Barrett's esophagus and new therapeutic modalities

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Barrett's esophagus is a metaplastic change of the epithelium of the esophagus, caused by injury and inflammation related to gastroesophageal reflux disease. Metaplasia is defined as the transformation from one cell type to another cell type. In the case of Barrett's esophagus, the normal squamous epithelium is replaced by a columnar epithelium-containing goblet cells, deemed intestinal metaplasia (IM). Owing to a significantly elevated risk for the development of esophageal adenocarcinoma associated with the presence of IM, patients with this diagnosis undergo surveillance endoscopy with multiple biopsies of the diseased tissue every 2–3 years, in order to detect adenocarcinoma at the earliest possible tumor stage. Development of dysplastic cellular changes within the Barrett's epithelium often precedes the development of cancer. In cases of IM containing dysplasia, surveillance endoscopy is performed more frequently (every 3–12 months). For many patients with high-grade dysplasia, the esophagus may be removed surgically in order to preempt the development of cancer.

Keywords: ablation, adenocarcinoma, Barrett's, cancer, dysplasia, endoscopy, esophagus, gastroenterology, intestinal metaplasia, surveillance

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Removal of the Barrett's epithelium, prior to the development of cancer, is possible. Until recently, therapy of Barrett's esophagus was limited to those patients with the most severe form of dysplasia (high grade), and those therapies consisted of endoscopic mucosal resection, photodynamic therapy and surgical esophagectomy. However, each intervention, has been associated with specific risks to the patient. More recently, clinical data have become available regarding circumferential and focal ablation for completely removing the Barrett's epithelium. Such ablation is performed with the HALO ablation system, which is an endoscopic catheter system that applies ablative energy to the Barrett's epithelium in a controlled manner. Outcomes from clinical trials demonstrate that ablation with this device is safe and effective.

In this review, we will briefly explore the key issues related to Barrett's esophagus, including pathophysiology, histological grading, current management, natural history, morbidity associated with progression of the disease and methods historically used for removing the Barrett's epithelium. We will then summarize the key issues related to newer treatment options for Barrett's ablation, with a focused review of circumferential and focal ablation, for treating Barrett's esophagus, including the technical components of the devices, the endoscopic technique for ablation, preclinical study, results human clinical trial results, and the role this intervention may have for the management of patients having a diagnosis of Barrett's esophagus.

Barrett's esophagus

Definition

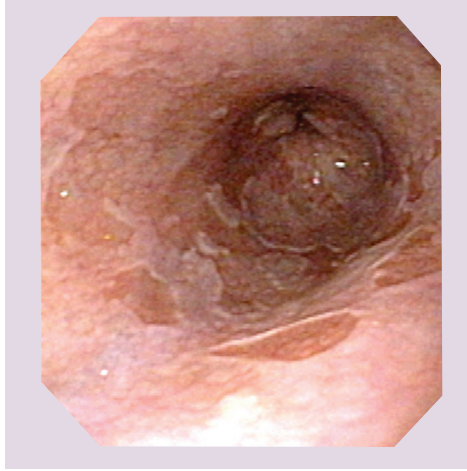
The normal esophagus is lined by a stratified squamous epithelium from the esophageal inlet to the gastroesophageal junction (GEJ), at which there is a transition to a cardiac or gastric mucosa which has a glandular histology. A diagnosis of Barrett's esophagus (BE) is initially suspected when a columnar-lined esophagus is seen during upper endoscopy, appearing as a salmon-colored epithelium, compared with the lighter-pink-colored, normal squamous epithelium (**Figure 1**). The diagnosis is confirmed with biopsy, with histology demonstrating an intestinalized mucosa containing goblet cells [1–4].

A Barrett's segment usually emanates from the GEJ and extends proximally into the esophageal body, is usually less than 6 cm total length and is configured as confluent circumferential disease, tongue-like projections, isolated islands or any combination thereof. The Prague Classification system is used to categorize a Barrett's esophagus. The length of circumferential (C) and noncircumferential (M) components are described *vis-à-vis* the GEJ. For example, a 4-cm circumferential segment plus any number of tongues projecting as high as 6 cm above the GEJ would be classified as C4 M6 [5].

Histology

If Barrett's esophagus is suspected based on the presence of a columnar-lined esophagus, biopsies are obtained via the endoscope for histopathological confirmation of the diagnosis. The *sine*

Figure 1. Endoscopic appearance of a Barrett's esophagus segment with salmon-colored islands and tongues.



The endoscope is positioned approximately 10 cm proximal to the gastroesophageal junction.

qua non of Barrett's esophagus is a glandular epithelium in the esophageal body with goblet cells containing mucous (**Figure 2**). This epithelium is also known as intestinal metaplasia (IM). Standard hematoxylin and eosin staining techniques are often adequate to confirm this diagnosis, although special staining with Alcian blue creates a unique staining pattern of the goblet cells, which may be useful in selected cases [4].

The histological features of IM are graded according to the presence or absence of dysplasia:

- No dysplasia
- Indefinite for dysplasia
- Low-grade dysplasia (LGD)
- High-grade dysplasia (HGD) [4,6–8].

Nondysplastic IM is an organized columnar epithelium with glandular crypts and goblet cells. Indefinite for dysplasia has IM with mild nuclear enlargement and stratification. Often, inflammatory changes owing to gastroesophageal reflux disease (GERD) can mimic early dysplastic changes. In LGD, the glandular crypt architecture tends to be preserved and nuclei are enlarged, hyperchromatic, crowded and stratified. In HGD, the glandular crypts are significantly distorted and may include branching, which is not found in LGD. Nuclei are markedly enlarged, hyperchromatic and display loss of polarity [4,6–8].

If neoplastic glandular tissue is present below the basement membrane, this is deemed invasive adenocarcinoma [4,8]. The earliest stage is intramucosal adenocarcinoma (IMC), defined as any neoplasia that penetrates the basement membrane, but does not extend below the muscularis mucosae. The mucosal layer is comprised of the epithelium, lamina propria and muscularis mucosae. The TNM system (based on the extent of the tumor [T] the extent of spread to the lymph nodes [N], and the presence of metastasis [M]) of the American Joint Committee on Cancer (AJCC) defines IMC as a T1 lesion or, more specifically, as a T1m, with 'm' referring to mucosa. A deeper T1 lesion invades the submucosa (T1sm), but not the muscularis propria. Such histological subclassification of T1 tumors is important in selecting the optimal treatment modality. A T2 lesion invades muscularis propria. A T3 lesion invades the esophageal adventitia. A T4 lesion invades mediastinal structures [4,8].

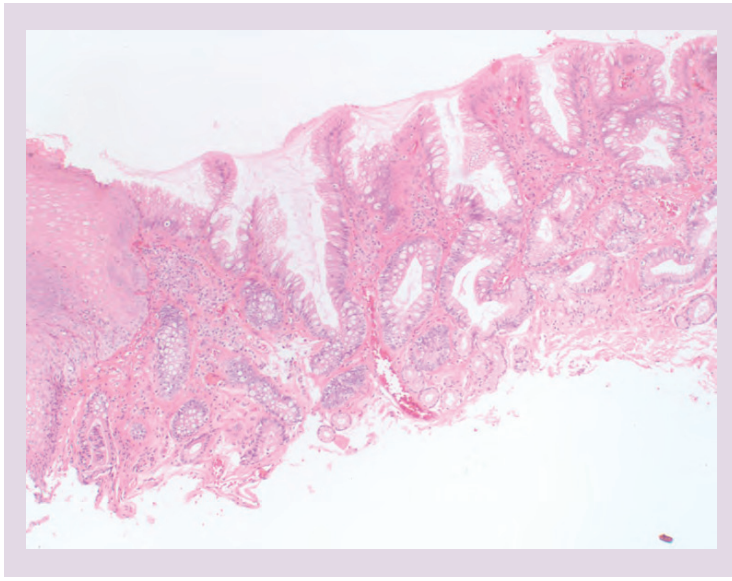
Pathophysiology & histogenesis

It is thought that metaplasia of the esophageal lining occurs as a result of recurrent mucosal injury related to GERD [4,9]. Injury to the squamous epithelium is a result of chronic exposure to gastric acid, enzymes and bile in the refluxate, resulting in chronic inflammatory changes, erosion and ulceration. This chronic injury and repair process and local inflammatory mediators may result in a genetic change in the epithelial cells, which then express the phenotype of a columnar or glandular epithelium [9]. Despite treatment of GERD via inhibition of acid production with antisecretory agents or antireflux surgery, once IM occurs, spontaneous regression is uncommon [10,11].

Demographics

The prevalence of Barrett's esophagus in the adult population is 0.4–1.6% [1,3,12,13]. Assuming a US adult population in 2007 of 220 million adults, between 880,000 and 3.5 million US adults, therefore, have Barrett's esophagus. There is an even higher prevalence reported in some recent studies, ranging between 6.8 and 30%, although these studies represent highly selected patient populations and the estimates cannot be extrapolated to the general population [14–16]. In addition to this rather alarming prevalence, the incidence of Barrett's esophagus is also rising. The frequency of new cases of Barrett's esophagus in one series rose from 2.9 to 8.9 cases per 1000 endoscopies over the last decade [17]. In another series, the number of new cases of Barrett's esophagus per 1000

Figure 2. Photomicrograph of intestinal metaplasia without dysplasia showing characteristic goblet cells.



Hematoxylin and eosin stain, 200x magnification.

endoscopies rose from 19.8 in 1997 to 40.5 in 2002, despite a reduction in the total number of endoscopies performed in that same time interval. The incidence of EAC rose by fourfold in this study during the same time period [18]. The incidence of Barrett's esophagus, as reported in the progression of GERD (ProGERD) study, is 0.65% per year for patients with GERD and 2.9% per year for those with severe forms of esophagitis [19].

The cause of this observed increase in the number of Barrett's esophagus cases is unclear, but it may be related to the increase in the prevalence of GERD and obesity in developed countries. In parallel with these observations of rising incidence and prevalence of Barrett's esophagus, the incidence of EAC is on the rise, marked by a 300–500% increase in annual new cases over the last four decades [101]. As described earlier, IM is the precursor cell type for EAC [20].

Natural history

An initial diagnosis of Barrett's esophagus may be accompanied by findings of dysplasia or even cancer on the initial biopsies from the Barrett's segment. In one report, Sharma *et al.* reported a multicenter cohort study of 1376 patients with a first-time diagnosis of Barrett's esophagus [21]. A significant number of these first-time Barrett's patients (17.0%) demonstrated grades of Barrett's esophagus other than 'no dysplasia': LGD (n = 101, 7.3%), HGD (n = 42, 3.1%), and cancer (n = 91, 6.6%). Once diagnosed, a nondysplastic Barrett's esophagus segment may still progress to dysplasia or cancer, and therefore regular surveillance endoscopy for the lifetime of the patient is recommended [22].

The rate of progression from nondysplastic IM to LGD, HGD and cancer is well documented [18,21,23]. Regarding the risk of progression from IM to cancer, in a meta-analysis of 25 studies, Shaheen *et al.* found this range to be 0.0 to 2.7% per patient-year of follow-up (mean: 1.0%) [23]. The authors adjusted the risk for progression to account for study-size bias (funnel plot analysis) and established the widely cited 'risk for progression' of 0.5% per patient-year of follow-up. In a prospective, population-based study (ProGERD study), the progression rate from nondysplastic IM to cancer was 2.5% over 2 years (1.3% per patient-year of follow-up) [18]. Lastly, Sharma *et al.* followed 66 nondysplastic IM patients for a mean of 8 years, during which time 5.0% progressed to cancer (0.6% per patient-year follow-up), suggesting that the rate of progression continues for at least a mid-term time interval [21].

Regarding progression from nondysplastic IM to dysplasia, which also changes patient management, Sharma *et al.* reported on a cohort in whom a first-time diagnosis of Barrett's was made. After eliminating all patients with a simultaneous diagnosis of dysplasia or cancer, they followed the remainder of the group with yearly surveillance endoscopy, eliminating all patients with new dysplasia or cancer in the first 12 months of follow-up. Of these, 618 patients were available who had at least one follow-up biopsy and who had IM with no dysplasia as their worst baseline diagnosis. After 2546 patient-years of follow-up (mean 4.2 years), 21.7% (n = 134) of patients progressed to LGD (16.2%), HGD (3.6%) or cancer (2.0%). This represents a 5.2% per patient-year of follow-up risk for disease progression. The aggregate risk for developing HGD or cancer was 1.4% per patient-year of follow-up [21].

There are several recognized methodological issues making the estimate of the exact risk of histological progression from nondysplastic IM to more advanced disease states difficult. These issues include biopsy sampling error, concordance rates for pathological interpretation and inflammatory changes masquerading as

dysplasia. Regardless, as shown in several of the cited studies, a diagnosis of IM (with or without dysplasia) significantly elevates the risk for developing esophageal adenocarcinoma.

Management of Barrett's esophagus

Treatment of gastroesophageal reflux disease & surveillance endoscopy

Current management of Barrett's esophagus begins with treatment of GERD symptoms and prevention of erosive injury to the esophageal lining, usually with long-term antisecretory drugs (histamine type-2 receptor antagonists, proton pump inhibitors) [1,3,24]. Antireflux surgery may be considered in those patients with refractory GERD symptoms or erosive esophagitis, despite a properly dosed antisecretory drug regimen [3]. Surveillance endoscopy with biopsy is performed on a regular basis in order to detect progression from earlier stages of IM to dysplasia or cancer, as such early detection can result in decreased morbidity and mortality [22,24]. Guidelines issued by the US-based gastroenterology societies recommend that patients with nondysplastic IM undergo surveillance endoscopy every 3 years, with four quadrant biopsies obtained every 2 cm of the Barrett's segment [22,24]. For LGD, the interval is shortened from every 3 years to every 6–12 months, and the number of biopsies per session doubled, given the higher likelihood of LGD progressing to HGD or cancer [21,22,24]. For HGD, a number of diagnostic interventions may be utilized to rule out concurrent invasive adenocarcinoma, such as repeating the biopsy session, endoscopic ultrasound, chest radiograph and chest CT. The standard of care for HGD has historically been surgical esophagectomy, given the high rate of occult adenocarcinoma [3]. More recently, ablation and endoscopic mucosal resection (EMR) have been applied in selected patients, which will be discussed later. Surveillance endoscopy every 3 months has been considered for selected cases of unifocal HGD, the elderly patient or significant comorbidities that render the patient ineligible for surgery [22].

Endoscopic therapeutic intervention

In addition to surveillance endoscopy, endoscopic therapeutic interventions have been studied with the intent of eliminating the Barrett's epithelium. These include photodynamic therapy (PDT) [25–30], EMR [31–37], laser ablation [38–43], argon plasma coagulation (APC) [44–48], multipolar electrocoagulation (MPEC) [48–52], cryotherapy [53] and, most recently, circumferential and focal ablation [54–66].

Photodynamic therapy

PDT, a photosensitizing agent, is administered and followed 48 h later by delivery of laser light energy to the Barrett's tissue via a fiber passed through the endoscope. Upon exposure to this laser energy, cells containing the photosensitizer form cytoplasmic oxygen metabolites that can result in cell death [26]. Porfimer sodium (Ps-PDT) is approved for treatment of HGD and cancer in the USA, while 5-aminolevulinic acid (ALA) is used outside the USA for HGD and early cancer [28,29].

Overholt *et al.* reported on 208 patients with HGD who were randomized to Ps-PDT (n = 138) versus control (n = 70) [25]. During 18-month follow-up, 75% of the Ps-PDT group were deemed free of HGD on at least one biopsy session, compared with 36% in the control group ($p < 0.0001$). Complications included: photosensitivity (69%), stricture (36%), vomiting (32%), chest pain (20%), pyrexia (20%), dysphagia (19%), dehydration (12%) and nausea (11%). The progression rate to cancer in the Ps-PDT group (13%) was less than that in the control group (20%), although HGD and IM remained in a significant percentage of the PDT group.

Pech *et al.* evaluated ALA-PDT in 66 patients with high-grade intraepithelial neoplasia (HGIN) or early adenocarcinoma. Although complete resolution of IM was not an end point of the trial, the complete response rate over 37 months for HGIN and cancer was 100 and 97%, respectively. Over time, disease-free survival for HGIN and cancer was 89 and 68%, respectively owing to recurrence. No major complications were observed [29].

Triadafilopoulos *et al.* found that Ps-PDT followed by surveillance was more cost effective than esophagectomy for treating HGD, despite incurring a greater lifetime cost (US$47,310 vs US$24,045), mainly owing to a higher quality-adjusted life years associated with Ps-PDT [27].

The issues that continue to be associated with PDT include patient tolerability (photosensitivity), safety (stricture, vomiting, pleural effusion, atrial fibrillation and dysmotility),

persistent IM despite elimination of dysplasia in the majority of patients and subsquamous IM [25–30].

Endoscopic mucosal resection

EMR is a technique utilized to diagnose, stage and sometimes completely remove HGD and early cancer in selected patients. There are multiple techniques, such as an endoscopic cap with internal snare device, a variceal ligation device or a monofilament snare in combination with lifting of the mucosa with a biopsy forceps [32]. Generally, EMR is performed after injection into the submucosal layer to lift the mucosa, although banding can be performed without injection. Once the tissue is snared, electrosurgical energy is used to cut out the mucosa. EMR produces a relatively large specimen (15–20 mm diameter) that allows histologic analysis of the lateral and deep margins, the latter of which is considered favorably by endoscopists and pathologists in staging more advanced disease, such as HGD and IMC.

Ell *et al.* evaluated EMR in 64 patients with early cancer (n = 61) or HGD (n = 3) [35]. After EMR, complete remission of the worst baseline diagnosis was achieved in 97% of patients with: lesion size of less than 2 cm; moderately or well-differentiated adenocarcinoma or HGD; and lesion limited to the mucosa. The complete remission rate was lower (59%) for: lesion size of greater than 2 cm; poorly differentiated adenocarcinoma; or infiltration of the submucosa.

EMR is an excellent modality for staging of an esophagus with a visible mucosal abnormality and for complete removal of focal disease or short segments of tissue. The favorable risk:benefit profile of EMR should be considered when considering esophagectomy in patients with HGD and early focal cancer, which may be amenable to endoscopic therapy. However, there are limitations to the extent of mucosa that can be resected with EMR before stricture formation is incurred [37]. When used for focal resection of focal nodules, plaques and early cancer, the residual Barrett's mucosa must still be considered 'at risk', and subsequent wide-field treatment with another modality should be considered.

Laser ablation

Reports of the use of laser ablation in Barrett's esophagus consist of small case series. In six of these reports [38–43], complete ablation of all IM was achieved in 0–62% of cases after multiple treatment sessions. Gossner found that 20% of patients had subsquamous IM after laser ablation [38]. Interest in the use of laser ablation for Barrett's esophagus has waned, and its use is limited to 'spot ablation' salvage for wide-field ablation techniques, such as PDT.

Argon plasma coagulation

APC is a system that delivers argon gas to the esophageal target epithelium via a through-the-scope catheter. As the gas exits the tip of the catheter, it is exposed to a monopolar electrosurgical electrode, which ionizes the argon gas and is carried to the tissue via the gas stream [44]. As the energy is conducted through the epithelium, coagulation occurs. Depth of ablative injury is variable and dependent upon gas flow rate, power setting, duration of application, tissue hydration and distance from probe tip to tissue [44].

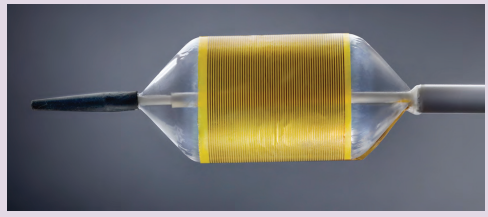
In ten published case series containing a diverse group of patients [44–48], with and without dysplasia, complete response rates for IM ranged widely from 0 to 99%. The observed inconsistency in results may be owing to variability in technique, treatment settings, number of ablation sessions and/or variation in ablation depth with APC. Dulai *et al.* recently reported a comparison study between APC and MPEC [48]. They report complete removal of IM in slightly over half of the patients: APC (58%) and MPEC (65%). The mean number of treatment sessions required were 3.8 (APC) and 2.9 (MPEC). Manner *et al.* performed a seven-center, 60-patient trial of APC for nondysplastic IM. They report a complete response rate of 77% at 14-month follow-up (per protocol analysis). Owing in part to a major complication rate of 9.8% (perforation, bleeding, stricture), the authors concluded that APC could not be recommended for treatment of nondysplastic IM [44].

Complications that have been reported related to APC for Barrett's esophagus include pneumatosis, pneumoperitoneum, subcutaneous emphysema, pain, ulceration, stricture, bleeding, perforation and death [44–48].

Multipolar electrocoagulation

MPEC involves the delivery of electrosurgery energy via a through-the-scope probe to provide point-coagulation of tissue. Energy travels between electrodes at the tip of the device, inducing tissue coagulation. Ablation depth is

Figure 3. Circumferential ablation catheter with electrode array (3 cm length) containing 60 isolated electrode rings.



Electrode rings are narrowly spaced, 250 µm apart.

variable, owing to dependence on operator technique and treatment settings. In four case series [49–52], 110 patients were treated with MPEC. The reported complete response rate for IM ranged from 75 to 100%. Multiple sessions are typically required. All studies report adverse postablation symptoms as common; specifically, Kovacs reported that 41% of patients experienced dysphagia, odynophagia or chest pain lasting up to 4 days [50]. As with APC and laser, MPEC is relegated to focal ablation of persistent IM after ablation with other modalities, such as PDT.

Cryotherapy

Cryotherapy is not a new modality, as it has been applied for tumor management in areas of the body other than the esophagus. More recently, cryotherapy has been studied in a limited manner for ablation of esophageal epithelium. Liquid nitrogen is sprayed onto the esophageal epithelium via a through-the-scope catheter. Johnston *et al.* treated 11 patients an average of 4.2-times each. Short-term follow-up of 6 months showed elimination of all IM in nine patients [53].

Circumferential & focal ablation

Devices

Circumferential and focal ablation for Barrett's esophagus are performed using the HALO ablation system (BÂRRX Medical, Inc., Sunnyvale, CA, USA). There are two distinct ablation devices in the HALO system, each distinctly designed for the treatment of a particular presentation of Barrett's esophagus. Circumferential ablation is performed using the HALO^{360} ablation system, which includes a sizing balloon, ablation catheter and energy generator. The sizing balloon catheter has a non-compliant 33.7-mm outer diameter (OD) clear balloon. When inflated to a low pressure (4 psi, 0.25 atm) using a pressure:volume measurement system integral to the energy generator, the inner diameter (ID) of the esophagus body is measured and displayed. The ablation catheter (**Figure 3**) has a 3-cm-long flexible electrode affixed to a balloon available in multiple sizes (22, 25, 28, 31, 34-mm OD). The electrode is comprised of multiple narrow bands (each 250 µm wide) with 250-µm spacing. The bands alternate in electrical polarity (plus/minus).

Focal ablation is performed using the HALO^{90} ablation system (BÂRRX Medical, Inc.), USA), which includes an ablation device (**Figure 4**) and energy generator. The device has a flexible strap that slides over the tip of the endoscope (compatible 8.6–12.8 mm). The view and function of the endoscope are preserved. The upper surface of the device is a 20-mm-long by 13-mm-wide platform covered by an electrode array, which is identical in pattern to that of the balloon-based ablation electrode. The endoscope is used to bring the electrode into contact with the targeted Barrett's tissue and the device platform is articulated so that the electrode remains flat against the tissue during ablation.

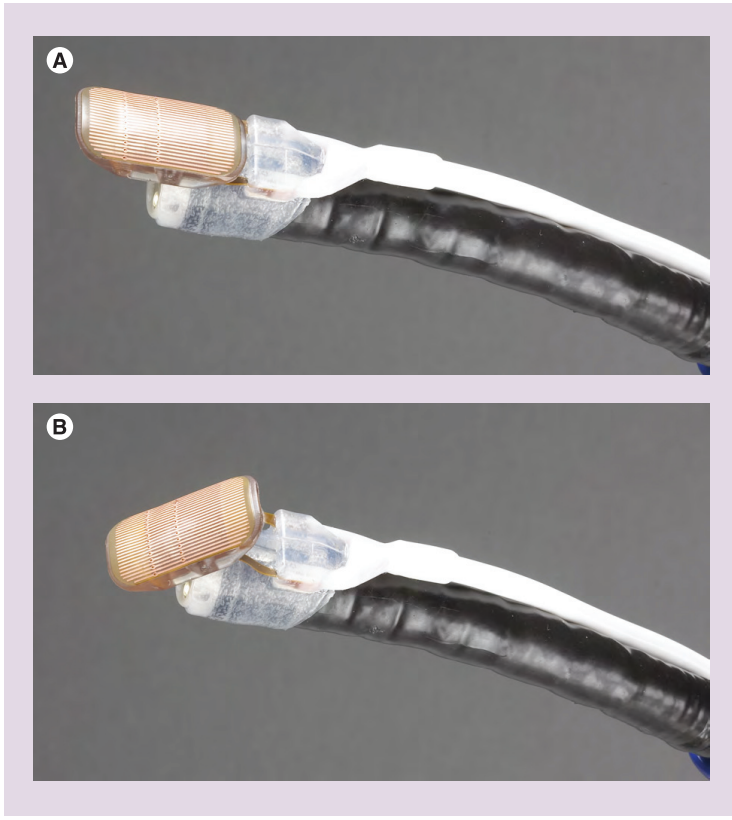
Circumferential ablation is applied as a primary intervention for a Barrett's esophagus segment that involves the entire circumference of the esophagus and is 2 cm or more in length. Focal ablation, on the other hand, is applied as a secondary (touch-up) intervention for residual Barrett's tissue after primary circumferential ablation, PDT, EMR or other modality. Focal ablation may also be applied as primary therapy in cases of noncircumferential Barrett's esophagus less than 2 cm in length.

Delivery of energy is automated for both ablation devices, thereby removing interoperator variation and presetting the ablation depth. High-power density (40 W/cm^2) allows the energy to be delivered rapidly (~250 ms) and a preset energy density (10/12 J/cm^2) ensures that each ablation zone is of uniform depth. Both systems have US FDA clearance and CE Mark (Europe) for treatment of Barrett's esophagus, specifically, and for coagulation of tissue in the gastrointestinal tract, in general.

Patient selection

Patients enrolled in clinical trials evaluating circumferential and focal ablation for Barrett's

Figure 4. Focal ablation catheter with electrode array mounted on an articulated platform.



(A) In repose without deflection. **(B)** In a deflected position as would occur with apposition to esophageal wall. Device fits on the end of a standard gastroscope. Electrode array is 13 mm wide by 20 mm long and has an identical electrode pattern to the circumferential ablation catheter.

esophagus have met the following general criteria: adult age, histological evidence of IM, and up to 10 cm Barrett's esophagus length. Specific trials have been conducted to evaluate each of the histological grades of Barrett's esophagus, including: no dysplasia, LGD, HGD and early cancer. In cases of nodularity, EMR is used to remove the lesion first, followed by ablation commencing 8 weeks later. To date, patients have not been eligible for clinical trials if they had esophageal stricture or varices, active esophagitis, prior ablation with another ablative modality, prior radiation therapy to esophagus or an implanted electrical device.

Circumferential ablation technique

Upper endoscopy is performed and the esophagus irrigated with 1% acetylcysteine in plain water to remove mucus. The total length of the Barrett's segment is measured from the top of gastric folds (TGF) to the proximal extent of visible Barrett's esophagus.

The sizing balloon catheter is introduced over a guidewire and positioned using measurement markings on the catheter shaft so that the balloon is 12 cm above the TGF. Using the automated pressure:volume system, the balloon is inflated and the ID of the esophagus measured. The measurement step is repeated in 1-cm increments moving distally until an abrupt increase in ID is noted, indicating that the balloon has migrated below the GEJ (**Figure 5A–D**).

Most esophageal bodies have a consistent ID, typically 25–31 mm. Based on the series of measurements, an appropriately sized (OD) ablation catheter is selected. If the esophagus ID is not consistent, a size appropriate for the smallest segment is selected. The ablation catheter is introduced over the guidewire, and the endoscope introduced in a side-by-side manner. The proximal margin of the electrode is positioned 1 cm above the proximal edge of the Barrett's segment. The balloon is inflated by the energy generator (7 psi, 0.5 atm) and energy delivered. The deflated electrode is advanced, the proximal edge aligned with the distal margin of the ablation zone and ablation repeated. Overlap of approximately 5 mm between treatment zones is performed to avoid missed areas. This is repeated until the ablation zone crosses the TGF, indicating that all Barrett's tissue has received one application of energy (**Figure 6A–F**).

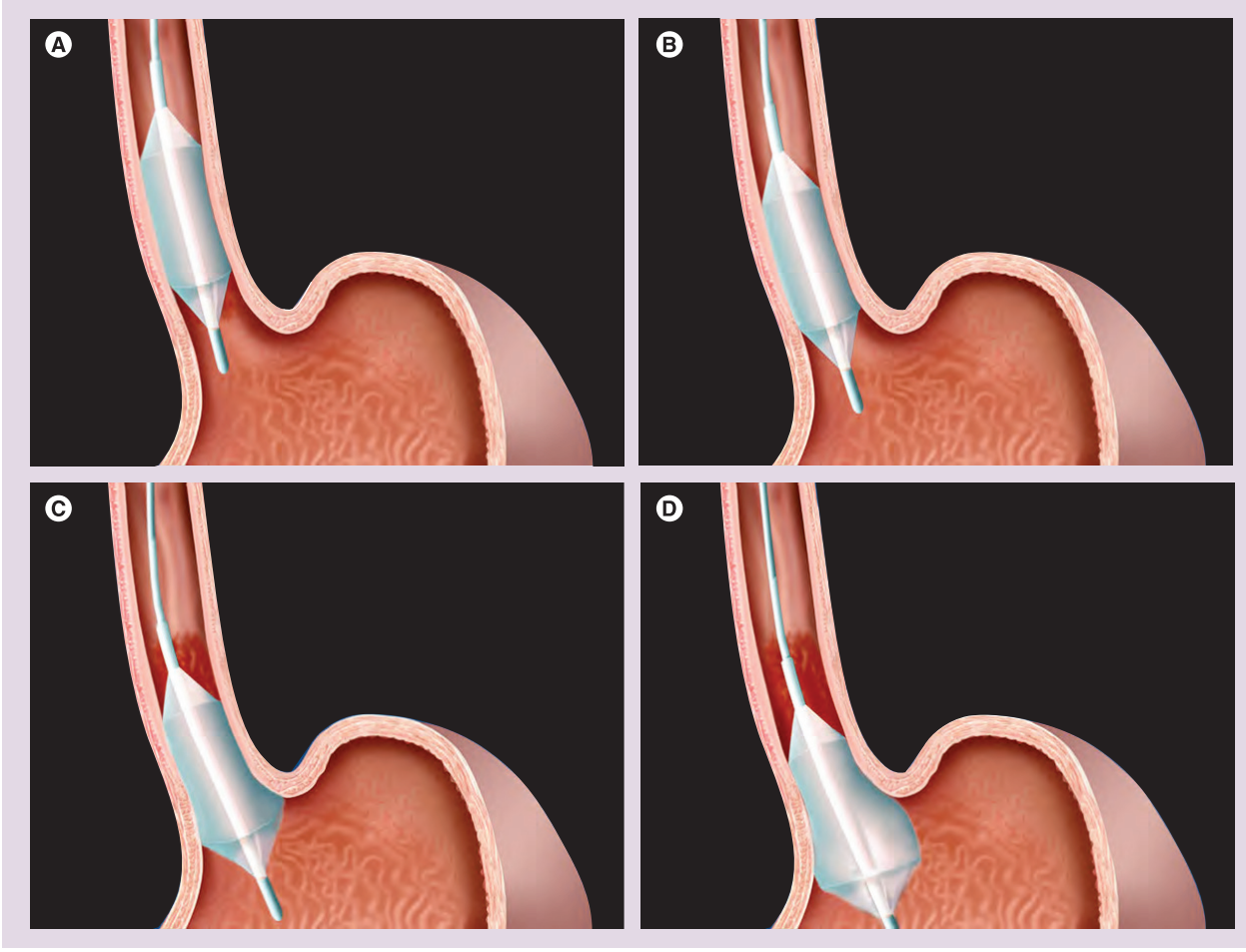
The balloon is inflated outside the body and the electrode cleaned of all coagulated tissue. The endoscope is reintroduced and the ablation zone cleaned of all adherent coagulum as well. Techniques used to clean the ablation zone include: irrigation and suction using the endoscope; irrigation via a spray catheter; and use of a soft EMR cap.

The ablation catheter and endoscope are reintroduced. The proximal margin of the electrode and ablation zone are aligned, the balloon inflated and ablation delivered. The entire ablation zone is treated in a proximal to distal manner until the ablation crosses the TGF. All Barrett's tissue has thus received two applications of energy, deemed '2×'. **Figure 7A** shows the treated segment after circumferential ablation, with no adherent coagulum and a tan color to the treated tissue.

Focal ablation technique

The focal ablation device is mounted on the tip of a gastroscope (**Figure 3**), with the electrode platform oriented at the 12 o'clock position in the video image (**Figure 7B**). The maximum

Figure 5. Sizing procedure.



(A) Sizing balloon catheter is positioned proximal to gastroesophageal junction. **(B–C)** Serial measurements are made, moving the balloon distally in 1 cm increments between measurements. **(D)** As the balloon enters the cardia of the stomach, an abrupt increase in measured size is noted as the balloon is no longer contained by esophageal body. An ablation catheter size is selected based on the measurements of the tubular esophageal body, obtained proximal to the abrupt increase in size.

deflection capability of most endoscopes is designed to be in the upward (12 o'clock) direction, actuated by rotating the large control wheel backwards or counterclockwise.

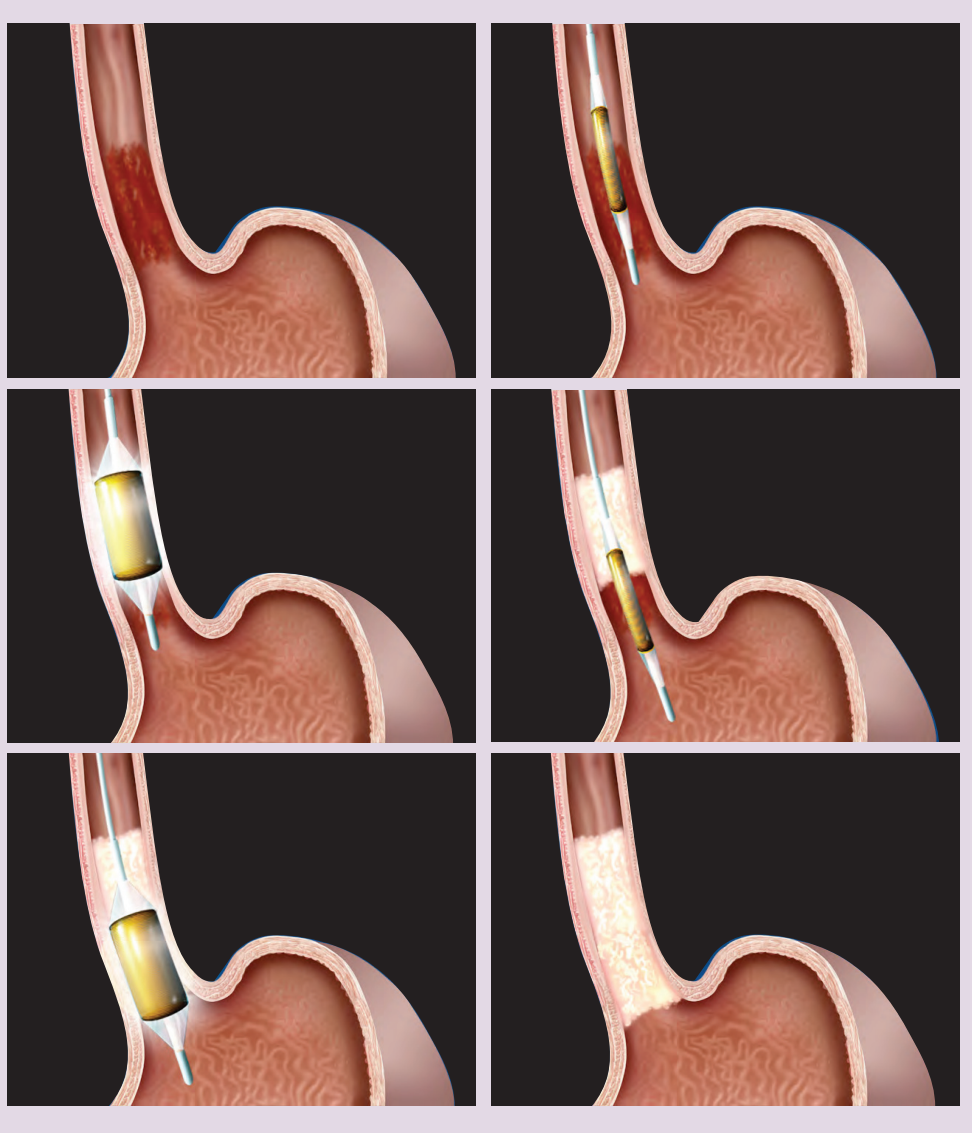
Introduction is performed with the endoscope in the natural position in the endoscopist's hand, which positions the electrode surface against the dorsum of the tongue. As the endoscope is advanced, the tip is deflected around the base of tongue (upward in the video image). At this point, the larynx is visualized and the electrode is facing anteriorly. Upward deflection is relaxed as the endoscope is advanced into the esophageal inlet posterolaterally.

The esophagus is irrigated with 1% acetylcysteine. Visible Barrett's tongues or islands are targeted first by rotating the endoscope so that the targeted tissue is above the electrode. The endoscope is deflected upward and ablation energy applied twice in succession. In the clinical trials to date, the squamocolumnar junction (SCJ) is empirically treated in a circumferential manner. All ablated areas are cleaned of coagulum and debris using the rounded leading edge of the electrode platform. The endoscope is removed and the electrode surface cleaned. The endoscope and device are reintroduced and all areas treated twice again. All areas thus receive four applications of energy.

Postablation discharge instructions & antisecretory regimen

After treatment, patients receive a high-dose antisecretory therapy (i.e., esomeprazole 40 mg twice-daily), and a mixture of antacid and liquid

Figure 6. Ablation steps.



(A) 4 cm Barrett's esophagus segment. **(B)** Ablation catheter positioned at the proximal portion of the Barrett's esophagus segment. **(C)** Balloon inflated and ablative energy delivered. **(D)** Ablation catheter repositioned distally in untreated segment. **(E)** Balloon inflated and ablative energy delivered. **(F)** Final appearance of ablated segment.

lidocaine, and liquid acetaminophen with or without codeine, as needed for discomfort. Patients are instructed to avoid noncardiac doses of aspirin and NSAIDs for 7 days before and after ablation.

Postablation follow-up

Postablation follow-up has four objectives:

- Perform additional focal ablation procedures at 2–3-month intervals until complete endoscopic resolution of all Barrett's is achieved;
- Upon achieving complete endoscopic resolution, biopsy to confirm complete histological resolution;
- Perform surveillance endoscopy using regimen appropriate for the baseline diagnosis to detect recurrence of Barrett's esophagus;
- Perform additional ablative procedures for any new Barrett's esophagus in order to maintain normal esophageal lining for the lifetime of patient.

Figure 7C shows a follow-up endoscopy after circumferential and focal ablation, with no evidence of Barrett's tissue and no IM on biopsy.

Clinical trials evaluating circumferential & focal ablation

Studies involving the circumferential ablation device were initially conducted in the porcine animal model to determine dosing and technique parameters. Subsequently, a number of prospective clinical trials were conducted involving patients with all grades of Barrett's esophagus (nondysplastic IM, LGD, HGD and early cancer).

Ganz *et al.* conducted a dosimetry study in the porcine esophagus using circumferential ablation. They varied energy density and power density to determine the optimal dose to achieve complete epithelial ablation without excess ablation depth or complications. Endoscopy was performed 1 month after ablation, and there were no strictures evident in the ablation zones treated using energy densities of 8, 10 and 12 J/cm^2 (40 W/cm^2). Higher energy densities (>20 J/cm^2) developed strictures. Acute histology showed complete ablation of the epithelium without submucosal injury at 8, 10 and 12 J/cm^2. The deepest injury achieved at this dose range was the muscularis mucosae. Deeper injury to the submucosa was evident at greater than 20 J/cm^2, hence the propensity for stricture formation at this dose [54].

Ganz *et al.* performed a pilot human clinical trial in patients scheduled for esophagectomy for the indication of EAC or HGD. They created circumferential ablations within the squamous-lined portion of the esophagus using 10 or 12 J/cm^2. The patient underwent esophagectomy 24–48 h later. Complete removal of all epithelium was achieved at both doses with no submucosal injury [54].

Dunkin *et al.* created multiple circumferential ablation zones in the squamous portion of the esophagus of patients prior to esophagectomy for EAC or HGD. In this trial, single and double treatments to the same site were evaluated, deemed 1× and 2×, respectively. It was hypothesized that multiple low-energy passes, as opposed to one higher-dose pass, would provide more effective removal of the epithelium without excessive ablation depth. Histology demonstrated complete removal of epithelium at 10 J/cm^2 (2×) and 12 J/cm^2 (1× or 2×), without injury to the submucosa. Areas treated with 10 J/cm^2 (1×) showed only partially ablated epithelium [55].

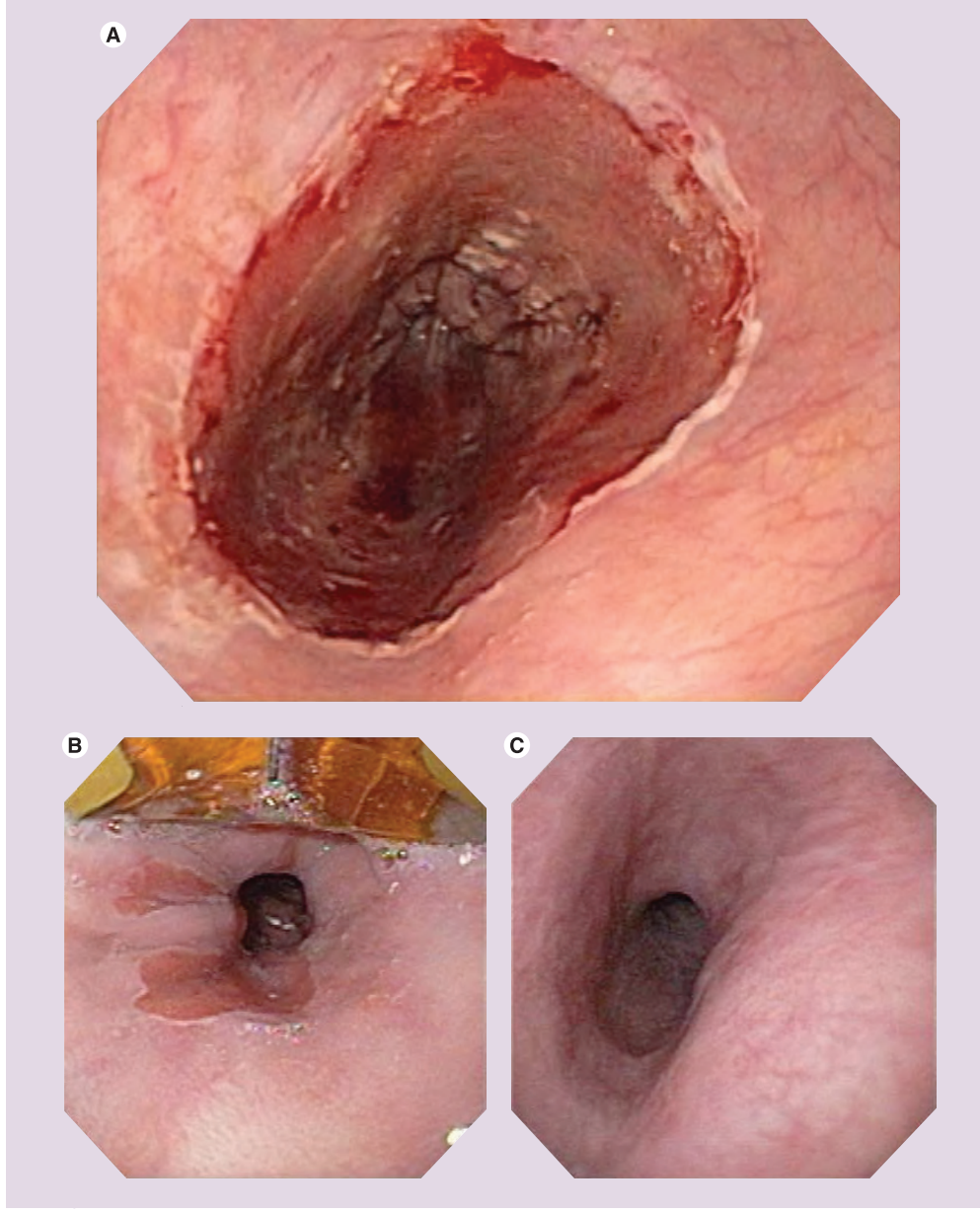
Smith *et al.* used a similar 'ablate and resect' protocol to Dunkin, but created multiple circumferential ablation zones in segments of HGD, followed by esophagectomy. Segments were randomized to 10, 12 or 14 J/cm^2 and 2×, 3× or 4× applications. The maximum ablation depth was the lamina propria or muscularis mucosae in all zones, although there was evidence of superficial submucosa edema in the ablation zone treated at the highest dose (14 J/cm^2, 4×). Complete ablation of all IM and HGD was achieved in all but one ablation zone (12 J/cm^2, 2×), likely owing to incomplete overlap [56].

After completion of the pilot dosimetry trials involving ablation and esophagectomy, the Ablation of Intestinal Metaplasia (AIM) Trial was commenced as the first study to enroll patients with Barrett's esophagus who would retain their esophagus after ablation. The AIM Trial was conducted in two serial phases, a dosimetry phase (AIM-I; n = 32) and an effectiveness phase (AIM-II; n = 70). All patients had nondysplastic IM. The dosimetry phase evaluated the dose–response and safety of delivering circumferential ablation using 6–12 J/cm^2 (1×) in patients with up to 3 cm of Barrett's esophagus. There were no dose-related serious adverse events and the outcomes at 1 and 3 months, along with the experience form previous esophagectomy studies, permitted the selection of 10 J/cm^2 (delivered 2×) for the subsequent effectiveness phase of the study [57].

The effectiveness phase involved circumferential ablation using 10 J/cm^2 (2×) in patients with up to 6 cm of Barrett's esophagus. Patients underwent endoscopy with biopsies at 1, 3, 6, 12 and 30 months. Focal ablation was applied after 12 months for any residual IM. The primary end point for AIM-II was histology-based and defined as complete response (CR) for IM at 12 and 30 months. A CR-IM means all biopsies for a patient show no evidence of IM at that time interval. The percentage of patients free of IM at 12 and 30 months are reported as the efficacy rate (percentage CR-IM). At 12 months (n = 69; mean: 1.5 sessions), a CR-IM was achieved in 70% of patients. At 30 months, as a result of providing focal ablation, a CR-IM was achieved in 98% of patients. There were no strictures or buried glandular mucosa at 12 or 30 months. There were no serious adverse events [57,58].

Sharma *et al.* used step-wise circumferential and focal ablation for patients with Barrett's esophagus containing LGD. Circumferential ablation was performed at baseline and repeated at 4 months for any residual IM. Focal ablation was performed after 12 months for any residual IM. Endoscopy with four quadrant biopsies every 1 cm was performed at 1, 3, 6, 12 and

Figure 7. Ablation effect.



(A) Acute appearance after two passes with circumferential ablation, note clean surface without residual coagulum or epithelium. **(B)** Videoendoscopic appearance of focal ablation device mounted on gastroscope, small areas of residual Barrett's tissue are visible at 6 o'clockand 9 o'clock and will be targeted with the focal device. **(C)** Follow-up appearance of esophagus after circumferential and focal ablation with no evidence of visible Barrett's tissue and all biopsies negative for intestinal metaplasia (IM).

24 months. This trial used similar histology-based end points, including CR-dysplasia (all biopsies negative for IM containing dysplasia) and CR-IM. At 2 years, CR for dysplasia was 100% and CR for IM was 90%. There were no strictures and no evidence of buried glands [59].

Inadomi *et al.* performed a cost–effectiveness analysis comparing circumferential and focal ablation versus annual surveillance endoscopy alone for patients with LGD. In a base case 50-year-old patient followed to age 80 years or death, they found that ablative therapy may be the most cost–effective option, reporting that ablation was preferred to surveillance based on extended dominance [60]. Das *et al.* conducted a similar cost-effectiveness analysis using a

Markov model in a base case 50-year-old patient with nondysplastic IM [61]. They compared three strategies:

- Natural history (no intervention)
- Surveillance
- Circumferential and focal ablation

The assumptions were conservative, using estimates of CR-IM that were intentionally lower than the published studies have reported (50% rather than more than 90%). The authors found that patient age, cost of ablation and effectiveness rate (CR-IM) associated with ablation were critical determinants of its cost–effectiveness. Within a range of these parameters, ablation for nondysplastic Barrett's esophagus is a cost-effective strategy in this model [61].

Bergman *et al.* have conducted several studies evaluating the safety and efficacy of circumferential and focal ablation for patients with the most advanced stages of Barrett's esophagus, including LGD, HGD and early cancer. In one report, 23 patients (17 men; median age: 66 years) were enrolled (median Barrett's esophagus length 7 cm; interquartile range: 4–10cm). EMR of visible abnormalities was performed in 13 patients, demonstrating mucosal carcinoma (n = 4), HGD (n = 6) and LGD (n = 3). Worst pathological grade of the remaining Barrett's segment after EMR and prior to ablation was LGD (n = 3) and HGD (n = 20). After circumferential and focal ablation, a CR-dysplasia was achieved in 22/23 patients (96%) and CR-IM in 21/23 patients (92%). No biopsy showed evidence of buried glandular mucosa [62].

Bergman *et al.* reported on a group of patients (n = 10) with HGD who underwent circumferential and focal ablation with pre- and post-ablation assessment of genetic abnormalities associated with Barrett's dysplasia and cancer, including immunohistochemistry for Ki67 and p53, and FISH for numerical chromosomal changes and loss of p16/p53. All patients demonstrated baseline abnormalities on both immunohistochemistry and FISH. After ablative therapy, CR-dysplasia and CR-IM was achieved in all patients (100%). No patient showed persistent abnormalities of Ki67 or p53, and all FISH probes were normal [63].

Bergman *et al.* performed pre- and post-ablation testing of the esophagus to determine if the function of the esophagus was impaired by circumferential ablation. Using the inner diameter measurement feature of the HALO ablation system, standard perfusion manometry and impedance planimetry (compliance), they found that there was no change in any of these parameters comparing the baseline and postablation results. Thus, ablation did not impair the functional integrity of the esophagus [64].

A patient registry involving 16 US centers and 142 patients with a diagnosis of HGD was conducted from 2004 to 2007. After a mean follow-up of 12 months after circumferential ablation only, complete eradication of HGD was achieved in 90% of patients. The stricture rate was less than 1%. As with other reported studies, there were no cases of buried glandular mucosa [65].

Rothstein *et al.* conducted a retrospective review of all focal ablation procedures performed in the USA during 2006. A total of 508 cases were reviewed, 182 of which were compiled from prospective clinical trials. These cases represent primary and secondary treatments for all stages of Barrett's esophagus. For the trial cases, 14-day symptom diaries were completed by the patient, querying chest pain, dysphagia, odynophagia, throat pain and abdominal pain. Median scores for each symptom were less than 10/100 on day 1 and returned to 0/100 by day 4 after ablation, therefore, symptom severity after ablation; was minor. There were no perforations, mucosal lacerations, bleeds, stricture formation or other adverse events. One patient (0.5% of the ablation cases conducted in a prospective clinical trial) reported symptoms of esophageal spasm on day 1 and was admitted for pain control [66].

Discussion

Barrett's esophagus is a metaplastic change occurring within the esophageal epithelium and resulting from chronic mucosal injury associated with GERD. Once the metaplastic change occurs, spontaneous reversion back to a normal squamous epithelium is uncommon. The propensity to develop dysplasia and adenocarcinoma in a Barrett's esophagus segment is the basis for recommending surveillance endoscopy with biopsy at regular intervals for the lifetime of the patient, in order to detect such progression at the earliest possible stage. If progression is detected, the management approach is adjusted accordingly. If HGD or cancer is discovered, these patients have historically undergone esophagectomy, although ablation and EMR have played a more dominant role in the last 5 years.

There are many reports of the progression rate of a Barrett's esophagus segment to dysplasia or cancer. As described earlier in this report,

Sharma *et al.* found that 21.7% of patients with nondysplastic IM progressed to LGD, HGD or cancer during a 4.2-year mean follow-up (5.2% per patient-year follow-up) [21]. In a meta-analysis of 25 studies by Shaheen *et al.*, the per-patient per-year progression rate for nondysplastic IM to cancer was 0.5% (range: 0.0–2.7%) [23].

This review briefly summarized the endoscopic techniques that have been evaluated for ablating Barrett's esophagus, such as APC, MPEC, laser, cryotherapy and PDT. Issues that have limited the use of these approaches have been related to nonuniform ablation (residual IM or buried IM), excessive ablation depth (stricture formation and other complications), and patient tolerability (photosensitivity and postablative symptoms).

A more-detailed review was provided related to circumferential and focal ablation for Barrett's esophagus. Both devices incorporate a tightly spaced electrode, high-power short-duration energy delivery and controlled energy density, which combine to provide uniform ablation of the esophageal epithelium. Uniform in this context refers to complete removal of all treated epithelium, without significant injury to underlying structures. Clinical trials of this device in patients with Barrett's esophagus (dysplastic and nondysplastic) have demonstrated very promising complete response rates for IM and dysplasia (defined as percentage of patients having no evidence of IM or dysplasia on follow-up biopsy), no buried glands, a very low rate of stricture formation or other complications and good patient tolerability.

As data become available for the use of circumferential and focal ablation for Barrett's, we as clinicians are faced with the challenge of determining which patients with Barrett's esophagus should be treated. Certainly, the patient with HGD and/or early cancer may benefit from endoscopic therapy combining EMR and ablation, as described by Bergman *et al.* The patient with LGD may also be eligible, as these patients are at higher risk than nondysplastic IM patients for developing HGD and cancer, they require more frequent surveillance, and the pathological interpretation of LGD remains problematic. The patient with nondysplastic IM represents, perhaps, the most challenging clinical decision. As longer-term trial outcomes become available for this technique, if the current safety and efficacy results remain favorable and durable, and if cost–effectiveness studies are favorable, we may offer this therapy to selected patients with nondysplastic IM to reduce their risk for progression to dysplasia and cancer.

Yet another challenge we face is how to manage the treated patient, regardless of baseline histology grade, who no longer has evidence of IM on repeated follow-up biopsies. First, it is important to recognize that Barrett's developed originally owing to GERD, and that the ablative intervention has done nothing to correct the pathophysiology of GERD. Therefore, a lifelong GERD management strategy must be tailored for each patient. For most, this will include an antisecretory regimen most likely consisting of a PPI of adequate dose to control GERD symptoms and avoid esophagitis. Antireflux surgery may be elected for some patients who are inadequately controlled on a properly escalated antisecretory drug regimen. Second, the role of long-term surveillance endoscopy must be considered. We advocate continuing a surveillance endoscopy regimen for all patients. A patient with nondysplastic IM converted to 'no IM' will continue surveillance every 3 years. A HGD or LGD patient converted to 'no IM' will continue surveillance every 3 and 12 months, respectively, for the short-term, but may lengthen their surveillance interval as serial biopsies continue to show no IM over time.

With the collective experience and clinical evidence from multiple clinical trials, and the addition of the focal ablation device to this armamentarium, we typically perform a circumferential ablation procedure at baseline, followed by a focal ablation procedure every 2–3 months as necessary in order to achieve a complete response for dysplasia and IM. Regardless of baseline grade of Barrett's esophagus, our clinical objective is elimination of all IM in a given patient. As we continue to study this technology, we may discover that elimination of all IM in a given patient reduces their lifetime risk for developing dysplasia and cancer.

Future perspective

Historically, the early stages of Barrett's esophagus IM and low-grade dysplasia (LGD) have been managed with expectant surveillance endoscopy in order to detect progression to HGD and cancer at the earliest stage, while later stages (HGD and cancer) have been managed with surgical esophagectomy. More recently, EMR and ablative techniques have garnered a significant role in this management paradigm, particularly with HGD and early cancers.

In the next 5–10 years, we envision a number of exciting developments in the field of Barrett's esophagus, which we believe will significantly improve patient care. First, assessing Barrett's tissue for molecular oncogenentic abnormalities will allow us to stratify the risk of the nondysplastic IM and LGD patient population for disease progression. Such stratification will allow us to offer EMR and ablation to the highest risk patients, thereby eliminating the precursor lesion, the oncogenetic abnormalities and, ultimately, the risk for cancer progression. The lowest-risk groups may be able to avoid future surveillance (and therapy) altogether. Second, advanced endoscopic imaging techniques (capsule, transnasal endoscopy, magnification and optical biopsy) may allow earlier diagnosis of Barrett's esophagus and, as a result, perhaps fewer undiagnosed Barrett's patients will progress insidiously to cancer. Lastly, as additional experience is gathered with the combination of EMR and endoscopic ablation in all stages of Barrett's, surgery for the indication of HGD and early cancer may no longer be necessary.

Finally, from a world-health perspective, it is exciting to consider the opportunity to extend what has been learned from the collective experience with EMR and ablation in Barrett's esophagus and EAC to the treatment of esophageal squamous dysplasia and squamous cell carcinoma. Squamous dysplasia has an even higher rate of progression to cancer than Barrett's esophagus, and squamous cell carcinoma of the esophagus is diagnosed in over 400,000 people every year worldwide, dwarfing the number of new EAC cases.

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Executive summary

- Barrett's esophagus is a cellular change of the esophageal epithelium, deemed intestinal metaplasia (IM), and is related to chronic gastroesophageal reflux disease (GERD).
- The disease is categorized histologically as nondysplastic IM, low-grade dysplasia or high-grade dysplasia.
- The IM cell is the precursor to esophageal adenocarcinoma.
- Management of a patient with Barrett's esophagus includes surveillance endoscopy to detect progression to cancer, treatment of GERD symptoms and, more recently, endoscopic therapy for selected patients to remove the diseased epithelium.
- A review of the endoscopic therapies for Barrett's esophagus is presented, with a focus on step-wise circumferential and focal ablation using the HALO ablation system.

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