

REVIEW

Endoscopic Therapy for Barrett's Esophagus

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Recent retrospective cohort data and a prospective randomized sham controlled trial have clearly documented the impact of endoscopic ablation therapy on dysplasia and Barrett's esophagus (BE). The clinical indications for ablation of BE includes high-grade dysplasia and intramucosal adenocarcinoma. The techniques of resection of mucosal irregularities and of ablation are reviewed, primarily thermal and photodynamic ablation. Ablation of BE with neoplasia has appropriately entered the clinical arena.

Endoscopic therapy for Barrett's esophagus (BE) has been used for 20 years. It has been applied increasingly around the world although it has been met with skepticism by some. A recent retrospective cohort series of surgery versus endoscopic therapy and a prospective randomized sham controlled trial of endoscopic therapy have catapulted this intervention into the clinical arena. This article reviews the indications for BE ablation; the techniques for ablation; their advantages, disadvantages, and level of documentation; and the goals of endoscopic therapy.

Retrospective cohorts from one high-volume institution have reported equivalent results from surgery and endoscopic therapy for BE with high-grade dysplasia (HGD).¹ Seventy patients underwent esophagectomy and 129 patients underwent photodynamic therapy (PDT). The majority of the PDT patients also underwent endoscopic resection (ER) of mucosal lesions. The overall mortality in each group was similar (9%) over a 5-year follow-up period. There were no deaths from esophageal adenocarcinoma in either cohort.

In addition, a prospective randomized sham controlled trial of radiofrequency ablation (RFA) was conducted in 22 centers and has been reported in abstract form.² The 1-year interim analysis of 101 patients with HGD and low-grade dysplasia (LGD) showed a reduction of neoplasia progression (LGD to HGD or HGD to cancer) from 19% to 5%. In addition, 77% of treated patients had clearance of intestinal metaplasia (IM) (ie, BE) versus none in the sham arm. These 2 major studies represent the beginning of the documentation of the efficacy of Barrett's ablation.

Indication for Endoscopic Ablation of Barrett's Esophagus

Careful T and N staging of neoplasia is necessary to determine if endoscopic ablation is appropriate for a patient. Patients with HGD do not have lymph node involvement.³ Patients with intramucosal adenocarcinoma (IMC) have a 3% or less metastasis to lymph nodes (T1a). Once the cancer is beyond

the muscularis mucosa and into the submucosa (T1b), the rate of nodal involvement is 15% or greater. Thus, HGD or early adenocarcinoma above the muscularis mucosa is eligible for endoscopic ablation. Spread below the muscularis mucosa usually is taken as an indication for surgery. However, there is a 19-patient series that suggests that endoscopic therapy of the first level of the submucosa (sm1) is beneficial. These patients had invasion of the upper third of the submucosa, no lymphatic or venous infiltration, histologically well or moderately differentiated, and macroscopically not ulcerated.⁴ However, classifying submucosal penetration depth by thirds often is inaccurate because only part of the submucosa is available for histologic assessment in ER specimens.⁵ Currently, the most effective T staging is accomplished by ER of any mucosal irregularity. T staging is directly histologically determined. N staging still is accomplished most accurately by endoscopic ultrasound. Nodal involvement indicates that a patient with adenocarcinoma is not resectable for cure. With the histologic documentation of adenocarcinoma, computed tomography of the chest and abdomen also is appropriate for staging, especially for distant metastases.

LGD that is persistent and confirmed by a second expert pathologist also potentially is treated with ablation. The RFA trial includes patients with LGD and shows a significant reduction in neoplastic progression. There is no justification for ablation of nondysplastic BE other than in a trial of novel therapy. The neoplastic progression of nondysplastic Barrett's is less than the complication rate of any ablation technique.

Techniques of Endoscopic Ablation

ER has been discussed as a staging technique. It also can be used to eliminate BE.⁶ When applied circumferentially, strictures commonly occur. ER also has been used as a curative therapy of early esophageal adenocarcinoma, defined as having a diameter of 2 cm or less, no lymphatic or vascular invasion, and well or moderately differentiated histologically.⁷ One hundred consecutive such patients were treated with ER and followed up for a mean of 3 years with a calculated 5-year survival

Abbreviations used in this paper: APC, argon plasma coagulation; BE, Barrett's esophagus; ER, endoscopic resection; HGD, high-grade dysplasia; IM, intestinal metaplasia; IMC, intramucosal adenocarcinoma; LGD, low-grade dysplasia; MPEC, multipolar electrocoagulation; PDT, photodynamic therapy; PPI, proton pump inhibitor; RFA, radiofrequency ablation.

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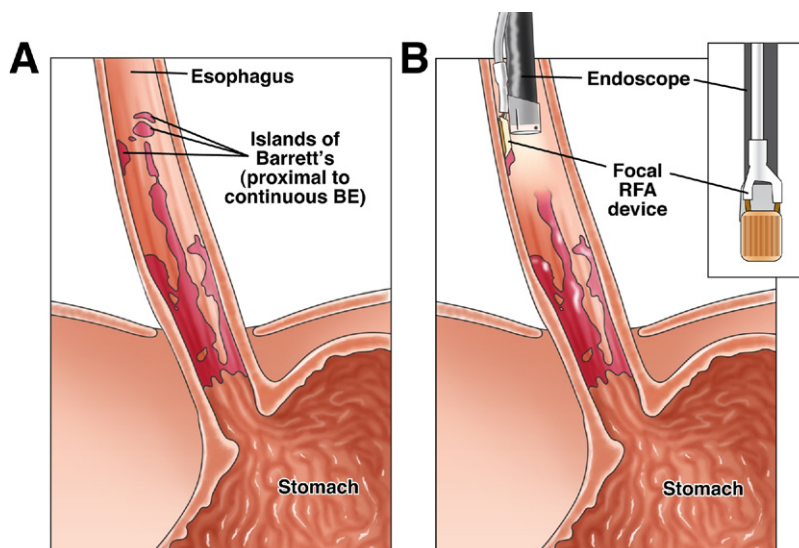


Figure 1. Targeting all columnar appearing esophageal lining.

rate of 98%. Sixty-nine percent of the patients had short-segment BE. The recurrent or metachronous cancer rate was 11% with successful re-treatment with ER. The great advantage of ER over mucosal ablation is that the tissue that is removed is available for careful documentation of the stage of the lesion.

Thermal therapies have been the most common type of ablation therapy used. These include multipolar electrocoagulation (MPEC), which was the earliest used; argon plasma coagulation (APC), which is the most commonly used; and RFA, which is the most recently used. MPEC and APC are basically point-and-shoot techniques, with MPEC requiring contact and APC requiring near contact (within 1–1.5 mm of the mucosa for the electrical charge distribution). RFA uses a 3-cm balloon specifically sized for the diameter of the esophagus for circumferential therapy and a focal device that fits over the tip of the endoscope with a 1.5- by 2-cm surface area.

In a preliminary trial of MPEC, only half of the circumference of the BE segment was treated to document the ability of ablation and acid reduction to lead to squamous re-epithelialization.⁸ The dose of proton pump inhibitor (PPI) was adjusted to reduce the esophageal acid exposure to a pH lower than 4 for less than 4.2% of a 24-hour period. Subsequently successful removal of BE was documented in a larger series of patients: 22 of 27,⁹ 14 of 14 patients with antireflux surgery,¹⁰ and 45 of 58 patients in a multicenter study.¹¹

Twelve large trials of APC ablation of BE have been published with sample sizes varying between 15 and 94 patients. Additional trials have used APC in combination with laparoscopic fundoplication.^{12,13} The most remarkable results were in 70 patients treated with high-power APC (90 W) and high-dose PPIs (omeprazole 40 mg 3 times a day)—69 patients had complete squamous regeneration.¹⁴ In a long-term follow-up evaluation of this same series—66 patients followed up for a mean of 51 months—only 12% of APC ablated patients had evidence of IM on biopsy evaluation of endoscopically suspected BE.¹⁵ This firmly shows the durability of reversal of BE with ablation and PPI therapy. Eighty-three percent of these patients were treated with a PPI adjusted to symptoms or laparoscopic fundoplication. Maintenance of a reduced acid environment in the

esophagus seems important for maintenance of the new squamous epithelium.

APC also has been used to treat HGD.¹⁶ In the largest series 29 patients were treated with APC with a mean follow-up period of 37 months.¹⁷ Twenty-five patients had elimination of HGD and 22 patients had elimination of BE. Most importantly, the estimated 5-year survival was 82%, which was not different from the expected survival of a similarly aged population. The major limitation of MPEC and APC is the limited area treated. The *painting technique*, withdrawing the endoscope with the treatment catheter in position, is tedious and subject to both overlap and missed areas. Major complications such as stricture, bleeding, or perforation are very uncommon.

RFA has been applied to nondysplastic BE and to HGD in a registry and a randomized trial. In an open prospective study of 70 patients with BE, 70% of patients had BE eliminated at 1 year.¹⁸ At a 30-month follow-up evaluation after additional focal ablation of histologic intestinal metaplasia (IM), 97% of 61 available patients had no residual IM by intention-to-treat analysis.¹⁹ A 3-cm balloon-based radiofrequency device was used for circumferential ablation. A registry of 92 patients with documented HGD underwent the same circumferential ablation. At a median follow-up period of 12 months 90% had no HGD, 80% had no dysplasia, and 54% had no IM.²⁰ There was a randomized, multicenter trial of RFA versus sham in BE patients with dysplasia (LGD and HGD) reported in abstract form.² All histology was centrally confirmed by an expert GI pathologist. Circumferential 3-cm balloon and focal (2 × 1.5 cm) RFA ablation (Figure 1B) was used and accompanied by twice-daily PPI. A total of 101 patients were assessed in a 12-month interval analysis.² Neoplastic progression in the sham arm was 18.5% (LGD to HGD, 3 of 19 patients; HGD to cancer, 4 of 18 patients) versus 4.7% (LGD to HGD, 2 of 39 patients; HGD to cancer, 1 of 25 patients) ($P < .05$). In an intention-to-treat analysis 77% of these RFA patients had complete elimination of IM versus none of the sham ($P < .001$). RFA has the advantage of treating a larger surface area than MPEC and APC. It also is subject to overlap and missed areas but is technically less challenging. Short-term follow-up evalu-

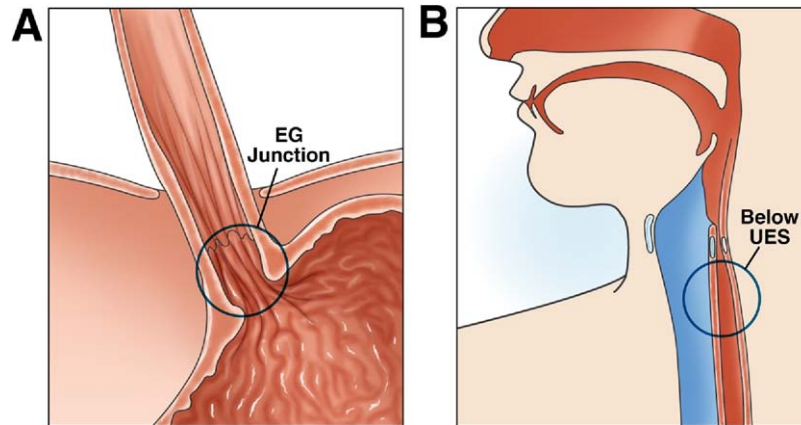


Figure 2. Technical challenges in ablation therapy of Barrett's esophagus.

ation suggests that perforation and bleeding are rare, and stricture occurs in 6%.

PDT has been used to treat BE neoplasia. The largest randomized trial of ablation therapy was performed in the United States using intravenous porfimer sodium as the photosensitizer accompanied by PPI therapy. A total of 205 patients with HGD were randomized 2 to 1 to PDT or no PDT. At 24 months in the PDT arm 77% had no HGD versus 39% in the no-PDT arm. In a secondary analysis, 13% in the PDT arm developed cancer versus 28% in the non-PDT arm ($P < .006$).²¹ The 5-year follow-up evaluation of the study showed similar results: PDT significantly reduces but does not eliminate cancer.²² The reduction of HGD, the primary end point of the study, is significant, but the variable natural history of HGD is shown in the loss of HGD in the non-PDT arm.

In Europe an oral photosensitizer for PDT, 5-aminolevulinic acid, has been applied with success; this was first reported in 32 patients²³ and subsequently in 66 patients with HGD or early cancer.²⁴ In the latter trial with a mean follow-up period of 37 months there were 8 local recurrences re-treated, but no tumor-related deaths. In a light dosimetry study 5-aminolevulinic acid was used in patients with HGD, most successfully in the highest dose.²⁵ Forty patients with LGD had dysplasia eliminated with 5-aminolevulinic acid.²⁶ The effect was maintained in a mean follow-up period of 53 months. At 3 years 1 patient developed cancer in an untreated area of BE, highlighting the need to eliminate all BE. The advantages of 5-aminolevulinic acid versus porfimer included brief skin photosensitivity (range, 2 days versus 3 months) and no stricture formation versus 30%.

The latest technique of ablation therapy applied to BE with the least experience in human beings is cryotherapy. Two systems have been used: one sprays liquid nitrogen through an open-tip catheter,²⁷ the other forces a cryogenic refrigerant (carbon dioxide) through a catheter that also provides venting.²⁸ The former technique was used to treat 11 patients with no dysplasia, LGD, or HGD. At the 6-month follow-up evaluation 9 patients had BE eliminated. This technique also has been used to treat early cancer and palliate more advanced cancer.

The technical challenges of all modalities of endoscopic therapy include experience with the modality, experience of the operator, the availability of all the necessary accessories, and an experienced assistant. Additionally, the treatment of the

esophagogastric junction and below the upper esophageal sphincter pose special challenges. The junction flares to the right and is not always easy to target. The upper esophagus is below the closing end of the sphincter, again a difficult to target area (Figure 2).

Choice of Endoscopic Therapy

Mucosal irregularity necessitates ER, so this technique must be in the armamentarium of someone performing endoscopic therapy (Table 1).

The techniques of choice for elimination of all IM is a function of availability of equipment, cost, complications, and the experience of the endoscopist. APC is the thermal technique that has been used most widely and is available in many endoscopy laboratories for treating bleeding lesions. Excess application time and/or excess pressure can uncommonly lead to perforation.

RFA has the advantage of treating a larger surface area than other thermal techniques. This is obvious for the balloon, but is also true of the focal disease. Thus, although it is a contact technique, it is not a point technique. The major complication rate also is low: 6% strictures versus 30% in PDT with porfimer sodium.

PDT has the highest-quality fully published data supporting its efficacy. Yet, its side-effect profile, technical difficulty, and expense are likely to lead to the elimination of its clinical use.

Goal of Endoscopic Therapy

The proximate goal of endoscopic therapy is to eliminate neoplasia. The ultimate goal is to prevent the development

Table 1. Endoscopic Ablation Modalities

Thermal
MPEC
APC
RFA ablation
Cryotherapy
Photodynamic therapy
5-aminolevulinic acid
Porfimer sodium
Mechanical
Endoscopic resection

of invasive cancer. First eliminating the dysplasia or IMC is important but insufficient. Residual IM means the potential for the continued harboring of clonal abnormalities^{29,30} and the ultimate development of recurrent dysplasia and potentially adenocarcinoma. Therefore, the pragmatic goal is to eliminate all IM (Figure 1A). This leads to the issue of IM buried under neosquamous epithelium. In a recent extensive evaluation of more than 33,000 biopsy specimens in the PDT trial, the most advanced dysplasia was never solely beneath the squamous overgrowth.³¹ Thus, with a 4-quadrant, 2-cm biopsy protocol, the most advanced diagnosis always was present in a surface Barrett's biopsy. Although yet to be proven, it is reasonable to project that the elimination of all IM will result in the avoidance of progression to cancer.³² This is the underlying, if unstated, assumption of esophagectomy: eliminate the majority of the organ, including the distal esophagus harboring IM, and a cancer-free survival will result. This is also the assumption of the result of eliminating all IM with endoscopic ablation. Preliminary data supporting elimination of all IM comes from the most experienced group in the world reporting on endoscopic therapy in 349 patients with HGD and mucosal adenocarcinoma.³² In patients with ablative therapy after treatment of neoplasia 16.5% had metachronous neoplasia versus 29.7% in those receiving no ablation.

We have entered a new era of the more widespread application of endoscopic therapy for HGD and IMC in BE. We still await the long-term follow-up data to document the effectiveness of this form of therapy. The evidence is building and clinical practice is shifting.

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Reprint requests

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Conflicts of interest

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