How I Treat Patients With Barrett Esophagus When Endoscopic Ablation Fails

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Overview

- Endoscopic ablation is highly effective for treating dysplastic Barrett esophagus, but there are a number of patients who only partially respond.
- Reflux control should first be optimized in these patients with double-dose proton pump inhibitor therapy and use of mucosal protective maneuvers.
- If initial ablation was started with radiofrequency ablation, switching to cryotherapy as an alternative appears to be successful in most cases.
- In the most recalcitrant patients with persisting Barrett esophagus, endoscopic resection techniques can be employed.

Endoscopic ablation has become an accepted therapy for Barrett esophagus with malignant potential. This has been established through multiple large, multicenter, prospective, randomized studies that provide level 1 evidence that Barrett esophagus with both high-grade dysplasia and low-grade dysplasia can be treated with a significant reduction in the degree of dysplasia with either thermal therapy with argon plasma coagulation, photodynamic therapy, or radiofrequency ablation.[1-3] However, upon reviewing these studies, it is clear that none of these therapies are entirely successful in eradicating all of the intestinal metaplasia in every patient. In cases where therapy is not entirely successful, it is important to understand when it may become necessary to use other therapies. Treatment is targeted toward patients who have good performance status and expected longevity to be able to take advantage of the cancer prevention that endoscopic therapy often entails.

There are no standard definitions of treatment failure or persistent Barrett esophagus. However, one can adopt the definitions used in the prior randomized trials regarding the number of treatments needed to achieve predefined endpoints.[1,3] At the Mayo Clinic, my colleagues and I define a patient with persistent Barrett esophagus as someone who has undergone 3 ablation attempts without a reduction in the degree of dysplasia from the index therapy or who has failed to achieve at least a 50% reduction in the length of Barrett esophagus.[4] This generally indicates that the patient will require multiple additional treatments and would be defined as a treatment failure in the previously mentioned radiofrequency ablation study.[1] The definition of recurrent Barrett esophagus also varies in the literature because there is an intrinsic bias depending on the histologic confirmation and location of intestinal metaplasia. Past literature has defined potential recurrence as any intestinal metaplasia or dysplastic columnar tissue found in the tubular esophagus after even a single endoscopy with negative biopsies. Both the previously mentioned prospective, randomized radiofrequency ablation trial and the randomized photodynamic therapy trial depended on achieving clearance of dysplasia or intestinal metaplasia in a single endoscopic procedure.[1,3] In reviewing our own data, we found that one-third of patients who achieved an endpoint of clearance of dysplasia or intestinal metaplasia had a "recurrence" at the next endoscopy.[5] For this reason, we have defined a patient with recurrent Barrett esophagus as someone without evidence of Barrett esophagus or dysplasia for 2 consecutive endoscopies who developed Barrett esophagus or dysplasia afterward.[6] Another category of failure of endoscopic therapy is progression while receiving ablation. This is usually evidence of very aggressive disease and necessitates consideration of esophagectomy or chemotherapy and radiotherapy for control of the disease before it disseminates further. If the

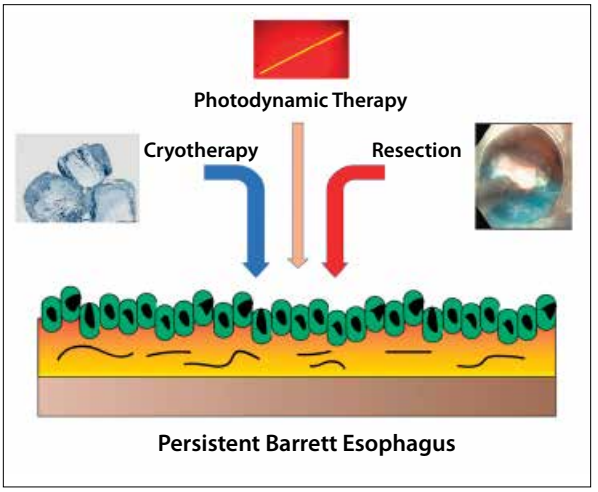

Figure 1. Alternative therapies for persistent Barrett esophagus. Cryotherapy (cold therapy) has been the therapy most frequently used after the failure of thermal therapies such as radiofrequency ablation. Photodynamic therapy can also be applied, although it has limitations similar to when it is used as primary therapy. Resection techniques such as endoscopic mucosal resection or endoscopic submucosal dissection can be used postablation and are quite feasible for smaller lesions.

progression still appears to be endoscopically treatable, it is advisable to obtain consultation from surgeons and discuss the case at a tumor board, as good outcomes are possible if the disease can be removed rapidly.

It has been established that any residual esophageal intestinal metaplasia is a risk factor for progression or recurrence of dysplasia in Barrett esophagus. As early as 2000, my colleagues and I found that genetic abnormalities present in dysplastic tissue persisted in the residual intestinal metaplasia even after dysplasia apparently resolved.[7] Risk factors for recurrent dysplasia have also been found to include persistent intestinal dysplasia.[8] The issue of whether or not cardia metaplasia indicates substantial risk of progression to cancer is unclear. However, recent evidence from the Cancer Genome Atlas has established that esophageal cancer is genetically identical to gastroesophageal junction cancers and is unlike distal gastric cancers.[9] Findings from this program suggest that the presence of persistent or recurrent intestinal metaplasia after ablation may indicate significant pathology. This has not been established conclusively, but the body of evidence favors a more aggressive approach to the cardia after ablation.

Retrospective studies have suggested that improved control of reflux disease could enhance response to ablation.[10,11] It is on this basis that intensive antireflux medications are prescribed to ensure the best possible response. Based on the response rate of patients who were on suitable proton pump inhibitor therapy compared to patients who were not, control of acid reflux appeared to provide benefit by preventing regrowth of intestinal metaplasia. However, prospective trials that have been conducted to address the question of acid control have not found that more intensive acid control increased response rates using thermal therapy and mucosal resection techniques.[12] In select cases of large diaphragmatic hernias or prior pyloroplasty with bile reflux, there have been reports of response after fundoplication. Improved control of acid and bile reflux needs to be considered in cases where these types of reflux are particularly intense, such as after gastric sleeve procedures or partial gastrectomy.

Photodynamic Therapy

The treatments available for persistent Barrett esophagus are similar to those for primary therapy (Figure 1). However, it seems reasonable to change therapeutic modalities because persistent disease usually has developed a mechanism to escape thermal damage. Photodynamic therapy is an older technology that can be helpful with persistent Barrett dysplasia. Although there are limited data regarding its use in this situation, photodynamic therapy was the first ablation modality approved by the US Food and Drug Administration for the treatment of Barrett esophagus with high-grade dysplasia, based on a prospective randomized trial of 208 patients. The treatment was reasonably successful, as it decreased dysplasia and reduced progression to adenocarcinoma in 77% of patients, compared with a control group that used only acid suppression as therapy.[3] A photosensitizing agent (sodium porfimer) is given intravenously 2 days prior to photodynamic therapy. During the endoscopy, light is delivered through a cylindrical diffusing fiber that can easily be placed through the biopsy channel of a diagnostic endoscope. A red light (630-nanometer wavelength) is applied from a diode laser through the diffusing fiber, which activates the photosensitizer that is present in the mucosa. This light produces extensive necrosis that becomes visible after 1 to 2 days. In the original study,[3] a second light was applied 48 hours after the first to areas that did not respond, but due to the expense and lack of demonstrated benefit, this practice has largely been abandoned. The advantages of photodynamic therapy are that it is easy to apply with little technical skill required and can reach into the submucosa, making it capable of even treating nodular disease. It has been suggested that the therapy potentially has efficacy in treating early cancers as well. However, most gastroenterologists no longer use this therapy because of the higher costs, the resulting photosensitivity that causes patients to avoid sunlight for approximately a month, and the relatively high stricture

Figure 2. Spray cryotherapy with liquid nitrogen freezes the tissue. Frost is seen on the surface, as well as on the decompression tube in the central lumen that is needed to remove excess nitrogen gas.

Figure 3. Cryotherapy balloon treatment with nitrous oxide causes freezing inside a compliant transparent balloon. The endoscope is positioned to examine the mucosa through the cap to visualize the area for treatment.

rates that can occur. Pain after therapy can also be severe, requiring the administration of narcotics.

Cryotherapy

Another treatment with a different mechanism of action is cryotherapy. This therapy can destroy cells through supercooling, which causes crystallization within the cell membrane and results in cell expansion. Upon thawing, the tissue fractures and undergoes necrosis, which is usually very effective for epithelial tissue treatment. As with photodynamic therapy, cryotherapy-induced changes are fairly subtle initially, with a blanching of the tissue with ischemia from thrombosis in small vessels, but become much more apparent once the necrosis is visible after a day. Currently, cryotherapy can be delivered by 2 methods. One method involves spray liquid nitrogen (CSA Medical), which is a liquid at the temperature of -320° F but rapidly converts to a gas at room temperature. The nitrogen unit uses a temperature of -20° C or -4° F for tissue treatment, and spray liquid nitrogen is delivered through a 7-French catheter placed through the endoscope that is usually within a centimeter of the tissue to allow for rapid cooling. Usually, a cap is fitted on the end of the endoscope to help prevent frosting of the endoscope's optics. The treatment provides rapid cooling of tissue and superficial tissue freezing, as seen in Figure 2. When frost is seen on the tissue surface, freezing is continued for a period of 20 seconds, which can be adjusted by the user depending on the intended application, and then thawing is allowed for a minute or until the frost is cleared. This is repeated for multiple cycles in order to ensure tissue destruction, as it is the repeated freezing and thawing that produces maximum effect. The tissue becomes ischemic after therapy and undergoes necrosis. The advantages of this treatment are that it produces little pain compared with other ablation techniques and produces fewer cases of esophageal stricture. In the setting of preexisting stricture produced by prior thermal ablation, spray cryotherapy ablation is the therapy I prefer to use. However, continued suction of the stomach lumen is needed to prevent the accumulation of gas in the stomach, which can potentially cause rupture of the gastrointestinal tract as over 9 L per minute of gas is introduced into the stomach. There are also technical issues with loss of cooling due to freezing within the endoscope channel, which acts like a thermal sink. This requires the periodic need to defrost the catheter to achieve sufficient cooling. Overall, treatment efficacy seems to be similar to other ablation methods in terms of decreasing dysplasia in 80% to 90% of patients and eliminating intestinal metaplasia in 70% to 90%, although numerically the ability to completely eliminate intestinal metaplasia appears to be less than with radiofrequency ablation.[13]

The other type of cryotherapy, balloon cryotherapy (Pentax Medical), is delivered through a small handheld unit and, in its most recent iteration, a foot pedal that controls balloon inflation, rotation of the cooling jet, and administration of the cryogen. A therapeutic endoscope is required due to the size of the catheter that is passed through the biopsy channel. The catheter has a compliant balloon at the distal end that will expand and allow delivery of a jet of nitrous oxide to a focal area for a user-adjustable period. Usually for Barrett esophagus, it takes approximately 8 seconds to freeze tissue through the Joule-Thomson effect. The gas throttling cools the tissue and causes a rapidly expanding area of freezing, as seen in Figure 3. The spray nozzle can rotate a full 360° within the balloon, allowing for treatment of an entire segment with focal application. In preliminary cohort research, balloon cryotherapy has been shown to eliminate dysplasia in 80% to 100% of cases and completely eliminate intestinal metaplasia in 60% to 90%.[13] Some of the published case series include both treatment-naive and previously

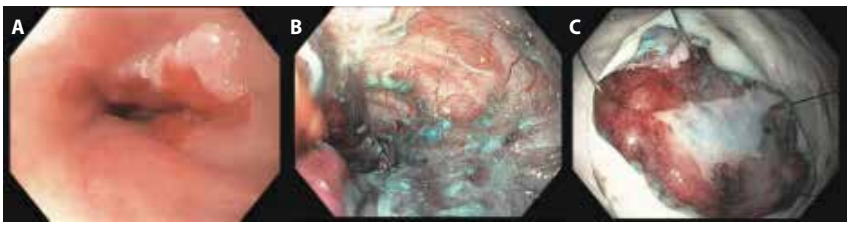

Figure 4. Resection is advised for lesions that are neoplastic in appearance or polypoid. An endoscopic mucosal resection had been performed in the center of the lesion, which is why it appears ulcerated in **A**. **B** shows the degree of fibrosis present, which makes secondary therapy with dissection much more difficult. The fibrosis is intimately associated with the circular muscle layer of the muscularis propria, which can be seen in the base of the ulcer in **B**. The endoscopic mucosal resection scar is epithelialized with squamous tissue, as can be seen by the 6-cm endoscopic submucosal resection performed in **C**.

treated patients. These small series have not found differences in efficacy between the treatment groups, despite prior therapy with radiofrequency ablation.[14,15] However, more pain has been reported after balloon cryotherapy than after spray cryotherapy. In addition, the esophageal stricture rate reported in some series has been higher than with radiofrequency ablation. It is unclear why balloon cryotherapy acts differently, although the distension of the lumen of the esophagus and potential thinning of the esophageal wall may be a potential source of increased wall damage.

Additional Thermal Therapies

Recurrences generally are small areas, and, if nondysplastic, mucosa near the gastroesophageal junction can be treated with further thermal ablation. Thermal ablation methods include focal radiofrequency ablation (Medtronic), argon plasma coagulation (APC), hybrid APC (Erbe), and multipolar coagulation. All of these treatments involve focal devices that can adequately treat small islands of nondysplastic low-grade dysplasia or nonnodular high-grade dysplasia in Barrett esophagus if they recur. Hybrid APC, the newest technique, allows for injection of fluid into the submucosa to lift the mucosa first prior to cautery with APC to potentially provide more safety by not damaging muscle tissue and even enhancing ablation efficacy. Most reports of recurrences generally indicate that additional thermal ablation methods are effective in eliminating intestinal metaplasia, although they have not been formally studied.[5,16]

Endoscopic Resection

When disease is recurrent but submucosal, the lesions are not endoscopically visible except as nodules under squamous mucosa. The resection of these lesions can be diagnostic as well as therapeutic. Submucosal lesions are frequently dysplastic and can often be the first manifestation of cancer even if the original lesion was not thought to contain cancer. If there are biopsies suggesting carcinoma, both endoscopic resection and surgical esophagectomy should be considered. I have generally favored endoscopic submucosal dissection in cases of submucosal dysplasia or carcinoma, as the extent of the lesion is not apparent and it is very beneficial if the lesion can be removed in its entirety. In addition, these lesions are in a field of extensive fibrosis due to the prior ablation, and endoscopic mucosal resection techniques are less effective due to tissue scarring. Rarely is very extensive circumferential resection required for these recurrences, and complications can be controlled, although this requires a high level of expertise and familiarity with endoscopic submucosal dissection techniques. Traditional mucosal tissue planes are not visible after extensive ablation, and the submucosal space is generally obliterated with fibrotic tissue, making dissection much more technically challenging and complications more common.

Lesions may also persist despite ablation attempts, as they are not really amendable to this therapeutic approach. Care and patience are required to remove these lesions. If the patient is not considered to be a surgical candidate, endoscopic resection can be performed of the residual Barrett esophagus. Endoscopic mucosal resection has been performed to treat Barrett esophagus, but piecemeal circumferential resection has led to very high stricture rates and is rarely used as primary therapy. However, in the face of extensive nodular mucosa, widespread resection can be considered along with traditional esophagectomy. If the patient is a good surgical candidate, esophagectomy should be considered because endoscopic therapy will require multiple sessions and likely cause more complications.

It is important to recognize that areas of nodularity cannot be treated with radiofrequency ablation because of the required depth of injury. Nodules need to be resected,

Table. Comparison of Alternative Therapies

Treatment Modality	Relative Cost[a]	Efficacy[a]	Strength(s)	Technical Skill Required[a]	Complication(s)	Relative Contraindications
Spray Cryotherapy	+++	+++	Fewer strictures, less pain	++	Gas distention	Mucosal breaks that permit gas entry
Balloon Cryotherapy	++++	+++	Ease of application	++	Pain, strictures	Strictures
Photodynamic Therapy	+++++	++	Ease of application	+	Severe pain, strictures, phototoxicity	Strictures
Endoscopic Mucosal Resection	+	++++	Tissue obtained from nodular or submucosal lesions	+++	Bleeding, strictures, perforation	Strictures, nonlifting lesions, circumferential lesions
Hybrid Argon Plasma Coagulation	++	Unknown	Ease of application	++	Pain, strictures	Large areas of tissue
Argon Plasma Coagulation	+	+++	Ease of application	++	Pain, strictures	Large areas of tissue
Multipolar Coagulation	+	++	Ease of application	++	Pain, strictures	Large areas of tissue
Endoscopic Submucosal Dissection	+	+++++	Large tissue samples, ability to dissect fibrosis	++++	Bleeding, strictures, perforation	Very fibrotic strictures

[a]The increasing number of plus symbols correlates with an increase in relative cost, efficacy, or technical skill required.

and if an area has many nodules scattered throughout, then complete resection is needed, as subsequent resection will encounter the fibrosis created by the initial attempt. In general, if the lesion cannot be removed in its entirety by the treating gastroenterologist, it should probably only be carefully inspected with a magnifying endoscope to determine if it is neoplastic. If this cannot be determined, biopsies can be obtained carefully to establish the presence of neoplasia before the patient is sent to undergo resection by an expert in endoscopic submucosal dissection who can remove the entire lesion. Although previous treatment with ablation or resection creates fibrosis in the submucosa, extensive ulceration from reflux esophagitis can produce a similar effect, which often can be very resistant to ablation techniques. Endoscopic resection of fibrotic lesions is a very technically challenging procedure that requires several hours to achieve and has a much higher complication rate than nonfibrotic lesions. Figure 4 shows a lesion that had undergone endoscopic mucosal resection but had residual nodules, necessitating the removal of the mucosal resection site as well as the nodules with endoscopic submucosal dissection. Fibrosis had deformed the esophageal lumen and had to be released to achieve the en bloc resection.

Summary

If initial ablation fails, it is usually beneficial to switch to a different mode of therapy. The Table shows the relative advantages and disadvantages of the alternatives to thermal ablation. Usually, thermal therapy with radiofrequency ablation is the first treatment modality. If the treatment fails to show demonstrable results after 3 applications in terms of decreasing both the Barrett mucosa and the degree of dysplasia, my preference is to use cryotherapy if there is persisting intestinal metaplasia. If there is persisting high-grade dysplasia or cancer or if nodules have arisen, then endoscopic resection is ideal, with endoscopic submucosal dissection being my first choice for complete removal. With recurrent disease, focal thermal therapy seems most cost-effective for small amounts of nondysplastic or low-grade dysplasia, whereas high-grade dysplasia or cancer usually is resected to ensure histologic confirmation of the adequacy of treatment. Submucosal recurrences and those of larger size generally require endoscopic submucosal dissection. All of these treatments should only be considered when the patient is expected to have sufficient longevity and health to be able to benefit. Otherwise, a strategy of surveillance or

watchful waiting can be considered in patients with extensive serious comorbidities.

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