

Mucosal ablation of Barrett esophagus

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Abstract | The management of Barrett esophagus is evolving with the emergence of new endoscopic technologies. Traditionally, patients with high-grade dysplasia or cancer were referred for esophagectomy. However, with the advent of endoscopic ablative therapies for Barrett esophagus, the treatment paradigm has shifted. Patients with high-grade dysplasia and intramucosal carcinoma are increasingly offered esophagus-sparing therapies. Endoscopic ablative therapies can be categorized into tissue-acquiring and non-tissue-acquiring modalities. Visible lesions in the setting of dysplasia should be treated with a tissue-acquiring modality to stage and resect the lesion appropriately. One or more modalities may be used to eradicate the entire region of affected esophagus totally. Total eradication treats all of the at-risk epithelium and, therefore, treats any metachronous or synchronous lesions. Success of treatment may be gauged by complete remission of cancer, dysplasia, or Barrett esophagus. In addition to procedure-related complications, the risk of residual Barrett esophagus or subsquamous Barrett esophagus remains to be addressed. Endoscopic surveillance and acid suppression is still currently required after ablation.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the prognosis of Barrett's esophagus.
- 2 Distinguish the most effective treatment for Barrett's esophagus with high-grade dysplasia and visible lesions on endoscopy.
- 3 Describe the technique and efficacy of endoscopic mucosal resection.
- 4 Compare newer ablative therapies for high-grade dysplasia associated with Barrett's esophagus.

Introduction

Barrett esophagus occurs when the normal squamous lining of the esophagus undergoes conversion to specialized, intestinal, columnar epithelium. The incidence of esophageal adenocarcinoma in patients with

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nondysplastic Barrett esophagus is approximately 0.5% per year.¹ The only feature that is currently widely accepted as a clinical marker of risk of progression to cancer is the presence of high-grade dysplasia on histological examination of esophageal biopsy specimens. The risk of progression to adenocarcinoma among patients with high-grade dysplasia and Barrett esophagus is approximately 6.6 cases per 100 patient-years.²

Traditional management of patients with Barrett esophagus involved surveillance protocols for those without dysplasia or with low-grade dysplasia. Patients who had high-grade dysplasia or resectable cancer underwent esophagectomy. Over the past few years, this approach to management of Barrett esophagus has changed, owing to the emergence of endoscopic ablative therapies. Patients with Barrett esophagus and high-grade dysplasia or intramucosal carcinoma are now offered esophagus-sparing therapies at centers where these advanced endoscopic therapies are available.

The role of endoscopic therapy

Traditionally, patients with Barrett esophagus and high-grade dysplasia underwent immediate esophagectomy because of the estimated risk that 40% of such patients harbored occult cancer.^{3–5} A 2008 systematic review analyzed the risk of esophageal cancer in 441 patients with Barrett esophagus and high-grade dysplasia who underwent prophylactic esophagectomy for treatment of their high-grade dysplasia. Although the pooled, average rate of occult adenocarcinoma in the esophagectomy specimens was 39.9%, the rate of proven invasive cancer, as defined by the presence of submucosal invasion or beyond, was only 12.7%.³ The remainder of the adenocarcinomas were intramucosal carcinomas, which have a low risk of nodal metastasis (approximately 0–3%) and

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Key points

- Total eradication of Barrett esophagus provides treatment not only for known lesions, but also for metachronous and synchronous lesions in the remainder of the at-risk epithelium
- Visible lesions in the setting of high-grade dysplasia or intramucosal carcinoma should be treated with a tissue-acquiring modality to stage and treat the lesion appropriately
- Ablative therapies, such as photodynamic therapy, radiofrequency ablation and cryotherapy, hold promise for the treatment of Barrett esophagus
- The diagnosis of neoplasia in Barrett esophagus should be confirmed by expert gastrointestinal pathologists

may be amenable to local therapy, such as endoscopic mucosal resection.^{6,7} Given that risk of mortality for patients who undergo esophagectomy is approximately 3–4%, even in experienced centers, the risk:benefit ratio of using endoscopic approaches to treat high-grade dysplasia and intramucosal carcinoma was comparatively reduced.⁸ Improved understanding of the risk of occult invasive cancer and advances in endoscopic technologies have, therefore, provided the rationale for the use of endoscopic therapy to manage high-grade dysplasia and intramucosal carcinoma in patients with Barrett esophagus.⁹ The low risk of cancer for patients with Barrett esophagus without dysplasia or with low-grade dysplasia, combined with the risk of possible complications that are associated with endoscopic therapy, suggests that ablative therapies do not provide the same level of benefit to this group of patients as they do for patients with high-grade dysplasia.¹⁰

Appropriate evaluation before treatment

Screening endoscopies are performed in patients with long-standing reflux to look for endoscopic and histological evidence of Barrett esophagus. Patients who have Barrett esophagus then undergo surveillance endoscopies to look for neoplasia. The standard endoscopic protocol for mapping and surveillance of Barrett esophagus involves biopsy of all visible lesions as well as four-quadrant mapping biopsies every 1–2 cm to look for evidence of occult neoplasia. In patients with known high-grade dysplasia, mapping biopsies should be performed every 1 cm.

All biopsy specimens with dysplasia should be evaluated by an expert gastrointestinal pathologist. Nevertheless, significant variation in pathological interpretation and poor interobserver agreement, even between expert gastrointestinal pathologists, has been reported.¹¹ Even when protocols for biopsy of Barrett esophagus are correctly followed, sampling error is still a concern as the vast majority of the epithelium is not sampled.

In addition to high-grade dysplasia, other factors that can increase the risk of harboring adenocarcinoma in an individual with Barrett esophagus have also been identified. The length of the Barrett esophageal segment and the presence of multifocal high-grade dysplasia,

visible lesions, large hiatal hernias and a *de novo* diagnosis of Barrett esophagus with high-grade dysplasia have all been associated with an increased risk of adenocarcinoma.^{3,12–14} The classification of Barrett esophagus on the basis of the endoscopic appearance of visible lesions is now becoming increasingly standardized between countries, and nonprotruding lesions are typically thought to be associated with a raised risk of adenocarcinoma. The updated Paris endoscopic classification of superficial neoplastic lesions is based on the Japanese scheme for classification of gastric lesions.^{15,16}

According to the updated Paris classification, lesions identified as superficial on the basis of their endoscopic appearance can be graded as either protruding, pedunculated (type 0–Ip), protruding sessile (0–Is), slightly elevated (0–IIa), completely flat (0–IIb), slightly depressed (0–IIc), excavated (0–II), or of a mixed pattern.¹⁶ Among focally resected visible lesions, type 0–Ip and type 0–IIc lesions are associated with an increased risk of submucosal penetration of carcinoma.¹⁷ Standard endoscopic procedures for obtaining biopsy samples have several limitations, including limited tissue sample size and depth, and artifacts that result from compression of the specimen. Appropriate diagnosis and staging of visible lesions in Barrett esophagus is, therefore, achieved by use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection—techniques that yield large and intact tissue specimens and can provide a more reliable diagnosis than is possible with standard procedures. These techniques are discussed in further detail below.

In the absence of visible lesions, the Barrett esophageal mucosa can be further characterized by use of enhanced endoscopic imaging. Areas suspected to include high-grade dysplasia or intramucosal carcinoma may be examined with modalities such as magnification endoscopy, high-resolution endoscopy, narrow band imaging, multiband imaging, autofluorescence imaging and chromoendoscopy. By use of magnification chromoendoscopy with indigo and carmine dye-staining and narrow band imaging, Sharma *et al.* demonstrated that the presence of an irregular, distorted pattern accurately predicts the presence of high-grade dysplasia.^{18,19} Such enhanced endoscopic imaging modalities not only accurately characterize mucosa in the absence of lesions, but may also be less time-consuming than standard endoscopic techniques that require four-quadrant biopsies to be obtained every 1–2 cm. These methodologies, therefore, serve as an important adjunct to standard biopsy protocols. Further staging of Barrett esophagus may be performed with use of endoscopic ultrasonography and/or a CT scan before endoscopic therapy of lesions is initiated.

Endoscopic ablative therapies

Endoscopic ablative therapies can be divided into tissue-acquiring and non-tissue-acquiring methods. Tissue-acquiring methods include focal EMR, complete

eradication of Barrett esophagus by EMR and endoscopic submucosal dissection. Non-tissue-acquiring methods include photodynamic therapy, radiofrequency ablation and cryotherapy. Visible lesions in patients with Barrett esophagus and high-grade dysplasia or intramucosal carcinoma should be treated with a tissue-acquiring modality so that lesions can be appropriately staged and resected. After all areas of localized neoplasia are removed and appropriately staged, the remainder of the Barrett epithelium may be eradicated by ablation to treat metachronous or synchronous lesions. Molecular abnormalities can persist in the remaining epithelium even after targeted ablation has been performed, which is sufficient reason to treat the whole of the 'at-risk' esophagus by complete eradication of the Barrett esophagus epithelium.²⁰

The success of therapy may be gauged by evidence of complete remission of cancer in the case of tissue-acquiring modalities, or remission of dysplasia or Barrett esophagus for all ablative modalities. The occurrence of complications during or after the endoscopic procedure, the presence of buried intestinal metaplasia on surveillance endoscopy and progression to cancer are points of particular concern. As increased experience with these procedures is gained, assessments of 5-year survival will offer an improved measure of the long-term outcome of using endoscopic ablative therapies to treat lesions of esophageal adenocarcinoma and their precursors. Some centers are beginning to report 5-year survival rates for patients who have received endoscopic therapies such as EMR and photodynamic therapy; the results suggest that endoscopic ablative therapy is a safe and curative approach for the treatment of Barrett esophagus and high-grade dysplasia or intramucosal carcinoma.^{21,22} Large studies with >5 years of follow-up might be needed to assess how these endoscopic approaches affect progression to cancer.

The myriad of nascent technologies in this arena is exciting, but these technologies have varied potential clinical applications and availability. The optimum approach to the treatment of patients with Barrett esophagus and high-grade dysplasia no longer involves routine esophagectomy. Local expertise with the different endoscopic modalities and patient-specific factors, such as age, preferences and the presence of comorbidities, should guide decisions about whether an individual undergoes intensive surveillance or esophagectomy, or receives endoscopic management.²³ The treatment approach to Barrett esophagus with dysplasia should be deliberate and have resources available to provide an appropriate work-up and management. Given the rigorous examination needed to detect neoplasia, the requirement for tissue-acquiring techniques, and the need to monitor patients' responses after administration of ablative therapies, at this point in time these endoscopic modalities are best provided by centers that have multiple diagnostic and therapeutic modalities available and in the context of clinical studies.

Tissue-acquiring ablative therapies

Advantages of a tissue-acquiring modality

The advantage of EMR compared with traditional endoscopic biopsy sampling is acquisition of a suitable histological specimen to stage disease and determine need for further treatment. As mentioned above, biopsy specimens obtained by conventional endoscopic approaches have a limited size and depth, and include artifacts that result from compression of the tissue. The differences between intramucosal and submucosal carcinomas often cannot be seen on histological examination of biopsy specimens. EMR provides a specimen of sufficient area and depth from which to make an accurate diagnosis. *En bloc* resections obtained by EMR or ESD may allow for a better assessment of lateral margins than can piecemeal resections. Positive, lateral margins of the resection area may be managed with further endoscopic treatment. Positive, deep margins that penetrate into the submucosa may, however, be an indication for esophagectomy.

Again, the importance of ensuring that histopathological analysis is performed by an expert gastrointestinal pathologist who is experienced in Barrett esophagus pathology must be highlighted. Factors such as duplication of the muscularis mucosa, a common feature of Barrett epithelium, may contribute to misdiagnosis of the depth of invasion.²⁴ Evidence of lymphatic-vessel involvement is correlated with increased risk of lymph-node metastasis in esophageal squamous-cell carcinomas.²⁵ Extrapolation of this finding to adenocarcinomas suggests that histological evidence of lymphatic-vessel involvement could be useful for stratification of cancer risk.

Some controversy exists about whether determination of the depth of tumor invasion should use qualitative or quantitative indices. Unlike the full-thickness specimens obtained by esophagectomy, endoscopically resected tissue might not include sample the entire submucosa and the specimens themselves are subject to artifacts from contraction and stretching. The submucosa (sm) can be qualitatively divided into three layers—sm1, sm2 and sm3, with sm1 indicative of 'superficial' submucosal invasion. The quantitative, empirical cut-off for the superficial submucosa of the esophagus is 200 μm . Regardless of whether a quantitative or a qualitative approach is used, the depth of submucosal invasion should somehow be evaluated. One study demonstrated complete remission of Barrett esophagus in 95% of patients ($n = 19$) with low-risk submucosal adenocarcinoma lesions (sm1, moderate to high differentiation with no vessel invasion, and type I or II endoscopic lesions) who were treated with endoscopic resection, with or without additional ablative therapy.²⁶ However, experience with endoscopic resection of esophageal adenocarcinomas with superficial submucosal invasion is limited, and the role of endoscopic therapy of these lesions is yet to be defined.²⁷

Endoscopic mucosal resection

EMR may be accomplished with *en bloc* or piecemeal resections. Commonly used EMR techniques

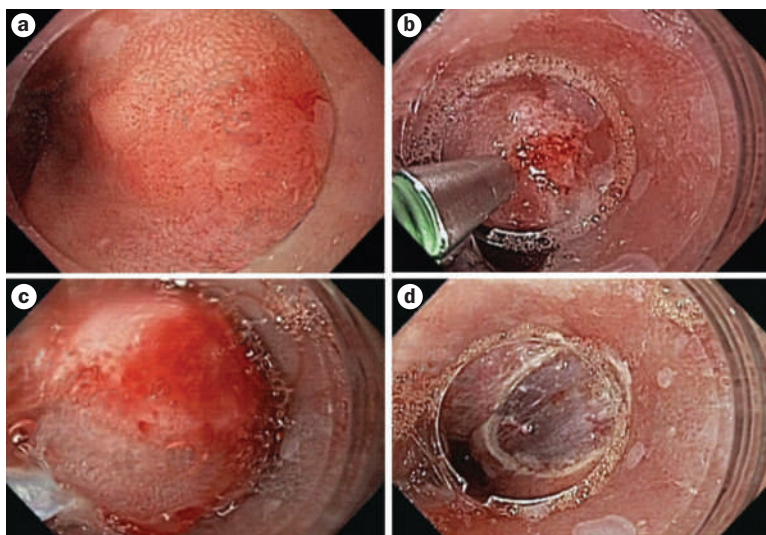


Figure 1 | Endoscopic mucosal resection of a lesion with use of the cap-assisted technique. **a** | A flat lesion of Barrett esophagus selected for endoscopic mucosal resection. **b** | The mucosa is lifted with an injection of saline. **c** | The lesion is then resected using a cap-assisted snare technique. **d** | The resection site is carefully inspected for complications.

can be injection-assisted, cap-assisted or ligation-assisted.²⁸ Injection-assisted techniques may be performed either with an injection of saline and ‘free-handed’ snare cautery to cut the tissue (also known as an inject and cut approach), or with an injection of saline and a dual-channel endoscope that uses forceps to grasp tissue through one channel and a snare to resect the tissue through the other channel (also known as an inject, lift and cut approach). The cap-assisted technique uses a cap that has a groove fitted on the tip of the endoscope. A submucosal injection of saline causes the tissue to lift, and a crescent-shaped snare is then inserted and placed into the groove of the cap. Suction is applied, the snare is closed, and cautery is applied to resect the tissue (also known as a suck and cut approach, Figure 1). Ligation-assisted resection may be performed by using a variceal band to first ligate the target tissue before a snare is used to resect it (also known as a band and cut approach). Comparison of the cap-assisted and band-ligation techniques revealed that they are equivalent in terms of their safety, efficacy and the size of tissue specimen that they can obtain.^{29,30}

A modified version of the ligation-assisted technique, the multiband mucosectomy technique, uses a modified multiband variceal ligator. This technique enables piecemeal resections to be performed efficiently, because the endoscope does not need to be withdrawn to place each snare. However, the resection specimens obtained with use of this technique are smaller in diameter than those obtained with the standard ligation-assisted approach.^{31,32}

Complications of EMR include stricture formation, bleeding and, rarely, perforation. Most stenoses and bleeding are amenable to endoscopic management. Initial reports from studies that have used EMR to eradicate

lesions are promising. Complete remission of neoplasia has been reported in 97–100% of cases.^{21,33–36}

Ell *et al.* reported on their long-term experience with EMR in 100 patients who had low-risk, early esophageal adenocarcinoma lesions (<20 mm, types I, IIa, IIb or IIc, with no lymphatic or vascular invasion, and moderate to high differentiation).³⁷ Complete remission was achieved in 99% of patients. 11% of the cohort had metachronous lesions that were successfully treated endoscopically. 5-year survival was 98%; the two deaths resulted from causes other than esophageal cancer. No major complications occurred in the study group.

Complete endoscopic mucosal resection

Complete Barrett eradication EMR (CBE-EMR) is a technique that uses extended EMR to eradicate the entire length of the Barrett esophagus epithelium. This technique is used to treat all lesions that may be occult or synchronous and should prevent the development of any metachronous lesions as the entire at-risk epithelium is removed. Several studies have investigated the effect of this technique on Barrett esophagus. Seewald *et al.* described effective ablation of Barrett esophagus in 12 patients by a median of 25 sessions of CBE-EMR.³⁷ Peters *et al.* demonstrated complete remission of Barrett esophagus in 89% of patients ($n = 39$) after a median of three sessions, Larghi *et al.* demonstrated complete remission of Barrett esophagus in 87.5% of patients ($n = 24$) after a median of three sessions and Lopes *et al.* described complete remission of Barrett esophagus in 75.6% of patients ($n = 41$) after the first CBE-EMR session and in 90% of patients after the second session.^{38,39} Esophageal stenoses occurred in 2–26% of cases in the above CBE-EMR studies, but all were amenable to endoscopic treatment.^{33–36}

Endoscopic submucosal dissection

Endoscopic submucosal dissection allows for *en bloc* dissection of neoplastic lesions. This technique has been predominantly used to remove superficial gastric cancers in Japan. Endoscopic submucosal dissection may, therefore, be a suitable modality to manage lesions that are located at the gastroesophageal junction. However, the use of this technique in the distal esophagus should be approached with caution, given the potential for reflux-induced submucosal fibrosis.⁴⁰ Yoshinaga *et al.* performed endoscopic submucosal dissection at the gastroesophageal junction in 24 patients for the treatment of adenocarcinoma (15 of these patients had Barrett esophagus). No recurrence of adenocarcinoma was observed during the 30-month follow-up.⁴¹

Non-tissue-acquiring ablative therapies

Photodynamic therapy

Photodynamic therapy is an ablation method that involves exposure of the tissue to a photosensitizing agent before light is delivered to it. This approach stimulates the formation of oxygen radicals and subsequent cell death. The photosensitizing agent approved by the FDA,

porfimer sodium, is administered intravenously and accumulates in esophageal tissue. 5-aminolevulinic acid is another photosensitizing agent that is administered orally and accumulates superficially in the mucosa. Light is delivered to the tissue by use of either bare, cylindrical diffusing fibers or balloon-diffusing fibers. Patients need to avoid exposure of skin to sunlight after the procedure. Complications of photodynamic therapy include skin photosensitivity, esophageal stricture, vomiting, noncardiac chest pain and dysphagia.

Overholt *et al.* described their experience of administering photodynamic therapy to 103 patients (mean follow-up 4 years).⁴² Complete remission was achieved in 78% of patients with high-grade dysplasia. The overall rate of stricture formation was 30%.⁴² A randomized, controlled trial, which included 208 patients with Barrett esophagus and high-grade dysplasia in the intention-to-treat population, compared the effect of administration of photodynamic therapy plus omeprazole with that of omeprazole alone.²² After 5 years, complete remission of high-grade dysplasia had been achieved in 77% of patients who received combination therapy compared with just 39% of patients who received omeprazole alone. Of note, the rate of progression to cancer was lower in the combination therapy group than it was in the omeprazole monotherapy group (15% and 29%, respectively).²² In this study, patients required up to three sessions to complete therapy. No controlled trials have compared photodynamic therapy and surgical therapy for the treatment of Barrett esophagus; however, a retrospective study of 199 patients demonstrated that mortality and long-term survival achieved by these modalities are comparable.⁴³

As mentioned above, esophageal strictures occur in approximately 30% of patients treated with photodynamic therapy. The risk of stricture development correlates with history of prior stricture, administration of EMR before photodynamic therapy, and use of multiple photodynamic treatments in a given session.⁴⁴ Whether esophageal strictures that develop after photodynamic therapy are benign (that is, a consequence of this treatment) or malignant (that is, owing to progression to adenocarcinoma) can be difficult to determine. Buried glands contain foci of Barrett epithelium that are covered by squamous epithelium and are another important feature to identify. The significance of buried glands is unknown, but the development of adenocarcinomas under squamous epithelium has been reported.^{42,45} In one study that examined histological and pathological specimens after photodynamic therapy, buried glands were found under the squamous epithelium in 51% of patients; 27% of these harbored dysplasia or carcinoma.⁴⁶

The ability of certain biomarkers to predict response of Barrett esophagus to ablation, such as with photodynamic therapy, has also been investigated. Panjehpour *et al.* demonstrated that administration of photodynamic therapy to patients with Barrett esophagus and high-grade dysplasia significantly reduced expression of the transcription factor p53 in the neosquamous epithelium.⁴⁷

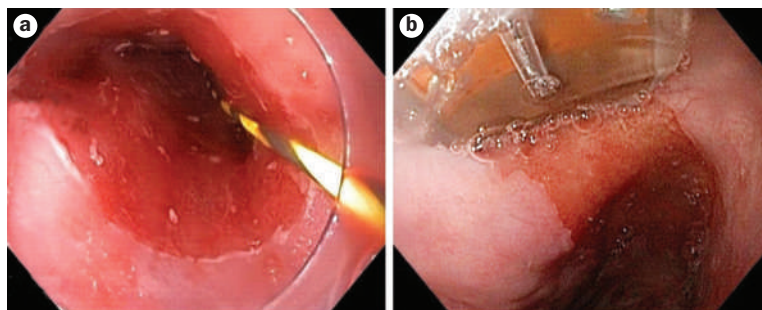


Figure 2 | Treatment of Barrett esophagus by radiofrequency ablation. **a** | Endoscopic image that illustrates a segment of Barrett esophagus after a circumferential application of radiofrequency ablation. **b** | Focal administration of radiofrequency ablation to a tongue-like lesion of Barrett esophagus.

Prasad *et al.* determined that patients with a loss of chromosome p16, as determined by fluorescence *in situ* hybridization, were less likely to respond to photodynamic therapy than were patients without such a loss.⁴⁸ Future investigations into different molecular markers that predict response to therapy may help to stratify patients who will probably respond to photodynamic therapy, and may improve dosimetry for all patients. The development of new photosensitizing agents may also improve the risk:benefit ratio for photodynamic therapy.⁴⁹

Radiofrequency ablation

Radiofrequency ablation uses a balloon-based catheter, such as that used by the Halo³⁶⁰ System (BÂRRX Medical Inc., Sunnyvale, CA), which delivers a high-energy pulse to the esophageal lining. An inflatable device that is sequentially inflated at multiple levels of the esophagus is used to determine the safest balloon size for the patient. The ablated tissue, as depicted in Figure 2a, is then removed by use of a scraping motion with a soft cap on the endoscope. The circumferential balloon device described above was subsequently supplemented with a focal radiofrequency ablation device, the Halo⁹⁰ System, also from BÂRRX Medical Inc., to treat residual areas of Barrett esophagus (Figure 2b).

Porcine and human epithelia were successfully ablated without causing submucosal injury by use of radiofrequency ablation at 10 J/cm² and 12 J/cm².⁵⁰ The depth of ablation correlates linearly with the density of energy delivered. Complications associated with radiofrequency ablation include chest pain, mucosal lacerations and stenosis.

The Ablation of Intestinal Metaplasia (AIM) trial assessed the safety and efficacy of radiofrequency ablation using the Halo³⁶⁰ System circumferential balloon device in patients with Barrett esophagus. Complete remission was achieved in 70% of patients ($n = 48$) with non-dysplastic Barrett esophagus 12 months after treatment.⁵¹ The AIM II trial used the Halo⁹⁰ System to treat residual Barrett esophagus after administration of circumferential radiofrequency ablation. With this approach, complete remission was achieved in 98% of patients ($n = 69$) with Barrett esophagus without dysplasia.⁵² No evidence of

buried glands was found on surveillance endoscopy in any patient.⁵²

A US, multicenter, registry study investigated 142 patients with Barrett esophagus and high-grade dysplasia who underwent radiofrequency ablation. 24 of these patients had previously received EMR. Complete remission of high-grade dysplasia was achieved in 90% of patients with high-grade dysplasia and complete remission of intestinal metaplasia was achieved in 54% of patients.⁵³ Shaheen *et al.* conducted a randomized, controlled trial in 127 patients to compare the efficacy of radiofrequency ablation with surveillance plus administration of a PPI versus that of sham ablation with surveillance plus administration of a PPI.⁵⁴ 1 year after administration of radiofrequency or sham ablation, 67% of patients who received radiofrequency ablation had achieved complete remission of dysplasia, compared with 0% of patients who received sham ablation. The rate of esophageal stricture formation after radiofrequency ablation was 6%—considerably lower than rates reported with use of photodynamic therapy.

Gondrie *et al.* investigated the efficacy of radiofrequency ablation for the treatment of Barrett esophagus in patients who had a maximum pathological stage of high-grade dysplasia after EMR of visible lesions. After receiving stepwise circumferential and focal radiofrequency ablation, complete remission of dysplasia and intestinal metaplasia was reported in 100% of patients.^{55,56} An additional study by the same researchers examined markers of apoptosis and proliferation, and evaluated histological changes in the esophageal tissue of 10 patients with high-grade dysplasia who received circumferential followed by focal radiofrequency ablation. All patients in this study achieved complete remission of their dysplasia and intestinal metaplasia, and no evidence of buried glands was found in biopsy samples. Interestingly, further analysis of the biopsy samples revealed alterations in markers of cell proliferation and apoptosis and demonstrated chromosomal abnormalities.⁵⁷ The clinical relevance of these changes are still unclear.

Cryotherapy

Cryotherapy uses a low-pressure spray of liquid nitrogen to freeze the epithelium to a depth of 2 mm. The spray is applied focally to targeted areas, and freezing and subsequent thawing of this tissue disrupts its intracellular structures and causes ischemic necrosis. Cryotherapy requires placement of a decompression tube in the lumen of the esophagus to prevent overinflation. Therapy sessions may be repeated every 4–6 weeks.

The use of cryotherapy to treat Barrett esophagus has been less extensively studied than have other modalities, but preliminary findings from studies of this modality are promising. In one study, 11 patients with Barrett esophagus that varied from no dysplasia to high-grade dysplasia underwent cryotherapy. Complete remission of Barrett esophagus was achieved in 78% of patients.⁵⁸ No complications were reported and no evidence of buried

glands was found after 6 months. Other pilot studies reported in abstract form have described cryotherapy to be a relatively safe treatment for Barrett esophagus.^{59,60}

Argon plasma coagulation

Argon plasma coagulation uses a high-frequency, monopolar current of ionized argon gas to ablate the epithelium. The depth of tissue injury is approximately 1–3 mm. Adverse effects and complications include chest pain, odynophagia and perforation of the esophagus. Many of the initial studies that used argon plasma coagulation are limited to the treatment of intestinal metaplasia; however, a few studies have investigated this technique for the treatment of dysplastic Barrett esophagus.

Studies that have combined argon plasma coagulation with PPI therapy for nondysplastic Barrett esophagus have reported success rates of 58–100%.^{61,62} Two studies examined the efficacy of argon plasma coagulation in combination with surgical fundoplication for the treatment of nondysplastic Barrett esophagus, with success rates of 70–100%.^{63,64} Attwood *et al.* investigated the efficacy of argon plasma coagulation for the treatment of high-grade dysplasia; 22 of 29 patients (76%) achieved complete remission of their Barrett esophagus.⁶⁵

On the basis of previous studies and experience, we now know that argon plasma coagulation should not be used to treat nondysplastic Barrett esophagus because of the high rate of relapse, continued progression to cancer, and a poor risk:benefit ratio.^{66–68} Currently, argon plasma coagulation is reserved as a ‘touch up’ therapy to treat areas of intestinal metaplasia left behind by other ablative modalities.⁶¹

Multipolar electrocoagulation

Multipolar electrocoagulation was one of the earliest ablative methods studied for the treatment of Barrett esophagus. This technique uses a heated catheter to contact the mucosa and to induce focal thermal injury. Studies have demonstrated the ability of multipolar electrocoagulation to eradicate Barrett esophagus; however, this technique has now largely been replaced by other ablative methods.^{69,70} The use of multipolar electrocoagulation may be considered in patients with implantable devices, such as defibrillators who have areas of focal or residual Barrett esophagus that need to be ablated.

Laser therapies

Laser therapies use an intense beam of light to produce a contact injury in the targeted esophageal epithelium. Neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers produce an injury with a depth of 3–4 mm, whereas potassium titanyl phosphate (KTP) lasers and KTP YAG lasers produce an injury with a depth of 1 mm.

Complications of laser therapy include retrosternal pain, dysphagia, odynophagia, nausea, vomiting, fever, epigastric pain, sore throat, headache, esophageal strictures, bleeding and esophageal perforation. Short-term success rates for the treatment of Barrett esophagus

with use of laser therapy have been variable. The rate of residual Barrett esophagus in patients after this treatment ranges from 0% to 85%, and rates of buried glands range from 0% to 90%.^{71–73}

Management of complications

Specific complications associated with each of the ablative therapies have been mentioned above. The overall complication profile of endoscopic therapy is better than that of esophagectomy. Appropriate endoscopic management of Barrett esophagus requires the availability of accessible resources to evaluate and manage potential immediate and delayed complications. Esophageal-stricture formation is a common complication of several ablative modalities, but can be treated endoscopically with dilation. Postprocedural admission for observation may be indicated in patients with severe chest pain. Mucosal tears or lacerations may be endoscopically managed with placement of covered stents or clips; these complications can be evaluated immediately with radiological procedures. Surgical expertise should be readily available in the event of perforation.

Surveillance and maintenance of remission

Safe and effective eradication of the entire Barrett esophagus epithelium has been made possible with increasing experience of ablative modalities. Total eradication of Barrett esophagus is advantageous in that the entire at-risk epithelium is treated. Occult, synchronous lesions and metachronous lesions that may develop subsequently over time are, thereby, effectively managed. Thus, the use of a technique or a combination of modalities to achieve complete eradication of the Barrett esophagus epithelium is more likely to maintain remission than are local therapies.

Life-long surveillance by performance of biopsy sampling throughout the location of the eradicated Barrett esophagus is required to monitor for recurrence of this condition, the presence of buried glands and the development of neoplasia. All ablative therapies also need to be accompanied by acid-suppression therapy, which prevents injury of the distal esophagus, avoids recurrence of Barrett esophagus and hence progression to dysplasia. All patients who have received ablative therapy should, therefore, also receive life-long, high-dose PPIs to control reflux symptoms. Acid suppression may also decrease the risk of progression to dysplasia in patients with Barrett esophagus.⁷⁴ Improved understanding of how other factors, such as genetic and molecular abnormalities,

influence the development of Barrett esophagus and neoplasia is also necessary. Increased understanding of underlying pathogenic factors might affect risk stratification and management of patients in the future.

Conclusions

The development of endoscopic ablative therapies has rapidly changed the management of Barrett esophagus. Visible lesions in patients with dysplasia should be endoscopically resected to obtain a histological specimen with which to properly stage disease and gauge treatment response. Intramucosal carcinoma should be treated by endoscopic mucosal resection; histopathological examination of deep and lateral margins will dictate whether the lesion is amenable to endoscopic therapy and the need for further treatment, respectively. Total eradication of the Barrett esophagus epithelium would treat not only the known lesions, but also any metachronous or synchronous lesions in the remainder of the at-risk Barrett epithelium. A combination of modalities might be needed to achieve complete eradication.

Further investigations with endoscopic ablative therapies are needed to characterize rates of clinical remission of neoplasia and Barrett esophagus, long-term survival, risk of buried glands, risk of progression to cancer, and procedure-related complications of the different modalities. Although the significance of buried glands is incompletely understood, they can harbor dysplasia or even cancer under squamous epithelium. Further studies are, therefore, required to elucidate the role and consequence of buried glands.

The role of ablative therapies for the treatment of low-grade dysplasia and nondysplastic Barrett esophagus is yet to be defined, and life-long surveillance remains the current recommendation for affected patients. Although further research into ablative technologies is required, esophagus-sparing approaches will evidently become the mainstay of therapy for patients with high-grade dysplasia and intramucosal carcinoma.

Review criteria

MEDLINE and PubMed search engines were used to select both original articles and review articles published from 1990 to December 2008. Search terms were “Barrett esophagus”, “ablative therapies”, “radiofrequency ablation”, “photodynamic therapy”, “endoscopic therapy”, “endoscopic mucosal resection”, and “cryotherapy”. Further articles were selected from the reference lists of these articles.

1. Shaheen, N. J., Crosby, M. A., Bozyski, E. M. & Sandler, R. S. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* **119**, 333–338 (2000).
2. Rastogi, A. *et al.* Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest. Endosc.* **67**, 394–398 (2008).
3. Konda, V. J. A. *et al.* Is the risk of concomitant invasive esophageal cancer in high grade dysplasia in Barrett's esophagus overestimated? *Clin. Gastroenterol. Hepatol.* **6**, 159–164 (2008).
4. Ferguson, M. K. & Naunheim, K. S. Resection for Barrett's mucosa with high-grade dysplasia: implications for prophylactic photodynamic therapy. *J. Thorac. Cardiovasc. Surg.* **114**, 824–829 (1997).
5. Pellegrini, C. A. & Pohl, D. High-grade dysplasia in Barrett's esophagus: surveillance or operation? *J. Gastrointest. Surg.* **4**, 131–134 (2000).
6. Feith, M., Stein, H. J. & Siewert, J. R. Pattern of lymphatic spread of Barrett's cancer. *World J. Surg.* **27**, 1052–1057 (2003).
7. Rice, T. W. *et al.* Esophageal carcinoma: depth of tumor invasion is predictive of regional node status. *Ann. Thorac. Surg.* **65**, 787–792 (1998).

8. Swisher, S. G. *et al.* Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. *J. Thorac. Cardiovasc. Surg.* **119**, 1126–1132 (2000).
9. Tadiparthi, R., Bansal, A. & Sharma, P. What's new in columnar lined esophagus (Barrett's metaplasia)? *Curr. Opin. Gastroenterol.* **24**, 516–520 (2008).
10. Wani, S. *et al.* Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. *Am. J. Gastroenterol.* **104**, 502–513 (2009).
11. Kerkhof, M. *et al.* Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. *Histopathology* **50**, 920–927 (2007).
12. Palazzo, F., Fisichella, P. M. & Patti, M. G. Management of high-grade dysplasia. *Curr. Gastroenterol. Rep.* **10**, 240–245 (2008).
13. Tharavej, C. *et al.* Predictive factors of coexisting cancer in Barrett's high-grade dysplasia. *Surg. Endosc.* **20**, 439–443 (2006).
14. Buttar, N. S. *et al.* Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology* **120**, 1630–1639 (2001).
15. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition. *Gastric Cancer* **1**, 10–24 (1998).
16. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* **37**, 570–578 (2005).
17. Peters, F. P. *et al.* Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. *Gastrointest. Endosc.* **67**, 604–609 (2008).
18. Sharma, P. *et al.* Non-biopsy detection of intestinal metaplasia and dysplasia in Barrett's esophagus: a prospective multicenter study. *Endoscopy* **38**, 1206–1212 (2006).
19. Sharma, P. *et al.* The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. *Gastrointest. Endosc.* **64**, 167–175 (2006).
20. Hage, M. *et al.* Molecular evaluation of ablative therapy of Barrett's oesophagus. *J. Pathol.* **205**, 57–64 (2005).
21. Pech, O. *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* **57**, 1200–1206 (2008).
22. Overholt, B. F. *et al.* Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. *Gastrointest. Endosc.* **62**, 488–498 (2005).
23. Wang, K. K. & Sampliner, R. E. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus; Practice Parameters Committee of the American College of Gastroenterology. *Am. J. Gastroenterol.* **103**, 788–797 (2008).
24. Lewis, J. T., Wang, K. K. & Abraham, S. C. Muscularis mucosae duplication and the musculo-fibrous anomaly in endoscopic mucosal resections for Barrett esophagus: implications for staging of adenocarcinoma. *Am. J. Surg. Pathol.* **32**, 566–571 (2008).
25. Eguchi, T. *et al.* Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: analysis of 464 surgically resected cases. *Mod. Pathol.* **19**, 475–480 (2006).
26. Manner, H. *et al.* Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. *Am. J. Gastroenterol.* **103**, 2589–2597 (2008).
27. Konda, V. J. *et al.* Low rate of invasive cancer in patients undergoing mucosectomy for Barrett's esophagus (BE) and high grade dysplasia (HGD) or intramucosal carcinoma (IMC) [Abstract]. *Gastrointest. Endosc.* **67**, AB76 (2008).
28. ASGE technology committee *et al.* Endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointest. Endosc.* **68**, 11–18 (2008).
29. Abrams, J. A. *et al.* Depth of resection using two different endoscopic mucosal resection techniques. *Endoscopy* **40**, 395–399 (2008).
30. May, A. *et al.* A prospective randomized trial of two different endoscopic resection techniques for early stage cancer of the esophagus. *Gastrointest. Endosc.* **58**, 167–175 (2003).
31. Soehendra, N. *et al.* Use of modified multiband ligator facilitates circumferential EMR in Barrett's esophagus. *Gastrointest. Endosc.* **63**, 847–852 (2006).
32. Peters, F. P. *et al.* Multiband mucosectomy for endoscopic resection of Barrett's esophagus: feasibility study with matched historical controls. *Eur. J. Gastroenterol. Hepatol.* **19**, 311–315 (2007).
33. Ell, C. *et al.* Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterology* **118**, 670–677 (2000).
34. May, A. *et al.* Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. *Eur. J. Gastroenterol. Hepatol.* **14**, 1085–1091 (2002).
35. May, A. *et al.* Intraepithelial high-grade neoplasia and early adenocarcinoma in short-segment Barrett's esophagus (SSBE): curative treatment using local endoscopic treatment techniques. *Endoscopy* **34**, 604–610 (2002).
36. Conio, M. *et al.* Endoscopic mucosal resection for high-grade dysplasia and intramucosal carcinoma in Barrett's esophagus: an Italian experience. *World J. Gastroenterol.* **11**, 6650–6655 (2005).
37. Ell, C. *et al.* Curative endoscopic resection of early esophageal adenocarcinoma (Barrett's cancer). *Gastrointest. Endosc.* **65**, 3–10 (2007).
38. Larghi, A. *et al.* Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. *Endoscopy* **39**, 1086–1091 (2007).
39. Peters, F. P. *et al.* Stepwise radical endoscopic resection is effective for complete removal of Barrett's esophagus with early neoplasia: a prospective study. *Am. J. Gastroenterol.* **101**, 1449–1457 (2006).
40. Seewald, S., Ang, T. L., Gotoda, T. & Soehendra, N. Total endoscopic resection of Barrett esophagus. *Endoscopy* **40**, 1016–1020 (2008).
41. Yoshinaga, S. *et al.* Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. *Gastrointest. Endosc.* **67**, 202–209 (2008).
42. Overholt, B. F., Panjehpour, M. & Halberg, D. L. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. *Gastrointest. Endosc.* **58**, 183–188 (2003).
43. Prasad, G. A. *et al.* Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. *Gastroenterology* **132**, 1226–1233 (2007).
44. Prasad, G. A. *et al.* Predictors of stricture formation after photodynamic therapy for high-grade dysplasia in Barrett's esophagus. *Gastrointest. Endosc.* **65**, 60–66 (2007).
45. Van Laethem, J. L., Peny, M. O., Salmon, I., Cremer, M. & Deviere, J. Intramucosal adenocarcinoma arising under squamous re-epithelialisation of Barrett's oesophagus. *Gut* **46**, 574–577 (2000).
46. Ban, S. *et al.* Histopathologic aspects of photodynamic therapy for dysplasia and early adenocarcinoma arising in Barrett's esophagus. *Am. J. Surg. Pathol.* **28**, 1466–1473 (2004).
47. Panjehpour, M., Coppola, D., Overholt, B. F., Vo-Dinh, T. & Overholt, S. Photodynamic therapy of Barrett's esophagus: ablation of Barrett's mucosa and reduction in p53 protein expression after treatment. *Anticancer Res.* **28**, 485–489 (2008).
48. Prasad, G. A. *et al.* Utility of biomarkers in prediction of response to ablative therapy in Barrett's esophagus. *Gastroenterology* **135**, 370–379 (2008).
49. Wang, K. K. *et al.* Photodynamic therapy for Barrett's esophagus: does light still have a role? *Endoscopy* **40**, 1021–1025 (2008).
50. Ganz, R. A. *et al.* Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. *Gastrointest. Endosc.* **60**, 1002–1010 (2004).
51. Sharma, V. K. *et al.* Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. *Gastrointest. Endosc.* **65**, 185–195 (2007).
52. Fleischer, D. E. *et al.* Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. *Gastrointest. Endosc.* **68**, 867–876 (2008).
53. Ganz, R. A. *et al.* Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U. S. multicenter registry. *Gastrointest. Endosc.* **68**, 35–40 (2008).
54. Shaheen, N. *et al.* A randomized, multicenter, sham-controlled trial of radiofrequency ablation (RFA) for subjects with Barrett's esophagus (BE) containing dysplasia: interim results of the AIM dysplasia trial [Abstract]. *Gastroenterology* **134**, A37 (2008).
55. Gondrie, J. J. *et al.* Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. *Endoscopy* **40**, 370–379 (2008).
56. Gondrie, J. J. *et al.* Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. *Endoscopy* **40**, 359–369 (2008).
57. Gondrie, J. J. *et al.* Balloon-based circumferential ablation followed by focal ablation of Barrett's esophagus containing high-grade dysplasia effectively removes all genetic alterations [Abstract]. *Gastroenterology* **132**, A64 (2007).

58. Johnston, M. H. *et al.* Cryoablation of Barrett's esophagus: a pilot study. *Gastrointest. Endosc.* **62**, 842–848 (2005).
59. Greenwald, B. D. *et al.* endoscopic cryotherapy ablation is safe and well-tolerated in Barrett's esophagus, esophageal dysplasia, and esophageal cancer [Abstract]. *Gastrointest. Endosc.* **67**, AB76 (2008).
60. Canto, M., Dunbar, K., Okolo, P., Jagannath, S. & Kantsevov, S. Low flow CO₂-cryotherapy for high risk Barrett's esophagus (BE) patients with high grade dysplasia and early adenocarcinoma: a pilot trial of feasibility and safety [Abstract]. *Gastrointest. Endosc.* **67**, AB179–AB180 (2008).
61. Dumot, J. A. & Greenwald, B. D. Argon plasma coagulation, bipolar cautery, and cryotherapy: ABC's of ablative techniques. *Endoscopy* **40**, 1026–1032 (2008).
62. Van Laethem, J. L., Cremer, M., Peny, M. O., Delhaye, M. & Devière, J. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. *Gut* **43**, 747–751 (1998).
63. Bright, T. *et al.* Randomized trial of argon plasma coagulation versus endoscopic surveillance for Barrett esophagus after antireflux surgery: late results. *Ann. Surg.* **246**, 1016–1020 (2007).
64. Pinotti, A. C. *et al.* Endoscopic ablation of Barrett's esophagus using argon plasma coagulation: a prospective study after fundoplication. *Dis. Esophagus* **17**, 243–246 (2004).
65. Attwood, S. E., Lewis, C. J., Caplin, S., Hemming, K. & Armstrong, G. Argon beam plasma coagulation as therapy for high-grade dysplasia in Barrett's esophagus. *Clin. Gastroenterol. Hepatol.* **1**, 258–263 (2003).
66. Kahaleh, M., Van Laethem, J. L., Nagy, N., Cremer, M. & Devière, J. Long-term follow-up and factors predictive of recurrence in Barrett's esophagus treated by argon plasma coagulation and acid suppression. *Endoscopy* **34**, 950–955 (2002).
67. Basu, K. K., Pick, B., Bale, R., West, K. P. & de Caestecker, J. S. Efficacy and one year follow up of argon plasma coagulation therapy for ablation of Barrett's oesophagus: factors determining persistence and recurrence of Barrett's epithelium. *Gut* **51**, 776–780 (2002).
68. Manner, H. *et al.* Ablation of nonneoplastic Barrett's mucosa using argon plasma coagulation with concomitant esomeprazole therapy (APBANEX): a prospective multicenter evaluation. *Am. J. Gastroenterol.* **101**, 1762–1769 (2006).
69. Sharma, P. *et al.* A randomised controlled trial of ablation of Barrett's oesophagus with multipolar electrocoagulation versus argon plasma coagulation in combination with acid suppression: long term results. *Gut* **55**, 1233–1239 (2006).
70. Sampliner, R. E. *et al.* Effective and safe endoscopic reversal of nondysplastic Barrett's esophagus with thermal electrocoagulation combined with high-dose acid inhibition: a multicenter study. *Gastrointest. Endosc.* **53**, 554–558 (2001).
71. Yeh, R. W. & Triadafilopoulos, G. Endoscopic therapy for Barrett's esophagus. *Gastrointest. Endosc. Clin. North Am.* **15**, 377–397 (2005).
72. Johnston, M. H. Technology insight: ablative techniques for Barrett's esophagus—current and emerging trends. *Nat. Clin. Pract. Gastroenterol. Hepatol.* **2**, 323–330 (2005).
73. Gossner, L. *et al.* KTP laser destruction of dysplasia and early cancer in columnar-lined Barrett's esophagus. *Gastrointest Endosc.* **49**, 8–12 (1999).
74. El-Serag, H. B. *et al.* Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am. J. Gastroenterol.* **99**, 1877–1883 (2004).

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