Endoscopic work-up of early Barrett’s neoplasia

Introduction

In recent years, endoscopic therapy of early Barrett’s esophagus neoplasia has become a safe and effective alternative to esophagectomy [1–4]. Only patients with high-grade intraepithelial neoplasia (HGIN) or mucosal cancer are eligible for curative endoscopic treatment. Lesions that invade the submucosa are associated with a significant risk of lymph node metastases and are therefore preferably to be treated surgically.

There are two main types of endoscopic therapy: endoscopic resection and endoscopic ablation. An important difference between these two modalities is that endoscopic resection permits histopathological evaluation of the resection specimen, whereas this safeguard is missing with endoscopic ablation therapy. A practical approach is to resect the areas with endoscopically visible lesions by endoscopic resection followed by ablation of residual Barrett’s esophagus [5–8]. This assumes that if the histopathological evaluation of the most involved areas is favorable, the chances that the residual Barrett’s esophagus harbors more advanced neoplasia elsewhere are small and thus additional ablation therapy without histological correlation is justified. It is, therefore, crucial that the most involved area in the Barrett’s esophagus is indeed identified and resected rather than overlooked and ablated, since this may lead to undertreatment of submucosal lesions.

In this review, we will discuss the endoscopic work-up for diagnosis and staging of early neoplasia in Barrett’s esophagus (i.e., HGIN or mucosal cancer), including the role of advanced imaging techniques and the importance of histopathological evaluation by endoscopic resection.

Diagnosis

Endoscopic detection of early neoplasia in Barrett’s esophagus

The goal of endoscopic surveillance of patients with Barrett’s esophagus is the detection of early neoplastic lesions. To ensure the detection of early neoplastic lesions there are three rules that should be followed. These rules relate to the endoscopic equipment used, the “detecting eye” of the endoscopist, and a systematic, meticulous approach.

Rule 1: Use the best endoscope you have available

Technological improvements have made high-resolution endoscopes available with charge-coupled devices (CCD) containing up to one million pixels, compared with the 300 000 pixels of standard endoscopes [9]. Studies suggest that high-resolution endoscopy may have higher sensitivity for the detection of early neoplasia in Barrett’s esophagus than do standard video endoscopy systems [10,11]. Since early Barrett’s esophagus neoplasia often presents as flat lesions with only subtle mucosal abnormalities, most experts agree that high-resolution endoscopy is the preferred method for the endoscopic evaluation of Barrett’s esophagus.

Rule 2: You do not detect what you see, you detect what you recognize

Up to 80% of patients referred for work-up of high-grade dysplasia or early Barrett’s esophagus cancer without visible abnormalities will have at least one visible abnormality detected in their Barrett’s esophagus upon endoscopic inspection by expert endoscopists [10,12]. Although early Barrett’s esophagus neoplasia generally presents as subtle flat lesions that may be difficult to detect, most state-of-the-art endoscopes do show these abnormalities to the experienced eye. Early
neoplasia in Barrett’s esophagus is, however, relatively rare and most endoscopists do not encounter these lesions on a regular basis. The lack of familiarity of most endoscopists with the appearance of early gastrointestinal neoplasia thus becomes the limiting factor in the detection: “You do not detect what you see, you detect what you recognize.” Knowledge of the endoscopic appearance of early Barrett’s neoplasia is thus essential for its diagnosis. Fig. 1 shows a variety of subtle early neoplastic Barrett’s esophagus lesions that may help endoscopists to recognize these lesions better in future.

Rule 3: Perform a systematic endoscopic inspection
The detection of gross mucosal abnormalities such as elevations, ulcerations, and nodularities in overview is fairly easy. For the detection of subtle abnormalities, a more careful and thorough inspection following a systematic approach is imperative. After intubation, the esophagus should be carefully cleaned out to remove any mucus or saliva. If excessive or viscous mucus is present, spraying with acetylcysteine (1 %) may be helpful, but generally simple water flushes will do the job. Then, it is important to remove all gastric secretions to prevent reflux into the esophagus that may interfere with inspection. Subsequently, the endoscope should be gradually withdrawn to examine the inflated Barrett’s segment in overview for any mucosal irregularities and to describe the extent of the Barrett’s esophagus according to the validated Prague C&M classification [13]. After initial inspection, the inflated esophagus should be gradually deflated to reveal any irregularities that may have been stretched out during inflation (Fig. 2). Special attention should be paid to the area between 12 and 6 o’clock in the endoscopic view, since the majority of neoplastic lesions are located there [14]. Finally, it is important to inspect the transition of the Barrett’s esophagus into the hiatal hernia in the retroflexed position, since abnormalities in this area are easily overlooked in the antegrade view (Fig. 3).

Following the inspection and classification of all visible lesions, biopsies should be obtained from each visible abnormality followed by random four-quadrant biopsies, always starting distally and working upwards, so that the view is not obscured by bleeding. We follow the rule “look longer, biopsy less,” since in our experience targeted biopsies performed after a thorough inspection contribute 80%–90% of the diagnosis of dysplasia [10,12,15]. At the present time, in the absence of visible abnormalities, random biopsies should still be performed.

Macroscopic appearance of early neoplasia in Barrett’s esophagus
Macroscopically visible lesions in Barrett's esophagus are classified according to the Paris classification, adopted from the Japanese Gastric Classification of Gastric Carcinoma [16,17]. In this classification, superficial lesions are classified as 0 and divided into three categories (Fig. 4): 0-I for protruding or polypoid lesions, 0-II for nonprotruding or nonexcavated lesions [i.e., flat lesions, smaller than the height of the closed cups of a biopsy forceps (2.5 mm)], and 0-III for excavated or ulcerated lesions. Category 0-I can be subdivided into pedunculated (0-Ip) and sessile lesions (0-Is). Type 0-II has three subtypes: slightly elevated (0-IIa), completely flat (0-IIb), and slightly depressed (0-IIc). The three subtypes can be present in all combinations, e.g., 0-IIa + IIc or 0-IIa + IIb, with the first mentioned being the more predominant type. Most of the early neoplastic lesions in Barrett’s esophagus are of the superficial type (0-II) [14,18].

The clinical relevance the above classification is the correlation of the macroscopic classification with the infiltration depth, which predicts the risk of submucosal invasion and thus the risk of lymph node involvement. Type 0-I and 0-IIc lesions carry a greater risk of submucosal invasion than do type 0-IIa, type 0-IIb, or combined types [14,18]. Type 0-II-III lesions always have deep submucosal invasion and are accompanied by a dense fibrous reaction, and are therefore not suitable for endoscopic treatment.

Advanced endoscopic imaging modalities for detection of early neoplasia in Barrett’s esophagus
In recent years several new imaging technologies have been introduced to improve the detection of early neoplasia in Barrett’s esophagus [19]. An elaborate discussion of all techniques is beyond the scope of this review; we will briefly discuss the most promising technologies.

High-definition endoscopy
Next to high-resolution endoscopes, the introduction of high-definition television (HDTV) that can generate up to 1080 scanning lines — compared with 480–576 scanning lines by standard analog systems (PAL or NTSC) — is a further improvement in daily endoscopy practice, enabling increased image quality or projection on a larger screen while retaining image quality. Arguably, the most important improvement in endoscopic imaging today is the significant increase in image resolution through the development of high-resolution and high-definition endoscopes.

Chromoendoscopy
In the past decade high-resolution endoscopy has been combined with staining agents such as methylene blue, indigo carmine, and acetic acid (i.e., chromoendoscopy). However, for none of the chromoendoscopy techniques has a distinctly improved detection rate for early neoplasia been unequivocally demonstrated in comparison to high-resolution endoscopy [19]. These disappointing results partly reflect the fact that the use of these agents and the subsequent interpretation can be labor-intensive and operator-dependent, making chromoendoscopy a technique for experienced endoscopists rather than for routine use.

Narrow-band imaging
Narrow-band imaging (NBI) (Olympus) is a technique that utilizes short wavelength light (essentially, blue light), which enhances the superficial imaging of the mucosa without the use of staining agents. NBI can be activated by the push of a button on the endoscope handle and may therefore not be subject to some of the practical disadvantages of chromoendoscopy. Early studies investigating NBI showed promising results in terms of distinguishing NBI images of nondysplastic Barrett’s esophagus from those containing early neoplasia [20, 21]. A recent publication with a tandem study design suggested that NBI improves detection of all dysplasia by approximately 10 %, but the control arm used standard-resolution endoscopy [15]. Results of ongoing multicenter randomized trials are awaited and may help define the utility of NBI for neoplasia in Barrett’s esophagus. Recently, other endoscopy manufacturers have introduced electronic enhancement techniques (FICE, Fujinon; I-scan, Pentax) which on the basis of postprocessing techniques may also enable improved contrast enhancement without the use of dyes [22].
Fig. 1 Collection of subtle early neoplastic Barrett’s esophagus lesions. Early neoplastic lesions are encircled. Reproduced with permission from www.endosurgery.eu.
Autofluorescence imaging

Autofluorescence imaging (AFI) is based on the principle that certain endogenous substances emit fluorescence when they are excited with short wavelengths of light. It has been demonstrated that nondysplastic tissue has a different fluorescence spectrum from that of early Barrett’s esophagus neoplasia. A video endoscopy system that enables real-time full endoscopic view AFI in combination with high-resolution endoscopy appears to improve the detection of early neoplasia at the expense of a relatively high false positive rate [23, 24]. Currently a trimodal endoscopy system is commercially available that incorporates high-resolution endoscopy, AFI, and NBI in a single system. In a recent international multicenter feasibility study with this system, AFI increased the sensitivity for detecting early neoplasia with high-resolution endoscopy from 53% to 90%, and subsequent inspection with NBI of areas that looked suspicious on AFI reduced the false positive rate from 81% to 26% [12]. The true additional value of this trimodal imaging system needs to be established in currently ongoing randomized crossover studies.

Confocal microscopy

A recent exciting development in endoscopic imaging is the possibility of in vivo histology using confocal laser microscopy. Kieslich et al. were the first to demonstrate that in vivo histological assessment of Barrett’s esophagus is feasible with high accuracy and high interobserver agreement. They used a confocal endomicroscopy system integrated into a conventional endoscope [25]. Initial results are promising but await confirmation from multicenter studies. In addition, clinical studies are required to elucidate the clinical relevance and cost-effectiveness of in vivo pathology as a decision-making tool during endoscopy.

Histopathological diagnosis of early neoplasia in Barrett’s esophagus

Histopathological diagnosis of biopsies obtained during Barrett’s esophagus surveillance determines the individual management strategy. However, histopathological evaluation is a subjective process in which multiple morphological characteristics have to be interpreted by the pathologist. This subjective interpretation is reflected by poor interobserver agreement in relation to the histopathology of Barrett’s esophagus, especially for discriminating indefinite for dysplasia from low-grade intraepithelial neoplasia (LGIN) and differentiating HGIN from well-differen-
of differentiation grade and the involvement of lymphatic and blood vessels – all prognostic factors for successful outcomes after endoscopic treatment. Endoscopic resection is thus the most reliable way to ensure an optimal histological diagnosis of endoscopically visible abnormalities in Barrett’s esophagus.

### Staging

#### Depth of infiltration

The most important risk factor predicting lymph node metastasis in early neoplasia of Barrett’s esophagus is the depth of infiltration of the lesion. Mucosal lesions are subdivided into three categories: T1m1, which is limited to the epithelial layer; T1m2, with infiltration into the lamina propria; T1m3, with infiltration into the muscularis mucosae. The submucosa is divided into three equal parts, giving: T1sm1, infiltration into the superficial one-third; T1sm2, infiltration into the intermediate one-third; T1sm3, infiltration into the deepest third. Assessment of infiltration depth is of importance for determining the treatment strategy for the individual patient. Patients with mucosal carcinoma (T1m1–3) are considered to have a negligible risk of lymph node metastasis and are therefore eligible for endoscopic treatment [32,33]. Patients with deep submucosal invasion are generally considered to be at risk of lymphatic dissemination and should therefore be considered for surgical treatment. Recent studies suggest that T1sm1 tumors show a much lower risk (0–8%) of lymph node involvement than T1sm2–3 tumors (26%–67%) [32,33]. Given the risks of esophagectomy and relatively poor outcome when there are positive lymph nodes, this suggests that endoscopic treatment may also be a valid treatment option for patients with superficial submucosal invasion in their endoscopic resection specimens.

### Endoscopic ultrasound in the staging of early neoplasia in Barrett’s esophagus

Endoscopic ultrasonography (EUS) is the most important and accurate technique for T and N staging of advanced esophageal cancer and is superior to computed tomography scanning (CT) [34,35]. The overall accuracy of standard EUS in the assessment of the infiltration depth of advanced cancers is approximately 75%, and is distinctly better when performed by experienced endoscopists [35–37]. For staging of early Barrett’s neoplasia, however, other rules apply.

#### Rule 1: Endoscopic inspection for T-staging in early Barrett’s esophagus neoplasia

The resolution of standard EUS is not sufficient to distinguish mucosal lesions from deeper invading tumors [35]. Although high-frequency EUS miniprobe improves the accuracy of T-staging in superficial squamous cell carcinomas, these results cannot be extrapolated to early Barrett’s esophagus neoplasia [38,39]. To differentiate mucosal lesions from lesions infiltrating into the submucosa is much more difficult in Barrett’s esophagus than in the squamous esophagus: the tissue architecture with crypts and villi is more heterogeneous than the layered architecture of squamous epithelium, and Barrett’s esophagus neoplasia is associated with significant inflammation and the presence of a double muscularis mucosae. Furthermore, most Barrett’s lesions are situated in the distal esophagus close to the cardia, where EUS interpretation is known to be difficult [40,41]. May et al. have clearly demonstrated that EUS has no additional value in
determining the T-stage of early Barrett’s esophagus neoplasia after endoscopic assessment of the macroscopic appearance by an expert endoscopist [40].

Rule 2: Endoscopic resection for N-staging in early neoplasia in Barrett’s esophagus
The diagnostic accuracy of EUS for N-staging in esophageal cancer ranges between 68% and 86% [35]. The addition of EUS-guided fine-needle aspiration (EUS-FNA) of suspect lymph nodes has been shown to increase the specificity of EUS N-staging and can increase the accuracy of EUS N-staging up to 90% in advanced esophageal carcinomas [42]. For the work-up and staging of patients with early neoplasia, N-staging is of crucial importance, since positive lymph nodes will exclude patients from endoscopic treatment. On the other hand, in appropriately selected patients the risk of local lymph node metastasis is so small that EUS may do more harm than good. Preliminary results of 62 patients with HGIN undergoing EUS prior to ablation therapy showed that the frequency of EUS findings altering management (1.6%) was balanced by the risk of a major complication [43]. Ultimately, the best method for assessment of the risk of lymph node involvement may be not EUS but a diagnostic endoscopic resection with assessment of the infiltration depth of the lesion.

Diagnostic endoscopic resection is vital for staging early neoplasia in Barrett’s esophagus
Endoscopic resection of early neoplasia in Barrett’s esophagus allows an objective, histological T-staging of the resected lesion. In addition, other prognostic factors such as differentiation grade and lymphatic and vascular involvement can be evaluated [18]. Endoscopic resection is thus the final step in the diagnostic work-up of early Barrett’s esophagus neoplasia that permits optimal triage of patients: if the endoscopic resection specimen shows poorly differentiated carcinoma, lymphatic involvement, involved vertical margins, or deep submucosal invasion, the patient is referred for surgical resection, whereas patients with mucosal cancers without these features are managed endoscopically with the diagnostic endoscopic resection also serving as the first step in their endoscopic treatment.

Computed tomography/positron emission tomography for staging of early neoplasia in Barrett’s esophagus
In the work-up and staging of esophageal adenocarcinoma, CT is mainly performed to detect distant metastases. The risk of distant metastasis is virtually absent in HGIN and mucosal carcinoma [1,32,33]. Pech et al. showed in 100 consecutive patients with suspected early Barrett’s esophagus neoplasia that CT had no influence on the TNM classification in any of these patients, and suggested that it may be possible to dispense with this staging method for HGIN and mucosal carcinoma [34]. The risk of distant metastasis increases with submucosal invasion, so therefore CT scanning of the abdomen and thorax, combined with an ultrasound study of the neck, should be performed for M-staging in patients with submucosal involvement detected at diagnostic endoscopic resection or EUS [32,44].

A systematic review of the staging performance of positron emission tomography (PET) showed only moderate accuracy for locoregional staging and reasonable accuracy for distant metastasis in esophageal cancer [45]. The role of PET in esophageal cancer staging is probably more important for advanced cancers and for evaluating the response to neoadjuvant treatment [46]. Therefore, PET does not appear to have a role in staging early Barrett’s esophagus neoplasia.

Summary
The importance of endoscopic work-up and staging of patients with suspected early Barrett’s esophagus neoplasia is to identify patients who are eligible for endoscopic therapy and to select those patients who require surgical management as curative treatment. The endoscopic work-up should be performed with high-resolution endoscopy by an endoscopist experienced in the recognition of early Barrett’s esophagus neoplasia, utilizing a systematic approach. Novel imaging modalities such as NBI, AFI, and confocal endomicroscopy may aid in the identification and characterization of early lesions, but currently their value over high-resolution/high-definition endoscopy in expert hands appears to be limited. The endoscopic work-up should focus on identifying the most suspicious areas in the Barrett’s segment which subsequently need to be removed by a diagnostic endoscopic resection. Endoscopic resection allows for optimal diagnosis and staging, is potentially curative, and guides the selection of patients for endoscopic therapy. Patients who are eligible for endoscopic therapy have HGIN or well or moderately differentiated cancers limited to the mucosa without lymphovascular invasion. EUS has a limited role in the T- and N-staging of early neoplasia in Barrett’s esophagus. CT and PET scanning have minimal value in locoregional staging of early neoplasia in Barrett’s esophagus.

Competing interests: None

Acknowledgment
The work of Wouter Curvers is supported by an unrestricted research grant from AstraZeneca BV, Netherlands.

References
8 Pouw RE, Sondermeijer C, ten Kate FJ et al. Stepwise circumferential and focal radiofrequency energy ablation of Barrett’s esophagus with early neoplasia: first European multi-centre trial. Gastrointest Endosc 2008; 67: AB137


