Published in final edited form as:

Endoscopy. 2011 January ; 43(1): 21–25. doi:10.1055/s-0030-1256021.

Reflux and Barrett's disease

S. D. Crockett^{1,2} and N. J. Shaheen^{1,2}

¹ Center for Esophageal Diseases and Swallowing, University of North Carolina, Chapel Hill, North Carolina, USA

² Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina, USA

Multispectral scanning during endoscopy guides biopsy of dysplasia in Barrett's esophagus (Qiu et al., Nat Med 2010 [1])

In this study, a team of Harvard researchers conducted human testing of a novel technique known as endoscopic polarized scanning spectroscopy (EPSS) in Barrett's esophagus. This technology relies on the fact that dense and enlarged epithelial nuclei are a key pathological feature of dysplasia. Because dysplastic nuclei scatter light differently from normal nuclei, the back-scattering of spectra can be analyzed to detect foci of dysplasia. Using polarized light, the researchers were able to isolate the spectroscopic signal of the epithelial layer, as light back-scattered from deeper tissues becomes depolarized and can therefore be cancelled out. The EPSS instrument uses a 2.5-mm stainless-steel probe, which can be inserted into the working channel of a standard upper endoscope (Fig. 1). Scanning of the Barrett's segment is accomplished by both linear and rotary movement of the probe, which is driven by an external control box. The instrument is able to collect spectra regardless of the orientation and distance between the probe tip and the esophageal wall, so the test results are not altered by peristaltic motion or the level of insufflation of the esophagus.

In this proof of concept study, EPSS data from five patients were compared with pathology results from standard of care 4-quadrant biopsies performed during endoscopic surveillance of Barrett's esophagus. A total of 95 biopsies were obtained from all patients, revealing 13 dysplastic sites (nine high grade dysplasia [HGD] and four low grade dysplasia [LGD]). The exact site of each biopsy was recorded with reference to the EPSS scanning grid, and the biopsy locations were then overlaid on the spectroscopic results using "pseudocolor maps" (Fig. 2). Blinded comparison was then performed to test the accuracy of the EPSS analysis at each of the biopsy sites. The EPSS technique had a sensitivity, specificity, and accuracy of 92%, 96%, and 96%, respectively. These test characteristics only reflect the performance of EPSS at each of the biopsy sites, however, not the accuracy of the entire scanned segment; it is also worth noting that localization of biopsies and matching of biopsy sites with EPSS maps was likely imperfect, which may have accounted for some false-negative and false-positive results. Additionally, the authors report that in one patient, the endoscopic examination (with high resolution endoscopy and narrow-band imaging) and 4-quadrant biopsies were negative for suspicious lesions or dysplasia, but the EPSS scan did reveal several probable dysplastic sites and the patient was recalled. EPSS-targeted biopsies were subsequently performed and confirmed HGD at three EPSS-positive sites (Fig. 2).

Corresponding author: S. D. Crockett, MD, MPH, University of North Carolina School of Medicine, CB#7080, Chapel Hill, NC 27599-7080, USA, Fax: +1-919-966-6842, sethc@med.unc.edu.

Competing interests: Dr Shaheen has served as a consultant to Astra Zeneca and CSA Medical, and has received research support from Astra Zeneca, Takeda, Procter & Gamble, BARRX Medical, CSA Medical, and Oncoscope.

This technique has several benefits over the current standard of care of random 4-quadrant biopsies every 1–2 cm. First, because this technology allows for scanning of the entire segment of Barrett's epithelium for dysplasia, it offers the potential for targeted biopsies at suspicious sites, and more efficient surveillance. Secondly, the possibility of sampling error is reduced, which is a downfall of the current standard of care biopsy approach. Thirdly, if this technology is shown to allow rapid scanning of the entire Barrett's segment with real-time reporting and ease of interpretation, it may be superior to other advanced microimaging technologies such as narrow-band imaging, optical coherence tomography, and confocal laser microscopy, which have been complicated by imperfect sensitivity and the need for methodical exams and specialized operator training. This technique may also be useful for dysplasia screening and surveillance challenges elsewhere in the gastrointestinal tract, such as high risk gastric cancer screening, gastric ulcer evaluation, polyposis syndromes, and inflammatory bowel disease. As with all new technologies, rigorous prospective studies are required until efficacy and safety can be assured, and practical aspects (e.g. ease of use, reliability of results, operator training needs, cost, and inter-operator variability) can be optimized. However, if the device can really achieve real-time targeting of biopsies for areas highly enriched in dysplasia, this technology is a potential game-changing tool for optimizing dysplasia surveillance in patients with Barrett's esophagus.

Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus (Prasad et al., *Gastroenterology* 2009 [2])

This retrospective cohort study from the Mayo Clinic reports the long-term outcomes of patients with T1a mucosal esophageal adenocarcinoma (EAC) associated with Barrett's esophagus who underwent esophagectomy or endoscopic mucosal resection (EMR) with or without adjuvant photodynamic therapy (PDT). All patients were rigorously characterized with cross-sectional imaging with or without positron emission tomography scans to exclude metastatic or locally invasive disease, and only patients with mucosal EAC were included in the study. Pathology was confirmed by at least two experienced gastrointestinal pathologists and interpreted according to standard criteria. The EMR technique varied based on time period, and included the band ligation and pseudopolypectomy technique, the endoscopic resection cap technique, and the multiband mucosectomy technique. Half of the EMR patients also received PDT therapy following the initial procedure (this practice was more common in the early phase of the study, 1998–2003), and all patients were placed on twice daily proton pump inhibitor (PPI) therapy following the procedure. The esophagectomy group was identified by retrospective review of all esophagectomies performed at the Mayo Clinic between 1998 and 2007, and was limited to those with EAC confined to the mucosa. Overall and cancer-free survival were compared between groups using Kaplan–Meier curves and Cox-proportional hazard modeling.

In total, 46 esophagectomy patients were compared with 132 patients who underwent EMR for T1a lesions. Those treated endoscopically tended to be older (mean age 71 years vs. 68 years in the surgery group), with shorter Barrett's segments and more co-morbidities. In the endoscopically treated group, the authors report that remission of cancer (defined as no evidence of cancer on two consecutive surveillance exams) was achieved in 124/132 patients (94%). It is worth noting, however, that most patients had persistent Barrett's esophagus (n = 114, 92%), and a substantial proportion had residual dysplasia following EMR with or without PDT (LGD n = 18, 15%; HGD n = 41, 33%). Eight patients who underwent EMR had persistent adenocarcinoma postprocedure and underwent esophagectomy. The authors report a 13% complication rate in the EMR group (18/132). Most complications were related to PDT therapy (e.g. strictures [n = 8] and photosensitivity

[n = 5]), but five patients developed procedure-related bleeding requiring hospitalization, transfusion, or endoscopic therapy. In the esophagectomy group, complications were expectedly higher: postoperative complications (e.g. anastomotic leaks or strictures) were common (17/46, 34%) and one patient died postoperatively.

There were 16 recurrent cancers in the EMR group, and only one in the surgery group. The 5-year cancer-free survival was significantly lower in the EMR group compared with the esophagectomy group (80% vs. 97%, $P = 0.01$ [log rank test]; Fig. 3). Overall 5-year survival was also lower in the EMR group, but the difference was not statistically significant (83% vs. 95%, $P = 0.15$ [log rank test]). Results of survival comparisons must be interpreted carefully given the retrospective design of this study and the inherent differences in the groups' co-morbidities because those treated with EMR tended to be older and sicker (i.e. may not have been good surgical candidates) and their survival might therefore be expected to be poorer. However, a difference in cancer-free survival persisted after adjustment for co-morbidities and propensity to receive EMR in multivariate Cox modeling. Other ablative therapy modalities (e.g. radiofrequency ablation [RFA]) may also have impacted the recurrence rate in the EMR group, as most patients had detectable HGD prior to their recurrence.

These results add to the growing body of literature that establishes a role for an EMR-based approach for early Barrett's cancer. Such an approach avoids much of the morbidity associated with esophagectomy. While the amount of residual Barrett's esophagus and dysplasia following EMR was substantial, adjuvant use of ablative technologies after EMR may now be applied to reduce this phenomenon. Nevertheless, this trial underscores the risk of recurrent cancer and need for continued surveillance following EMR for early Barrett's neoplasia, which may affect the cost-effectiveness of this approach.

Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated (Curvers et al., Am J Gastroenterol 2010 [3])

This study was an analysis of a Dutch registry of Barrett's patients within a network of six "non-university" hospitals. The authors selected only patients who were diagnosed with LGD and followed them prospectively to evaluate whether they had progression of dysplasia or development of EAC. All patients with a diagnosis of LGD were identified, and their pathology specimens were independently reviewed and graded using accepted criteria by two expert gastrointestinal pathologists with extensive experience in Barrett's neoplasia.

Between 2000 and 2006, 1198 patients with Barrett's esophagus were evaluated, and 147 (12%) were diagnosed with LGD. Strikingly, upon expert review, LGD was only confirmed in 22 patients (15%). One patient had HGD, 14 had indeterminate results, and 110 (75%) were downgraded to nondysplastic Barrett's esophagus. After excluding the patient with HGD, those who did not undergo endoscopic surveillance and those who were lost to follow-up, 274 surveillance endoscopies were performed in 122 patients (mean follow-up 51 months). Among the 19 patients with a consensus diagnosis of LGD who underwent endoscopic surveillance, eight progressed to HGD ($n = 6$) or EAC ($n = 2$). By contrast, among the 92 patients with a consensus diagnosis of nondysplastic Barrett's who underwent endoscopic surveillance, only two patients progressed to HGD or EAC. The overall rate of progression to HGD or EAC for those with a consensus diagnosis of LGD was 13.4% per patient-year compared with 0.5% for those who were downgraded to nondysplastic Barrett's. The cumulative incidence of HGD or EAC for those in the LGD group was 85% at 109 months (Fig. 4).

The results of this study indicate that LGD is overdiagnosed in community practice, but that a valid pathological diagnosis of LGD is associated with a clear risk of progression to HGD and EAC. These data suggest that previous estimates of progression rates in LGD may be artificially diminished due to “contamination” by patients with nondysplastic disease. Most importantly, this report underscores the need for careful review of dysplastic Barrett’s esophagus specimens by at least two pathologists (one of whom should be an expert gastrointestinal pathologist), as is currently advocated by published guidelines [4]. Failure to do so could commit patients with Barrett’s esophagus to a surveillance program that is not appropriately tailored to their actual risk of cancer progression.

Safety and efficacy of endoscopic spray cryotherapy for Barrett’s esophagus with high-grade dysplasia (Shaheen et al., *Gastrointest Endosc* 2010 [5])

Endoscopic spray cryotherapy or cryoablation is a novel form of Barrett’s ablation in which liquid nitrogen is used to destroy Barrett’s epithelium. Analogous to other ablative techniques, destruction of Barrett’s esophagus followed by acid suppression generally results in regeneration of neosquamous epithelium.

This retrospective cohort study reported safety and efficacy data on 98 patients from nine sites across the USA who underwent cryoablation for Barrett’s esophagus with associated HGD. The study cohort included a number of patients in whom previous therapies had failed, including one patient who had a Nissen fundoplication, two patients with partial esophagectomies for HGD, and 14 patients who had previous unsuccessful ablative therapy (i.e. PDT, RFA, or argon plasma coagulation [APC]); 22 patients had undergone previous EMR.

Cryoablation was directed at the entire Barrett’s segment with the intention of eradicating any dysplastic foci in addition to the background intestinal metaplasia. The CSA cryotherapy system (CSA Medical, Baltimore, Maryland, USA) was used for all procedures. This apparatus utilizes a 7-Fr polyamide spray catheter, which can be inserted through the working channel of the upper endoscope. Affected areas were sprayed with liquid nitrogen with a maximum treatment dosimetry of 40 seconds (two cycles of 20 seconds or four cycles of 10 seconds) with intervening thaw cycles to ensure tissue reperfusion (Fig. 5). Follow-up exams (with 4-quadrant biopsies taken according to the standard of care) were performed every 2–3 months until eradication of Barrett’s esophagus was confirmed, or until treatment was halted for clinical reasons or patient preference.

Of the 98 patients reported in this retrospective study, 60 had completed planned cryoablation therapies (mean of 4 treatments). Of these, HGD was eradicated in 58 (97%), all dysplasia (HGD or LGD) was eradicated in 52 (87%), and all intestinal metaplasia was eradicated in 34 patients (57%). No serious adverse events were reported, and there were no perforations. Three patients (3% of patients, 1% of treatments) developed strictures, all of which were successfully dilated endoscopically. One patient had postprocedure bleeding, and two patients experienced chest pain.

A number of endoscopic ablative therapies have been previously studied including APC, electrocoagulation, laser therapy, PDT, EMR, and RFA, in addition to cryotherapy. Many of these techniques are now less commonly used for various reasons, and EMR is generally reserved for Barrett’s esophagus associated with nodules or early cancers. It is unclear whether cryotherapy will emerge as a first-line therapy for flat dysplastic Barrett’s esophagus. While this report is promising, the excellent results and side effect profile of RFA present a formidable standard to reach. Further trials will be needed to clarify whether

one technology is superior to the other in terms of safety, efficacy, tolerability, and cost, and additional studies are needed to clarify the durability of the cryoablation effect. However these results suggest that cryoablation may have a role in endoscopic ablation of Barrett's esophagus associated with dysplasia.

Argon plasma coagulation of cervical heterotopic gastric mucosa as an alternative treatment for globus sensations (Bajbouj et al., Gastroenterology 2009 [6])

Globus sensation is characterized by a fullness or "lump" in the throat that can be an extra-esophageal manifestation of gastroesophageal reflux disease (GERD). The etiology of this disorder is incompletely understood, but studies have suggested a role of esophageal acid, with evidence of abnormal pH/impedance findings in patients with globus [7], and improvement of symptoms with PPI therapy [8]. Furthermore, an association between gastric inlet patches (GIP) and globus sensation has been reported [9], but the significance of this finding has been uncertain.

This randomized, sham-controlled trial of APC therapy from Germany is the first to test the hypothesis that ablation of GIPs may result in improvement in symptoms for patients suffering from globus. Enrolled patients had globus sensation for ≥ 3 months in addition to histologically verified GIPs and symptoms that had not responded to previous PPI therapy. Patients were given a standardized symptom assessment questionnaire prior to the initial procedure and at 3 months postprocedure, and were randomized in blinded fashion to undergo either APC or a sham procedure.

The study was terminated early after an interim analysis found evidence of a statistically significant treatment effect. Symptom improvement was found in 9/11 patients (82%) in the APC group compared with 0/10 patients (0%) in the sham arm. In the APC group, the median globus score and symptom score had decreased significantly by the follow-up examination (Fig. 6). At the conclusion of the study, patients in the sham arm were offered APC, and 8/10 elected to pursue this. In total, the authors reported that 18 patients received APC for their GIPs, and eradication was successful in all. At 6-month follow-up, 13/17 contactable patients (76%) who had received APC reported symptomatic improvement. Based on the response in the initial phase of the study, the authors report an impressive number needed to treat of 1.2. The APC therapy was well tolerated with no strictures, bleeding, or perforations.

This study demonstrates that APC may be an effective treatment for patients with globus sensation who also have cervical heterotopic gastric mucosa patches visible on endoscopy. Although there appears to be a subset of patients who do not respond to GIP ablation and who may have a different etiology of their symptoms (e.g. a psychological component), given the paucity of treatments for globus and the relative safety of APC therapy, this provides the clinician and patient with a promising alternative in the management of this condition.

Acknowledgments

This research was supported, in part, with a grant from the National Institutes of Health (T32 DK07634).

References

1. Qiu L, Pleskow DK, Chuttani R, et al. Multispectral scanning during endoscopy guides biopsy of dysplasia in Barrett's esophagus. *Nat Med.* 2010; 16:603–606. [PubMed: 20383155]

2. Prasad GA, Wu TT, Wagle DA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. *Gastroenterology*. 2009; 137:815–823. [PubMed: 19524578]
3. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol*. 2010; 105:1523–1530. [PubMed: 20461069]
4. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2008; 103:788–797. [PubMed: 18341497]
5. Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc*. 2010; 71:680–685. [PubMed: 20363409]
6. Bajbouj M, Becker V, Eckel F, et al. Argon plasma coagulation of cervical heterotopic gastric mucosa as an alternative treatment for globus sensations. *Gastroenterology*. 2009; 137:440–444. [PubMed: 19410576]
7. Bajbouj M, Becker V, Neuber M, et al. Combined pH-metry/impedance monitoring increases the diagnostic yield in patients with atypical gastroesophageal reflux symptoms. *Digestion*. 2007; 76:223–228. [PubMed: 18174685]
8. Dore MP, Pedroni A, Pes GM, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci*. 2007; 52:463–468. [PubMed: 17211695]
9. Alaani A, Jassar P, Warfield AT, et al. Heterotopic gastric mucosa in the cervical oesophagus (inlet patch) and globus pharyngeus – an under-recognised association. *J Laryngol Otol*. 2007; 121:885–888. [PubMed: 17166326]

Fig. 1. Endoscopic polarized scanning spectroscopy (EPSS) of Barrett's esophagus. **a** Illustration of probe inserted into working channel of upper endoscope with yellow arrows indicating linear rise of probe tip before each scan and rotary motion during scanning. **b** Endoscopic image showing actual EPSS probe during scanning of Barrett's esophagus segment showing illumination spot on the esophageal wall at the upper right of the image. (Reproduced with permission from Macmillan Publishers Ltd. ©2010. Qui et al., Nat Med 2010; 16: 603–606.)

Fig. 2.

Pseudocolor maps produced from endoscopic polarized scanning spectroscopy (EPSS) data overlaid with circles indicating biopsy sites and confirmed pathology. Vertical axis indicates the angle of rotation from the start of each rotary scan, and the horizontal axis indicates distance from upper incisors. Blue and green areas are sites unlikely for dysplasia, and pink/red areas are sites suspicious for dysplasia as determined by EPSS. Color of circles indicates pathology results (green, nondysplastic; pink, low grade dysplasia; red, high grade dysplasia). The two images depicted represent one patient whose initial exam was negative for dysplasia based on standard-of-care 4-quadrant biopsies (i.e. all green circles) but whose EPSS map identified several areas suspicious for dysplasia (pink and red areas). The patient was recalled and three EPSS-guided biopsies confirmed high grade dysplasia. (Reproduced with permission from Macmillan Publishers Ltd. ©2010. Qui et al., *Nat Med* 2010; 16: 603–606.)

Fig. 3.

Overall and cancer-free survival from Prasad et al., in patients treated with esophagectomy (gray lines) and with endoscopic mucosal resection (EMR) (black lines). Kaplan-Meier curves show superior cancer-free survival in the esophagectomy group compared with the EMR group (right panel), but similar overall survival in the two groups (left panel). (Reproduced with permission from Elsevier. Prasad et al., *Gastroenterology* 2009; 137: 815–823.)

Fig. 4. Kaplan-Meier curve demonstrating cumulative rate of progression to high grade dysplasia (HGD) or cancer (Ca) for the entire cohort, and those with low grade dysplasia (LGD), indefinite dysplasia (ID), and nondysplastic Barrett's esophagus (NDBE). (Reproduced with permission from Macmillan Publishers Ltd. ©2010. Curvers et al., *Am J Gastroenterol* 2010; 105: 1523–1530.)

Fig. 5. Endoscopic images from an endoscopic spray cryotherapy session. **a** Dual-channel decompression tube in place with a friction-fit cap before administration of liquid nitrogen therapy. **b** Postcryotherapy image demonstrating white frost on the targeted dysplastic mucosa. (Reproduced with permission from Elsevier. Shaheen et al., *Gastrointest Endosc* 2010; 71: 680–685.)

Fig. 6.

Box plot showing change in median globus score before (blue) and after (green) therapy in each study arm of a trial of argon plasma coagulation (APC) ablation of cervical inlet patches for treatment of globus sensation. (Reproduced with permission from Elsevier. Bajbouj et al., *Gastroenterology* 2009; 137: 440–444.)