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Review

Advanced endoscopic imaging in Barrett's oesophagus

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ABSTRACT

Barrett's oesophagus is a metaplastic condition with an inherent risk of progression to adenocarcinoma. It is essential to identify dysplastic changes within Barrett's oesophagus in order to individualise surveillance strategies and establish which patients warrant endoscopic treatment. There is a trend towards endoscopic resection of focal high-grade dysplasia followed by whole segment ablation. However, endoscopic identification of dysplastic lesions is unreliable and subjective making targeted therapy extremely difficult. In addition, the current practice of taking random quadrantic biopsies may miss dysplastic disease and intramucosal adenocarcinoma. Several advanced endoscopic imaging techniques have been described and tested in clinical trials in an effort to improve the detection of early lesions, although none are routinely used in clinical practice. In this article we will review these techniques and discuss their potential for clinical implementation. We will also discuss the potential benefits of multimodal imaging and highlight several newer techniques which have shown early promise for *in vivo* diagnosis.

1. Introduction

The incidence of oesophageal adenocarcinoma in the Western World has increased by 500% over the past 40 years.[1,2] Significantly, survival rates have failed to improve during this period and outcomes for symptomatic cancers remain bleak with 5 year survival figures of just 8%–15%.[3,4]

Early detection of premalignant high-grade dysplasia (HGD) is essential to improve patient outcomes and prevent progression to invasive malignancy.[3] For this reason patients with Barrett's oesophagus are kept under endoscopic surveillance so that endoscopic therapy can be instigated early in those with progressive disease.[5]

There has been tremendous progress in the endoscopic treatment of Barrett's neoplasia over the past decade. Endoscopic resection of focal neoplastic lesions enables accurate histological classification of dysplasia, improves detection of synchronous intramucosal cancers (IMC) and can achieve complete eradication of dysplastic lesions in 82.5%–95% of patients with high-grade dysplasia (HGD).[6–9]

Increasingly clinicians are favouring a policy of endoscopic resection of visible early neoplastic lesions (IMC (T1a adenocarcinomas) and HGD) followed by whole segment ablation to destroy the neoplastic field change. This approach has been shown to reduce recurrence rates compared to single modality therapy.[10] However, these essential diagnostic and therapeutic benefits of endoscopic resection are only possible where lesions are detectable endoscopically.

Endoscopic detection of Barrett's neoplasia is notoriously difficult using conventional white light endoscopy. A variety of diagnostic endoscopic techniques have been developed in an attempt to improve the accuracy of neoplasia recognition in Barrett's oesophagus and enable targeted biopsy or endoscopic resection (ER) of neoplastic lesions. This article reviews the evidence-base that supports the better established diagnostic techniques and discusses their prospective role in clinical practice, including the potential for multimodality imaging. With an eye further to the future several alternative novel tools in early stages of clinical development are also reviewed.

2. Endoscopic approach to Barrett's oesophagus

A thorough and systematic inspection of the mucosa is essential. Lavage should be performed using water or 1% acetylcysteine to remove blood, saliva and refluxate from the oesophagus and adequate insufflation should ensure that any mucosal abnormalities can be clearly inspected. Particular care must be taken to identify the oesophagogastric junction in patients with a hiatus hernia to avoid missing the distal extent of a metaplastic segment in these patients. Endoscopists should also consider that the majority of early neoplastic lesions arise between 6 o'clock and 12 o'clock in the endoscopic view.[11]

The endoscopic appearance of the Barrett's segment should be recorded using the Prague C&M criteria as defined by the

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International Working Group on Barrett's oesophagus.[12] This records the lengths of the circumferential (C) and maximum extent (*M*) of the Barrett's segment. It is also essential that clinicians record precisely the site of each biopsy as this may be important for future endoscopic therapy and is crucial for correct histological classification. In addition, where possible lesions should be characterised according to the Paris classification (Table 1).

3. Endoscopic recognition of early neoplasia: The problem

Endoscopic recognition of dysplasia and IMC within Barrett's oesophagus is subjective and difficult even for skilled endoscopists. Progression to dysplasia or IMC in Barrett's oesophagus is rare and the lack of familiarity of most endoscopists with the typical appearances of early neoplasia is a significant limiting factor in its detection.[4,13–15] Guidelines therefore advise that multiple biopsies are taken whenever Barrett's oesophagus is identified at endoscopy.[5] Most endoscopists take four quadrant biopsies every 2 cm of Barrett's oesophagus, or fewer.

This policy samples less than 5% of the mucosa and may miss up to 57% of early neoplastic lesions.[16] In addition, patients with HGD are known to have a 30–40% chance of occult adenocarcinoma which may be missed by sampling error in up to 50% of patients when using a standard biopsy regimen. Several studies have compared the results of endoscopic biopsy assessment to surgical pathology following oesophagectomy for the detection of adenocarcinoma in dysplastic Barrett's segments. Falk et al demonstrated that over a third of cancers (38%) were missed when quadrantic biopsies every 2 cm were taken from patients with HGD. Jumbo biopsy forceps made little difference to detection rates (67% versus 62%).[17] Cameron and Carpenter found 2/19 (10.5%) unsuspected adenocarcinomas following quadrantic 2 cm biopsies in patients who subsequently underwent oesophagectomy.[18] Similarly, Reid et al showed that this biopsy regimen would have missed 13/26 (50%) of cancers in their cohort. They also demonstrated that targeted biopsies of endoscopically visible suspicious lesions were only able to establish the correct diagnosis in 15 out of 45 (33%) patients who were subsequently proven to have cancer.[19]

In addition to the sampling error of standard biopsy regimens and the low sensitivity of targeted biopsies when using standard white light endoscopy, diagnostic difficulties are further compounded by limited inter-observer agreement between pathologists ($k = 0.2–0.6$), especially for distinguishing HGD from LGD.[20,21]

There is a clear clinical need for advanced imaging tools that could improve endoscopic detection of HGD and IMC and enable targeted treatment.

4. Wide-field detection techniques

4.1. High resolution endoscopy

Modern high resolution endoscopes which generate up to one million pixel images (compared to the 300,000 pixel images of traditional scopes) have been shown to have a higher sensitivity than standard white light endoscopy for the detection of early Barrett's neoplasia provided they are used by expert endoscopists.[22,23] So not to negate their effect these endoscopes should be used in conjunction with a high definition television to further enhance the projected image quality and prevent loss of resolution when larger images are required.

Even in the hands of experts, Kara et al showed that targeted biopsy using HRE was only capable of detecting 79% of dysplasia, and differentiation from LGD for the purposes of targeted treatment was difficult.[22] HRE should replace standard WLE where possible. Although to significantly improve endoscopic diagnosis of dysplasia, HRE may be best utilised in conjunction with additional endoscopic imaging technology.

Table 1
Paris classification of superficial (0) lesions. Most dysplastic Barrett's lesions are type 0-II.

0	Superficial lesions
0-I	Protruding / polypoid lesions
0-Ip	Pedunculated
0-Is	Sessile lesions
0-II	Non-protruding / non-excavated lesions
0-IIa	Slightly elevated
0-IIb	Completely flat
0-IIc	Slightly depressed
0-III	Excavated / ulcerated lesions

4.2. Chromoendoscopy

Chromoendoscopy involves exogenous administration of stains to the oesophageal mucosa in order to improve tissue characterisation during endoscopy. Absorptive stains (such as methylene blue) cross-epithelial membranes selectively, whereas contrast stains (such as indigo carmine) permeate into mucosal crevices highlighting surface topography and mucosal irregularities.[24]

Studies utilising chromoendoscopy in Barrett's oesophagus have had mixed results and have highlighted problems such as difficulties in uniformly coating the oesophageal mucosa with the stain, and excessive times necessary for stain spraying.[20,25,26] The technique has not been shown to consistently out-perform HRE in the detection of early neoplastic lesions.[27]

Chromoendoscopy is relatively widely available and does not require any particular equipment except for a spray catheter which is easy to use and cheap to purchase. However, chromoendoscopy is often both labour-intensive and operator-dependent and is therefore unlikely to become widely utilised.

4.3. Narrow band imaging

Narrow band imaging (NBI) illuminates the mucosa with blue and green light in order to enhance the resolution of the mucosal surface by relying on the principal that longer wavelengths of light penetrate deeper into tissue than shorter wavelengths. Narrow band blue light displays the superficial capillary networks, while green light displays the sub-epithelial vessels, and a combination of the two images produces an extremely high definition image of the mucosal surface allowing visualisation of subtle mucosal irregularities and alterations in vascular patterns consistent with dysplasia and IMC.[28]

NBI is a widely available technique which avoids the need for staining or intravenous contrast agents. It has shown promise in detection of dysplastic lesions when in the hands of experienced users.[29,30] A recent review of NBI with magnification demonstrated high accuracy for the diagnosis of HGD in Barrett's oesophagus based on recognition of irregular mucosal pit patterns and/or irregular microvascularisation.[31] However, NBI is time-consuming and results have been mixed due to high levels of inter-observer variability.[27,29] Overall, data on the accuracy of NBI in Barrett's oesophagus are inconclusive and results of multicentre randomised controlled trials are awaited.

4.4. Autofluorescence imaging

AFI detects fluorescence radiation following excitation of tissue using light of short wavelengths. Variation in the type and concentration of fluorophores enables differentiation between normal, metaplastic and neoplastic tissue. Several studies have

suggested that AFI is sensitive for detection of HGD in Barrett's oesophagus although the technique appears limited by low specificity.[32–34] Curvers et al demonstrated an increased detection rate of HGD/IMC using AFI compared to WLE alone (53% Vs 90%) but this came at the expense of a high false positive rate of 81%.[35]

Further trials are necessary to demonstrate improvements in specificity through combination with other imaging techniques such as confocal microscopy.

4.5. Optical coherence tomography

OCT is similar to ultrasound but can produce higher quality images as it relies on backscattering of near-infrared light (as opposed to radio waves) to generate cross-section images of epithelial and sub-epithelial tissues.

OCT is performed using probes passed through the instrument channel of endoscopes. It does not require the use of exogenous contrast and, unlike with ultrasonography, tissue contact is not required.

Several studies have assessed the role of OCT in the detection of dysplasia. In a study of 55 patients with Barrett's oesophagus, OCT was shown to delineate between HGD and adenocarcinoma with a sensitivity of 83% and a specificity of 75%.[36] Another study of 33 patients demonstrated a diagnostic accuracy of 78% for the identification of dysplastic Barrett's oesophagus, however considerable user discrepancy (56%–98%) was demonstrated.[37]

Further clinical evaluation is required to assess the diagnostic performance of OCT in the oesophagus. In the future the technique may have a greater role in the staging of early oesophageal tumours rather than in the detection of dysplasia, however the considerable time required to acquire and interpret the images may become a significant limiting factor.

4.6. Labelling of biomarkers

Visually tagged probe molecules have been engineered which selectively bind to neoplastic cells.[38,39] Lu et al identified a cell-surface peptide specific to adenocarcinoma which they labelled using a fluorescein-tagged antibody delivered topically. The oesophagus was then washed to remove any unbound antibody and a fluorescence endoscope was used to visualise neoplastic disease.[40]

Similarly, Fitzgerald et al recently demonstrated that alterations in cell-surface glycans during progression to adenocarcinoma could be identified through changes in their lectin binding properties.[41] Selective binding of a candidate lectin (wheat germ agglutinin) sprayed into an ex vivo oesophagus enabled visualization of high-grade dysplastic lesions, which were not detectable by conventional endoscopy (Fig. 1B).

These highly promising molecular techniques require further work in order to identify novel molecular targets to improve sensitivity and specificity before clinical implementation can be considered.

5. Point measurement techniques

5.1. Confocal microscopy

CM magnifies the mucosa 1000-fold enabling real-time visualisation of cellular structures. CM has shown considerable potential in Barrett's oesophagus with reported accuracy of up to 97.4% for the detection of dysplasia.[42] However, due to considerable inter-user variation these results have not been universally matched.[43] The technique has also been criticised for being both time-consuming and expensive as well as requiring considerable training to interpret and relying on the use of exogenous contrast to demonstrate the irregular neovascularisation that is characteristic of neoplastic tissue. Further trials are required before this technique can be recommended for widespread use.

5.2. Elastic scattering spectroscopy (ESS)

ESS uses a fibre-optic probe passed through the instrument port of an endoscope to generate morphological information about the nature of the Barrett's segment. White-light is elastically scattered from the mucosa and submucosa with varying signal depending on the size and shape of the cell nuclei and the degree of cellular crowding.

Spectral signal can be acquired in short acquisition times which approach 'real-time' imaging.

Dysplastic and malignant tissues have been shown to have a characteristic ESS signature however, due to signal interference from deeper structures the accuracy of ESS appears limited to around 85%.[44] Lovat et al measured spectra from 181 tissue sites from 81 patients which were correlated with consensus histopathology. ESS identified HGD with a sensitivity of 92% and a specificity of 60% and was able to differentiate these sites from inflammation with a sensivity and specificity of 79%.[45] This current level of accuracy is probably not sufficient to support clinical uptake of ESS unless it can be improved through refinement of the technology or the use of a concomitant imaging modality.

5.3. Raman spectroscopy

Raman spectroscopy relies on the principle of inelastic scattering in order to generate a biochemical profile of the oesophageal mucosa (Fig. 1A). Neoplastic lesions have been shown to display subtle changes in molecular composition which can be detected and used to objectively classify the tissue.[5,10,46–49] Although some way off wider clinical implementation, several groups have recently conducted *in vivo* trials attempting to utilise this technology endoscopically.[48,50] Early results appear encouraging with Huang et al reporting overall accuracy of 96% for detecting oesophageal adenocarcinoma.[48] However, future work is necessary to assess the diagnostic accuracy of RS for distinguishing between LGD and HGD.

6. Discussion

Endoscopic detection of Barrett's-associated HGD and early adenocarcinoma is crucial to prevent missed disease and to enable early curative endoscopic, or surgical, therapy. However, it is clear that detection of early neoplasia in Barrett's oesophagus is reliant on a number of factors including the experience of the endoscopist and their adherence with a comprehensive biopsy regimen. The search continues for a one-stop technique that can accurately identify and objectively grade neoplastic disease.

A variety of endoscopic imaging tools, at various stages of development, have been trialled for use as diagnostic aids. None of these have yet made the transition to widespread clinical practice reflecting a variety of limitations including limited diagnostic accuracy, considerable multi-user variation and long operator times. In an attempt to address these difficulties several multi-modality imaging systems have been described and have begun evaluation in randomised trials.[51,52] Curvers et al compared detection of dysplasia using endoscopic trimodal imaging (ETMI) and standard WLE in 99 patients who underwent both procedures 6–16 weeks apart. ETMI (HRE, AFI and NBI) was shown to improve targeted identification of dysplasia following detection of 22

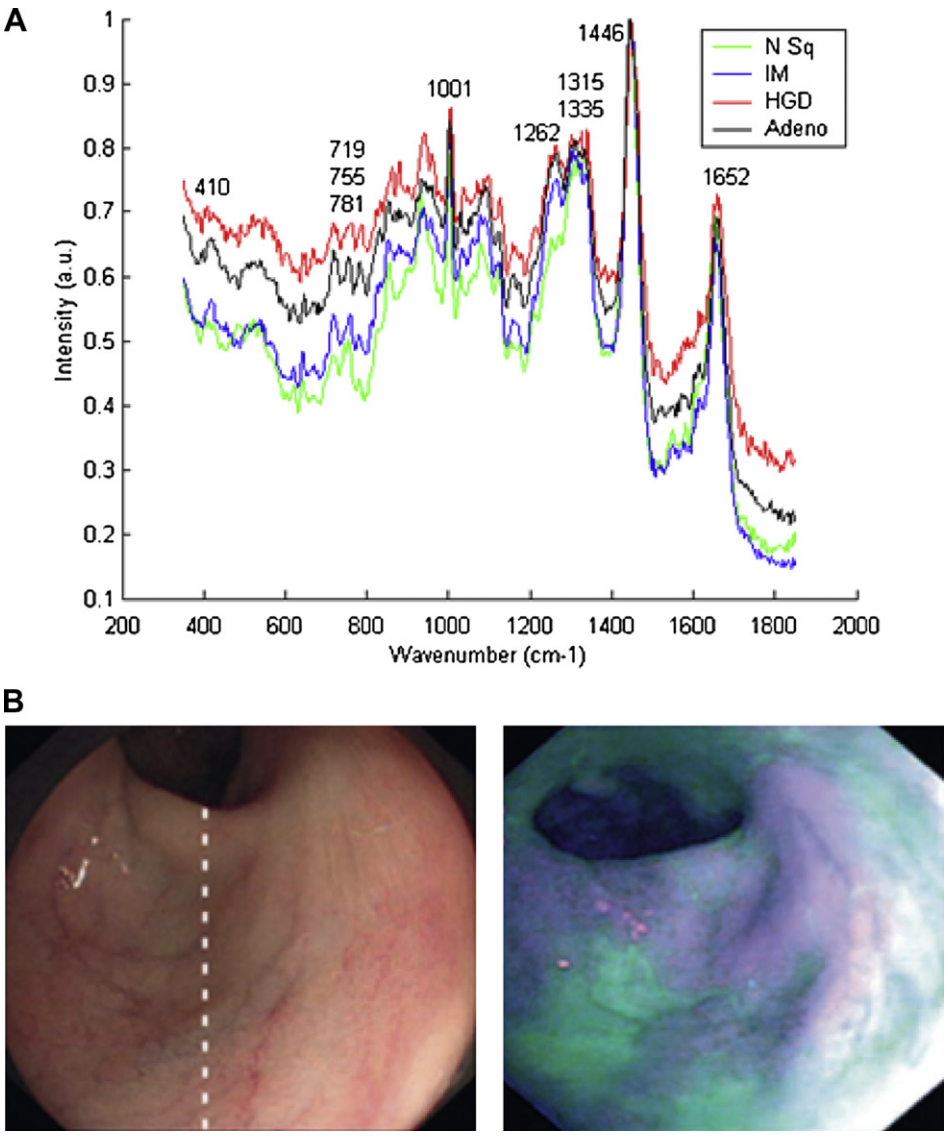

Fig. 1. Novel endoscopic techniques currently in development. (A) Raman spectra for normal squamous mucosa (NSq), intestinal metaplasia (IM), HGD and adenocarcinoma (Adeno). Each pathology has a slightly different spectral signature due to differences in biochemistry enabling objective diagnosis in 1 s or less. (B) Ex vivo oesophageal imaging. Figure modified from Fitzgerald et al. NatMed 2012 with permission from RightsLink.[41] ex vivo endoscope images using white-light endoscopy (left), and fluorescence imaging after application of a fluorescently-tagged lectin (right). Areas of HGD, corresponding to areas of low lectin binding, appear purple. The dashed white line was used to orientate the image.

additional early neoplastic lesions. However, ETMI did not improve overall neoplasia detection rates when compared to WLE plus random biopsies, and its greater role may be in targeting neoplastic lesions for endoscopic resection.[53]

Huang et al recently described a multimodal imaging system combining endoscopic Raman spectroscopy with AFI, NBI and standard white light endoscopy.[54] This trimodal wide-field imaging system was used to guide point Raman measurements of suspicious areas and was shown to identify oesophageal cancer with a sensitivity of 97.0% and specificity of 95.2%.[48]

The disadvantage of multimodality imaging systems such as these is their expense, and the increase in time required to utilise and interpret the different technologies. However, the principal of combining wide-field techniques with high sensitivity, and point measurement techniques with high specificity is conceptually promising.

It is perhaps unlikely that any of the techniques described will become recommended for the assessment of Barrett's oesophagus in non-specialist centres. Although the prevalence of Barrett's oesophagus in the West is increasing, the expense and training required to support widespread use of additional endoscopic tools may be impractical particularly given the low risk of neoplastic progression.[13–15]

Surveillance strategies are likely to move towards inclusion of only those patients deemed to be at a higher risk of progressive disease. These patients may be identified based on long Barrett's segments (>5 cm), the presence of dysplasia, and potentially the genetic profile of the Barrett's cells. Endoscopic technology would then be utilised to aid targeted detection and treatment of early lesions in these patients.

It is important to stress that the key to detecting early neoplasia in Barrett's oesophagus is a thorough and careful inspection of the metaplastic segment supported by a sound knowledge of the characteristics of suspicious lesions. The greatest role for additional endoscopic technologies may prove to be in identifying these lesions for targeted endoscopic therapy.

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Author contribution

Max Almond conducted the literature search and wrote the paper. Hugh Barr made amendments to the paper content before submission.

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References

1. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1468–70. doi:10.1158/1055-9965.EPI-10-0012.
2. *National cancer institute's surveillance, epidemiology, and end results database*, http://seer.cancer.gov/statistics/; 2011.
3. Rees JR, Lao-Sirieix P, Wong A, Fitzgerald RC. Treatment for Barrett's oesophagus. *Cochrane Database Syst Rev* 2011:004060.
4. Third Annual Report. *Third Annual Report. National Oesophago-Gastric cancer audit* 2010.
5. A Report of the Working Party of the British Society of Gastroenterology, principal authors Watson A, Heading RC, Shepherd NA. *Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus* 2005.
6. Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 2008;**57**:1200–6. doi:10.1136/gut.2007.142539.
7. ASGE TECHNOLOGY COMMITTEE, Kantsevoy SV, Adler DG, Conway JD, Diehl DL, Farraye FA, et al. Endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointest Endosc* 2008;**68**:11–8. doi:10.1016/j.gie.2008.01.037.
8. Ciocirlan M, Lapalus MG, Hervieu V, Souquet JC, Napoleon B, Scoazec JY, et al. Endoscopic mucosal resection for squamous premalignant and early malignant lesions of the esophagus. *Endoscopy* 2007;**39**:24–9. doi:10.1055/s-2006-945182.
9. Inoue H, Fukami N, Yoshida T, Kudo SE. Endoscopic mucosal resection for esophageal and gastric cancers. *J Gastroenterol Hepatol* 2002;**17**:382–8.
10. Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. *Clin Gastroenterol Hepatol* 2010;**8**:23–9. doi:10.1016/j.cgh.2009.07.003.
11. Curvers WL, Bansal A, Sharma P, Bergman JJ. Endoscopic work-up of early Barrett's neoplasia. *Endoscopy* 2008;**40**:1000–7. doi:10.1055/s-0028-1103409.
12. Sharma P, Dent J, Armstrong D, Bergman JJ, Gossner L, Hoshihara Y, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology* 2006;**131**:1392–9. doi:10.1053/j.gastro.2006.08.032.
13. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;**365**:1375–83. doi:10.1056/NEJMoa1103042.
14. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. *Am J Epidemiol* 2008;**168**:237–49. doi:10.1093/aje/kwn121.
15. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 2011;**103**:1049–57. doi:10.1093/jnci/djr203.
16. Vieth M, Ell C, Gossner L, May A, Stolte M. Histological analysis of endoscopic resection specimens from 326 patients with Barrett's esophagus and early neoplasia. *Endoscopy* 2004;**36**:776–81. doi:10.1055/s-2004-825802.
17. 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.
18. Cameron AJ, Carpenter HA. Barrett's esophagus, high-grade dysplasia, and early adenocarcinoma: a pathological study. *Am J Gastroenterol* 1997;**92**:586–91.
19. Reid BJ, Blount PL, Feng Z, Levine DS. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. *Am J Gastroenterol* 2000;**95**:3089–96. doi:10.1111/j.1572-0241.2000.03182.x.
20. Shaheen NJ, Richter JE. Barrett's oesophagus. *Lancet* 2009;**373**:850–61. doi:10.1016/S0140-6736(09)60487-6.
21. Kerkhof M, van Dekken H, Steyerberg EW, Meijer GA, Mulder AH, de Bruine A, et al, CYBAR study group. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. *Histopathology* 2007;**50**:920–7. doi:10.1111/j.1365-2559.2007.02706.x.
22. 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. doi:10.1055/s-2005-870433.
23. Kara MA, Smits ME, Rosmolen WD, Bultje AC, Ten Kate FJ, Fockens P, et al. A randomized crossover study comparing light-induced fluorescence endoscopy with standard videoendoscopy for the detection of early neoplasia in Barrett's esophagus. *Gastrointest Endosc* 2005;**61**:671–8.
24. Canto MI, Kalloo A. Chromoendoscopy for Barrett's esophagus in the twenty-first century: to stain or not to stain? *Gastrointest Endosc* 2006;**64**:200–5. doi:10.1016/j.gie.2006.03.921.
25. Lim CH, Rotimi O, Dexter SP, Axon AT. Randomized crossover study that used methylene blue or random 4-quadrant biopsy for the diagnosis of dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2006;**64**:195–9. doi:10.1016/j.gie.2005.07.025.
26. Ragunath K, Krasner N, Raman VS, Haqqani MT, Cheung WY. A randomized, prospective cross-over trial comparing methylene blue-directed biopsy and conventional random biopsy for detecting intestinal metaplasia and dysplasia in Barrett's esophagus. *Endoscopy* 2003;**35**:998–1003. doi:10.1055/s-2003-44599.
27. 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. doi:10.1053/j.gastro.2008.01.003.
28. 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**:155–66. doi:10.1016/j.gie.2005.11.049.
29. 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**:167–75. doi:10.1016/j.gie.2005.10.044.
30. Anagnostopoulos GK, Yao K, Kaye P, Hawkey CJ, Ragunath K. Novel endoscopic observation in Barrett's oesophagus using high resolution magnification endoscopy and narrow band imaging. *Aliment Pharmacol Ther* 2007;**26**:501–7. doi:10.1111/j.1365-2036.2007.03374.x.
31. Filip M, Iordache S, Saftoiu A, Ciurea T. Autofluorescence imaging and magnification endoscopy. *World J Gastroenterol* 2011;**17**:9–14. doi:10.3748/wjg.v17.i1.9.
32. Niepsuj K, Niepsuj G, Cebula W, Zieleznik W, Adamek M, Sielanczyk A, et al. Autofluorescence endoscopy for detection of high-grade dysplasia in short-segment Barrett's esophagus. *Gastrointest Endosc* 2003;**58**:715–9.
33. Kara MA, Peters FP, Fockens P, Ten 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**:176–85. doi:10.1016/j.gie.2005.11.050.
34. 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**:679–85.
35. 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**:167–72. doi:10.1136/gut.2007.134213.
36. Evans JA, Poneros JM, Bouma BE, Bressner J, Halpern EF, Shishkov M, et al. Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2006;**4**:38–43.
37. Isenberg G, Sivak Jr MV, Chak A, Wong RC, Willis JE, Wolf B, et al. Accuracy of endoscopic optical coherence tomography in the detection of dysplasia in Barrett's esophagus: a prospective, double-blinded study. *Gastrointest Endosc* 2005;**62**:825–31. doi:10.1016/j.gie.2005.07.048.
38. Pierce MC, Javier DJ, Richards-Kortum R. Optical contrast agents and imaging systems for detection and diagnosis of cancer. *Int J Cancer* 2008;**123**:1979–90. doi:10.1002/ijc.23858.
39. Thekkek N, Anandasabapathy S, Richards-Kortum R. Optical molecular imaging for detection of Barrett's-associated neoplasia. *World J Gastroenterol* 2011;**17**:53–62. doi:10.3748/wjg.v17.i1.53.
40. Lu S, Wang TD. In vivo cancer biomarkers of esophageal neoplasia. *Cancer Biomark* 2008;**4**:341–50.
41. Bird-Lieberman EL, Neves AA, Lao-Sirieix P, O'Donovan M, Novelli M, Lovat LB, et al. Molecular imaging using fluorescent lectins permits rapid endoscopic identification of dysplasia in Barrett's esophagus. *Nat Med* 2012. doi:10.1038/nm.2616. 10.1038/nm.2616.

42. Goetz M, Kiesslich R. Confocal endomicroscopy: in vivo diagnosis of neoplastic lesions of the gastrointestinal tract. *Anticancer Res* 2008;**28**:353–60.
43. Pohl H, Rosch T, Vieth M, Koch M, Becker V, Anders M, et al. Miniprobe confocal laser microscopy for the detection of invisible neoplasia in patients with Barrett's oesophagus. *Gut* 2008;**57**:1648–53. doi:10.1136/gut.2008.157461.
44. Haidry R, Butt MA, Lovat LB. Advances in endoscopy. *Medicine* 2011;**39**:279–83.
45. Lovat LB, Johnson K, Mackenzie GD, Clark BR, Novelli MR, Davies S, et al. Elastic scattering spectroscopy accurately detects high grade dysplasia and cancer in Barrett's oesophagus. *Gut* 2006;**55**:1078–83. doi:10.1136/gut.2005.081497.
46. Kendall C, Hutchings J, Barr H, Shepherd N, Stone N. Exploiting the diagnostic potential of biomolecular fingerprinting with vibrational spectroscopy. *Faraday Discuss* 2011;**149**:279–90. discussion 333–56.
47. Kendall C, Stone N, Shepherd N, Geboes K, Warren B, Bennett R, et al. Raman spectroscopy, a potential tool for the objective identification and classification of neoplasia in Barrett's oesophagus. *J Pathol* 2003;**200**:602–9.
48. Bergholt MS, Zheng W, Lin K, Ho KY, Teh M, Yeoh KG, et al. In vivo diagnosis of esophageal cancer using image-guided Raman endoscopy and biomolecular modeling. *Technol Cancer Res Treat* 2011;**10**:103–12.
49. Bergholt MS, Zheng W, Lin K, Ho KY, Teh M, Yeoh KG, et al. Characterizing variability in in vivo Raman spectra of different anatomical locations in the upper gastrointestinal tract toward cancer detection. *J Biomed Opt* 2011;**16**:037003. doi:10.1117/1.3556723.
50. Wong Kee Song LM, Molckovsky A, Wang KK, Burgart LJ, Dolenko B, Somorjai RJ, et al. Diagnostic potential of Raman spectroscopy in Barrett's esophagus. *Proc SPIE* 2005;**5692**:140–6.
51. 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**:1106–14. doi:10.1053/j.gastro.2010.06.045.
52. Curvers WL, van Vilsteren FG, Baak LC, Bohmer 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**:195–203. doi:10.1016/j.gie.2010.10.014.
53. Thomas T, Singh R, Ragunath K. Trimodal imaging-assisted endoscopic mucosal resection of early Barrett's neoplasia. *Surg Endosc* 2009;**23**:1609–13. doi:10.1007/s00464-009-0429-z.
54. Huang Z, Teh SK, Zheng W, Mo J, Lin K, Shao X, et al. Integrated Raman spectroscopy and trimodal wide-field imaging techniques for real-time in vivo tissue Raman measurements at endoscopy. *Opt Lett* 2009;**34**:758–60.