited significance since they harbor only flat mucosal neoplasia that will be effectively eradicated by ablation<sup>32</sup>.

Staging of early neoplastic lesions implies evaluation of invasion depth. Advanced imaging techniques have limited value in distinguishing mucosal from submucosal cancers. Several studies have demonstrated that EUS provides no clinically relevant information over endoscopic inspection with HD-WLE<sup>46-48</sup>. CLE has a limited scanning depth and is therefore not suited for assessment of depth invasion. Histological evaluation of the resected specimen not only provides the ultimate proof of invasion depth, but also allows diagnosis of poorly differentiated cancers and lymphatic invasion, features that are virtually impossible to detect otherwise.

Prior to endoscopic resection, lesions have to be delineated from the surrounding mucosa. Series on attempted en-bloc resection show positive lateral resection margins in >50% of resections<sup>49,50</sup>.

Advanced imaging techniques may facilitate delineation of lesions prior to endoscopic resection, but formal studies are lacking<sup>37,51,52</sup>. Delineation of lesions should meet the purpose of endoscopic resection of Barrett's neoplasia: removal of the most involved area to finalise staging and rendering the Barrett's segment flat for subsequent ablation therapy<sup>7,53</sup>. In our opinion, NBI is superior to HD-WLE for this purpose. Detailed inspection with NBI allows for identification of the demarcation line (*Figure S4*), separating the area with an irregular mucosal and vascular pattern from its normal surroundings, like the delineation performed for resection of early gastric



neoplasia<sup>54</sup>. Lesions with a clear demarcation line usually harbour invasive cancer. Visible lesions containing HGIN or LGIN often do not display irregular mucosal or vascular patterns and therefore lack a clear demarcation line. Their endoscopic detection is triggered by slight elevation. Such subtle differences in surface relief are better appreciated by NBI than with HD-WLE (*Figure S4*). For delineation, the demarcation line and surface relief should both be used; the latter is generally more important in determining the size of the resection (*Figure 3*).

Optical chromoendoscopy techniques also have an important role in the follow-up of patients after ablation, allowing for the detection of small residual islands of Barrett's mucosa that are easily overlooked with HD-WLE. Recent studies suggest that detailed inspection with NBI of the post-RFA neo-squamous epithelium is probably more useful than obtaining random biopsies<sup>55</sup>.

## FUTURE PERSPECTIVES

Detection of early neoplasia can be improved by optimizing the endoscopists' recognition of "the face of Barrett's neoplasia" but there are few tools to aid this<sup>7,8</sup>. The international workgroup for the classification of oesophagitis<sup>56,57</sup> is working on a training program for "Barrett's oesophagus related neoplasia" (BORN-project) that will be dispersed to the gastroenterology community.

In the near future, molecular markers may enable us to predict which patients will develop neoplasia well before morphological changes can be observed histologically. Advanced imaging techniques may aid this risk stratification by detecting areas containing relevant biomarkers or to provide biophotonic information on an underlying field defect<sup>58,59</sup>.

A recently emerged concept is the administration of fluorescently labelled peptides or lectins that bind to specific molecular targets for malignant progression<sup>60</sup>. Lectins have a low toxicity, high stability, are inexpensive to produce and have a good sensitivity for detecting early neoplasia in combination with fluorescence endoscopy<sup>61</sup>.

Another promising technique is optical frequency domain imaging (OFDI). OFDI enables high-speed and high-resolution image acquisition of the whole Barrett's segment<sup>62,63</sup>. Preliminary studies suggest that specific OFDI characteristics correlate with neoplasia<sup>63</sup>. Moreover, an integrated laser may allow marking of distinct areas based on OFDI features<sup>64</sup>. Theoretically, this may enable automated detection and marking, and even delineation and treatment of early Barrett's neoplasia.

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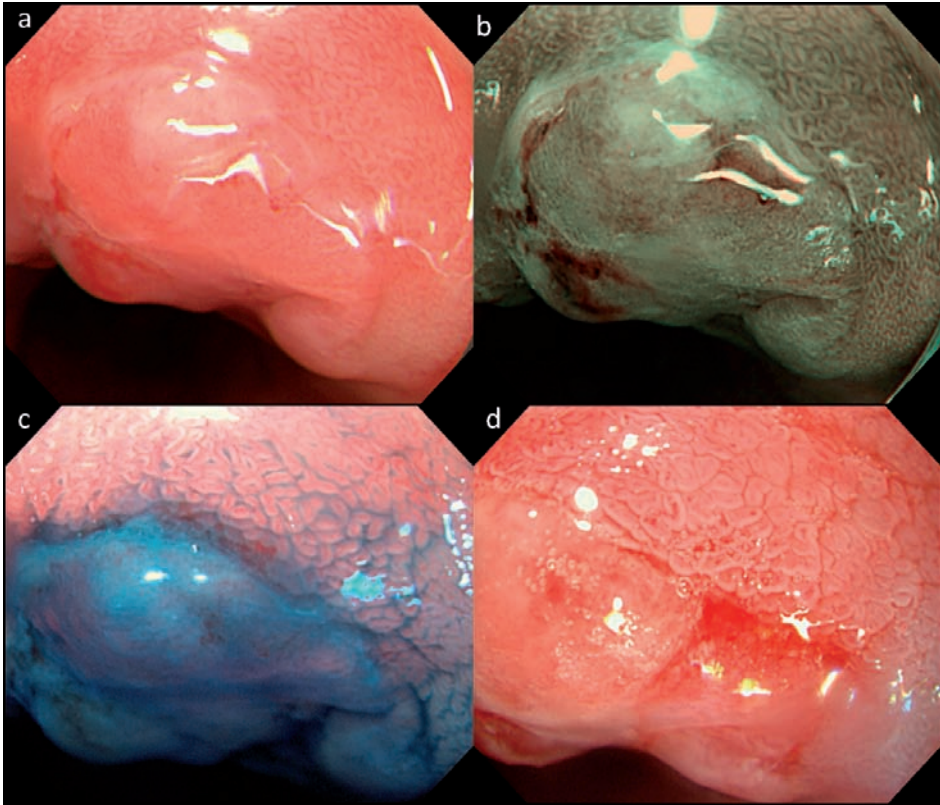


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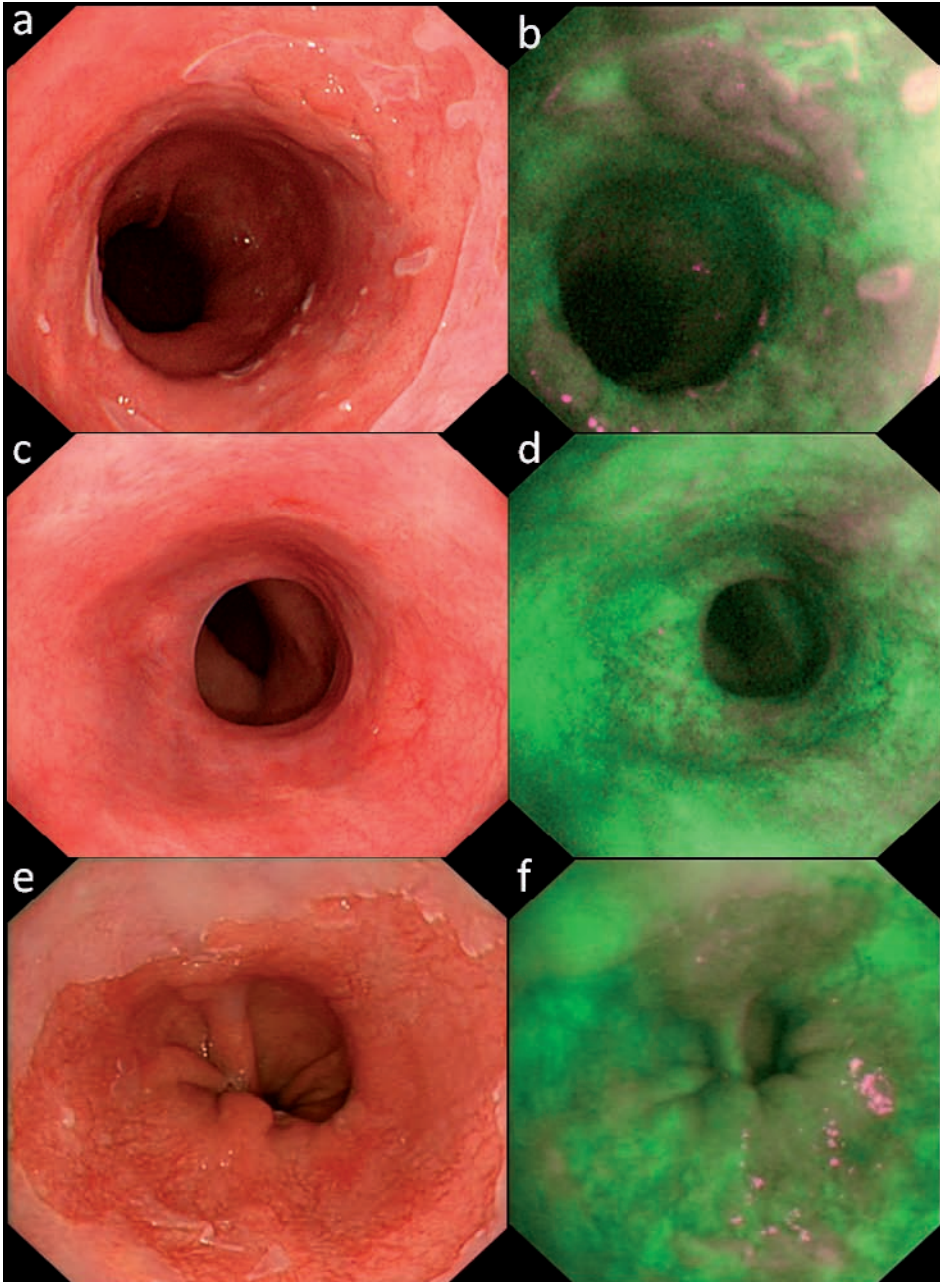
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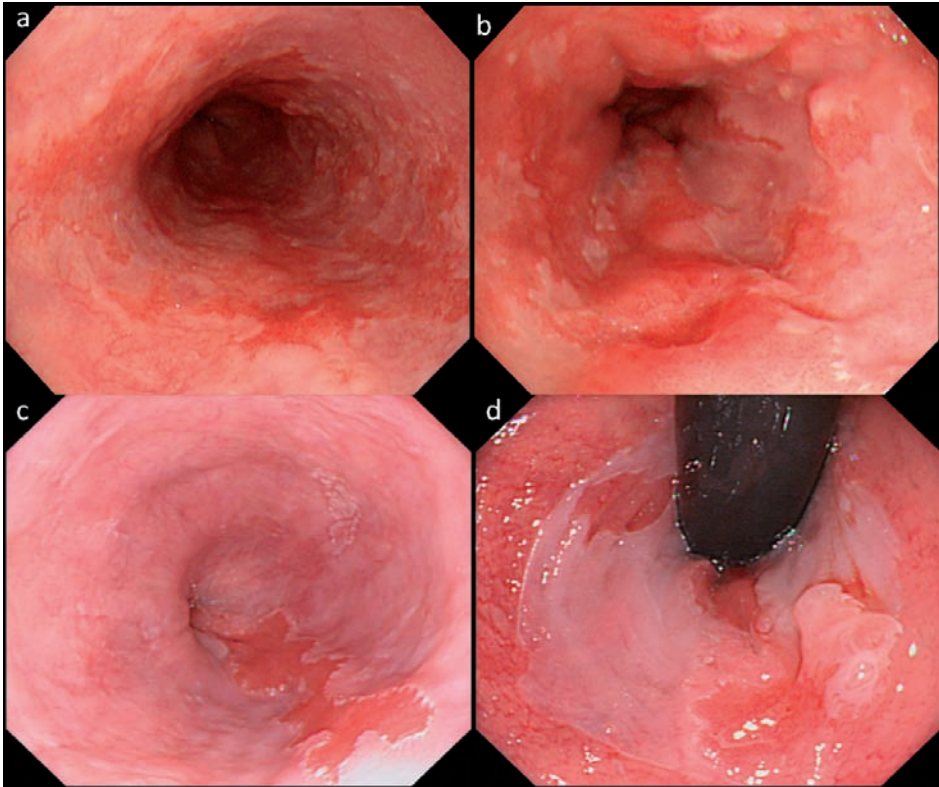
## SUPPLEMENTARY FIGURES



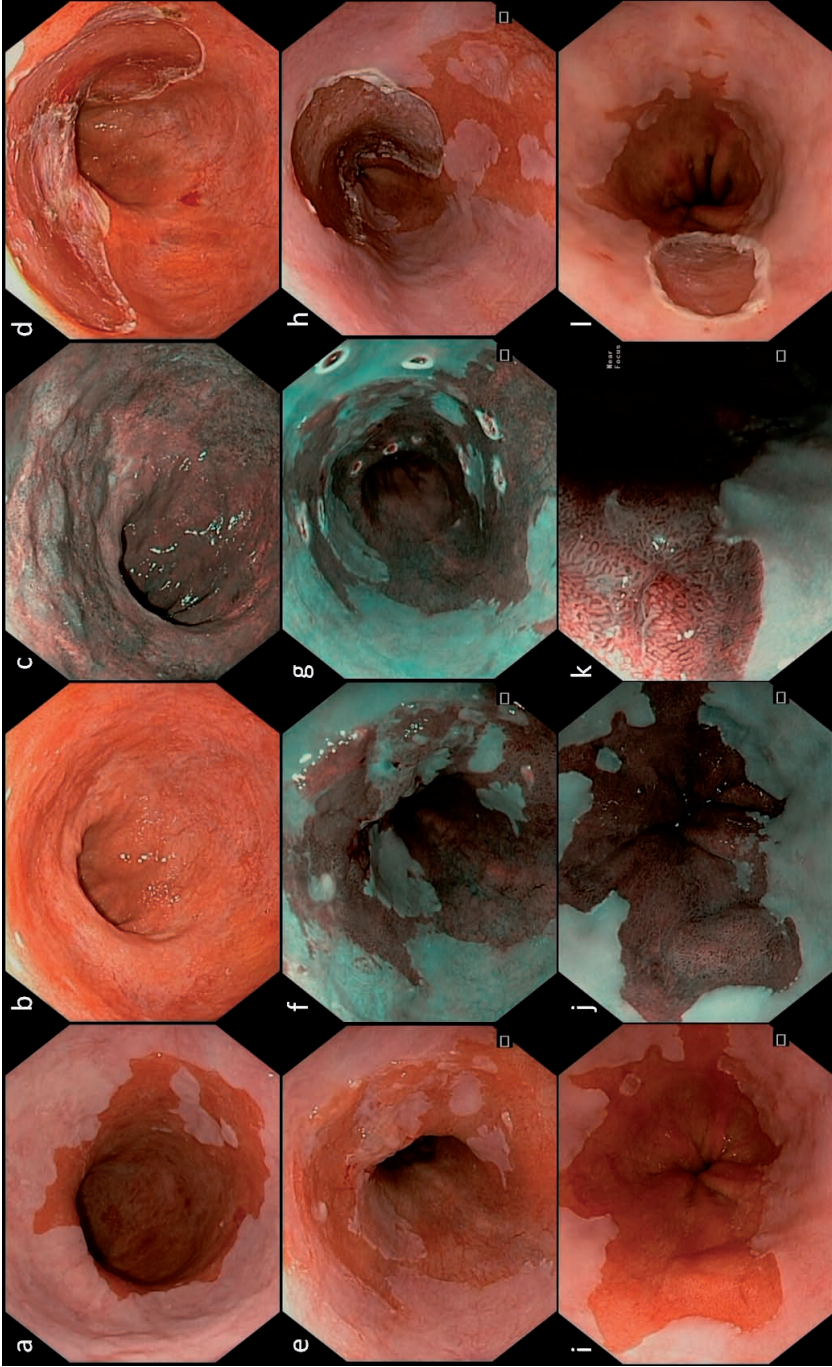
**Figure S1.** Image of an early neoplastic lesion in the distal esophagus, a) with high resolution white light endoscopy, b) with narrow band imaging, c) after indigo carmine spraying, d) after acetic acid spraying.



**Figure S2.** Three examples of a neoplastic lesions in Barrett's esophagus, with white light endoscopy (WLE; a,c,e) and autofluorescence imaging (AFI; b,d,f). In c) and d), the lesion is hard to detect with WLE, but can be clearly appreciated with AFI. In e) and f) the lesion is located at the gastric folds, which makes the AFI interpretation difficult, resulting in high false positive rates for AFI.



**Figure S3.** Images of an early neoplastic lesion in Barrett's esophagus, that is difficult to appreciate when the esophagus is fully inflated. By alternating inflation and suction, the lesion becomes more apparent (a,b). By looking in retroflex, lesions at the distal esophagus may be detected that would have been missed when only antegrade inspection would have been performed (c,d).



**Figure 54.** Narrow band imaging (NBI) facilitates not only the evaluation of the mucosal and vascular patterns, but also enhances visualization of the mucosal relief, a distinct and recognizable feature of NBI (c,f,j,k). While the mucosal and vascular patterns may be regular, the relief can be used to assess the extension of the lesion to direct the delineation (g) prior to endoscopic resection (d,h,l).