Chapter 14
Barrett's Esophagus: Treatment Options

Ajaypal Singh and Irving Waxman

Abstract Barrett's esophagus (BE) is an asymptomatic condition, but it is the most significant known risk factor for the development of esophageal adenocarcinoma (EAC). More than half of short segment BE patients do not have any reflux symptoms. Cancer develops in BE through a sequence of genetic and epigenetic changes that activate oncogenes and silence tumor suppressor genes and cause progression from metaplasia through dysplasia to esophageal adenocarcinoma. Treatment approaches to BE mainly focus on eradication of high-grade dysplasia and neoplasia as well as prevention of progression of metaplasia to neoplasia. The treatment options for BE have undergone a significant change over the last few years due to improvement in our understanding of pathogenesis and progression of Barrett's esophagus as well as availability of endoscopic treatment modalities.

Keywords *Gastroesophageal reflux disease* • Barrett's esophagus • Metaplasia • Low -grade dysplasia • High-grade dysplasia • Radiofrequency ablation • Endoscopic mucosal resection • Cryotherapy • Esophagectomy

Barrett's esophagus (BE) is an asymptomatic condition, but it is the most significant known risk factor for the development of esophageal adenocarcinoma (EAC). More than half of short segment BE patients do not have any reflux symptoms. Cancer develops in BE through a sequence of genetic and epigenetic changes that activate oncogenes and silence tumor suppressor genes and cause progression from metaplasia through dysplasia to esophageal adenocarcinoma.

A. Singh, MD • I. Waxman, MD, FASGE (✉)
Department of Medicine, Center for Esophageal Diseases, University of Chicago Pritzker School of Medicine, 5700 S. Maryland Avenue, MC 8043, Chicago, IL 60637, USA
e-mail: iwaxman@medicine.bsd.uchicago.edu

P.M. Fisichella et al. (eds.), *Esophageal Diseases*,
DOI 10.1007/978-3-319-04337-1_14,

Treatment approaches to BE mainly focus on eradication of high-grade dysplasia and neoplasia as well as prevention of progression of metaplasia to neoplasia. The treatment options for BE have undergone a significant change over the last few years due to improvement in our understanding of pathogenesis and progression of Barrett's esophagus as well as availability of endoscopic treatment modalities.

Medical Treatment

Acid Suppression Therapy: All patients with BE and symptoms of GERD or reflux esophagitis seen on endoscopy should be treated with high-dose proton-pump inhibitor (PPI) therapy, unless there are contraindications for the use of PPIs in which case H2 receptor blockers should be used. The use of PPI therapy in patients with BE but no symptoms of reflux or endoscopic evidence of reflux esophagitis is not clear. The main argument for the use of PPIs in this group will be only to reduce the risk of progression of dysplasia or development of cancer. There are a few observational and retrospective studies that have shown that the use of PPIs is associated with lower risk of developing high-grade dysplasia (HGD) and adenocarcinoma and even partial regression of intestinal metaplasia, but no randomized controlled trials are available to support these findings. The American Gastroenterology Association (AGA) recommends discussion of risks and potential benefits of long-term acid suppression therapy with BE patients in the context of their overall health status and medication use. Currently we recommend acid suppression therapy for all patients with BE unless there are specific contraindications. The assessment of reflux symptoms in patients on high-dose acid suppression therapy has not shown to be a reliable indicator of acid suppression, and up to 40 % of these patients can have persistent acid reflux as judged by 24-h pH studies despite resolution of reflux symptoms. Even though pH monitoring might be needed to titrate doses of acid suppression, routine pH monitoring to confirm efficacy of acid suppression therapy is not currently recommended.

Aspirin and Nonsteroidal Anti-inflammatory Drugs: Multiple published studies have shown that aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDS) might have potential chemopreventative effects in patients with BE. Both ASA and NSAIDs have been shown to reduce the risk of developing esophageal adenocarcinoma by as much as 33 %. Currently no prospective, randomized control trials to support this chemopreventative effect are available, but a large clinical trial is currently underway, the results of which are eagerly awaited. Most of the patients with BE are elderly males with obesity or other cardiovascular risk factors, so use of low-dose aspirin should be considered in patients with cardiovascular risk factors and BE. The biggest concern for the use of ASA is risk of bleeding, but the patients with BE should also be on a PPI, which should minimize the gastrointestinal toxicity associated with aspirin use.

Endoscopic Treatment

Who to Treat and Who to Watch?

The patients at highest risk for the development of invasive cancer are candidates for eradication of Barrett's epithelium. Currently the best available marker for predicting development of cancer in BE is dysplasia. The incidence of adenocarcinoma in high-grade dysplasia (HGD) is around 6 % per year with one study showing incidence of 19 % in 1 year. Thus, endoscopic eradication is recommended in all patients with HGD. Intense endoscopic surveillance every 3 months is an option for patients who decline eradication therapy or those who are not candidates for Barrett's eradication. The incidence of lymph node metastases is only 1–2 % in adenocarcinomas confined to the mucosa but increases to around 15 % with submucosal involvement. Thus, endoscopic therapy is also currently recommended in all patients with intramucosal carcinoma (IMC). This underlines the importance of accurate T-staging of the esophageal adenocarcinoma. Endoscopic ultrasound has been shown to have an accuracy of only 50–60 % in identifying the T-stage of early esophageal cancers. However, preoperative EMR specimens have excellent agreement with histology from esophagectomy specimens in patients with BE and neoplasia. Hence, in addition to being a therapeutic procedure, endoscopic mucosal resection is a very important staging tool. The incidence of adenocarcinoma is very low (0.1 % per year) in low-grade dysplasia (LGD) and there is no international consensus regarding eradication therapy, but most societies do not recommend eradication therapy in this patient population. One of the issues with managing low-grade dysplasia in BE is the interobserver variability among pathologists regarding the diagnosis, with studies reporting only 15 % cases of low-grade dysplasia that were confirmed by expert pathologists. A recent cost-effectiveness study concluded that radiofrequency ablation of low-grade dysplasia might be cost-effective if the diagnosis is accurate and it is assumed that risk of progression to cancer for low-grade dysplasia is at least 50 % more than that for non-dysplastic BE. In its latest medical position statement, the American Gastroenterological Association (AGA) "strongly supports the concept of shared decision-making where the physician and patient together consider whether endoscopic surveillance or eradication therapy is the preferred management option."

Surveillance for Barrett's Esophagus

The main aim of surveillance is to detect progression of dysplasia as well as early esophageal cancer. Even though there are no randomized, prospective trials showing direct benefits of regular surveillance, there are multiple retrospective studies that have shown improved survival if esophageal cancer is detected endoscopically rather than when it is symptomatic. Esophageal cancers detected during

surveillance have a lower staging and improved survival. All patients with new diagnosis of BE should have two endoscopies within the first year and if no dysplasia is noted on either, they can be followed by serial endoscopy every 3–5 years. Due to high variability in reporting of low-grade dysplasia, if LGD is noted on biopsies, this diagnosis must be confirmed by an expert GI pathologist. Once low-grade dysplasia is confirmed, a repeat endoscopy is recommended within 6 months to make sure there is no high-grade dysplasia. All patients with low-grade dysplasia should undergo annual surveillance endoscopy until non-dysplastic BE is noted on two consecutive occasions after which surveillance can be done as for non-dysplastic BE (every 3–5 years). As mentioned above, all high-grade dysplasia patients should undergo eradication therapy unless they are not candidates for this or they decline treatment, in which case, surveillance endoscopy should be done every 3 months.

During surveillance endoscopy, current guidelines recommend 4-quadrant biopsies every 1–2 cm of the Barrett's segment (Seattle protocol). All areas of nodularity or mucosal irregularity should be sampled separately. Strict adherence to Seattle protocol is important since only around 40 % of high-grade dysplasia and esophageal adenocarcinomas were identified as endoscopically suspicious locations during high-definition white light endoscopy in one study. But due to multiple number of biopsies needed, adherence to the Seattle protocol in community practice has been low, with some studies reporting an adherence of only 30 % with BE of more than 10 cm (notably, this population is at higher risk of esophageal cancer). The time spent during inspection of Barrett's epithelium has been shown to be directly proportional to the number of suspicious lesions as well as HGD/EAC lesions identified, with 1 min per centimeter of Barrett's epithelium suggested as optimal Barrett's inspection time. Given the poor adherence to dysplasia surveillance by extensive biopsies, other markers of dysplasia as well as endoscopic imaging techniques are being studied. Currently the use of biomarkers for detection of dysplasia is only in the investigational stages and no professional gastroenterology society recommends their use for clinical decision-making. Various different modalities including chromoendoscopy, narrow band imaging with magnification, and confocal laser endomicroscopy are being study to identify high-risk lesions during visual inspection. The AGA currently recommends detailed examination under white light endoscopy and these additional imaging techniques are not currently recommended. The endoscopic surveillance should be performed using high-definition, high-resolution endoscopes and strict adherence to the biopsy protocol should be followed. We utilize these resources as adjuncts to our endoscopic examination to help us target the biopsies toward areas of interest.

How to Treat?

An international, multidisciplinary, systematic, evidence-based review of management strategies for BE in 2012 recommended that endoscopic treatment of BE with HGD or T1m esophageal adenocarcinoma is preferred over surveillance strategies or surgical treatment. It further went on to recommend that endoscopic treatment of HGD or T1m BE should be performed in tertiary referral centers after proper

training of both endoscopists and pathologists involved. The goal of all endoscopic therapies is complete eradication of intestinal metaplasia leading to regeneration of squamous epithelium.

Endoscopic Treatment

Endoscopic treatment of BE includes endoscopic ablative therapies and endoscopic mucosal resection (EMR).

Ablative Therapies

The ablative therapies include thermal therapies (argon plasma coagulation, radiofrequency ablation, cryotherapy) and photodynamic therapy that utilizes photochemical energy. Even though the ablative methods are technically easier to adopt, they do not provide any tissue for histopathological analysis. Another major concern about ablative therapies is that they can leave behind foci of metaplastic Barrett's epithelium that is covered by squamous epithelium during regeneration and is thence not visible during routine endoscopic surveillance. These residual columnar foci, also known as buried glands, have neoplastic potential and can cause progression of BE despite complete Barrett's eradication visually.

Radiofrequency Ablation (RFA)

Radiofrequency ablation (RFA) involves mucosal ablation via superficial thermal injury generated by a high-frequency electromagnetic field from electrodes placed in an ablation catheter. Commercially available RFA catheters as Barrx ablation system, it includes an RFA energy generator and RFA delivery catheters. There are three kinds of ablation catheters: a balloon catheter (Barrx 360) for circumferential ablation, over the scope catheters of various sizes (Barrx 90, Barrx 60, and Barrx Ultra Long Catheter) and a recently developed through the scope catheter (Barrx Channel RFA Catheter). RFA is currently the most commonly used mucosal ablation technique for BE given its efficacy, ease of use, and low risk of complications. After cleaning the esophageal mucosa with 1 % *N*-acetylcysteine, the RFA catheter is applied to the surface at a dose of 12 J/cm^2. A second round of ablation is done after cleaning the mucosa and removing the debris. Some endoscopists use 10 J/cm^2 for low-grade dysplasia. Usually multiple sessions of RFA are required till complete ablation of dysplastic mucosa is achieved. It is very important to note that RFA is indicated only for flat Barrett's mucosa and patients with nodular disease should undergo resection of visible nodular lesions for staging purposes before the remaining flat Barrett's mucosa is ablated.

In a multicenter, randomized, sham-controlled study from the United States, complete eradication of intestinal metaplasia at 12 months was achieved in 74 % patients with high-grade dysplasia and 81 % patients with low-grade dysplasia. Progression of high-grade dysplasia to esophageal cancer was reduced from 19 % in shams to 2.4 % in the ablation group, though the total number of cancers in the study population was low. The number of high-grade dysplasia patients needed to treat (NNT) to prevent one esophageal cancer in the study was 6. Major complication of RFA is esophageal stricture that is seen in 6–8 % of cases, while bleeding and mediastinitis have been reported but are uncommon. The major disadvantage of RFA is the lack of tissue for histopathology. Though there is no long-term data about the durability of RFA, a recent study showed 93 % complete remission of intestinal metaplasia and neoplasia at 5 years in patients treated with a combination of EMR and RFA. Further, buried glands were found only in the 0.08 % of neosquamous biopsies. The recurrence can be successfully treated with repeat RFA sessions with good results. Further follow-up data is still needed to confirm the long-term efficacy of eradication and the optimal interval for surveillance endoscopies in these patients.

Argon Plasma Coagulation

Argon plasma coagulation (APC) was the most common eradicative therapy before RFA became widely available. APC utilizes a monopolar high-frequency probe that causes surface coagulation of the epithelium through ionized argon plasma. In a single center from the United Kingdom, 86 % remission of Barrett's metaplasia was seen after a mean follow-up period of 37 months, while 14 % developed esophageal adenocarcinoma over a follow-up period of 90 patient-years. Other studies have also shown that buried glands are noted in up to 30 % of patients treated with APC therapy, which is much higher than that reported for radiofrequency ablation. Stricture formation is the most common adverse event, while the risk of perforation is very low. Currently APC is not widely used as a primary ablative therapy for HGD but has an important role as an adjunct to endoscopic mucosal resection where it is used to ablate the edges of the resection.

Photodynamic Therapy

Photodynamic therapy (PDT) was one of the earliest used modalities for Barrett's ablation. It involves systemic administration of a photosensitizer that is activated during endoscopy by using light waves of appropriate wavelength. The photosensitizer can be administered either orally or intravenously. Porfimer sodium is the most extensively studied photosensitizer for BE and has been approved by the U.S. Food and Drug Administration. It is administered intravenously at a dose of 2 mg/kg approximately 48 h before the procedure. The required wavelength is delivered to the esophagus under endoscopic visualization using a cylindrical balloon advanced

over a wire. The desired dose for successful therapy is 130 J/cm that allows calculation of application time if the power density of the instrument is known. The mucosal injury is usually evaluated 2 days after PDT when an additional dose of 50 J/cm can be delivered to the skip areas. The side effects of PDT include chest pain (20 %), nausea (11 %), vomiting (32 %), hiccups (10 %), dysphagia (19 %), esophageal perforation (less than 1 %), pleural effusion (2 %), and photosensitivity reaction (7–18 %). The major complication of PDT is stricture formation occurring 3–4 weeks after PDT, with a reported incidence of up to 36 % in some studies. These are more commonly seen in areas of treatment overlap and in patients with long segment BE and are treated with serial dilations. Patients should also avoid sun and bright light for at least 30 days and sometimes up to 90 days due to risk of photosensitivity. Known history of porphyria and porphyria sensitivity is a contraindication for PDT. In an international, multicenter, partially blinded phase III trial of PDT in 208 patients with HGD, 77 % patients with PDT had complete ablation of HGD at 2 years compared to 39 % in the control arm ($p < 0.0001$). The incidence of esophageal adenocarcinoma decreased from 28 % in the control arm to 13 % in the PDT group ($p = 0.006$). A 5-year follow-up study of the same patient cohort was subsequently published and it confirmed the long-term efficacy for HGD ablation (77 % for PDT vs. 39 % for control group, $p < 0.001$) and lower risk of progression to cancer after PDT (15 % vs. 29 %, $p = 0.027$).

Due to systemic absorption of porfimer sodium and high incidence of photosensitivity after exposure to sunlight, various other photosensitizers have been studied. Aminolevulinic acid has been used as an oral photosensitizer administered on the day of photoradiation and has lesser systemic absorption along with shorter duration of skin photosensitivity (24–48 h). In one of the earlier studies using ALA, eradication of HGD and mucosal cancer was noted in 100 % (10/10) and 77 % (17/22) patients, respectively, after a mean follow-up of 9.9 months. In a subsequent study to evaluate the long-term efficacy of PDT with ALA, 66 patients with HGIN and early adenocarcinoma were treated with PDT using ALA and complete response was documented in 97 and 100 % patients, respectively, at 37 months. Currently ALA is not approved for use in the United States. Further randomized studies comparing PDT with other ablation modalities are required. Given its ease of application, better adverse effect profile, and good efficacy at Barrett's eradication, radiofrequency ablation has replaced photodynamic therapy as the most commonly used ablation technique.

Cryotherapy

It is a noncontact ablation technique that induces cell damage with minimal fibrosis by using alternating cycles of rapid freezing and slow thawing. It is a relatively newer technique and has the most limited experience of all the ablation techniques. Commonly used gases include liquid nitrogen and carbon dioxide. In a multicenter, retrospective cohort study, 98 patients with BE and HGD underwent 333 cryotherapy treatment sessions with 97 % complete eradication of HGD and

57 % complete eradication of all intestinal metaplasia after a mean of 3.4 treatments per patient. Two percent patients developed severe chest pain requiring narcotics and 3 % patients developed esophageal strictures treated with endoscopic dilation. There were no perforations in the study population. Cryotherapy has also been shown to provide complete luminal response in patients with intramucosal cancer who failed or refused conventional therapy. But long-term data on the efficacy is lacking and this modality is available only at select centers in the country.

Endoscopic Mucosal Resection

Endoscopic mucosal resection or EMR refers to endoscopic removal of neoplastic epithelium using the standard polypectomy technique usually after raising the area of interest by saline injection. EMR has been shown to be effective and safe along with the advantage of providing tissue of histological evaluation, making it both a therapeutic and a staging procedure as discussed above. All patients with any nodular disease and absence of submucosal disease should undergo EMR. Currently it is being widely used for treatment of mucosal adenocarcinoma in patients with BE. The role of EMR in diagnosis of dysplasia and early cancer as well as staging of BE is very important. Any area of mucosal irregularity noted on endoscopy for Barrett's surveillance should ideally be removed by EMR. Endoscopic biopsies of these areas have several limitations including small sample size, lesser depth, poor orientation, and crush artifact. The EMR has the advantage of providing larger and well-oriented specimens. Diagnosis and staging of dysplasia in BE is a difficult decision and has shown to be observer dependent. Analysis of EMR specimens has shown to improve the interobserver agreement for diagnosis of dysplasia when compared to endoscopic biopsies.

The most commonly used techniques for EMR are the cap-assisted technique and multiband ligation technique. The cap technique is the more commonly used of the two and it uses a transparent cap (flat or oblique) and a snare to resect the mucosa. The target area is first lifted by injection of a fluid in the submucosal layer (saline or diluted epinephrine). After that a snare is fitted into the inside of the cap, the injected mucosa is suctioned into the cap, captured by already placed snare, and resected using blended current electrocautery. In the band and ligate technique, which can be performed without submucosal injection, a banding device (modification of the traditional variceal bander) is used to band areas of interest creating pseudopolyps which are then resected using a snare and electrocoagulation. In a randomized trial comparing cap technique with submucosal injection and band ligation without submucosal injection for early esophageal cancers, no difference in efficacy or safety profiles were noted. Multiband technique has been shown to be more efficient for resection of larger mucosal specimens, but the final decision is usually based on the endoscopist's preference, level of comfort, and experience with a particular modality.

Most of the initial studies used EMR focally for the treatment of mucosal adenocarcinoma. Long-term success with complete response rates of around 95 % at 5

years had been reported for focal EMR done to treat intramucosal carcinoma (IMC). In one of the earlier studies of focal EMR for patients with IMC (only 3 patients in the study with HGD), local recurrence or metachronous carcinoma was noted in up to 17 % patients after a mean follow-up interval of 10 months. Other studies have shown recurrence rate as high as 47 % after focal EMR. Seewald et al. for the first time reported successful use of circumferential EMR (75 % of luminal circumference at one setting) in patients with HGD and IMC but no visible lesions. Complete eradication of BE was noted in all patients after a median follow-up of 9 months. This technique is also known as stepwise radical endoscopic resection or wide area EMR and involves resection of the entire Barrett's segment. Multiple studies have shown the effectiveness of complete Barrett's eradication using EMR only with reported success rate of 76–100 %. Esophageal strictures are very common after circumferential EMR with one study reporting an incidence of up to 88 %. These can be successfully treated using serial dilations.

Combination or Hybrid Therapy

Complete eradication of Barrett's using EMR should be performed only at high volume referral centers with adequate surgery backup (Fig. 14.1). A combination approach is used in a significant number of cases, where all visible lesions are treated with EMR while the remaining of Barrett's epithelium is treated with ablative therapies (RFA being the most common) (Fig. 14.2). This approach has been shown to have good outcomes with neoplasia and metaplasia eradication rates of 83–95 % and 79–88 %, respectively. This might be a safer alternative to long segment BE with segments longer than 10 cm where risks of esophageal strictures is very high after complete eradication using EMR.

Surgical Options

Fundoplication

Fundoplication is primarily performed in patients with refractory reflux symptoms not responding to medical therapy. Some surgeons have suggested that fundoplication might be more effective than acid suppression therapy in preventing cancer in BE patients, but published literature on this topic is limited. Nissen fundoplication has been associated with regression of low-grade dysplasia at 12–18 months in up to 93 % patients compared to 63 % in patients treated with medical therapy alone. In addition to promoting regression of Barrett's metaplasia, some studies have demonstrated lower risk of progression to adenocarcinoma after fundoplication in Barrett's patients. This has been proposed to be secondary to decreased exposure of the esophageal epithelium to bile acids, in addition to gastric secretions. Currently,

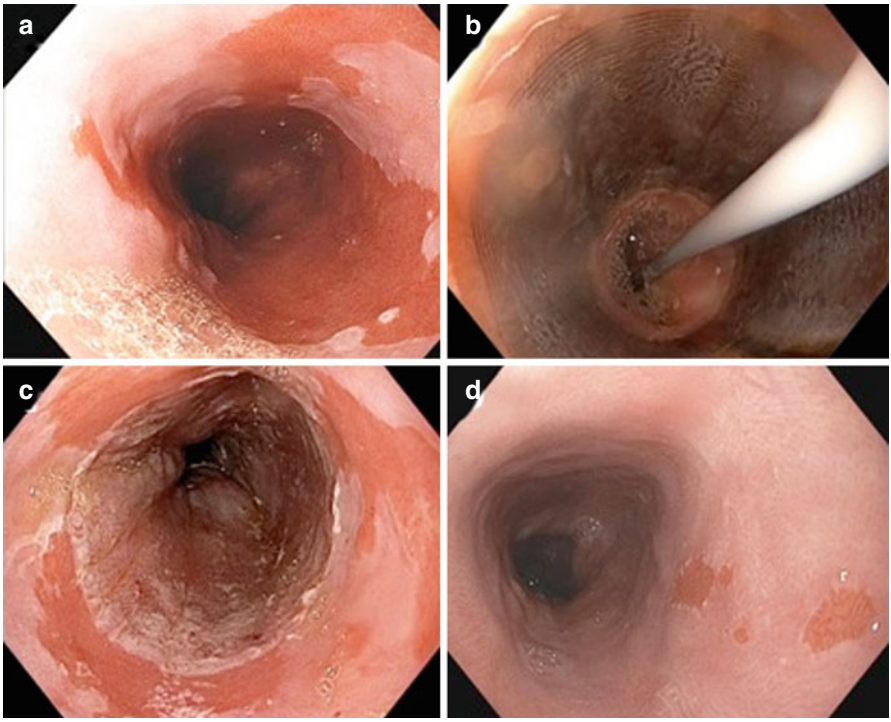

Fig. 14.1 (**a**) Patient with long-standing BE with focal high-grade dysplasia above the GE junction that was previously treated with focal EMR. (**b**) Barrett's ablation using 360° RFA balloon catheter. (**c**) Endoscopic view immediately after RFA. (**d**) Neosquamous epithelium with few islands of BE after 9 months and 3 RFA sessions. The Barrett's islands were treated with focal RFA

surgical attempts at reducing acid exposure solely for the purpose of reducing cancer risk in BE are not recommended.

Esophagectomy

Esophagectomy was the standard of care for patients with high-grade dysplasia and intramucosal carcinoma till the endoscopic eradication techniques became more available. Even though esophagectomy can be done using a laparoscopic and thoracoscopic approach now, it is still associated with significant morbidity and long hospital stays compared to endoscopic treatment that can be done as an outpatient. Patients who were treated with a combination of photodynamic therapy and endoscopic mucosal resection were shown to have similar 5-year mortality as those who underwent esophagectomy for high-grade dysplasia (9 % vs. 8.5 %). None of the deaths in either group was from esophageal adenocarcinoma. Intramucosal cancer (m1) has only 1–2 % incidence of lymph node metastasis, while submucosal

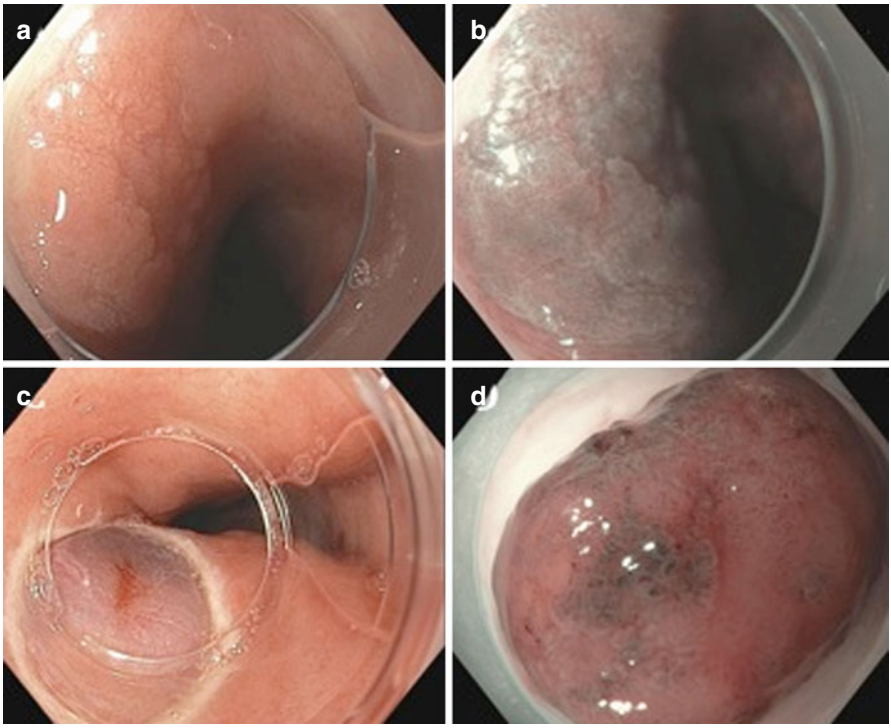

Fig. 14.2 (**a**) A flat area of nodularity (IIA) noted during surveillance endoscopy for BE (white light with magnification). (**b**) Same lesion seen under narrow band imaging and magnification. (**c**) Endoscopic mucosal resection (EMR) using saline injection followed by cap and snare was performed. (**d**) Mucosectomy specimen, pathology was consistent with high-grade dysplasia

involvement is associated with 15 % incidence of nodal involvement. When performed in appropriately selected patients, esophagectomy has a mortality of less than 5 % with good quality of life; it should be discussed with all patients who have high-grade dysplasia, especially for younger, otherwise healthy patients.

Follow-Up After Ablation

Close follow-up and surveillance of patients is needed after eradication therapy, but no guidelines have been established due to lack of data about recurrence of metaplasia and dysplasia after eradication. After eradication therapy, these patients should initially have surveillance according to the highest grade of dysplasia that was noted. Biopsies should be obtained from entire area of prior BE at appropriate intervals until complete ablation is documented on at least three consecutive endoscopies with reasonable certainty, following which the surveillance intervals can be increased.

Summary

- High-dose proton-pump inhibitor therapy for acid suppression is recommended for all patients with BE.
- Patients with HGD should undergo eradication therapy, either endoscopic ablation or endoscopic resection.
- All patients with non-dysplastic BE and LGD should undergo regular surveillance endoscopies with high-definition scopes and adequate Barrett's inspection time.
- All visible or nodular lesions should be treated with endoscopic mucosal resection and the residual BE can be eradicated with either ablation or mucosal resection depending on the endoscopists' skills and preference.
- Intramucosal carcinoma can be successfully treated with endoscopic resection.
- Complete Barrett's eradication by using only endoscopic mucosal resection is possible but is associated with high stricture rate, which can be easily treated endoscopically.
- All patients who undergo eradication therapy should have appropriate surveillance endoscopies.