



# Clinical Update

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*Commentary: Barrett's esophagus (BE) with associated high-grade dysplasia (HGD)/early cancer (EC) has generally been treated by surgical esophagectomy. However, even at highly experienced surgical centers, <1> esophagectomy carries a significant risk of morbidity and mortality. The ideal therapy for BE with HGD/EC would be one that is minimally invasive and associated with a low risk of major complications. Within the past decade, various forms of minimally invasive endoscopic therapies have been developed. In this Clinical Update, Dr Frank Gress reviews these new potential endoscopic therapies for BE with HGD/EC. In addition, Dr Gress discusses the advantages and disadvantages of each therapy and the evidence that supports their use.*

– Richard C. K. Wong, MD, FASGE, Editor

## ENDOSCOPIC MANAGEMENT OF BARRETT'S ESOPHAGUS

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Barrett's esophagus (BE) is a well-known premalignant condition that can be associated with the development of dysplasia and adenocarcinoma. In the past, esophagectomy was the standard treatment for patients with BE with high-grade dysplasia (HGD) and early cancer (EC). However, subtotal esophagectomy carries high mortality and morbidity rates (3%-5% and 20%-50%, respectively), even when performed at high-volume centers.<sup>1</sup> Esophagectomy is no longer the only treatment option for HGD and EC. Over the last decade, a number of endoscopic therapies were developed for the management of BE. These include EMR and thermal ablation techniques that use laser, multipolar electrocoagulation, argon plasma coagulation (APC), photodynamic therapy (PDT), and, more recently, radiofrequency ablation (RFA).

BE, or specialized intestinal metaplasia (IM), is a cellular change that occurs in the epithelium of the esophagus in which squamous mucosa is replaced by a specialized intestinal columnar mucosa. It occurs as a complication of long-standing GERD. IM has the potential to become dysplastic and to progress to high-grade dysplasia (HGD), which is considered the precursor of esophageal adenocarcinoma. Patients diagnosed with HGD are usually referred to surgery for esophagectomy. The surgical approach is supported because some studies revealed unrecognized cancer in 38% to 73% of patients having surgery for BE with

HGD.<sup>2,3</sup> However, in the case of BE with HGD/EC, the risk of lymph-node involvement or metastasis to distant sites is small. For cancer limited to the mucosa, the risk for lymph-node metastases is 0%.<sup>4</sup> Hence, local endoscopic therapy might be an effective and minimally invasive alternative for some patients with BE with HGD/EC limited to the mucosa. This review will discuss endoscopic management options currently available for BE with HGD/EC. Recently, some early data were reported that suggest a possible role of endoscopic ablative therapies for eradicating nondysplastic BE.<sup>5</sup> These studies are very preliminary and lack long-term follow-up. Until there are well-designed prospective clinical trials with long-term follow-up, the eradication of nondysplastic BE should remain investigational.

### ENDOSCOPIC TREATMENT OF BE WITH HGD/EC

Several endoscopic-based approaches have been developed for the management of BE with HGD/EC. These include endoscopic ablation therapy and EMR. Endoscopic ablation therapy includes thermal modalities such as multipolar electrocoagulation, laser ablation, APC, cryotherapy, and PDT (with the use of photosensitizers, such as porfimer sodium, a hematoporphyrin derivative, and 5-aminolevulinic acid [5-ALA]). However, these techniques can lead to nonuniform ablation, which can result in per-

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sistent or residual IM and “buried glands” (defined as specialized columnar epithelium covered by a layer of squamous epithelium with no communication with the surface). Buried glands can progress to occult invasive carcinoma, and the squamous reepithelialization that occurs after these therapies might compromise the early diagnosis of neoplastic changes that arise from the buried glands. These ablative modalities can lead to excessively deep ablation as well, which result in stricture formation and, rarely, in perforation. In an effort to overcome these pitfalls, a new endoscopically guided RFA device was also recently developed.<sup>5</sup>

## ENDOSCOPIC ABLATION THERAPY

### *Thermal-probe–based ablation therapies: laser and APC*

Photothermal lasers were the first tools used for endoscopic ablation of BE. The laser-light sources frequently used include Nd:YAG (1064 nm),<sup>6</sup> potassium-titanyl-phosphate (532 nm),<sup>7</sup> or argon (514.5 nm) lasers. These techniques, although easier to use, can result in nonuniform ablation with disappointing long-term results.

APC has been used for BE with HGD/EC. This technique permits non-contact application of a monopolar electrocautery conducted to the tissue by a flow of ionized argon gas, with a limited depth of penetration that minimizes the risk of perforation. Vargo<sup>8</sup> reviewed 10 case series of APC for BE that totaled to 304 cases and reported a complete macroscopic eradication of BE in 82.6% of the cases; however, the rate of buried glands was very high in this subgroup (50%).

The main disadvantage of thermal-probe–based ablation techniques is that they represent “point-and-shoot” methods, which provide nonhomogeneous ablation of the mucosa, with the subsequent risk of buried glands.

### *Cryotherapy*

Low-pressure spray cryoablation with liquid nitrogen under direct endoscopic visualization in patients with BE with HGD has also been studied. This technique is well tolerated, with no significant complications (eg, strictures). The device <3> produces a depth of injury of 2 mm. Johnston et al<sup>9</sup> performed a study on 11 patients with BE. In 78% of treated patients, a complete endoscopic and histologic reversal of BE was achieved, with no evidence of buried glands and no complications at the 6-month follow-up. Although this technique appears promising, there are still very limited data about its efficacy.

### *PDT*

PDT involves the administration of an inactive photosensitizing agent that has an affinity for dysplastic cells and is only activated by a wavelength-specific light directed at the esophageal tissue during endoscopy and triggers a photochemical reaction that results in mucosal damage and cell death from the formation of oxygen radicals. The photosensitizers more extensively evaluated for BE are porfimer sodium, meta-tetrahydroxyphenyl chlorine (mTHPC), <4> and 5-ALA. These photosensitizers differ in the depth of distribution at the tissue level and the clearing from the body. Porfimer sodium is distributed within the submucosal layer, whereas 5-ALA accumulates in the cells of the mucosa. Thus, strictures are much more frequent with porfimer sodium (36%)<sup>10</sup> than with 5-ALA, which does not appear to induce strictures.<sup>11</sup> Predictors of stric-

ture formation include EMR before PDT, a history of esophageal stricture, and more than one PDT session. Although the risk for strictures is reduced with 5-ALA–PDT, it does not reliably ablate BE. A major drawback for PDT is that it can produce significant skin photosensitivity, which results in skin burns from direct light exposure.

Porfimer sodium, at 2 mg/kg, <5> is typically given by IV 48 hours before PDT. It <6> may cause skin photosensitivity that lasts for up to 3 months. mTHPC, at 0.15 mg/kg, is given by IV 72 hours before PDT. mTHPC causes less skin photosensitivity than porfimer sodium.<sup>12</sup> The 5-ALA compound is given orally, at 60 mg/kg, 4 to 6 hours before treatment. Its rapid clearance (after 24–48 hours) reduces the risk of photosensitivity. In the United States, only porfimer sodium has received U.S. Food and Drug Administration approval for management of BE with HGD, whereas 5-ALA has more commonly been used in Europe.

Overholt et al<sup>10</sup> first reported the early results of a multicenter, randomized, pathology blinded trial that examined 208 patients with BE and HGD randomized to PDT with porfimer sodium plus omeprazole 40 mg/d versus omeprazole. There was an advantage in favor of PDT ablation of HGD. In a follow-up of this study, Overholt et al<sup>13</sup> showed that, at 5 years, PDT still maintained a benefit against omeprazole in eliminating HGD (77% vs 39%). In addition, the risk of cancer progression was lower with PDT compared with omeprazole (15% vs 29%).

Because of the procedural complexity of PDT, high cost to perform the procedure, suboptimal efficacy, possibility of buried glands, and high incidence of adverse effects (dysphagia, odynophagia, chest discomfort, stricture, and skin photosensitivity), PDT may be replaced by new incoming ablative techniques.

### *RFA*

A contact circumferential RFA system has been developed for BE management. This ablation system consists of a high-power radiofrequency energy generator, automated sizing balloon catheters (to measure the inner diameter of the esophagus), and ablation catheters. The circumferential ablation device (HALO<sup>360</sup> system; <7> is a balloon-based ablation catheter, with a 3-cm circumferential bipolar microelectrode on its surface that delivers a programmed amount of energy circumferentially to the targeted esophagus.

A focal ablation device (HALO<sup>90</sup> system; <Co. Name, City, State> <8> has also been developed to allow for more localized or focal ablation of residual BE after primary circumferential ablation with the HALO<sup>360</sup> system. This device is a 20-mm × 15-mm endoscope-mounted system that is affixed to the tip of the endoscope.

A recent prospective trial evaluated 100 patients by using the HALO<sup>360</sup> system in ablating nondysplastic BE, with 70% of patients achieving complete resolution of IM at 1-year follow-up.<sup>14</sup> More than 4,000 biopsy specimens were obtained, and none of the biopsy specimens met the criteria for buried glands. The balloon technique for RFA may allow for uniform contact of the electrode and lead to the consistent ablation depth. Energy density and power are controlled by the system, which eliminates operator variability. The high power of treatment permits rapid heating, thus preventing long “on” times and deep thermal conduction. As a result,

controlling depth confines the ablation injury to the level of the muscularis mucosa or superficial submucosa and may avoid stricture formation.<sup>5</sup> Other ablative modalities may leave Barrett's mucosa with persisting genetic anomalies; in contrast, a preliminary study suggests that RFA results in restoration of squamous epithelium without genetic abnormalities.<sup>15</sup>

Ganz et al<sup>16</sup> evaluated a multicenter U.S. registry of 142 patients who had BE with HGD (median length 6 cm) and who underwent circumferential ablation (median 1 session). Ninety-two patients had a least 1 follow-up biopsy session (median follow-up 12 months). A histologic complete response of patients with BE with HGD was safely achieved in 90.2%. No serious adverse events were reported.

Interim results from a nationwide dysplasia trial,<sup>17</sup> the first randomized controlled trial of RFA for subjects with BE that contained dysplasia at 19 U.S. centers, suggest that RFA is effective for BE with dysplasia. Subjects were randomized to RFA or sham (2:1) stratified by dysplasia grade (HGD or low-grade dysplasia) and BE length (<4 cm vs 4-8 cm). Stepwise circumferential and focal ablation was performed by using the HALO system <9> (maximum 4 sessions). Among those who received RFA, 85% were free of dysplasia at 12 months after treatment and 74% had no evidence of BE.

Ablation with the HALO<sup>360</sup> device appears to be a safe and effective modality for treating BE with HGD and may be an ideal adjunctive therapy for treating residual disease after other ablative modalities or EMR.

### EMR

EMR was developed as a potentially curative therapy for BE with HGD/EC, with similar success rates as esophagectomy. EMR provides tissue for assessment of the degree of differentiation of EC, the presence of lymphovascular invasion, and completeness of resection. EMR results in a change in the histopathologic diagnosis in approximately 25% of patients with BE with HGD/EC, lesions that can be either upstaged or downstaged.<sup>18</sup> If advanced neoplasia or incomplete resection of BE with EC is detected on evaluation of the EMR specimen, then the next logical step is surgical esophagectomy. For these reasons, EMR has some advantage over ablative therapies. EUS needs to be performed before EMR to assess the depth of mucosal involvement and to exclude regional nodal metastases.<sup>19</sup> Many techniques for EMR have been developed and include EMR without suction, such as the "inject-and-cut" technique and the "strip-biopsy" technique. Techniques with suction include "the simple snare resection" technique, cap-assisted EMR, the use of the esophageal EMR tube, and EMR with ligation.<sup>20</sup>

The first report of localized EMR for BE with HGD/EC in a cohort of 64 patients showed that, for low-risk patients (defined as lesion diameter <20 mm; macroscopically type I, IIa, or IIc lesions <10 mm; or well-differentiated or moderately differentiated adenocarcinoma or HGD limited to the mucosa), <10> EMR could achieve complete remission in 97% of cases. For high-risk patients (lesion diameter >20 mm and limited to the mucosa, and/or submucosal involvement) complete remission was achieved in only 59%. After 12 months, recurrent or metachronous carcinomas were found in 14% of cases.<sup>21</sup> In a prospective study of 100 patients with BE and EC treated with EMR (maximum of 3 resections), complete local remission was achieved in 99 of the 100 patients after 1.9

months (range 1-18 months).<sup>22</sup> Minor bleeding was the only complication. There was an 11% recurrence rate at a mean follow-up of 36 months, but successful repeated treatment with endoscopic therapy was possible in all cases.

EMR is very practical for BE with HGD/EC with a diameter <2 cm, because these lesions can be removed completely in an en bloc resection fashion. Furthermore, EMR is very useful for BE with obvious mucosal irregularities (eg, focal nodules) that may contain HGD/EC. However, EMR does not appear practical for long segments of BE or when multifocal HGDs/ECs are detected on random biopsy specimens from BE. Ablative endoscopic therapies are more appropriate for management in these settings, because, if EMR is performed, then a piecemeal approach cannot be avoided, which compromises complete removal of BE and interpretation of lateral margins of resection. Endoscopic submucosal dissection (ESD) has also been described. ESD was developed for en bloc removal of large (usually more than 2 cm) flat GI-tract lesions,<sup>23</sup> but the equipment to perform this technique is not yet commercially available in the United States.

### SUMMARY

Endoscopic therapy has become a very attractive option for patients with BE with HGD/EC, with an excellent long-term survival rate. Current available data suggest that the main role for endoscopic ablative therapies is for treating BE with HGD/EC. Although some early short-term studies suggest a potential role for endoscopic ablative therapies for treating nondysplastic BE, these studies are very preliminary, and, at this time, the eradication of nondysplastic BE remains investigational. Large, prospective, long-term clinical studies are needed to address this issue.

The management approach for BE with HGD/EC has to be based on lesion characteristics (length of BE, presence of focal nodular irregularities, unifocal or multifocal distribution of HGD/EC) and institutional expertise. EMR offers diagnostic and curative advantages over endoscopic ablative therapies for focal lesions and short-segment BE that contain HGD/EC. However, EMR is not practical for long-segment BE with HGD/EC detected on random forceps biopsy sampling. The different endoscopic ablative therapies can be more beneficial in these circumstances. There are several endoscopic ablative techniques that remain experimental, eg, cryotherapy, whereas other techniques, eg, RFA, have already demonstrated some advantages, including a favorable outcome with a low complication profile. The most-studied technique, PDT, has a high rate of postprocedure complications, such as stricture formation and the occurrence of buried glands. Recent studies suggest that such complications may be lower with RFA. Endoscopic therapies still remain investigational. Patients carry a minimal but possible risk of developing invasive carcinoma after ablative therapy and may still require life-long endoscopic surveillance. There is no clear consensus regarding the optimal management strategy for HGD/EC in BE. The decision on how to treat BE with HGD/EC must be made on a case-by-case basis; large series are needed to better define when endoscopic therapy or surgery is more appropriate.

## DISCLOSURE

The author reports that there are no disclosures relevant to this publication.

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