Diagnosis and Management of Barrett's Esophagus

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Introduction

Comprehensive knowledge regarding the diagnosis and management of Barrett's esophagus is essential since it is one of the most common conditions treated in every gastroenterologist's practice. Barrett's esophagus was first described in 1950 by Dr. Norman Barrett, a British thoracic surgeon. History of long-standing GERD, male gender, age >50, tobacco use, family history of esophageal cancer, and central obesity have all been identified as risk factors associated with the development of Barrett's esophagus.

Definition of Barrett's Esophagus and Screening Guidelines

Barrett's esophagus is defined by both endoscopic and histologic criteria. There must be endoscopic documentation of columnar appearing epithelium in the distal esophagus. The second component of the definition is pathologically confirmed intestinal metaplasia found on histologic evaluation of the biopsies taken from the columnar appearing epithelium.

Screening for Barrett's esophagus is a somewhat controversial topic as there are varying recommendations and no clear approach with proven efficacy. The American Gastroenterological Society (AGA) and the American College of Gastroenterology (ACG) do not recommend endoscopic screening for the general population of patients with GERD, although in practice many patients with GERD will ultimately undergo upper endoscopy.

It is helpful to be aware of the risk factors associated with the development of esophageal adenocarcinoma from Barrett's esophagus when deciding which patients to potentially screen. Risk factors include age 50 or older, male sex, white race, the presence of a hiatal hernia, chronic GERD symptoms, elevated BMI, and intra-abdominal distribution of body fat. The AGA position statement on the management of Barrett's esophagus recommends screening patients with multiple risk factors [1]. The position of the ACG is similar in recommending screening for high-risk patients. It is also recommended by the ACG that patients with any alarm symptoms such as dysphagia, unexplained weight loss, or signs of upper GI bleeding undergo upper endoscopy for further evaluation. The American College of Physicians recommends that screening may be indicated in men over age 50 with GERD symptoms for more than 5 years, plus additional risk factors including nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal distribution of fat [2].

None of the approaches to screening above has been proven in clinical trials to decrease mortality from esophageal cancer. Of note, approximately 40% of patients diagnosed with esophageal adenocarcinoma have no history of heartburn symptoms [3, 4].

The rate of progression to esophageal adenocarcinoma is approximately 0.2–0.5% per year with non-dysplastic Barrett's, approximately 0.7% per year with Barrett's with low-grade dysplasia, and approximately 7% per year with Barrett's with high-grade dysplasia [5].

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Endoscopic Documentation and Histologic Confirmation

Barrett's esophagus was traditionally endoscopically reported as long segment (extent of intestinal metaplasia at least 3 cm above the GEJ) versus short segment (extent of intestinal metaplasia of less than 3 cm) (Figs. 5.1 and 5.2). The AGA position statement regarding the management of Barrett's esophagus recommends the use of a system such as the Prague criteria which allows the endoscopist to provide more detailed information on the extent of Barrett's esophagus in the procedure report [1, 6]. The Prague *C* and *M* criteria document the circumferential extent (the *C* value) of the Barrett's esophagus and also the maximum extent (the *M* value) of the Barrett's esophagus. The maximum extent includes the tongues and islands of columnar appearing epithelia. For example, if the GEJ is located at 40 cm (from the incisors), the proximal extent of the circumferential columnar epithelium is located at 38 cm, and there are several islands of columnar epithelium between 36 cm and 38 cm; then, the Prague criteria will be C2M4 (Diagram 1).

Diagnosis of Barrett's esophagus depends on the histologic finding of intestinal metaplasia in the biopsies of the columnar appearing epithelium. It is important to appropriately identify the GEJ (an anatomic landmark) and the z-line (squamocolumnar junction), and take biopsies for diagnosis of Barrett's in the esophagus within the segment of columnar appearing epithelium. If biopsies are taken distal to the GEJ, in the stomach proper, intestinal metaplasia of the stomach may be reported (which is not able to be distinguished histologically from intestinal metaplasia of the esophagus). Intestinal metaplasia of the stomach can be caused by chronic H. pylori gastritis, among other causes. It is important to distinguish between these two conditions as surveillance is recommended for intestinal metaplasia of the esophagus (Barrett's esophagus), however, not for intestinal metaplasia of the stomach.

Surveillance of Barrett's Esophagus

Non-dysplastic Barrett's

All patients with Barrett's esophagus, including non-dysplastic Barrett's, should be treated with PPI therapy. Once daily PPI is adequate for most patients, with twice daily dosing only necessary for endoscopic findings of esophagitis or poor control of reflux symptoms.

The ASGE Standards of Practice Committee guideline on the role of endoscopy in Barrett's esophagus incorporates recommendations for surveillance intervals [7]. For non-dysplastic Barrett's esophagus, there are multiple possible management options to consider ranging from no surveillance, proceeding with endoscopic surveillance and endoscopic therapy (primarily aimed at ablation of dysplastic Barrett's esophagus) in selected cases. Endoscopic treatment of non-dysplastic Barrett's is a controversial topic and will be further discussed in a later section. If surveillance is decided on for non-dysplastic Barrett's, then EGD is typically performed every 3–5 years with 4-quadrant biopsies every 2 cm (Fig. 5.2). The AGA medical position statement on the management of Barrett's esophagus and the ACG clinical guideline regarding diagnosis and management of Barrett's esophagus also recommend EGD every 3–5 years for non-dysplastic Barrett's surveillance.

Dysplastic Barrett's

If biopsies are indeterminate for dysplasia, then PPI therapy should be initiated (or increased in dose if already on

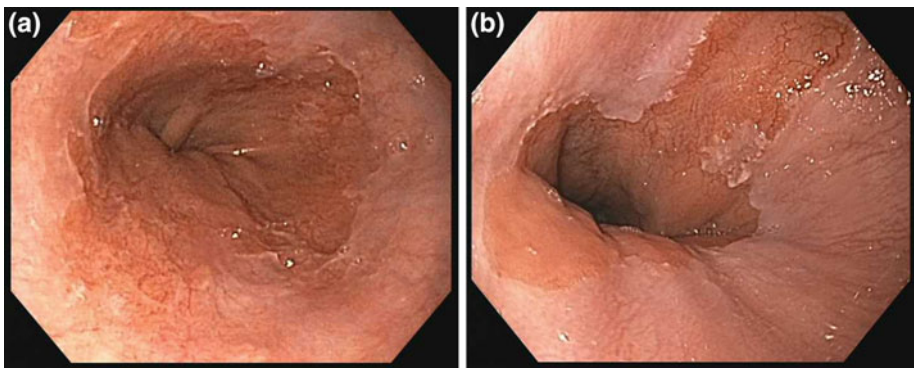

Fig. 5.1 **a**, **b** Endoscopic image of short-segment Barrett's esophagus

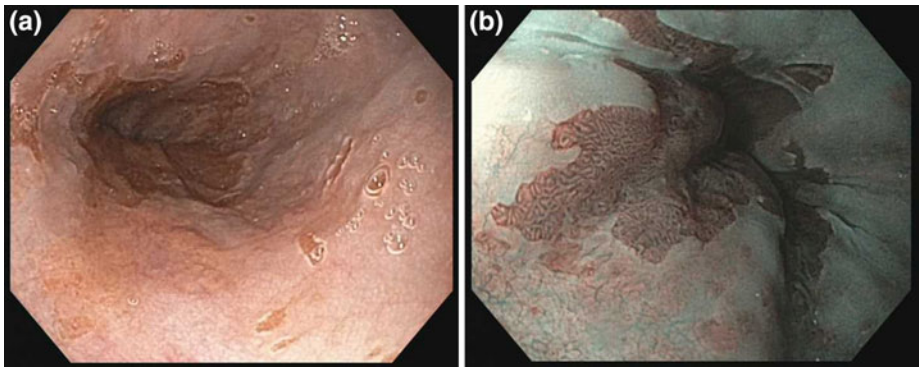

Fig. 5.2 **a** Endoscopic image of long-segment Barrett's esophagus. **b** Close-up image of same patient as (**a**), with narrow band imaging (NBI) applied

antisecretory medication), and repeat EGD with surveillance biopsies should be performed in 2–6 months to confirm or rule out the presence of dysplasia. Therapy with PPI is usually initiated at a standard dose (omeprazole 20 mg daily or equivalent) and increased only if needed based on reflux symptoms or if reflux esophagitis is present on endoscopy.

The finding of low-grade dysplasia should first be confirmed by an expert GI pathologist, and once agreed upon, repeat EGD should be performed in 6 months to confirm the presence of low-grade dysplasia and look for any signs of change (either progression or regression). Options for the management of patients with low-grade dysplasia include endoscopic eradication versus surveillance. Many patients with Barrett's esophagus with low-grade dysplasia will undergo ablative therapy, as discussed below. If patients choose to forgo ablation (for reason such as being unwilling to accept the risk of possible complications), then surveillance is a viable alternative option. If surveillance is performed, then the ASGE guidelines recommend 4-quadrant biopsies performed every 1–2 cm every 6–12 months. If surveillance is opted for, the ACG guidelines recommend 4-quadrant biopsies every 1 cm performed annually.

As with low-grade dysplasia, the finding of high-grade dysplasia should initially be confirmed by an expert GI pathologist. Surveillance is not typically performed as a first-line option for high-grade dysplasia as most of these patients undergo some type of treatment.

The Seattle protocol was initially described as a technique to differentiate high-grade dysplasia from early adenocarcinoma in patients with Barrett's esophagus [8]. The Seattle protocol continues to be widely utilized as a technique in Barrett's surveillance biopsies. In this protocol, targeted biopsies are first performed on mucosal abnormalities such as nodules. Four-quadrant biopsies are then obtained every 1 cm in the entire length of Barrett's esophagus. The ACG guidelines on diagnosis and management of Barrett's esophagus recommend biopsies every 1 cm in patients with history of any type of dysplasia, with biopsies every 2 cm in patients with no history of dysplasia.

Efficacy of Surveillance

Multiple studies have described the limited benefit of surveillance for non-dysplastic Barrett's esophagus [1, 6, 9, 10]. The cost-effectiveness of surveillance in non-dysplastic Barrett's is also controversial. The most recent AGA guidelines note that it is unclear whether endoscopic surveillance of non-dysplastic Barrett's esophagus reduces esophageal cancer incidence or mortality since no long-term trial designed to answer this question has yet been performed.

Although surveillance of non-dysplastic Barrett's esophagus is a controversial topic, it is common practice to perform surveillance as long as patients are fit-enough to ultimately undergo therapy if needed. The ACG specifically recommends that Barrett's surveillance should only be performed after counseling with patients regarding its risks and benefits [5]. The ASGE guidelines also suggest considering no surveillance in patients with non-dysplastic Barrett's esophagus.

Endoscopic Treatments: Description of Techniques and Discussion of Complications

There are two main categories of endoscopic therapies for Barrett's esophagus—mechanical treatments and ablative treatments. The mechanical treatments include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), while the most common ablative treatments include radiofrequency ablation (RFA) and cryotherapy.

Mechanical Treatments

Endoscopic Mucosal Resection (EMR)

The two most common methods of performing EMR are cap-assisted EMR and ligation-assisted EMR. Cap-assisted EMR involves submucosal injection, suction of the lesion

into a cap, and then snare electrocautery. The lesion is initially lifted with a submucosal injection. The submucosal injection can be performed with saline; however, other agents can also be utilized (use of hyaluronic acid; saline with the addition of epinephrine or dye such as methylene blue). After a submucosal injection with lifting has been performed, the lesion is suctioned into a clear plastic cap affixed to the end of the endoscope and then a snare is opened and positioned within the internal ridge of the cap (various snare shapes and sizes are available). The snare is then opened and the lesion is suctioned into the cap, allowing the snare to be closed around it. Electrocautery is then utilized to remove the lesion. Cap-assisted EMR mucosectomy devices with various different cap sizes (outer diameter ranging from 12.9 to 18 mm), shape (flat circular- or oval-shaped tip), and firmness (soft or hard) are available for this technique. (Olympus America, Center Valley, Pennsylvania)

Ligation-assisted EMR is another technique utilized to perform EMR. There are several single-use band ligation devices that are available, including the Duette Multi-Band Mucosectomy device (Cook Medical Inc., Winston-Salem, North Carolina) and the Captivator EMR device (Boston Scientific, Natick, Massachusetts). Both of these devices involve attaching the ligation device to the end of the upper endoscope (very similar in structure and function to standard banding device as would be used to treat esophageal varices). The lesion is then suctioned into the banding cap (typically without prior submucosal injection) and then a band is deployed around the lesion circumferentially. The result of this process is the creation of a pseudopolyp. The included snare can then be advanced though the working channel of the endoscope through the attached device (without having to remove the device), the snare placed around the pseudopolyp (either above or below the band, whichever is technically easiest in a given situation), and then the electrocautery can be applied to remove the lesion. If necessary, for larger lesions or additional lesions, multiple bands can be utilized and the lesion can be removed in a piecemeal fashion (Fig. 5.3).

Possible complications from EMR include bleeding, perforation, and esophageal stricture formation (which are often delayed in presentation). Rates of bleeding after EMR in the literature vary widely, partially dependent on how bleeding is defined by the individual study and how aggressive the EMR procedure under evaluation is. Bleeding after esophageal EMR was evaluated in a large single-center study including 681 patients who underwent 2513 EMR procedures [11]. Clinically significant bleeding, defined in this study as any bleeding requiring endoscopic intervention, blood transfusion, or hospitalization, was only reported in 1.2% of patients.

Perforation rates after esophageal EMR are overall low with rates <0.5% for endoscopists experienced in performing EMR. The perforation risk increases when piecemeal resection is required [12–14, 23].

Stricture formation has been reported to occur in as few as 6% of patients and in as many as 88% of patients undergoing esophageal EMR for Barrett's esophagus with HGD or intramucosal carcinoma in various studies [15–19]. The higher rates of stenosis are associated with patients who have undergone EMR with more extensive resection. A study of 73 patients undergoing EMR (for Barrett's esophagus with HGD or intramucosal carcinoma) found symptomatic strictures in 25% of patients, with strictures more common if the resection area involved more than 50% of the esophageal lumen (odds ratio 4.2, 95% CI 1.3–14) [20].

The strictures caused by EMR are typically able to be effectively managed with endoscopic dilation. In a study of 136 patients undergoing esophageal EMR, a total of 37 patients (27%) developed an esophageal stricture [21]. Of note, 65% of the patients who developed a stricture also had a history of RFA treatment, so the cause of the stricture was likely multifactorial. In the group of patients that did not develop stricture, 56% had history of RFA treatment, suggesting that even EMR combined with RFA does not always

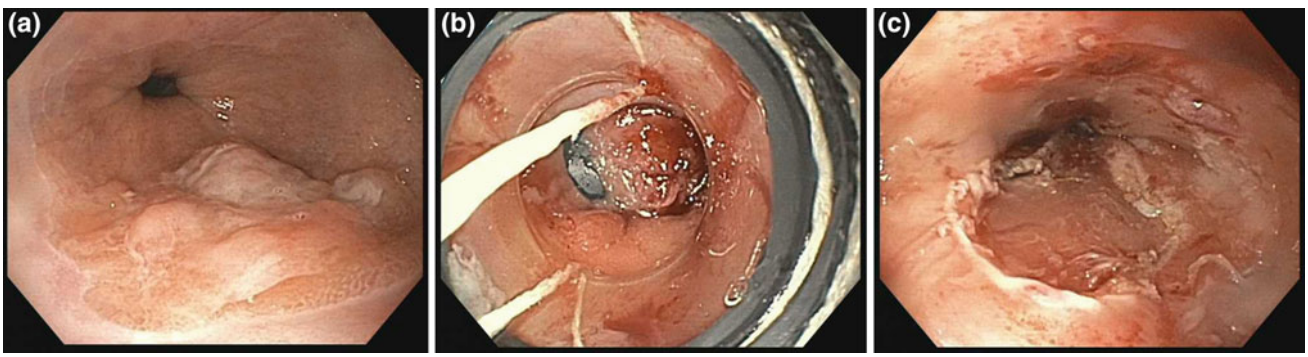

Fig. 5.3 **a** Intramucosal adenocarcinoma arising within Barrett's esophagus. **b** Band deployment during EMR of the intramucosal adenocarcinoma in the same patient as (**a**). **c** Status post-EMR in the same patient as (**a**, **b**)

lead to stricture formation. The authors note that all of the patients who developed stricture had resolution of dysphagia with endoscopic dilation. A median number of 2 dilations were needed per patient. Another study examining esophageal stricture post-EMR demonstrated similar findings with an average of 2.3 dilations required per patient [22].

Endoscopic Submucosal Dissection (ESD)

ESD is a technique that utilizes submucosal injection and then needle-knife for en bloc removal of larger (and possibly deeper) lesions. Many different types of needle-knife catheters are available for performing ESD. Overall complication rates, including perforation, are higher with ESD than with EMR. Bleeding during an ESD procedure is common and is typically able to be treated intra-procedurally with coagulation. Delayed bleeding is less common with esophageal ESD than with gastric ESD, in which rates up to 15.6% have been reported [23]. In a series of patients treated with esophageal ESD, delayed bleeding rates were reported in between 0 and 5.2% in the seven studies (with 568 cases) that provided this information [24].

Review of data from multiple series of esophageal EMR demonstrates a pooled perforation rate of 2.3% (19 of 816 cases), recognizing that most of these cases were performed by experts [25]. Almost all of these perforations were recognized during the procedure and were treated with placement of endoscopic clips. Strictures develop in approximately 12–17% of patients after esophageal ESD [26–29]. As with EMR, the stricture rate increases when more extensive and circumferential lesions are resected.

Since ESD is a technically difficult procedure with higher rates of adverse events than EMR, the utilization of ESD in the USA is limited to specialized centers with endoscopic expertise at performing this technique.

Ablative Treatments

Radiofrequency Ablation (RFA)

Radiofrequency ablation (RFA) is an endoscopic ablative therapy that delivers energy via a balloon (or catheter) with a series of closely spaced electrodes that generate a thermal injury with controlled depth and uniformity. Circumferential ablation and focal ablation are the two primary methods of performing RFA. Circumferential ablation (with an electrode-laden balloon) is typically performed in settings of more extensive areas to treat (such as long-segment Barrett's esophagus), while focal ablation (with an ablation catheter placed on the tip of the endoscope) is used to treat smaller areas. A smaller through-the-scope probe is also available for very small areas of Barrett's esophagus (Video 5.1).

Prior to performing ablation, the esophageal wall should first be irrigated with water to remove any mucus or other debris. Cleansing of the esophagus has traditionally performed using acetylcysteine; however, it has been demonstrated that water is just as effective at cleaning the esophagus [30]. The next step is careful identification of the esophageal-gastric landmarks, including the top of the gastric folds and the proximal extent of the Barrett's esophagus.

Prior to performing circumferential ablation, as the endoscope is positioned in the stomach, a stiff guidewire is placed through the working channel of the endoscope, and the endoscope is withdrawn as the wire is kept in place. The Barrx^{TM} 360 soft sizing balloon is then advanced over the wire and connected to the Barrx FLEX generator (Medtronic, Minneapolis, Minnesota). This sizing balloon is utilized to measure the inner diameter of the esophagus prior to performing ablation. Based on the measurements from the sizing balloon, an appropriate ablation balloon catheter is selected. The BARRX^{TM} 360 RFA balloon catheters (Medtronic, Minneapolis, Minnesota) are all 3 cm in length and are available in size diameters ranging from 18 to 31 mm.

The RFA balloon catheter is advanced over the wire and then the endoscope can be advanced adjacent to the wire and positioned proximal to the ablation balloon. With direct endoscopic visualization, the proximal edge of the balloon is positioned approximately 1 cm above the proximal extent of the Barrett's esophagus. The balloon is then inflated, and then radiofrequency energy (typically 12 J/cm^2) is activated by depressing a foot pedal attached to the generator. After the energy has been delivered, the balloon is repositioned more distally (allowing approximately 5–10 mm of overlap with the prior ablation area) and the same process repeated until the entire segment of Barrett's esophagus has been treated.

After the entire segment has been treated, the balloon catheter, wire, and endoscope are removed from the patient. A soft cap is attached to the end of the endoscope and the esophagus is then cleansed by removal of the coagulum with the soft cap combined with irrigation of the esophagus with water. After this is complete, the entire process is repeated (placement of wire, insertion of balloon catheter, and then ablation using the same settings as previously performed) as needed to treat the entire area of Barrett's esophagus.

A variety of different RFA catheters is commercially available and can be utilized to ablate smaller segments of Barrett's esophagus when non-circumferential disease is encountered. Several of the catheters (Barrx60, Barrx90, Barrx Ultra Long) can be attached to the end of the endoscope and one of the catheters (Barrx Channel) is a through-the-scope device for treatment of focal areas of Barrett's esophagus. When utilizing the attachments made to be affixed to the endoscope tip, the device is positioned at 12 o'clock on the endoscopic image. The endoscope and ablation catheter are advanced into the esophagus under direct

visualization for use. The through-the-scope RFA ablation catheter is rotatable and usable under direct endoscopic visualization as well.

Once the endoscope has been advanced to the target tissue, ablation is performed by using the wheels of the endoscope to bring the ablation catheter into close contact with the mucosa in the desired treatment area. RFA energy (typically 15 J/cm^2) is then delivered by depressing a foot pedal attached to the generator. Prior to moving the electrode away from the mucosa, a second delivery of energy (at the same setting) is applied. All of the remaining areas of Barrett's esophagus are then treated in a similar fashion. As with circumferential ablation, the coagulum should then be cleansed from the esophageal wall after each treatment. This can be performed by using the tip of the electrode catheter to scrape off the coagulum. The endoscope should then be completely removed from the patient and the catheter cleansed with water. The endoscope and catheter are then reinserted and another treatment is performed in the exact same manner as previously (another two pulses of ablation at each treatment station) (Fig. 5.4).

Post-RFA treatment care typically includes high-dose PPI treatment. All patients with Barrett's esophagus should already be taking a PPI agent; however, increased acid suppression therapy may help improve esophageal healing after an ablation session. A prospective study demonstrated that effective esophageal pH control (24-h pH monitoring was utilized) was associated with improved outcomes, including reduction in Barrett's esophagus surface area and complete eradication rate, after RFA treatment [31].

As patients may experience chest pain and/or dysphagia immediately after treatment, alteration in the diet for several days after treatment is generally recommended. Dietary recommendations after RFA typically include liquids only for the first day after the procedure, a soft-consistency diet on the second day, and slow advancement as tolerated after that time. Other medications that can be considered include sucralfate suspension and pain medications if needed.

RFA treatment is generally well tolerated. There are a multitude of studies describing complication rates after RFA for Barrett's esophagus. Overall stricture rates from RFA range between 0 and 6%, depending on the study. A multi-centered community-based study including 429 patients treated with RFA for Barrett's esophagus demonstrated a stricture rate of 1.1% of cases (2.1% of patients), with no serious adverse events (including no bleeding or perforation) [32]. In this study, the strictures resolved with a median of three endoscopic dilations. A large meta-analysis of 18 studies demonstrated that the most frequent complications from RFA include esophageal stricture (5%), chest pain (3%), and bleeding (1%) [33].

Cryotherapy

Cryotherapy is a technique that has been utilized in many different fields in medicine; however, this technology has only recently been adapted for use in endoscopy in general and Barrett's esophagus specifically. At this time, it is most commonly used for patients with refractory Barrett's esophagus who have failed or developed complications from RFA treatment (such as chest pain or stricture), or who are not candidates for RFA, or in patients who do not want to undergo RFA. Cryotherapy can also be utilized as a primary therapy for Barrett's esophagus treatment and can be used to treat esophageal cancer locally in nonsurgical candidates.

The two currently commercially available cryogens are liquid nitrogen and carbon dioxide. The destruction of the Barrett's epithelia is caused by freeze-thaw cycles using either of the cryogens. The available endoscopic systems for cryotherapy treatment include the CryoSpray Ablation system (CSA Medical, Baltimore, Maryland), Polar Wand cryotherapy (GI Supply, Camp Hill, Pennsylvania), and the Coldplay Focal Cryoballoon Ablation System (C2 Therapeutics, Redwood City, California).

Although there are different cryotherapy systems, in general a catheter is advanced through the working channel of the endoscope under direct endoscopic visualization. One system uses a cryogen-filled balloon to cool tissue; all others use a spray catheter. Administration of the cryogen is performed by depressing a foot pedal attached to the processor/pump, connected to a tank of cryogen, which

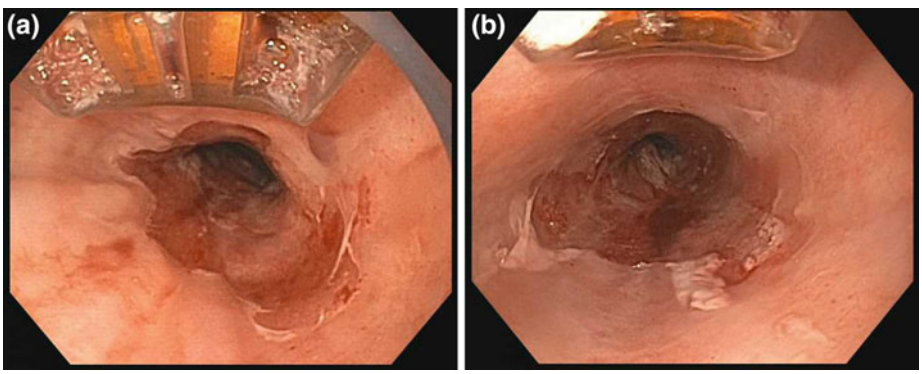

Fig. 5.4 **a** Initiation of RFA treatment with a BARRX90 catheter. **b** Image of the esophagus in the same patient as (**a**) after several ablation applications

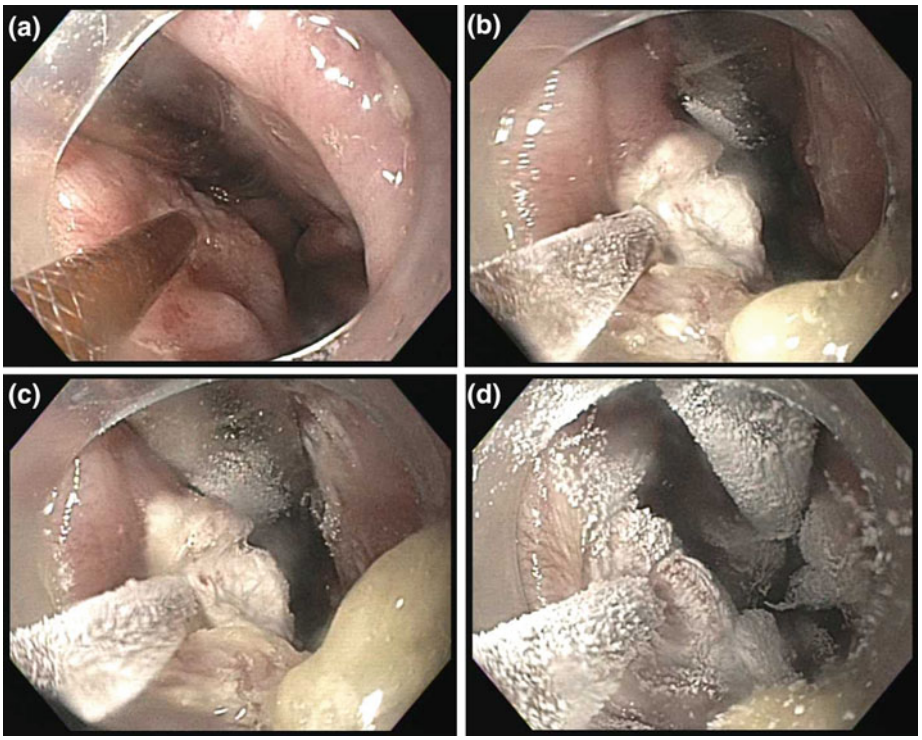

Fig. 5.5 **a** Small focus of esophageal adenocarcinoma in a patient with Barrett's esophagus undergoing cryotherapy with liquid nitrogen as cryogen. Note the spray catheter and suction tube visible in the image. Of note, the patient is not a surgical candidate. **b** Cryogen is applied and freezing begins. **c** Continued application of cryogen results in deep freezing. **d** As the freezing cycle ends, there is some diffuse, superficial freezing of tissue in the field although the focus is on the area of esophageal cancer

delivers the cryogen itself into direct contact with the target tissue. There are different regimens in performing cryotherapy treatment, but all involve several freeze/thaw cycles in a single endoscopic session. Three-to-four cycles per session are not uncommon (Fig. 5.5).

As cryotherapy is a more recently developed therapy for Barrett's esophagus, there are limited data with regard to outcomes when compared to that available for RFA. In general, endoscopic cryotherapy is well tolerated, but the technology has been slow to disseminate into widespread clinical practice. Also, there is no currently available method for accurate determination of dosimetry in cryotherapy, a major impediment to research in this field.

Based on numerous studies on the side effects from cryotherapy in Barrett's esophagus, the treatment is generally safe. In a series of sixty patients with Barrett's esophagus with HGD treated with cryotherapy, 2 patients (3.3%) experienced chest pain, 3 patients (5%) developed stricture, and there was 1 patient (1.7%) with GI bleeding [18]. Cryotherapy has demonstrated a favorable safety profile in multiple additional studies. A multi-center retrospective cohort study of 79 patients with esophageal cancer treated with spray cryotherapy with liquid nitrogen demonstrated no serious adverse events [34]. Ten patients developed benign strictures (12.6%); however, it was noted that 9 of the 10 patients had prior esophageal narrowing from other treatments (such as RFA). Twenty patients (25.3%) experienced chest discomfort that was treated with narcotic analgesics. A single-center retrospective study of 32 patients treated with spray cryotherapy for Barrett's esophagus with high-grade dysplasia noted esophageal stricture formation in 3 patients (9%), all of which responded to endoscopic dilation [35]. There were no serious adverse events.

Efficacy of Endoscopic Treatments

High-Grade Dysplasia/Intramucosal Carcinoma

Patients with Barrett's with HGD or intramucosal carcinoma should be all undergo treatment if they are good candidates for endoscopic therapy. Surgical esophagectomy is the historical first-line treatment for patients with Barrett's esophagus with high-grade dysplasia and/or intramucosal adenocarcinoma, and can still be discussed with patients as a potential option, especially if the disease is extensive or multifocal. Esophagectomy is the most definitive therapy as it removes the entire segment of neoplastic epithelium, a healthy margin of unaffected tissue, and regional lymph nodes. Esophagectomy, however, is a complex and extensive surgical undertaking and has high rates of morbidity, postoperative complications, and mortality, particularly in centers that do not perform high-volume number of procedures. Data from the Dutch National Registry demonstrated mortality rates from esophagectomy to be 12.1% (in centers performing 1–10 surgeries per year), 7.5% (11–20/year), and 4.9% (more than 50 per year) [25].

Most patients will prefer and select endoscopic therapy over surgical esophagectomy. If endoscopic therapy is performed, generally all mucosal irregularities (nodular mucosa) should initially be removed with EMR (endoscopic mucosal resection), and then the remainder of the Barrett's esophagus was treated with RFA, cryotherapy, or EMR. The initial EMR of any mucosal irregularities provides both therapy and staging information. Patients with submucosal depth of invasion (T1b) discovered on EMR should be referred for surgical consultation as endoscopic therapy in these patients will generally not be curative. Patients with EMR specimens revealing intramucosal cancer (T1a) will be candidates for endoscopic therapy.

Numerous studies have demonstrated the efficacy of RFA in the eradication of high-grade dysplasia/intramucosal carcinoma and intestinal metaplasia (complete eradication of Barrett's esophagus). A multi-center trial consisting of 127 patients with dysplastic Barrett's esophagus was randomized (2:1 ratio) to received RFA or a sham procedure (control). In the group of patients with high-grade dysplasia, eradication of dysplasia was achieved in 81% of patients in the RFA group, compared with 19% in the control group ($p < 0.001$) [36]. Among all patients with dysplasia, eradication of intestinal metaplasia was achieved in 77.4% of patients in the ablation group, compared with 2.3% in the control group ($p < 0.001$). The patients in the RFA group also had less disease progression (3.6 vs. 16.3%, $p = 0.03$) and fewer malignancies (1.2 vs. 9.3%, $p = 0.045$).

A systematic review including a total of 22 studies evaluated the efficacy of RFA and EMR for eradication of high-grade dysplasia and intramucosal carcinoma [37]. Eradication of dysplasia was achieved in 92% of patients after completion of RFA treatment (patients received a median of 2 RFA sessions). After medium follow-up of 21 months, the eradication of dysplasia was maintained in 94% of patients treated with RFA.

Endoscopic cryotherapy is an alternative therapy for ablation of Barrett's esophagus. Since it is a less fully developed and studied treatment for Barrett's esophagus, there is not nearly as much long-term follow-up data for cryotherapy as exists for RFA. Cryotherapy can be utilized as the first-line therapy for ablation of Barrett's esophagus and may also be used in patients that have been refractory to eradication of intestinal metaplasia with RFA or in patients having significant side effects from RFA (such as pain or stricture formation). In current practice, cryotherapy is most commonly used for patients with refractory Barrett's esophagus.

Several studies have evaluated the efficacy of endoscopic cryotherapy for treatment of Barrett's esophagus [35, 38, 39]. In a series of 32 patients with Barrett's esophagus with high-grade dysplasia treated with cryotherapy, there was complete eradication of high-grade dysplasia in 32 patients (100%) and complete eradication of intestinal metaplasia was seen in 27 patients (84%) at 2-year follow-up. Another study of 60 patients with Barrett's esophagus with high-grade dysplasia demonstrated complete eradication of high-grade dysplasia in 52 patients (87%) and complete eradication of intestinal metaplasia in 34 patients (57%). Sixty-four patients with Barrett's esophagus with high-grade dysplasia or intramucosal adenocarcinoma were treated with cryotherapy and demonstrated eradication of high-grade dysplasia in 60 patients (94%) and eradication of intestinal metaplasia in 35 patients (55%). Cryotherapy studies have yet to elucidate the exact dosimetry and timing of this treatment, although studies are ongoing.

EMR (endoscopic mucosal resection) has been discussed above as treatment/staging for the nodular areas of Barrett's esophagus (and then treatment of the remainder of Barrett's esophagus with ablative therapies). EMR can also be utilized as a primary therapy for resection of the entire area of Barrett's mucosa. This method is not as commonly performed as there are high rates of stricture formation when circumferential EMR is performed.

Complete resection of Barrett's mucosa with EMR versus resection of mucosal abnormalities with EMR followed by ablation of the remainder of Barrett's esophagus with RFA was evaluated in a study of 47 patients with Barrett's esophagus containing HGD or intramucosal cancer [40]. The complete endoscopic resection group demonstrated eradication of neoplasia in 100% of patients and eradication of intestinal metaplasia in 92% of patients. The EMR plus RFA group demonstrated eradication of neoplasia in 96% of patients and eradication of intestinal metaplasia in 96% of patients. The eradication rates between the two groups were similar; however, the stricture rate in the EMR only group was 88 versus 14% in the EMR plus RFA group ($p < 0.001$).

Low-Grade Dysplasia

Management options for Barrett's esophagus with low-grade dysplasia include endoscopic ablative treatment versus surveillance. Currently, more patients with Barrett's esophagus and low-grade dysplasia are recommended to undergo ablative therapy as numerous recent studies have demonstrated the benefits of ablation with regard to reducing the risk of progression to malignancy. If patients are not willing to accept the potential risks of ablative therapy such as pain and esophageal stricture formation, then surveillance alone without ablative therapy remains an option, recognizing that ablation may need to be discussed in the future if the patient shows signs of progression to high-grade dysplasia or intramucosal cancer.

A multi-center randomized trial comparing surveillance versus RFA (the SURF trial) specifically evaluated patients

with Barrett's esophagus with low-grade dysplasia and their risk of neoplastic progression [41]. This study included 136 patients with a diagnosis of Barrett's esophagus with low-grade dysplasia and randomized the patients (in a 1:1 ratio) to either RFA (treatment group) or endoscopic surveillance (control group). The group undergoing RFA demonstrated a marked reduced progression to HGD or adenocarcinoma during a 3-year follow-up (1.5% for the RFA group versus 26.5% for the control group; 95% CI, 14.1–35.9%; $p < 0.001$).

Another multi-center study retrospectively reviewed neoplastic progression rates in patients with Barrett's esophagus with low-grade dysplasia [42]. A total of 170 patients with confirmed Barrett's esophagus with low-grade dysplasia (45 patients who underwent RFA and 125 patients who underwent surveillance endoscopy) were reviewed and it was found that the annual rate of progression to HGD or adenocarcinoma was 0.77% in the RFA group (after mean follow-up of 889 days) and 6.6% (after a mean follow-up of 848 days) in the surveillance group. The group undergoing RFA demonstrated significantly lower risk of progression to HGD or adenocarcinoma than the surveillance group (adjusted hazard ratio = 0.06; 95% confidence interval 0.008–0.48).

Non-dysplastic Barrett's Esophagus

Endoscopic eradication therapy of non-dysplastic Barrett's esophagus is a controversial topic. In general, endoscopic therapy is not recommended for most patients with non-dysplastic Barrett's as the overall risk of progression to cancer is low. However, endoscopic therapy in select higher risk patients (young age with family history of esophageal cancer) can be considered, though there are no clear guidelines for these recommendations at this time.

The AGA medical position statement on the management of Barrett's esophagus recommends to consider endoscopic therapy in patients with non-dysplastic Barrett's who are thought to be at increased risk for progression to HGD or cancer, however notes that specific criteria to define this population have not been created as of this time. The ACG clinical guideline on management of Barrett's esophagus states that endoscopic ablative therapies should not be routinely applied to patients with non-dysplastic Barrett's esophagus. The ASGE standards of practice committee guideline note that endoscopic ablative therapies can be considered in non-dysplastic Barrett's in selected patients (such as patients with a family history of esophageal adenocarcinoma).

Non-dysplastic Barrett's esophagus can be a source of concern to patients who worry about their risk of developing cancer. Some patients with non-dysplastic Barrett's esophagus simply want to undergo ablation for peace of mind.

Surveillance After Treatment

Regardless of the treatment method, after complete eradication of intestinal metaplasia and complete eradication of dysplasia is achieved, surveillance endoscopy is recommended to evaluate for recurrence. The following recommendations from the ACG Clinical Guideline on Diagnosis and Management of Barrett's Esophagus are considered a strong recommendation, however, with low level of evidence [10].

Surveillance endoscopy for patients initially treated for Barrett's with high-grade dysplasia is recommended every three months for the first year (after eradication of both high-grade dysplasia and intestinal metaplasia), every 6 months for the second year, and then continued annually. Surveillance endoscopy for patients initially treated for Barrett's with low-grade dysplasia is recommended every 6 months for the first year (after eradication of both low-grade dysplasia and intestinal metaplasia), then continued annually.

Similar to initial surveillance endoscopy, it is generally recommended that surveillance endoscopy after eradication of intestinal metaplasia and dysplasia be performed with a careful examination of the esophagus with both white-light endoscopy and narrow band imaging. Four-quadrant biopsies are typically taken every 1 cm throughout the segment of prior Barrett's esophagus. Of note, the initial documentation of the length of Barrett's esophagus using a system such as the Prague criteria becomes very useful in the following Barrett's after treatment to know the location of the initial segment of abnormal mucosa so that it can be clearly evaluated on subsequent procedures after treatment.

Conclusion

There is general consensus among the American gastrointestinal societies regarding screening and surveillance of patients with Barrett's esophagus. Endoscopic screening should not be performed on the general population. Screening should be considered for patients at higher risk for development of esophageal cancer, including patients with long-standing GERD, male gender, age > 50, central obesity, history of tobacco use, and family history of esophageal cancer. Non-dysplastic Barrett's esophagus has a low risk of progression to esophageal adenocarcinoma, and endoscopic treatment is not generally recommended. Non-dysplastic Barrett's esophagus is most often followed with surveillance endoscopy and biopsies every 3-5 years. Patients with confirmed low-grade dysplasia, high-grade dysplasia, and intramucosal carcinoma are candidates for endoscopic therapy. The most common options for endoscopic therapy include ablative treatments (RFA and cryotherapy) and

Table 5.1 Surveillance of Barrett's esophagus

Non-dysplastic Barrett's	EGD every 3–5 years with 4-quadrant biopsies every 1–2 cm
Indefinite for dysplasia	Repeat EGD in 2–6 months to confirm or rule-out presence of dysplasia
Low-grade dysplasia	Confirm by GI pathologist. Repeat EGD in 6 months to evaluate for progression or regression. If LGD is confirmed, endoscopic treatment recommended. Alternative is surveillance every 6–12 months with 4-quadrant biopsies every 1–2 cm
High-grade dysplasia	Confirm by GI pathologist if confirmed → endoscopic treatment

mechanical treatments (EMR and ESD). It is important to note that there is risk of recurrence after complete eradication of both intestinal metaplasia and dysplasia, and patients should continue to have endoscopic surveillance after treatment is complete (Table 5.1).

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