Chapter 16
Barrett's Esophagus Treatment: Radiofrequency and Other Ablation Modalities

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Introduction

Barrett's esophagus occurs as a sequela of gastroesophageal reflux disease (GERD), where continued irritation of the normally stratified squamous epithelial lining of the distal esophagus undergoes metaplasia to become intestinal-type columnar epithelium. Approximately 10–20% of patients with GERD have Barrett's esophagus [1, 2]. As such, treatment of GERD can halt the progression Barrett's esophagus, but does not necessarily eliminate it. A feared complication Barrett's esophagus is progression to esophageal adenocarcinoma. The risk of progression in patients with non-dyspBarrett's esophagus is 0.2–0.5% per year, approximately 0.7% per year in patient low-grade dysplasia, and about 7%

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M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_16

in patients high-grade grade dysplasia [2]. Guidelines have been established by the American College of Gastroenterology regarding surveillance and management of Barrett'srett's esophagus, and are summarized in Table 16.1 [2, 3].

Initially, a diagnosis of dysplasia, part high-grade dysplasia, carried with it a recommendation for esophagectomy. However, new evidence has become available and since endoscopic techniquest have improved, endoscopic eradication therapies have become the standard of care [4]. Successful endoscopic ablative low-grade high-grade dysplasia, as well as in cases of intramucosal carcinoma that have first been treated with endoscopic mucosal resection, aims to remove the entirety of the metaplastic tissue in the mucosa but preserve the submucosa in order to prevent complications such as stricture [2]. These include radiofrequency ablation, chemical photodynamic therapy, and cryotherapy. This chapter will discuss the techniques, complications, and outcomes of ablative therapies, as well as comparisons between them. Endoscopic mucosal resection is discussed elsewhere.

Table 16.1 ACG guidelines for surveillance and management of Barrett's esophagus according to histology

Surveillance and ManagemenBarrett'sett's Esophagus					
Pathologic Finding	Barrett's without dysplasia	Indefinite for dysplasia	Low grade dysplasia	High grade dysplasia or T1a esophageal adenocarcinoma	Esophageal adenocarcinoma T1b or greater
Recommendation	Four quadrant biopsies every 2cm, every 3 to 5 years	Confirm the with second pathologist, repeat endoscfour-quadrant quadrant biopsies every 1cm in 2 to 6 months	Endoscopic eradication; endoscopic surveillance is an acceptable alternative	Endoscopic eradication	Referral to oncology

Radiofrequency Ablation

Introduction

Radiofrequency ablation (RFA) has become the most frequently performed method of endoscopic eradication of Barrett's esophagus [5]. While very effective, it is imperative that any nodular abnormalities or raised lesions in the presence of dysplasia be resected via endoscopic mucosal resection (EMR). EMR ensures that a flat concentric surface is present for maximal effectiveness of the RFA procedure so that it can adequately penetrate through to the submucosa, and in turn, RFA augments the effectiveness of the EMR, which alone would only remove a focal segment, and overcomes the risk of leaving behind a small focus of residual dysplasia [6].

RFA is usually accomplished initially with a circumferential balloon-based bipolar electrode catheter, followed by focal ablation of residual Barrett's esophagus endoscope mounted articulating bipolar device [7, 8]. In the past, circumferential ablation consisted of a two-step procedure, which first involved placing a sizing balloon, placement of an appropriately-sized ablation catheter, followed by the deli preset amount of radiofrequency energy density set at 300 W to the electrode of the ablation catheter [7]. This device uses an adjustable pneumatic stable balloon that can fir the diameter of the esophagus, usechan adjustable pneumatic stable balloon that can fit the diameter of the esophagus. This balloon contains catheter electrodes around the circumference, thereby eliminating the need for a sizing step and reducing procedure time for two-step procedure. The catheter consists of a 4 cm segment of circumferential copper sheet of bipolar electrodes. The balloon has a variable diameter from 1 to 31 mm, and automatically inflates to 3 PSI when activated via foot pedal with pneumatic dilation. The catheter is then actiavated and delivers radiofrequency energy at a preset setting of 10 J/cm^2, with the generator adjusting energy delivery by measuring tissue impedance [9].

Indications

Generally, the ideal candidate for an RFA is a patient with a high-grade dysplasia. As mentioned previously, patients with nodular Barrett's esophagus or with visible lesions require EMR prior Long-term data is not yet available for RFA alone in the treatment of flat intramucosal carcinoma, so care must be taken to rule out intramucosal carcinoma in the set high-grade dysplasia. It is generally recommend high-grade dysplasia be confirmed with two separate endoscopic four-quadrant biopsies eery 1 cm, within 2 months of RFA [8, 10]. In the case that intramucosal carcinoma is identified, RFA can proceed after EMR. In the preset low-grade dysplasia, RFA can be offered. A randomized controlled trial comparing RFA to observation in patients with Barrettlow-gradew grade dysplasia showed a significantly decreased rate of progress high-grade dysplasia or adenocarcinoma compared to control, and while rates of complication (mainly stricture) were higher in the intervention group, the study was terminated early due to the superiority of ablation [11]. However, observation is still considered a viable alternative, and is considered an acceptable option by the American College of Gastroenterology [2]. For intestinal metaplasia, ongoing surveillance is still recommended, as outlined above.

Technique

Circumferential RFA is usually performed on an outpatient basis, generally under monitored anesthesia care. The patient is placed into the left lateral decubitus position, and the endoscope is inserted. The esophagus is prepped with 1% acetylcysteine and flushed with water to clear away excess mucus in order to help the balloon catheter maximize contact with the mucosa. The length of the segment of Barrett's esophagus is measured, from the proximal extent to the proximal gastric mucosa (Fig. 16.1a, b). A guidewire is then passed, and the scope retracted proximally above the segment of Barrett's

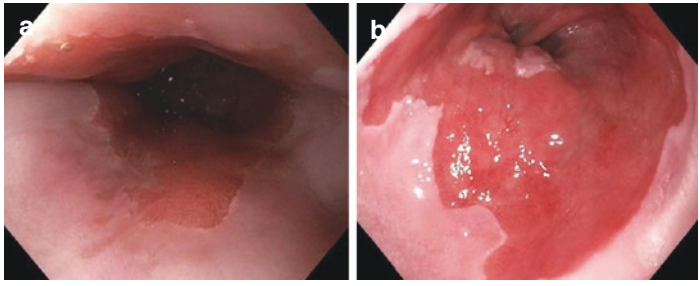

FIGURE 16.1 (**a**) Barrett's esophagus. (**b**) Barrett's esophagus with high-grade dysplasia on biopsy

esophagus. The balloon of the radiofrequency ablation catheter is then inserted under vision, with approximately 1 cm overlap onto normal esophageal squamous mucosa [6]. The catheter is then inflated, and when mucosal contact is confirmed under vision, the electrode is activated and the ablation commences. If the segment of Barrett's esophagus exceeds the catheter electrode length of 4 cm, the balloon is deflated and advanced to the distal end of the previously ablated segment with 5 mm of overlap from the previous segment [6]. The endoscope is then, removed and the balloon is cleaned. A cap is applied to the endoscope, and it is reinserted. The cap at the end of the endoscope is then used to gently clean away the coagulated mucosa from the first application of radiofrequency energy, and this area is rinsed with water. When the entire segment has been cleaned, the guidewire is reintroduced, and the balloon catheter is again inserted over the guidewire and placed into position under endoscopic guidance, and a second round of RFA is performed. A completion endoscopy is then performed to inspect the area of ablation, and the procedure is complete (Fig. 16.2a–c). Repeat endoscopy at 12 weeks is recommended, and if there is either residual circumferential Barrett's esophagus or multiple foci, repeat circumferential ablation is performed. If small or scattered foci are present, then focal RFA is performed.

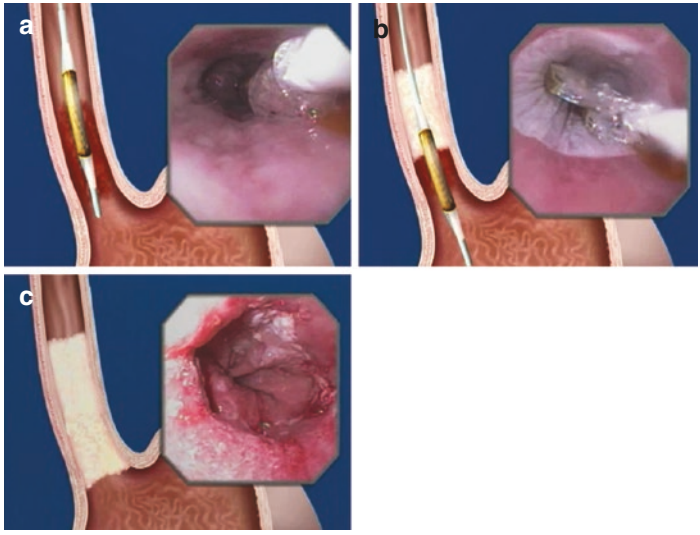

FIGURE 16.2 (**a**) Placement of RFA balloon. (**b**) Balloon deployment. (**c**) Completion endoscopy

Focal RFA is accomplished via a mounted catheter attached to the end of the endoscope, with the electrode at the 12 o'clock position. The endoscope and catheter are then inserted, and the targeted area of Barrett's esophagus is oriented at the 12 o'clock position on the video monitor. The electrode is then placed directly onto the tissue and RF energy is applied at 15 J/cm^2. This is repeated for each focal segment present. Historically, the catheter was then cleaned, the coagulum lifted, and another double set of ablation was performed. However, recently a simplified triple ablation without cleaning or removal of the coagulated tissue has shown noninferiority compared to the standard regimen [12]. The Z line is also recommended to be ablated circumferentially to ensure complete eradication of any residual Barrett's esophagus [6]. The procedure is then completed, and the endoscope is withdrawn.

Post procedurally, it is important to maintain patients on acid suppression, as persistent GERD is an independent risk factor for poor response to RFA [13]. Generally, patients are placed on a 2–4 week regimen of twice daily PPI, nightly ranitidine, and sucralfate four times daily, with continuation of the proton pump inhibitor. Patients should be on a liquid diet for the first day after the procedure, and then gradually advance as tolerated to a soft and then regular diet. As an adjunctive antireflux intervention, antireflux surgery should be considered if indicated to further prevent reflux following an ablative procedure.

Complications

Common symptoms post RFA are sore throat, chest pain, dysphagia, and nausea/vomiting. For pain and discomfort, patients are advised to take liquid acetaminophen or ibuprofen as needed, and if severe, may require codeine with lidocaine. On meta-analysis, complications after RFA included stricture (5%), pain (3%), and bleeding (1%) [14]. Perforation is theoretically possible but rare, and imaging should be obtained if clinical suspicion is high.

Rates of stricture, the most common adverse event after RFA, range from about 5–8%. This rate is higher in phototherapy but similar or lower in cryotherapy (Table 16.2). Factors that predict stricture after RFA include long segment length (>9 cm), longer longitudinal length of involved segment, and higher treatment area [15]. Treatment usually includes balloon dilation.

Table 16.2 Summary of endoscopic eradication methods

Therapeutic technique	Barrx	Photodynamic therapy	Cryotherapy
Stricture rate	5–8%	36%	3–9%
Eradication of dysplasia	78–95%	54–78%	81–97%
Reversion to squamous epithelium	93%	75–80%	57–84%
Incidence of buried Barrett's	0.9%	14.2%	3%
Recurrent metaplasia or dysplasia	4–13%	24%	18–19%
Surveillance	High-resolution endoscopy at 3, 6, and 12 months, then annually	High-resolution endoscopy at 3, 6, and 12 months	High-resolution endoscopy every 3 months for the first year, every 6 months for years two to three, then annually

Outcomes

There has been a good amount of evidence from several studies, both prospective and in meta-analysis, as well as long-term follow-up data, that have shown RFA is safe and effective for treatment of Barrett's esophagus with dysplasia. The consistent depth of penetration yields reliable results, which has been verified in the literature.

The AIM dysplasia trial was a prospective trial of 119 patients with low or high-grade dysplasia randomized 2:1 to ablation versus sham endoscopic therapy, with outcomes looking at complete eradication of dysplasia and metaplasia, durability of response, disease progression, and complications [14]. RFA was performed a maximum of four times in the first year, with an option for an additional focal ablation at 15 months if residual metaplasia or dysplasia remained. Of the initial cohort, 106 subjects reached the 2-year follow-up mark, including crossover of 35 out of 39 patients from the sham arm to RFA at 1 year per the eligibility of the study. Of these 106 patients, 95% had complete eradication of dysplasia and 93% had complete eradication of intestinal metaplasia at 2 years. Of the patients with low-grade dysplasia, 51 of 52 (98%) had complete eradication of dysplasia and metaplasia.

Of patients with high-grade dysplasia, all dysplasia was eradicated in 50 of 54 (93%) and intestinal metaplasia was eradicated in 48 of 54 (89%). Fifty-six patients continued to participate through 3 year follow-up, showing complete eradication of dysplasia in 55 of 56 patients (98%), and complete eradication of intestinal metaplasia in 51 of 56 patients (91%) [14]. Five of 119 patients (4.2%) experienced disease progression—three progressed from low to high-grade dysplasia, one patient with low-grade dysplasia developed esophageal adenocarcinoma, and one patient with high-grade dysplasia developed esophageal adenocarcinoma. Four adverse events of the 119 patients receiving RFA occurred: one patient on dual antiplatelet therapy developed bleeding requiring endoscopic management, and three patients required admission for management of chest pain that resolved with supportive care. Nine of 119 patients (7.6%) developed stricture, and there were no perforations or procedure-related mortalities [14].

Similarly, a meta-analysis consisting of 18 studies with 3802 patients reporting efficacy and 6 studies with 540 patients

reporting durability, complete eradication of intestinal metaplasia was seen in 78% of patients (95% CI, 70–86%), complete eradication of dysplasia was seen in 91% of patients (95% CI, 87–95%), recurrence of intestinal metaplasia was 13% (95% CI, 9–18%), and 0.7% of patients progressed to esophageal adenocarcinoma after achieving complete eradication of intestinal metaplasia [13]. The most common adverse events were stricture (5%), followed by pain (3%), and bleeding (1%).

Surveillance endoscopy regimens depend on the degree of dysplasia. For patients that had complete eradication of high-grade dysplasia or intramucosal carcinoma, surveillance with high-resolution endoscopy and narrow band imaging is recommended at 3 months, 6 months, and 12 months, with annual endoscopies every year for 5 years, whereas patients with low-grade dysplasia are recommended to have surveillance endoscopy at 3 months and 12 months [3].

Special Considerations

A concern after RFA is that underneath the neo epithelium that arises after the metaplastic and dysplastic tissues are eradicated, residual glands containing Barrett's esophagus may progress to esophageal adenocarcinoma underneath, known colloquially as "buried Barrett's" [6]. A systematic review of patients undergoing photodynamic therapy versus RFA found that baseline prevalence of buried Barrett's before endoscopic eradication ranged from 0 to 28%, and that buried Barrett's was seen in 14.2% of patients after photodynamic therapy compared to 0.9% of patients after RFA [16]. Despite the limitations of the study, such as non-uniformity of biopsy depth, there is a clear and significant difference in the incidence of buried Barrett's after RFA compared to photodynamic therapy.

Conclusion

RFA with Barrx FLEX (Medtronic, Minneapolis, MN) is the most commonly performed endoscopic eradication method for Barrett's esophagus with low or high-grade dysplasia. It consists initially of circumferential radiofrequency ablation followed by targeted focal ablation. It has been proven to be safe and effective with a good initial response as well as durability of response at 3–5 year follow-up, and it is considered the gold standard treatment for Barrett's with dysplasia.

Chemical Photodynamic Therapy

Chemical photodynamic therapy (PDT) combines a chemical, sodium porfimer (Photofrin), with argon laser phototherapy to activate and induce mucosal damage. Indications for treatment include Barrett's esophagus with low- or high-grade dysplasia, as well as intramucosal esophageal adenocarcinoma (T1, N0, M0).

Sodium porfimer, the chemical cytotoxic agent, is given intravenously 48–72 h prior to planned endoscopy. Endoscopy is then performed at the appropriate time period, usually under conscious sedation or monitored anesthesia care. After confirming the position on endoscopy, a windowed esophageal centering balloon is placed over a guidewire and inflated at the desired position, and a cylindrical diffuser is passed through the center channel of the balloon. 630 nm light from an argon-pumped laser dye is then applied to the targeted area of esophageal mucosa via the cylindrical diffuser [17]. The light energy activates the chemical agent, inducing mucosal damage via free radical formation [4, 18]. Endoscopies are usually repeated at 48 h to determine if further light treatment is required, and again at 1 week. Endoscopies to check for healing and for biopsies to confirm eradication are then performed at 3, 6, and 12 months [17].

Follow-up data has shown complete eradication of dysplasia to range from 54 to 78%, and complete eradication of

intestinal metaplasia with conversion to squamous epithelium to range from 75 to 80% [17, 19]. Rates of stricture are 28 to 34%, with the increased stricture rate thought to be secondary to the multiple exposures of the argon laser from the overlapping of treatment margins [9, 16]. Perforation is rare but has been described [16]. Other adverse reactions included photosensitivity, vomiting, and odynophagia. Anecdotally, this is often a major concern for patients, as they are advised to avoid sun exposure for at least 30 but up to 90 days [17]. Thus, although photodynamic therapy is a minimally invasive treatment option for Barrett's esophagus with dysplasia, its side effect profile limits its widespread use, and its efficacy is less than that of RFA.

Cryotherapy

Cryotherapy, also known colloquially as spray cryotherapy, works by spraying liquid nitrogen onto Barrett's tissue, causing the disruption of cell membranes, leading to apoptosis and thrombosis in the mucosa [3, 18]. The procedure is performed under conscious sedation or monitored anesthesia care. Endoscopy is performed, and the target area of Barrett's esophagus tissue is identified. A catheter is then placed through the endoscope, and a pressurized system sprays −196 °C liquid nitrogen onto the target tissue, with duration controlled by pressing a foot pedal [20]. The targeted site is treated with 40s total duration, either in two treatments of 20s or four treatments of 10s, with time between to allow for reperfusion of the tissue [20]. Depending on the total length of Barrett's tissue present, treatment of three to five target areas may be required (Fig. 16.3) [21]. The procedure is then repeated every 2–3 months until the Barrett's esophagus is eradicated, confirmed both on endoscopy and histology [20]. Surveillance is done with high-resolution endoscopy every 3 months for the first year, followed by every 6 months for years 2–3, then annually [22].

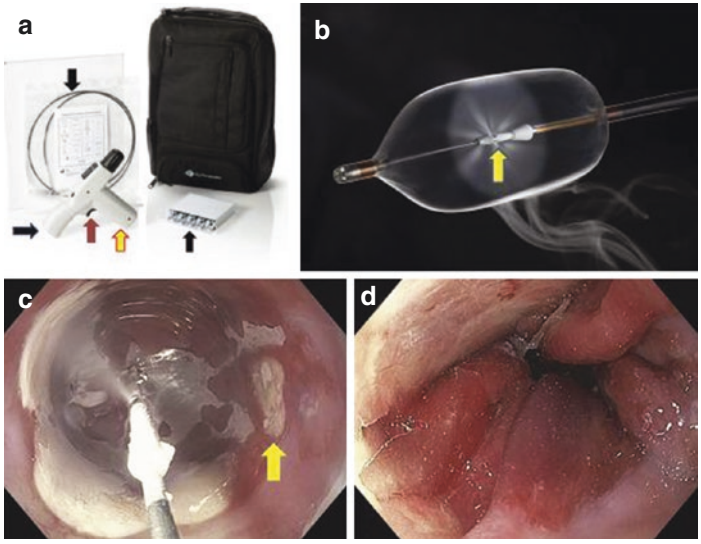

Figure 16.3 (**a**) Controller (left image) with handle that holds the nitrogen cartridge (yellow arrow), trigger (red arrow), and attachment site (black right arrow) for the balloon catheter (black down arrow). The catheter is attached to a reusable light weight portable handle, which controls the delivery of liquid nitrous oxide stored in a small cartridge. (**b**) External view of focal cryoballoon ablation catheter (30 mm) with diffuser (arrow) and nitrous oxide spray. (**c**) Endoscopic view of focal cryoballoon ablation through the balloon using a high-definition endoscope showing the cryogen released from the diffuser within the balloon and resulting ice patch. The active ablation is the fourth one applied in a clockwise circumferential fashion, with the first ice patch melting (arrow). (**d**) Endoscopic view of the distal esophageal and gastric cardia mucosa with red color change and edema immediately after cryoablation. (Figure and text description taken from the following reference, permission pending: Canto MI. Cryotherapy for Barrett's esophagus. Gastrointestinal Endoscopy Clinics. 2017 July 1;27(3):503–13)

In a series of 60 patients with Barrett's esophagus and high-grade dysplasia, 58 (97%) had complete eradication of high-grade dysplasia, 52 (87%) had complete eradication of

dysplasia overall, and 34 (57%) had complete eradication of intestinal metaplasia, with mean follow-up of 10.5 months [20]. Three percent of patients were found to have buried Barrett's. Three patients (3%) developed strictures, and no perforations occurred. Another retrospective series of 32 patients aiming to look at long-term data for cryotherapy in Barrett's esophagus with high-grade dysplasia found that at 2-year follow-up, all 32 patients (100%) had complete eradication of high-grade dysplasia, and 27 patients (84.4%) had complete eradication of intestinal metaplasia [22]. Six patients (19%) developed recurrent high-grade dysplasia and received either RFA (four patients) or argon plasma coagulation (one patient, with eradication in all treated patients. One of the six progressed to esophageal adenocarcinoma. At long-term follow-up (mean 37.8 months), complete eradication of high-grade dysplasia (counting the patients that had repeat treatment for high-grade dysplasia with subsequent eradication after treatment) was seen in 31 patients (97%), but if considering only cryotherapy, the durability of response was 81% [22]. Three patients (9%) had strictures, and no serious adverse events occurred.

Cryotherapy is a quick and overall safe minimally invasive method for endoscopic eradication of Barrett's esophagus with dysplasia, considering its ease of use and side effect profile. Most data is not long term, however, and so the overall durability remains to be seen and should be further studied.

Conclusion

Barrett's esophagus is an unfortunately common condition that carries with it a risk of malignant transformation, especially in the setting of dysplasia. Endoscopic treatments offer a minimally invasive treatment for a disease process that historically mandated esophagectomy, a procedure with significant morbidity. While technologies associated with endoscopic therapies are constantly evolving, the current most

common method of endoscopic eradication of Barrett's esophagus, radiofrequency ablation with Barrx FLEX (Medtronic, Minneapolis, MN) technology, remains the most studied therapy with durable long-term results showing eradication of dysplasia and metaplasia, along with a relatively safe side effect profile. The depth of penetration of the treatments is directly related to stricture rates. Despite the effectiveness of these procedures, ongoing surveillance is required. Antacid therapy should be continued in the form of medications, or one can consider antireflux procedures 3–6 months after the ablative therapies to prevent ongoing gastroesophageal reflux.

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