Original Article

Endoscopic Therapy of Esophageal Premalignancy and Early Malignancy

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Key Words

Endoscopic therapy, Barrett's esophagus, esophageal cancer, esophageal adenocarcinoma, radiofrequency ablation, endoscopic mucosal resection

Abstract

Esophageal adenocarcinoma (EAC) is an often deadly cancer with a rising incidence in Western countries. Chronic gastroesophageal reflux disease is associated with the metaplastic transformation of normal squamous epithelium to premalignant specialized intestinal metaplasia within the esophagus (Barrett's esophagus). Barrett's esophagus may progress to low-grade dysplasia (LGD), high-grade dysplasia (HGD), or even EAC. Although nondysplastic Barrett's esophagus progresses to EAC at a rate of 0.5% per year, rates of progression for true LGD and HGD are significantly higher. Treatment is mandatory for HGD and may be appropriate in select patients with nondysplastic Barrett's esophagus and many with LGD. Thus, accurate pathologic assessment is necessary before considering endoscopic therapy. Previously, only esophagectomy was offered to patients with HGD or EAC. However, esophagectomy has significant morbidity and mortality, and therefore endoscopic therapies have been advocated for early Barrett's neoplasia. These methods include endoscopic mucosal resection (EMR) and ablative techniques. Ablation techniques include argon plasma coagulation, multipolar electrocoagulation, laser therapy, photodynamic therapy, radiofrequency ablation, and cryotherapy. Of these, radiofrequency ablation has experienced the greatest adoption for the treatment of dysplastic Barrett's esophagus because of excellent published outcomes. The use of EMR to resect suspicious areas or raised lesions is mandatory to provide histology. In contrast, ablation techniques such as radiofrequency ablation have been shown to effectively eradicate large areas of dysplastic tissue with relative ease but do not allow for histologic assessment of the treated area. Combination EMR with radiofrequency ablation is thus advocated to resect visible lesions via EMR (providing histology) and ablate the remainder of the Barrett's esophagus. As always, the appropriate treatment is best determined after careful discussion with patients in a multidisciplinary environment. However, endoscopic therapy offers an attractive alternative to esophagectomy for early Barrett's neoplasia. (*JNCCN* 2011;9:890–899)

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Esophageal adenocarcinoma (EAC) is an often deadly cancer with an incidence in Western countries that has continued to rise in the past few decades.[1,2] In 2004, 8000 incidences of EAC occurred in the United States, representing a 2- to 6-fold increase in the past 20 years.[3] In general, EAC affects Caucasian men (men are affected 6 to 8 times > women, and Caucasians 3 to 4 times > African-Americans) in their 50s to 60s, with an annual increase of 4% to 10% since the 1970s, making EAC the fastest rising malignancy among white men in the United States.[2,4,5] Risk factors include both genetic and environmental factors, including central obesity, smoking, and diet.[2,6] The 5-year survival rate for esophageal and gastroesophageal junction cancers is low at only 15% to 20%.[7]

Chronic gastroesophageal reflux disease is associated with the metaplastic transformation of normal squamous epithelium to specialized intestinal metaplasia within the esophagus (Barrett's esophagus).[1] This premalignant condition of Barrett's esophagus can progress to low-grade dysplasia (LGD) or high-grade dysplasia (HGD), and in some cases to EAC.[8] Gastroesophageal reflux disease affects approximately 20% of adults in the United States,[9] with Barrett's esophagus diagnosed in 10% to 15% of these patients with reflux disease who undergo endoscopy, and 5.6% of patients without chronic reflux

symptoms.[10] However, patients without chronic reflux may also develop Barrett's esophagus, suggesting the presence of multiple associated risk factors.[11] Currently, Barrett's esophagus is the only recognized pathologic precursor to EAC.[12] Barrett's esophagus is associated with a 0.50% to 0.75% risk of progressing to EAC per year, with the greatest risk in patients with dysplastic Barrett's. Because esophagectomy may be associated with significant morbidity, endoscopic therapies for premalignant Barrett's esophagus and early EAC have been developed and studied.

Pathology of Barrett's Esophagus

With the emergence of new modalities for treating EAC and preinvasive lesions, accurate pathologic diagnosis and staging have become critically important.

The seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual[13] redefines Tis (carcinoma in situ) as equivalent to HGD in glandular mucosa in the esophagus. Although the term *carcinoma in situ* is not favored by gastrointestinal pathologists as a diagnostic term in Barrett's esophagus, having been supplanted by the terms *high-grade dysplasia* and *intramucosal carcinoma* (Table 1), it is retained for tumor registry reporting purposes as specified by law in many states. Invasion into the lamina propria is characterized by the finding of single neoplastic cells or small clusters of cells, separate from the larger dysplastic glands, without extension into deeper layers.

The alteration of the microanatomy of the superficial layers of the esophagus is an underappreciated finding that may result in erroneous staging on endoscopic ultrasound (EUS).[14] The muscularis mucosa varies in organization from relatively sparse bundles of smooth muscle in the cervical esophagus to a thickened reticulated network in the distal esophagus. The muscularis mucosa is commonly duplicated and thickened in Barrett's esophagus; the thicker outer muscularis mucosa layer, considered the original muscularis mucosa, may be confused with the muscularis propria and lead to overestimation of the depth of invasion on both endoscopic evaluation and examination of endoscopic mucosal resection (EMR) specimens. Although limited data are available on risk of metastasis related to subdivisions of T1a lesions, studies of esophagectomy specimens indicate that, overall, a low risk is present, ranging from 0% to 1.3% for T1a carcinomas compared with 18% to 22% for T1b tumors.[15,16] Early studies[17] attributed the link between depth of tumor invasion and increasing risk of metastasis to a richer lymphatic network in the submucosa than in the lamina propria. However, recent work reporting immunohistochemical studies specific for lymphatic endothelium suggests that the lamina propria in the normal esophagus in fact has an extensive network of lymphatic vessels,[18] and the increasing risk of metastases in T1b lesions cannot be entirely explained based on lymphatic density.

Table 1 Pathologic Evaluation of Neoplasia in Barrett's Esophagus

Term	Description	Comments
Negative for dysplasia	No evidence of neoplastic transformation	
Indefinite for dysplasia	Glandular architectural and nuclear changes equivocal for dysplasia	Morphologic changes overlap with reactive change
Low-grade dysplasia	Enlarged nuclei with increased nuclear to cytoplasmic ratio, mucin depletion, and lack of surface maturation	
High-grade dysplasia	Nuclear changes more pronounced than in low-grade dysplasia, with marked nuclear pleomorphism, architectural complexity, and loss of polarity	Equivalent to carcinoma in situ (Tis)
Intramucosal carcinoma	Neoplastic cells invade beyond the basement membrane into the lamina propria or muscularis mucosae	Equivalent to T1a, defined as invasion of lamina propria or muscularis mucosae
Invasive adenocarcinoma	Neoplastic cells invade through muscularis mucosae into the submucosa or deeper layers of esophagus	T1b is defined as invasion of submucosa; T2 is defined as invasion of muscularis propria

Disease Staging

EAC survival rates correlate with disease staging. Therefore, accurate staging of EAC is crucial because treatment varies according to the initial staging of the disease.[19–21] EUS, CT, and PET are typically the imaging modalities used to stage advanced EAC. The role of EUS in Barrett's dysplasia is limited, with most studies showing low yield.[22] Although EUS is appropriate in staging early adenocarcinoma to rule out lymph node metastasis, accurate assessment of depth of invasion is difficult.[23] The overall accuracy of EUS for T staging ranges from 72% to 76%.[21,24] The sensitivity, specificity, and accuracy for T1 disease were 80%, 100%, and 91%, respectively, and for T3 disease were 78%, 80%, and 80%, respectively ($P < .05$).[21] Given that the risk of lymph node metastasis significantly differs between T1a and T1b disease, this differentiation is important but can be difficult to ascertain via EUS.[25] Because of this difficulty, EMR of visible lesions is the current standard,[26] and allows both accurate staging and possible curative treatment at the same session.

Surveillance: The Importance of Novel Imaging Techniques

Determining which patients are appropriate to undergo endoscopic therapy for Barrett's esophagus is based on accurately identifying those who are at risk. Current guidelines recommend using systematic 4-quadrant biopsies every 2 cm for detecting dysplasia within Barrett's, because this technique had a 13-fold increase in yield over nonsystematic biopsies,[27] probably because the greater number of biopsies yields more tissue sampling for detecting dysplasia.[27] However, this approach is still random within the Barrett's mucosa and results in sampling error. Directed biopsies of suspicious dysplastic tissue are likely to have a higher yield for detecting dysplastic areas. Standard white-light endoscopic imaging is useful for detecting grossly visible lesions but may be less sensitive at detecting early or subtle mucosal changes.[28] Newer imaging techniques, including narrow band imaging (NBI), chromoendoscopy, optical coherence tomography, and laser confocal microscopy, are being evaluated to determine their possible advantages over standard white-light endoscopy in detecting dysplasia.[28]

NBI is a high-resolution endoscopic imaging modality used to better evaluate the more superficial mucosal surface. The shorter wavelength of red, green, and blue light in NBI limits the depth of light penetration, allowing visualization of more superficial detail.[29] In a study of 63 patients with Barrett's esophagus evaluating 200 mucosal areas showed that flat mucosa with regular mucosal and vascular patterns were associated with intestinal metaplasia, whereas irregular mucosal or vascular patterns or abnormal blood vessels were associated with high-grade intraepithelial neoplasm.[29] In this study, NBI had a high sensitivity (94%) with reasonable specificity (76%).[29] A second study with NBI showed similar sensitivity (100%) and specificity (98.7%).[30] Although NBI results are promising, the technology is generally used as an adjunct to standard 4-quadrant biopsies.[31] Other imaging techniques have been or are being studied, including endocytoscopy, optical coherence tomography, and confocal laser endomicroscopy, although these are largely being evaluated in the research setting and are not currently used in clinical practice.[31–37] Ultimately, improved imaging modalities may improve diagnostic yield and lessen the need for a large number of biopsy specimens.

Endoscopic Therapies

It is largely believed that a gradual progression occurs in Barrett's esophagus, from nondysplastic Barrett's esophagus to LGD to HGD to EAC.[38] As patients progress along this dysplasia spectrum, the risk for developing EAC increases. Patients with nondysplastic Barrett's esophagus have a 0.5% per year risk of progressing to EAC.[39,40] The literature on patients with LGD reflects variable reports[41,42] because of overdiagnoses leading to underestimation of progression risk. In a study of 147 patients diagnosed with LGD, only 15% cases were confirmed through expert pathology review, with a 13.4% per patient year incidence of progression to HGD or EAC, compared with 0.49% per patient year for patients who were downgraded to nondysplastic Barrett's esophagus.[43] Therefore, confirmation by an expert pathologist is key for patients with LGD, because true LGD indicates a substantially higher risk of EAC and should change management in these patients.[44]

For patients with Barrett's esophagus and HGD, esophagectomy has been the gold standard given the risk of occult invasive EAC, which has been estimated to be as high as 40%.[45,46] Esophagectomy was also previously the standard treatment for intramu-

cosal adenocarcinoma, even though the incidence of lymph node metastasis is less than 1% for these patients.[47] However, esophagectomy has significant surgical morbidity and mortality,[48,49] leading to the development of nonsurgical endoscopic alternatives.

EMR

EMR helps stage disease and resects tissue for therapeutic invention. EMR allows for complete histopathologic review of resected tissue that helps to better diagnostically stage disease.[50] If submucosal invasion is found, patients can then be referred for surgical resection, because these lesions have an 18% to 22% risk of lymph node metastasis depending on the depth of invasion into the submucosa.[50,51] If the lesion is confined to the mucosa and resection margins are clear, EMR can be curative because of the very low risk for lymph node metastases.[15,16] However, a 14% to 47% risk of synchronous or recurrent lesions exists within other areas of Barrett's tissue,[52] leading to the strategy of complete Barrett's eradication EMR (CBE-EMR) or target lesion–directed EMR combined with one of the ablative techniques described later. EMR can be performed using a variety of techniques, including free-hand, lift-and-cut, cap-assisted, or band-assisted (Figure 1).[52,53]

CBE-EMR has been used in some centers to resect the epithelial tissue of all Barrett's esophagus cases to reduce the risk of synchronous or metachronous lesions. Complete remission ranges from 94% to 97% for patients undergoing CBE-EMR for HGD or intramucosal adenocarcinoma, with focal radiofrequency ablation used in some cases.[54] However, stricture formation can occur in up to 50% of patients, along with bleeding or perforation.[52] Most of the esophageal strictures and bleeding were amenable to endoscopic treatment.[52] However, treating long-segment Barrett's esophagus with CBE-EMR may result in longer strictures that are more difficult to treat,[31] and therefore these cases may be best treated with focal EMR in combination with one of the ablations techniques described later.[31,55,56]

The major advantage of EMR over ablation is that it enables tissue acquisition for histopathologic staging, which may change or affect treatment options for the patient. One study showed that 45% of 49 patients had their pathologic diagnosis changed (14% upstaged, 31% downstaged) after review of the EMR specimens compared with the initial biopsy specimens.[54] In patients initially diagnosed with HGD who were upstaged, 4 had advanced pathology (intramucosal adenocarcinoma with lymphatic channel invasion or submucosal carcinoma) seen only after EMR, who were then properly referred for esophagectomy.[54] All 4 patients had visible nodular lesions on endoscopy.[54] EMR upstaging is likely the result of sampling error or limited biopsy specimen depth with forceps biopsy specimens.[54] EMR downstaging may be attributable to crush artifact with forceps biopsy specimens or complete resection of HGD or intramucosal adenocarcinoma foci.[54] Nonetheless, this study reinforces the importance of EMR for staging, because the 4 patients in this study would otherwise have been inappropriately treated with ablation for presumed HGD if their diagnoses had not been upstaged.[54] Thus, the esophagus must be carefully examined for nodules before initiation of therapy so that the appropriate initial technique is chosen.

Ablation Techniques

Argon Plasma Coagulation: Argon plasma coagulation (APC) is a thermal cautery device that uses a constant flow of ionized argon gas to transmit high-frequency current to the tissue to cause superficial

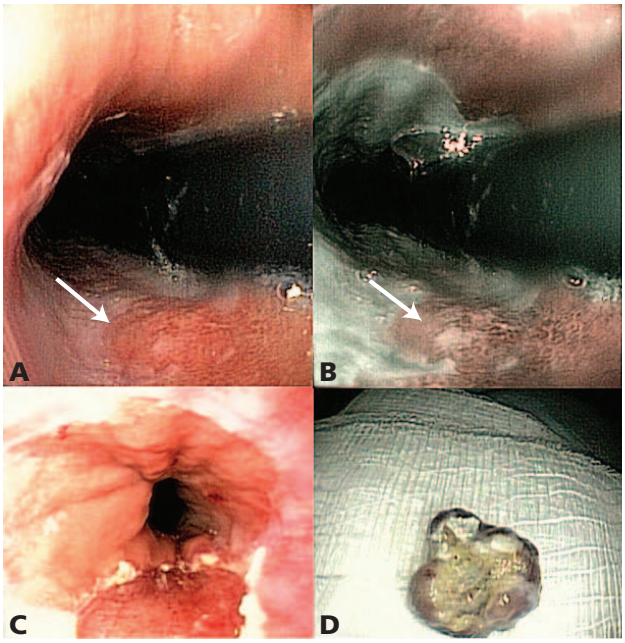

Figure 1 Endoscopic mucosal resection of an esophageal nodule. (A) Subtle area of nodularity seen at the gastroesophageal junction (arrow). (B) Esophageal nodule seen on narrow band imaging shows increased vascularity suspicious for carcinoma (arrow). (C) Nodule resected using band-assisted endoscopic mucosal resection. The area is inspected and no evidence of perforation is seen. (D) The full specimen is retrieved and submitted to pathology. Final diagnosis is intramucosal (T1a) carcinoma associated with Barrett's esophagus.

(2–3 mm depth) tissue destruction.[57] This allows the mucosal Barrett's esophagus to be treated without the concern for deeper cauterization that could incur more complications. Studies vary, with a rate of 84% to 100% for complete squamous reconstitution, and a relapse rate of 3% to 11% per year.[57,58] Some of this variability in results may be secondary to higher-powered APC (90W vs. 60W) and higher-dose proton pump inhibitors in different studies, although higher-powered APC may also induce more complications, including pleural effusions, strictures, and perforation.[57,58] A case has been reported of adenocarcinoma arising under the neosquamous mucosa after apparently successful APC; so called "buried adenocarcinoma."[59] This relates to the concern for "buried Barrett's esophagus" and "buried dysplasia" that may arise deeper to the neosquamous mucosa, which is produced by ablation. Given the varied Barrett's esophagus recurrence and procedure complication rate, APC is currently less routinely performed, because other techniques, such as radiofrequency ablation or cryotherapy, may be more beneficial.

Multipolar Electrocoagulation: Multipolar electrocoagulation (MPEC) uses a 50W energy source with a probe to apply firm pressure to the mucosa in areas of intestinal metaplasia until a white coagulum develops.[60] No studies have been performed in patients with HGD, and are only reported for ablation in patients with nondysplastic Barrett's esophagus. These studies show complete eradication rates of 89% to 100% but also show the highest adverse events of dysphagia (19%) and odynophagia (16%) compared with other ablative techniques.[50] MPEC is also very focal in its treatment areas and may be difficult to use in patients with long-segment Barrett's esophagus. MPEC is no longer routinely performed for this indication.

Laser Therapies: Some studies have used laser therapy for tissue destruction. The diode laser uses a continuous-wave 940-nm diode laser at a power of 40W with 2.1-mm diameter noncontact fibers that are positioned 1 cm from the mucosal surface to produce a whitening of tissue, signifying denaturation of proteins.[61] Using the diode laser therapy, a 65% complete ablation rate was achieved,[61] similar to the 67% complete ablation rate with the 1064-nm neodymium yttrium aluminum garnet (Nd:YAG) laser.[62] The 940-nm diode laser creates a more superficial ablation than the 1064-nm YAG laser, which may explain the higher complications of perforation, bleeding, and stricture noted with the YAG laser.[61–63] However, laser therapy has a limited area of treatment, and therefore requires numerous sessions to ablate large areas of metaplastic tissue, limiting its use in long-segment Barrett's esophagus.[61] Laser therapy is largely experimental and not used in clinical practice.

Photodynamic Therapy: Photodynamic therapy involves first administering a light-sensitizing agent that accumulates in the Barrett's esophagus tissue before performing light-activation therapy that causes free oxygen radical formation and ischemic necrosis for tissue destruction.[64,65] Porfimer sodium is the most commonly used photosensitizer and is given intravenously 48 hours before the procedure.[65] Alternatively, oral 5-aminolevulinic acid has been used.[65] Light activation is performed via endoscopy and the use of diffusing light fibers that are placed next to the target tissue, which causes excitation of the photosensitizer and tissue destruction as described earlier.[52] One study of 103 patients with LGD, HGD, or intramucosal adenocarcinoma found successful tissue ablation in 93%, 78%, and 44%, respectively.[66] Four patients (4.9%) had subsquamous ("buried"), nondysplastic, metaplastic tissue, and 3 patients (4.6%) had subsquamous adenocarcinoma.[66] An overall stricture rate of 30% was also seen, with a 50% stricture rate in patients receiving 2 sessions of photodynamic therapy.[66] These stricture rates are much higher than those with APC (2.9%) or radiofrequency ablation (1.9%).[50] Photosensitivity is also a major side effect in up to 69% of patients.[50] Given the subsquamous Barrett's esophagus tissue with neoplastic potential, reports of subsquamous adenocarcinoma, and high stricture rates, photodynamic therapy is now used less frequently because of the availability of alternative ablation techniques.[52]

Radiofrequency Ablation: Radiofrequency ablation uses either a cylindrical balloon with embedded electrodes or a focal ablation device to deliver a preset amount of thermal energy to the target tissue for tissue ablation.[52,67] For patients with long-segment Barrett's esophagus, ablation using the balloon is preferred. In contrast, the focal ablation device is preferred in the presence of short-segment Barrett's esophagus or when areas of residual intestinal metaplasia remain after prior treatments. If balloon ablation is used, a sizing balloon is first inserted into

the esophagus to determine the optimal size for the circumferential ablation balloon to ensure adequate contact with the mucosa.[52] With both devices, ablation is then achieved by performing 2 separate applications of direct thermal energy using the ablation device, while cleaning the coagulation tissue from the ablation zone and electrodes in between ablations (Figure 2).[52,67] This allows for uniform ablation of Barrett's esophagus tissue.

Early studies with radiofrequency ablation focused on ablation of nondysplastic Barrett's esophagus tissue. In a study of 100 patients, a 70% complete remission rate of Barrett's esophagus was seen at 1 year, with no evidence of stricture formation or buried Barrett's esophagus among the 4306 biopsies evaluated.[68] At the time of this initial study, only balloon-based ablation was available, contributing to the lower complete remission rates. A follow-up study at 2.5 years showed a 98% complete remission rate of Barrett's esophagus after stepwise circumferential therapy with focal ablation therapy of remaining Barrett's esophagus.[69] The most recent follow-up study at 5 years has now shown a 92% complete remission rate of Barrett's esophagus, with 8% having nondysplastic Barrett's esophagus; however, focal radiofrequency ablation reinduced complete remission in all of these patients.[70] Furthermore, no buried Barrett's esophagus, dysplasia, strictures, or serious adverse events were seen in this group of patients.[70]

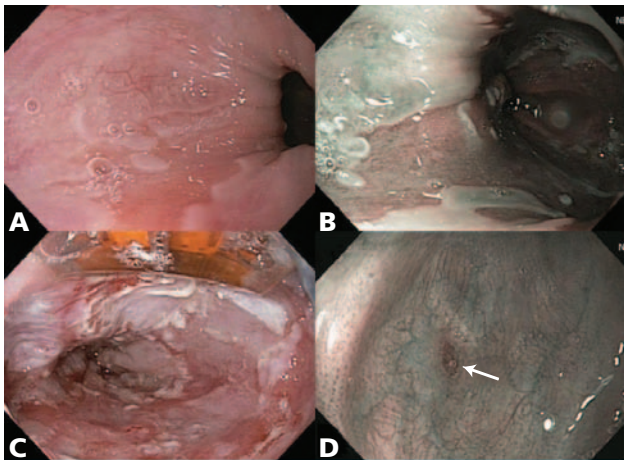

Figure 2 Radiofrequency ablation of dysplastic Barrett's esophagus. (A) Short-segment Barrett's esophagus is seen on high-definition endoscopy. (B) Narrow band imaging allows for easier detection of intestinal metaplasia and increases the ability to identify dysplastic areas. (C) Ablation is performed using the focal radiofrequency ablation device. (D) On surveillance at follow-up examination, only a focal area of Barrett's esophagus remains (arrow), best detected with narrow band imaging. This was successfully treated with repeat focal ablation.

A recent landmark multicenter, sham-controlled trial of 127 patients with dysplastic Barrett's esophagus were randomly assigned to undergo radiofrequency ablation or a sham procedure, with outcomes measured at 1 year.[67] In patients with LGD and HGD, complete eradication rates of dysplasia were 91% and 81%, respectively, in the radiofrequency ablation group compared with 23% and 19%, respectively, in sham procedure control groups.[67] Overall, complete eradication of Barrett's esophagus was 77% in the radiofrequency ablation group and only 2.3% in the control group, with less disease progression (4% vs. 16%) and cancers (1% vs. 9%).[67] Adverse events in the radiofrequency ablation group included more chest pain, one upper gastrointestinal bleed treated endoscopically, and a 6% esophageal stricture rate that were all successfully treated with endoscopic dilation.[67] Longer-term data from this cohort have only been published in abstract form, but the response seems to be durable. Based on the data, radiofrequency ablation should be given serious consideration as first-line therapy in patients with dysplasia,[71] with EMR used for resection of any visible nodules, as discussed later.

Cryotherapy: Cryotherapy, the most recent modality for endoscopic mucosal ablation, sprays liquid nitrogen on target areas to freeze tissue, causing intracellular disruption and ischemia with relative extracellular matrix preservation, resulting in less fibrosis.[72,73] Few studies have been conducted and no controlled studies have been published with cryotherapy. A recent study of 60 patients who completed all planned treatments with cryotherapy found a 97% complete eradication rate for patients with HGD and a 57% complete resolution rate of Barrett's esophagus.[74] The stricture rate in this study was 5% and subsquamous Barrett's esophagus was noted in 3% of patients.[74] Controlled trials are needed to evaluate this modality of treatment, although early results seem promising.

Combination EMR With Ablation Therapy

For patients with visible lesions in the setting of HGD or early EAC, a combination approach of EMR with additional ablation techniques has been used.[55,56,75–78] In a study of 44 patients with HGD or early EAC with visible (nodular) lesions, EMR was first used to

remove the visible lesion, then radiofrequency ablation was performed to ablate the remaining Barrett's esophagus tissue.[75] Initial EMR provided histologic evaluation in addition to flattening the mucosal surface before radiofrequency ablation for uniform tissue destruction.[75] Complete eradication of dysplasia and Barrett's esophagus was achieved in 98% of patients, with no dysplasia recurrence at 21-month follow-up.[75] Five adverse events occurred in patients after EMR: 4 mild bleedings managed endoscopically and 1 esophageal perforation managed endoscopically.[75] Complications after ablation included a 9% dysphagia rate, which improved with esophageal dilation (all had prior widespread EMR), and a 4% chest pain rate requiring hospitalization with conservative treatment.[75] The authors speculated that the higher rate of complications after ablation was likely related to ablation in areas of scarring from prior EMR. However, the controlled, uniform ablation with radiofrequency ablation resulted in minimal submucosal scarring, allowing for focal EMR after radiofrequency ablation for persistent Barrett's esophagus, representing a significant advantage over APC and photodynamic therapy, which cause submucosal scarring and make EMR difficult after ablation.[75]

A more recent multicenter study included 23 patients with early EAC or HGD with focal EMR followed by serial radiofrequency ablation.[76] In this study, "escape" EMR was permitted in which focal areas of visibly abnormal tissue were removed with EMR postablation.[76] Complete eradication of neoplasia and Barrett's esophagus was achieved in 95% and 88% of patients after radiofrequency ablation, respectively, and 100% and 96% of patients after radiofrequency ablation with escape EMR, respectively, with 22-month follow-up.[76] Of those who experienced complete Barrett's esophagus eradication, 3 patients (13%) had evidence of Barrett's esophagus on follow-up endoscopies, which supports current practice of continued surveillance endoscopies in patients after ablation.[76] However, follow-up biopsies of neosquamous epithelium in 22 patients after radiofrequency ablation showed resolution of genetic abnormalities and no buried glandular mucosa.[77]

Most recently, a multicenter, randomized control trial compared stepwise radical endoscopic resection (widespread EMR) with focal EMR followed by radiofrequency ablation in 47 patients with early EAC or HGD and a Barrett's esophagus segment of 5 cm or less with follow-up of 24 months.[78] Complete eradication of neoplasia was comparable (100% widespread EMR, 96% EMR/radiofrequency ablation) as was complete eradication of Barrett's esophagus (92% widespread EMR, 96% EMR/radiofrequency ablation).[78] However, an 88% stricture rate was seen in the widespread EMR group versus 14% in the EMR/radiofrequency ablation group, with all 14% in the EMR/radiofrequency ablation group developing strictures at the larger EMR resection sites.[78] Therefore, focal EMR followed by radiofrequency ablation may be a preferred approach, especially in patients with longer-segment Barrett's esophagus.[78] Overall, the combination of radiofrequency ablation and EMR has gained popularity for Barrett's esophagus eradication given the low stricture and complication rate, and now serves as an alternative to esophagectomy.

Surveillance Postendoscopic Treatment

Surveillance after completion of endoscopic therapy is critical because dysplastic Barrett's may recur after apparent complete eradication. Recurrence of "buried Barrett's" (subneosquamous intestinal metaplasia [SSIM]) or Barrett's esophagus at the neosquamous–columnar border is a major concern.[77] When SSIM occurs, it seems to reside in the deep epithelium or the lamina propria.[79] Therefore, biopsy specimens should include lamina propria tissue or be deeper to assess for this possible SSIM.[79] Biopsy depth and adequacy were compared using cold forceps in patients who were ablation-naïve (controls) versus those who had undergone photodynamic therapy or radiofrequency.[80] Approximately 90% of specimens from all groups were adequate to detect SSIM, showing this technique to be an appropriate surveillance approach after ablation.[80] In addition to SSIM or Barrett's esophagus recurrence at the neosquamous–columnar junction, a recent case report showed squamous cell dysplasia within the neosquamous epithelium on surveillance, 4-quadrant biopsies after prior cryoablation followed by radiofrequency ablation with complete response posttherapy.[81] Given the concerns for SSIM, Barrett's esophagus recurrence at the neosquamous–columnar junction, and neosquamous dysplasia, surveillance is critical after completion of endoscopic therapy. The exact timing and approach to surveillance after ablation are still unknown and further studies are needed before recommendations

can be made. However, patients should likely remain on their proton pump inhibitor therapy for life. Furthermore, consideration should be given to surgical therapy if persistent reflux is shown on esophageal testing to prevent disease recurrence.

Conclusions

EAC is an often deadly cancer with a rising incidence in Western countries. True LGD or HGD carry a much higher risk of progression to esophageal cancer, and therefore these patients should be treated more aggressively than those without dysplasia. Flat dysplastic Barrett's esophagus is now being treated with ablative techniques, with strong clinical data supporting the use of radiofrequency ablation. Furthermore, nodular Barrett's esophagus or early esophageal neoplasia (T1a disease) can safely be treated endoscopically with EMR. Endoscopists who treat dysplastic Barrett's esophagus should be familiar with both ablation and resection techniques, because both may be required in an individual patient. As always, appropriate treatment is best determined after careful discussion with patients in a multidisciplinary environment. However, endoscopic therapy offers an attractive alternative to esophagectomy, which was previously the only treatment for HGD and EAC.

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