Endoscopic approaches to Barrett’s oesophagus with high-grade dysplasia/early mucosal cancer

Gregory G. Ginsberg* MD
Professor of Medicine, University of Pennsylvania School of Medicine (Gastroenterology Division), and Executive Director of Endoscopic Services, University of Pennsylvania Health Systems
Hospital of the University of Pennsylvania, Gastroenterology Division, 3rd floor Ravdin Building,
3400 Spruce Street, Philadelphia, PA 19104, USA

This chapter will review the endoscopic approaches to the management of Barrett’s oesophagus with high-grade dysplasia/early mucosal cancer. Factors to consider when evaluating patients for endoscopic management are detailed. Ablation and resection methods for eradication of Barrett’s oesophagus with high-grade dysplasia/early mucosal cancer are reviewed. Strategies for combining therapies to achieve safe and effective eradication are discussed. Recommendations for complete eradication of all Barrett’s mucosa and follow-up considerations are put forward.

Key words: Barrett’s oesophagus; dysplasia; early oesophageal neoplasia; endoscopic mucosal resection; photodynamic therapy; radiofrequency ablation; cryotherapy; argon plasma coagulation.

INTRODUCTION

Barrett’s oesophagus (BE) is the condition in which specialised intestinal-type metaplasia (SIM) is present in the oesophagus and oesophagogastric junction.1 Replacement of the normal squamous mucosa by SIM is thought to occur in response to acid reflux injury to the oesophagus. The condition is recognisable endoscopically and can be confirmed with histopathology. Most BE is thought to be established by the third or fourth decade of life. Its extent is thought to remain static, with no spontaneous progression or regression in terms of its expanse.
BE is clinically significant because it is associated with an increased risk for the development of adenocarcinoma of the distal oesophagus and the oesophagogastric junction.\textsuperscript{2} The Barrett's cancer risk is estimated at 0.5% per year, at least a 30-fold increased risk over that in the general population. Barrett's cancer is increasing in Western populations (about four-fold over the past three decades) and doing so at a rate greater than that of any other type of cancer. The BE-to-cancer sequence is thought to occur over a continuum from non-dysplastic BE through low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal or early mucosal carcinoma (EMC), to advanced invasive carcinoma. For the purposes of this review, in that HGD and EMC may be indistinguishable histologically and often coexist they will be considered as one, except where designation in the published literature permits discrimination.

Advanced Barrett's cancer is highly lethal. Owing to the rich lymphovascular plexus that serves the oesophageal wall and the absence of a serosa, invasive oesophageal cancer is commonly at an advanced stage at the time of presentation. Among patients who present with symptomatic oesophageal cancer, the approximate 1-year and 5-year survival rates are a dismal 25% and 5% respectively. Conversely, patients with EMC have >90% 5-year survival. The goal of BE surveillance is detection of HGD/EMC. This affords an opportunity for cancer pre-emption and curative minimally invasive therapy. This chapter reviews the endoscopic approaches to management of Barrett's HGD/EMC.

EVALUATING THE PATIENT FOR ENDOSCOPIC MANAGEMENT OF BARRETT'S HGD/EMC

The consideration of endoluminal therapy for BE with HGD/EMC depends on its histopathological designation and staging, its length, configuration and morphology, the clinical condition of the patient, and the available expertise.

Histopathological designation and staging

HGD is the term used by pathologists to describe a degree of cellular disarray and deterioration of the architecture of the 'normal' gland structure. There is considerable heterogeneity within BE, such that when HGD is present it may be limited to an isolated focus (unifocal) or may be multifocal. Using standard white-light endoscopy, HGD may be detected with increased yield from biopsies from macroscopically recognisable lesions (e.g. nodular, depressed, hyperaemic); however, more often HGD is detected on random biopsies obtained from otherwise unremarkable-appearing Barrett's mucosa.\textsuperscript{3} Enhanced imaging techniques may permit improved detection of HGD/EMC.

Until recently, the standard of practice for pre-emptive therapy for BE patients with HGD has been operative oesophagectomy. The case for oesophagectomy for BE with HGD is based on the observation that 30–47% of patients with HGD, based on endoscopic forceps tissue sampling, will have unrecognised co-existent carcinoma/adenocarcinoma.\textsuperscript{4–6} Intra- and inter-observer variability even among expert histopathologists is recognised such that in many cases HGD and EMC may represent a continuum.\textsuperscript{7} Furthermore, 16–60% of patients with endoscopically detected BE with HGD will develop clinically apparent carcinoma within the next 5–7 years.\textsuperscript{3,8,9} However, while HGD may progress to invasive carcinoma, it may also remain stable or regress...
Moreover, true HGD represents pre-cancer; it is not invasive or capable of lymph-node metastasis, and can be eradicated with ablation or resection therapies. Therefore, owing to the subjective nature of dysplasia designation, the designation HGD should be confirmed by an expert gastrointestinal pathologist when management options are being considered.

HGD may be unifocal or multifocal, i.e. detected as limited to a single focus or at multiple levels or locations throughout the Barrett’s involved segment. Mapping studies suggest a field effect that may or may not be appreciated with directed and/or random biopsy forceps tissue sampling techniques. Multifocal (as compared with unifocal) dysplasia may be associated with a higher risk of cancer progression.

EMC is limited to the mucosal layer of the oesophageal wall. EMC is distinguished from the term ‘early oesophageal cancers’ which includes tumours involving the mucosa or submucosa, \( T_1N_0M_0 \). In that the \( T_1 \) classification does not distinguish mucosal versus deep submucosal invasion, the classification has been further divided. EMC is staged as \( T_{1M} \) and considered to have a risk of concurrent lymph-node metastasis of \(<1\%\) to \(3\%\). In contrast, submucosal invasion \( (T_{1SM}) \) carries a \(5–40\%\) risk of lymph-node metastasis, increasing with depth of invasion. Because a substantial percentage of patients with \( T_{1SM} \) lesions will have lymph-node involvement, they are not predictably amenable to curative endoscopic therapy. In contrast, the risk of concurrent lymph-node metastasis with EMC may be considered negligible and no greater that the risk of mortality associated with operative oesophagectomy. Accurate staging is therefore critical when considering management options for patients with BE and HGD/EMC.

Endoscopic ultrasound (EUS) is the most accurate imaging modality in staging oesophageal neoplasms (Figure 2). The role of EUS in evaluating BE with HGD/EMC is to exclude submucosal invasion. The accuracy of EUS for \( T_1 \) disease is approximately \(85\%). Several case series have demonstrated the ability of EUS to detect otherwise unsuspected submucosal invasion and/or lymph-node involvement. As such, EUS should be considered in selected patients with BE and HGD/EMC when non-operative therapy is being considered. The clinical evaluation of EUS in this setting has yielded

![Diagram](image)

**Figure 1.** Barrett’s dysplasia may progress through low-grade dysplasia (LGD), high-grade dysplasia (HGD), and early mucosal cancer (EMC) to invasive carcinoma. However, LGD and HGD may also remain stable or regress. Timely intervention with eradication therapies at the levels of HGD and EMC prevent development of invasive carcinoma.
conflicting results, however. Falk et al\textsuperscript{19} performed preoperative EUS on nine patients with high HGD/EMC. Four of the six patients with HGD were correctly diagnosed as T\textsubscript{0}. The two patients that were over-staged had mucosal nodularity. EUS identified tumour in only one of three patients with EMC. Conversely, a larger study by Scotiniotis et al\textsuperscript{20} reported more promising results. In 22 patients with BE and HGD/EMC, preoperative EUS findings were compared to surgical pathology. The emphasis in this study was the detection of endoscopically curable cases, specifically the presence or absence of submucosal invasion or regional lymphadenopathy. EUS accurately predicted the absence of submucosal invasion in 16 patients and correctly predicted submucosal invasion in five of six patients (83% positive predictive value) confirmed by surgical pathology. There was one false-positive prediction of submucosal invasion by EUS. The specificity of T stage was 94%. EUS over-staged suspected lymphadenopathy as malignant in four cases (18%) but did not under-stage in any of the cases. Subsequently, others have reported the utility of EUS-guided fine-needle aspiration (FNA) as effective in evaluating suspected lymphadenopathy in such circumstances.\textsuperscript{21}

The application of EUS in the evaluation of dysplastic BE appears to be greatest when EMC, nodules, and strictures are present versus the setting of flat indistinguishable HGD, where the yield is low. However, small superficial carcinomas may be subject to compression artefact from the balloon of a dedicated echoendoscope. High-frequency catheter ultrasound miniprobes have proved useful in this setting, with greater accuracy reported in some studies.\textsuperscript{17,22} However, imaging with miniprobes can be technically challenging and is not universally embraced. Computed tomographic (CT) and positron-emission tomographic (PET) scanning are used complementarily to assess nodal and distant metastases. In that metastases are apt not to be present in patients with HGD/EMC, their role in management has not been established, and they should be considered only on an individualised basis.\textsuperscript{23}

Endoscopic resection (also called endoluminal resection or endoscopic mucosal resection) provides a more substantial histopathological specimen and may be used to complement EUS staging (Figure 3). Endoscopic resection is particularly useful for
The staging of nodules. Endoscopic resection specimens lead to an upgrade in histopathology stage in up to 40% of instances. When EMC is present, the endoscopic resection specimen provides important histopathological prognosticators: degree of cancer differentiation, presence or absence of lymphovascular invasion, depth of cancer invasion, and the distance of cancer from the deep and lateral resection margins. These criteria aid in determining the suitability of curative endoluminal therapy. The low-risk criteria are: absence of submucosal invasion, low or moderately differentiated cancer, no lymphovascular invasion, clear margins, and size <2 cm. A variety of endoscopic resection techniques has been employed. The most common techniques employ a transparent suction cap, fitted to one end of the endoscope and used to aspirate otherwise flat tissue into the chamber following prior submucosal injection. This technique creates a pseudopolyp that is then resected by a snare polypectomy technique. The rubber-band ligation method is a variation on this technique that may be performed following submucosal injection.

Length, configuration, and morphology of BE with HGD/EMC

The expanse of Barrett’s involvement varies considerably among individuals, from limited focal SIM at the oesophagogastric junction to single or multiple islands and/or non-confluent tongues, or confluent (i.e. circumferential) SIM extending ≤2 cm (short-segment BE, SSBE) or >2 cm (long-segment BE, LSBE). The relative risk of cancer development varies with the length of the involved segment, but may be present in all distributions. The length and configuration of BE has implications for the options of endoscopic management. So too does the presence or absence of macroscopically recognisable lesions and focality of the HGD/EMC. These features should be mapped during a dedicated endoscopic planning procedure when endoluminal therapy is being contemplated.
Candidate patients should have been on effective acid-suppression therapy for at least 8 weeks prior to this planning endoscopy to ensure absence of active inflammation. Gastric aspirate pH analysis and ambulatory oesophageal pH studies are not routinely indicated but may be considered when there is evidence of active oesophagitis despite proton pump inhibitor pharmacotherapy. Effective acid suppression is essential to restoration of normal squamous mucosa coincident with endoluminal eradication therapy in BE with HGD/EMC.

The Prague C&M criteria have been proposed to standardise endoscopic reporting in BE. In this system the anatomic oesophagogastric junction is localised and the maximal length of any BE (M) and length of circumferential BE (C) are recorded. When mucosal irregularities are detected with standard white-light or image-enhanced endoscopy their locations should be recorded. I recommend establishing a neutral endoscope position and designating the lesion's distance from the bite-block and orientation on a clock face. Tissue sampling should be obtained from any mucosal irregularities and placed in as many so-designated individual specimen containers. Thereafter, four-quadrant biopsies should be obtained at intervals of 1–2 cm as per the 'Seattle protocol'. Ideally this is done with a large-capacity biopsy forceps. At referral centres like ours, focal or wide-area endoluminal resection is increasingly employed at this planning session based on previously documented endoscopic and correlating histopathological findings.

BE HGD/EMC is thought to arise as the result of an accumulation of genetic defects, fostering gross chromosomal instability and leading to loss of chromosomes and aneuploidy. These are late changes associated with cancer development. While ablative therapy has the ability to decrease histological changes of dysplasia, genetic abnormalities may persist. These persistent genetic abnormalities lead to recurrence of dysplasia and even cancer over time. This notion has been verified in clinical trial. In a randomised prospective study in patients undergoing ablation of BE with HGD, patients who were able to achieve complete elimination of their Barrett's mucosa did not progress to cancer, whereas those with any residual Barrett's mucosa had a significant chance of developing cancer. As such, endoluminal eradication therapy of BE HGD/EMC should involve total elimination of the Barrett's mucosa. An important part of the planning endoscopy, then, is to consider the technique(s) and sequence applied to eradicate all dysplastic and non-dysplastic BE. Not surprisingly, more limited expanses of BE with HGD/EMC are more easily and completely eradicated with endoscopic therapies compared to more expansive extents.

Clinical condition of the patient and the available expertise

The choice of operative versus non-operative therapy for BE with HGD/EMC is changing. Operative resection may still be preferred therapy for some young, fit patients with LSBE and multifocal HGD/EMC. For many years, non-surgical approaches were generally reserved for non-operative candidates. However, where the expertise is available endoscopic therapy is increasingly becoming the treatment of choice.

Operative oesophagectomy is not a meaningful option in patients with advanced age and co-morbid disease owing to the unacceptable mortality risk. Observation alone may be appropriate in debilitated patients with BE HGD, using periodic surveillance for detection of progression to EMC. Limited endoscopic resection may be appropriate in selected cases for focal macroscopically recognisable EMC. However, when feasible, eradication of all SIM should be the goal. Patients and physicians
must commit to a sequence of procedures needed to achieve complete eradication. The endoscopist must have access to and expertise with a variety of tools and techniques to achieve this end safely and effectively. Centres with expertise are apt to have clustered experience consisting of endoscopic expertise and equipment, experience with the histopathological evaluation of biopsies and resection specimens, and high-volume surgical profile. Such centres, therefore, are currently best positioned to perform endoluminal eradication therapy for BE HGD/EMC.

ENDOLUMINAL THERAPIES FOR BE WITH HGD/EMC

The concept of ablation or resection of oesophageal SIM with restoration of normal squamous mucosa in an an-acid environment was introduced in an elegant study by Gillen et al., and furthered by clinical observations by Brandt and Sampliner among others. Mucosal ablation has been most prominently achieved by thermal or cytotoxic means. Thermal ablative therapies have included contact (bipolar probes) and non-contact (laser and argon-beam coagulation) techniques. More recently, contact radiofrequency ablation therapy via tools developed for this explicit purpose have been introduced. Cytotoxic therapy is most prominently represented by photodynamic therapy, utilising a systemic or topically administered photosensitising agent and local exposure to a non-thermal laser light source. Cryotherapy and high-frequency ultrasound have also been considered for oesophageal mucosal ablation therapy. Resection therapies have included intraoperative stripping and endoluminal resection employing submucosal saline injection and suction-cap-assisted techniques. Multimodal endoluminal therapy combining resection and ablation techniques have also been described. The following is a selective review which emphasises the tools and techniques that the reader is most likely to consider on the basis of safety, efficacy, effectiveness and availability.

Thermal-probe-based ablation therapies

Thermal lasers were among the first tools to be used for the endoluminal eradication of BE, borrowing from experiences in palliative ablation of advanced oesophageal cancers and attempts at curative ablation of early oesophageal squamous-cell carcinoma. The choice of lasers varied, and included the neodymium:yttrium aluminium garnet (Nd:YAG) laser, potassium titanyl phosphate:yttrium aluminium garnet (KTP:YAG) and argon lasers. The later two have a more limited depth of penetration compared to Nd:YAG lasers. Contact multipolar electrocautery probes developed for endoscopic haemostasis have also been studied. Long-term results of laser and multipolar probe ablation have largely been disappointing because of ineffective eradication and complications, including perforation.

Argon plasma coagulation (APC) permits non-contact application of monopolar electrocautery with a limited depth of penetration sufficient to eradicate BE while minimising risk of perforation. The non-contact mode permits it to more easily ‘paint’ a broader surface area during a treatment session. A number of case series reported the use of APC in treating patients with varying lengths of Barrett’s oesophagus, including patients with low-grade dysplasia and EMC. Combining selected studies after a mean of 2.5 treatment sessions, using various methods of confirmation of success, ablation was noted in 68% of the 91 patients with 6–36 months’ follow-up. A better result was noted in patients with shorter, non-circumferential extensions of
Barrett’s. Particularly alarming, however, was a case of mucosal adenocarcinoma diagnosed 18 months after apparent complete squamous re-epithelialisation achieved with APC in a patient presenting initially with Barrett’s oesophagus without dysplasia. Attwood et al, in a carefully conducted cohort analysis, reported the outcome of APC eradication therapy in 32 patients (median age 66 years, range 44–85) with BE and HGD who were considered unfit ($n=28$) or were unwilling ($n=4$) to undergo oesophagectomy as primary therapy. Pre-treatment EUS was performed in 18 patients (56%). Enrolment occurred over 7 years, but only eight patients had exceeded 5 years of follow-up, and an additional four patients exceeded 3 years of follow-up. Some patients are within 1 year of follow-up. Non-contact thermal APC ablation of the involved segment was performed at 4–8-week intervals, on an outpatient basis, using routine endoscopic sedation, until HGD was no longer detected on succeeding biopsies. Acid suppression was provided by pharmacotherapy with a proton-pump inhibitor. Subsequent follow-up endoscopy and biopsy was performed at 3-, 6-, and 12-month intervals. Patients underwent a median of two treatment sessions (range

**Figure 4.** Following initial endoscopic resection for focal nodular Barrett’s with high-grade dysplasia (HGD), post-treatment biopsy surveillance identified focal residual specialised intestinal metaplasia. Argon plasma coagulation was used to complete eradication, as seen en face (a,b) and in retroflex (c,d) pre- and post-application.
HGD was eradicated in 22 patients (69%). Three patients continued on APC therapy for residual HGD in two and LGD in one. Three other patients underwent oesophagectomy for persistent HGD. Four patients progressed to carcinoma (13%) despite attempted eradication therapy. Oesophageal perforation occurred in one patient due to APC therapy prompting oesophagectomy from which the patient succumbed to postoperative complications. The authors emphasised that this complication occurred early in their experience and that no further treatment-related deaths occurred. Another series reported endoscopic and histological relapse rates of 62% at 24 months' follow-up.

The shortcoming of thermal probe-based ablation therapies is that they represent point-and-shoot techniques. The overlapping surface coagulation is not reliably or uniformly transmitted through to the submucosa. As such it is largely ineffective and has been abandoned as a single-mode therapy for eradication of BE with HGD/EMC. These techniques may play an adjunctive role in the spot treatment of small (3–5 mm), focal, residual islands of SIM following other more broad-field eradication therapies.

**Photodynamic therapy**

Photodynamic therapy (PDT) has been used considerably for endoscopic eradication of BE with HGD/EMC. PDT is a multistep process beginning with the administration of a photosensitising agent that is selectively retained in the target tissue. The tissue is then exposed to wavelength-specific light, triggering a photochemical reaction that generates oxygen radicals which lead to cell death. Technical details of PDT application have been well described. Biomedical lasers are the most common source of light energy, as laser light can be adjusted to specific wavelength and power to optimise results. Laser light is delivered via a cylindrical diffusion catheter of varying length so as to achieve a relatively uniform tissue exposure. The effect is endoscopically apparent after 12–24 h (Figure 5). Porfimer sodium has been the main photosensitiser used in the USA. Porfimer sodium is administered intravenously approximately 48 h prior to light exposure. In Europe, 5-aminolevulinic acid (5-ALA) has been more commonly used. It can be applied topically and within 4–6 h prior to light exposure but is more superficially active.

The published literature on 5-ALA PDT for BE with HGD/EMC, while reporting success rates of up to 90%, has been limited to small single-centre series. 5-ALA is not commercially available in the USA. Furthermore, there is little consensus with respect to the type and dosage of the photosensitiser, the interval between drug administration and subsequent illumination, light dosage and the illumination time. Owing to its more superficial effect, it has fewer associated side-effects. However, this same superficiality has been criticised as contributing to suboptimal SIM eradication.

Several single-centre series demonstrated efficacy of porfimer-sodium-based PDT for eradication of BE with HGD. Subsequently, in a well-powered, multicentre, randomised, controlled trial, 208 patients with confirmed BE and HGD were randomised (2:1) to porfimer-sodium-based PDT plus omeprazole 40 mg/day versus omeprazole alone. At 2-year follow-up, HGD was eradicated in 77% of study patients versus 39% in the control arm \( (P < 0.0001) \). Progression to cancer occurred in only 13% versus 20% respectively \( (P = 0.006) \). At 5-year follow-up analysis these results held up, with persistent eradication of HGD and reduced progression to cancer.
in the PDT group versus the control group: 15% and 29% respectively \( (P = 0.027) \).\(^{68}\) In a comparative analysis, long-term survival was equivalent among patients with BE and HGD following porphimer sodium PDT and operative oesophagectomy.\(^{69}\)

In a retrospective study, porphimer sodium PDT preceded by endoscopic mucosal resection of focal dysplasia or superficial cancer compared favourably to oesophagectomy, with slightly lower disease-free survival at 19 months (20/24 for PDT versus 64/64 for oesophagectomy) but also lower procedure-related morbidity despite greater co-morbidities at the time of treatment (4/24 for PDT versus 31/64 for oesophagectomy, \( P = 0.01 \)).\(^{70}\) Patient inclusion was determined by EUS for the endoscopic arm and surgical pathology for the oesophagectomy arm. Protocol pre-treatment tissue sampling was employed, with biopsies obtained from macroscopically distinguishable

---

**Figure 5.** (a) Long-segment Barrett’s oesophagus with high-grade dysplasia (HGD) was treated with porphimer sodium photodynamic therapy. (b) At 48 h after therapy, there is a sharply demarcated circumferential necroinflammatory response. (c) A symptomatic stricture at 6 weeks post-treatment was successfully dilated, and (d) the patient remained in complete remission with no residual or recurrent Barrett’s mucosa or dysplasia at 10-year follow-up.
abnormalities and from the four quadrants at 1-cm intervals. EUS was performed for T- and N-stage assessment. Suspicious lymph nodes were sampled by EUS-guided fine-needle aspiration cytology. Endoluminal therapy consisted of endoscopic resection and PDT. Endoscopic resection was performed on mucosal irregularities. Endoscopic resection was performed using the submucosal injection and cap-assisted aspiration snare resection technique. PDT was subsequently performed 48 h after intravenous administration of a photosensitising agent, at a single outpatient session, using an endoscopically guided cylindrical diffusing fibre and non-thermal laser light (630 nm, total energy 300 J/cm). Patients were maintained on pharmacological acid-suppressive therapy. Tumour stage and Barrett's segment length (mean 5.6 ± 0.8 cm) were comparable between the endoluminal and surgical treatment groups. Patient age (mean 68 ± 2 years) and co-morbid disease was greater in the endoluminal therapy group. While not specifically stated, it may be presumed that at least some of these patients were considered poor operative candidates. Combination endoscopic resection and PDT achieved elimination of carcinoma in 20/24 patients (83%). Of the four patients with residual carcinoma at the first follow-up endoscopy one had curative oesophagectomy, one had chemoradiotherapy (fate not stated), and two died from unrelated causes. Complications included photosensitivity (n = 2) and oesophageal stricture requiring dilation (n = 2, once and five times respectively). Oesophagectomy was curative in all cases. However, operative morbidity was considerably greater, compared to the endoscopic therapy group, and there was one surgery-related death (1.6%). Overall, the groups did not differ in mortality or cancer-related deaths.

These encouraging results aside, porfimer-sodium-based PDT has been disappointing on several levels. It is complex therapy requiring intravenous drug administration on day 0 and endoscopy with light therapy on days 2 and 4. Patients experience substantial chest discomfort with dysphagia and odynophagia, commonly requiring narcotic analgesia. Oesophageal stricture requiring dilation occurs in 20–30% of patients treated. Skin photosensitivity requires patient to avoid direct sunlight exposure for 4–6 weeks. PDT is expensive by most endotherapy standards and requires the acquisition and maintenance of biomedical lasers that find limited use in other applications. As a single-mode therapy, eradication of all SIM (i.e. non-dysplastic BE) by PDT is achieved in only ~50% of patients, and squamous overgrowth of subsurface BE occurs in up to 30% of treated patients. One perceived reason for this is the prospect of uneven light distribution at treatment. Centring balloon technology was developed to overcome this, but was not widely embraced and is no longer commercially available.71 Owing to the complexity of the therapy, its suboptimal efficacy, and the evolution of competing technologies, porfimer sodium and 5-ALA PDT for BE with HGD/EMC are poised for displacement.

**Radiofrequency ablation**

A contact radiofrequency ablation (RFA) system has been developed explicitly for BE ablation. The ablation system (HALO360 System; BARRX Medical, Inc, Sunnyvale, CA) consists of a high-power radiofrequency energy generator, sizing balloon catheters (sizes 22, 25, 28, 31, and 34 mm outer diameter), and ablation catheters (sizes 22, 25, 28, 31, and 34 mm outer diameter). The system received US Food and Drug Administration (FDA) clearance in 2001. The energy generator provides automated, pressure-regulated air inflation of the sizing balloon and ablation catheters, and rapidly delivers a preset amount of radiofrequency energy density (J/cm²) at 300 W to the
ablation catheter electrode. The sizing balloon catheters are used to measure the in-
ner diameter of the targeted oesophagus. At the distal end of the catheter there is
a non-compliant clear balloon and a guide-wire lumen. The ablation catheters are
used to deliver the ablative energy. As with the sizing balloon, the ablation catheter
has a non-compliant clear balloon and a guide-wire lumen. On the surface of the bal-
loon is a circumferential bipolar microelectrode 3 cm long. An adjunctive device
(HALO90 System) consists of a second, dedicated generator and a 20 × 15 mm tilt-
plate that is affixed to the tip of the endoscope developed for directed spot therapy
in the thoracic oesophagus and at the oesophagogastric junction (Figure 6).

To perform balloon-based RFA with the HALO360, patients undergo endoscopy to
assess the length of the treatment segment to determine the location of the most
proximal extent of BE. Before ablation, the oesophagus is irrigated with a mucolytic
agent (N-acetylcystine), a guide-wire is inserted through the accessory channel, and
the endoscope is removed, leaving the guide-wire in place with its tip well into the

---

Figure 6. (a) Long-segment Barrett’s oesophagus with high-grade dysplasia (HGD). (b) After treatment with
the HALO360, a transparent cap affixed to the tip of the endoscope is used to denude the coagulative ne-
crosis. (c) At 12 weeks’ follow-up, there is complete restoration of squamous mucosa.
stomach. The automated sizing balloon catheter is passed over a guide-wire and positioned within the oesophagus proximal to the uppermost margin of the BE. Sizing is performed with inflation of the balloon at 1-cm intervals, moving distally. The intention is to identify the optimal treatment balloon diameter so as to enhance uniform circumferential mural contact, but not at the expense of over-inflation risking perforation or mucosal tear. Based on these measurements, an appropriately sized ablation catheter is introduced over the guide-wire, and the endoscope is reinserted alongside. This permits direct visual positioning of the RFA catheter so that the proximal edge of the electrode coincides with the proximal margin of BE. By using the energy generator inflation function, the electrode balloon is inflated and energy was delivered to the tissue in <1 second. The electrode is moved distally ~3 cm, repositioned visually, and the ablation steps repeated until the top of the gastric folds is treated.

Treatment parameters have been based on accumulated dose-escalation studies. During a treatment session, two immediate sequential applications are performed per station. The balloon electrode catheter and its surface are wiped clean of debris with a damp cloth. The endoscope is reinserted and the treated surface is agitated to remove adherent coagulative necrosis, and the entire process is repeated a second time.

In contrast to PDT, the treatment effect of RFA is observed immediately, and there is no concern over photosensitivity. Patients can expect to experience post-treatment chest pain, dysphagia and odynophagia, but to a lesser degree than with PDT. Stricture formation has only rarely been reported. At follow-up endoscopy, in 6–12 weeks, in the presence of effective acid suppression, uniform squamous re-epithelialisation is expected. At follow-up endoscopy, the endoscopist will be prepared to treat any focal skip areas with the HALO90. Incremental circumferential applications at the oesophagogastric junction may be performed as well.

In an unblinded prospective effectiveness study of 70 patients with non-dysplastic BE, circumferential endoscopic ablation using a balloon-based radiofrequency device eliminated SIM completely in 70% and partially in 25% at 12 months. There were no strictures or subepithelial SIM after ablation. An as yet unpublished extension of this study has been completed, in which the addition of the HALO90 focal ablation device resulted in an increase in complete eradication to 98% at 2.5-year follow-up.

A multicentre registry from 16 academic and community endoscopic centres in the United States reports use of the HALO360 intended to achieve incremental circumferential complete RFA eradication of BE with HGD. Among 142 patients treated, with a median 12-month follow-up, there were no serious adverse events at the time of reporting. There was one asymptomatic stricture. Among 92 patients who had one or more follow-up biopsy sessions, there was complete histological remission of HGD in 90.2%. There has been no detection of subsurface BE.

In a small prospective series, six patients with BE and HGD underwent stepwise endoscopic resection of mucosal irregularities followed by circumferential (HALO360) and subsequent focal (HALO90) RFA to achieve 100% complete endoscopic and histological remission at a median of 14 months and two follow-up biopsy sessions after the last treatment.

Numerous clinical trials are under way evaluating circumferential and focal RFA for eradication of BE with HGD and combined with endoscopic resection for BE with EMC. At the time of writing, however, published results are limited. While preliminary results appear favourable, long-term follow-up is lacking. Should long-term results demonstrate equivalence or superiority to PDT, RFA will likely replace PDT for this indication.
Cryotherapy

Cryotherapy is the application of extreme cold to ablate tissue. Extreme freezing temperatures produce ice crystals within cells leading to cell organelle dysfunction and cell death. Cryotherapy has been used for decades in other disciplines such as dermatology and gynaecology for ablation of dysplastic epithelium. Two commercially available systems have been developed using compressed nitrous oxide and liquid nitrogen, respectively, as their cryogen. Both systems require use of an adjunct aspiration system to avoid over-distension associated with the use of compressed gases within the gut. Treatment regimens are nuanced, and optimal application recommendations are not as yet established. In a pilot study, liquid nitrogen cryotherapy successfully eradicated non-dysplastic BE in nine of 11 patients at 6 months’ follow-up. Clinical trials are under way.

Endoscopic resection

Endoscopic resection has been shown to be a safe and effective method for complete resection of superficial lesions, with the advantage of histopathological verification as detailed above. Techniques for oesophageal endoscopic resection have been well described elsewhere and include the cap technique after submucosal injection, ligation technique with or without pre-injection, and free-hand snare resection. Comparative analyses have not demonstrated substantive differences among these techniques in terms of volume of resected tissue and complications. Using these techniques, lesions with a diameter >2 cm can be removed en bloc (Figure 7). A piecemeal approach is required for more expansive wide-area endoscopic resection (Figure 8). Endoscopic submucosal dissection for more expansive en-bloc wide-area endoscopic resection has also been described for oesophageal and oesophagogastric junction BE with HGD/EMC, but this experience is largely limited to Japan at this time.

Figure 7. (a) Biopsies from this mucosal irregularity yielded histopathology: at least mucosal carcinoma; the depth of invasion cannot be determined. (b) En-bloc endoscopic resection was performed following submucosal injection of 10 ml normal saline solution using the large, soft, bevelled Olympus cap and crescent snare. The endoscopic resection yielded histopathology: well-differentiated carcinoma limited to the mucosa; deep and lateral resection margins are free of carcinoma; and no lymphatic or vascular invasion seen.
The group from Wiesbaden, Germany, have described their long-term follow-up on the efficacy and safety of endoscopic resection in patients with BE with HGD \((n = 44)\) and/or EMC \((n = 100)\) employing the cap technique after submucosal injection. Complete remission was achieved in 43/44 patients with macroscopically detectable HGD. EMC lesions were well to moderately differentiated, \(\leq 2\) cm in diameter, and with no lymphovascular invasion.\(^84\) \(R_0\) status was achieved in 99% of patients after 1.9 months. Recurrent or metachronous HGD was detected in 17% of patients, and recurrent or metachronous EMC was found in 11% of patients arising in persistent SIM during a mean of 36.7 months’ follow-up. All of these were successfully treated with additional endoscopic resection. The overall calculated 5-year survival rate for EMC patients was 98%. There were no major complications associated with endoscopic resection.

Incremental radical wide-area endoscopic resection using the cap technique after submucosal injection has been studied as monotherapy for BE with HGD/EMC encompassing \(\leq 5\) cm in length.\(^85\) With a median of three sessions at 6-week intervals, complete eradication of HGD/EMC was achieved in all 37 patients, and complete SIM eradication in 33/37 patients. Symptomatic strictures occurred in 26% of patients and were treated with endoscopic dilation therapy. There was one delayed bleeding complication and one asymptomatic perforation. There were recurrences at median follow-up of 11 months.

The Duette system (Cook Medical, Winston-Salem, NC) facilitates ease of use for rapid, confluent, piecemeal ligation endoscopic resection without pre-injection of the submucosa. Mucosal aspiration into the cap followed by rubber-band ligation creates a pseudopolyp. The muscularis propria layer is ‘squeezed’ out by the rubber band, permitting resection of the polyp, consisting of mucosa and submucosa, with the snare placed above or below the band. We applied this technique in 65 consecutive patients with BE with HGD/EMC, with a mean of four (range 1–6) resections per session and a mean of 1.5 endoscopic resection sessions.\(^86\) Using this technique as monotherapy,
HGD/EMC was eradicated in all patients, and complete SIM eradication was achieved in 60% at a median follow-up of 12 months. Patients with remaining SIM underwent adjunctive ablation therapies (PDT six, APC 18, RFA three) to achieve complete eradication. There were no perforations. Acute bleeding that responded to endoscopic haemostasis occurred in 4%. Stricture occurred in five patients (7.5%). Strictures occurred only when endoscopic resection encompassed >75% of the luminal circumference and responded to dilation.

Endoscopic resection is safe and effective for complete resection of focal nodular HGD/EMC. Larger lesions (those >2 cm in diameter), however, may require piecemeal resection compromising interpretation of the lateral margins of resection. Clinically significant bleeding is uncommon, and perforations are rare in the reported series. Single session and incremental endoscopic resection of >50–75% of the luminal circumference are associated with an increased stricture rate, although these strictures tend to respond to bouginage. Wide-area endoscopic resection appears to be safe and effective as monotherapy for BE with HGD/EMC ≤5 cm in length. Endoscopic resection functions equally well as part of multimodal endoluminal eradication therapy (Table 1).49,87–90

**CONCLUDING COMMENTS**

Endoscopic therapy for BE with HGD/EMC is appealing because, in appropriately selected cases, it has the potential to achieve the same curative effect as surgery, i.e., R0 status or no residual disease. In that oesophagectomy is associated with considerable morbidity and mortality, a minimally invasive option that yields the same benefit is obviously attractive. Case selection is crucial. Candidates for endoscopic therapy should be considered based on patient and lesion characteristics. Many or most patients considered for endoscopic therapies to this point have been poor operative candidates. As experience grows there will be a tendency, by patients and clinicians alike, to lower the bar for acceptable candidates for endoscopic therapy. BE with HGD/EMC is a curable condition. The overriding concern associated with endoscopic therapy for BE with

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients treated</th>
<th>Remission (%)</th>
<th>Follow-up (months)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacificoa</td>
<td>24</td>
<td>20 (83%)</td>
<td>12 ± 2</td>
<td>0</td>
</tr>
<tr>
<td>May</td>
<td>110</td>
<td>108 (98%)</td>
<td>34 ± 10</td>
<td>34 (39%)</td>
</tr>
<tr>
<td>Butter</td>
<td>17</td>
<td>16 (94%)</td>
<td>13 (3–48)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Peters</td>
<td>28</td>
<td>26 (93%)</td>
<td>19 (13–24)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Ginsberg</td>
<td>105</td>
<td>93 (89%)</td>
<td>32 (12–109)</td>
<td>17 (18%)</td>
</tr>
</tbody>
</table>

ER, endoscopic resection; PDT, photodynamic therapy; PS, porfimer sodium; ALA, aminolevulinic acid; mTHPC, meta-tetrahydroxyphenyl-chlorin; APC, argon plasma coagulation.

a All patients treated with ER and PS-PDT.

b ER in 66 patients; PDT in 32 patients (26 patients 5-ALA-PDT, four patients mTHPC-PDT, two patients 5-ALA + mTHPC-PDT), ER and PDT in ten patients, APC in three patients.

c All patients treated with ER and PS-PDT.

d ER in five patients, ER and 5-ALA-PDT in 19 patients, ER and APC in three patients.

e ER in 39 patients, PS-PDT in 12 patients, APC in four patients, ER and PS-PDT in nine patients, PS-PDT and APC in eight patients, ER and APC in 25 patients, PDT and ER and APC in eight patients.
HGD/EMC is the prospect of the patient developing invasive carcinoma with lymph-node metastases while undergoing non-operative treatment or post-treatment surveillance. Observations of residual foci of SIM with dysphasia and carcinoma beneath a surface epithelium of neosquamous mucosa are particularly vexing. For the elderly and co-morbidly infirm the risks compared to those of surgery may be acceptable. For younger fit patients there is insufficient evidence to support broad acceptance, and as such consideration should be individualised.

Following endoscopic eradication of oesophageal SIM, restoration of squamous mucosa requires an acid-free environment. Therefore, adequate acid suppression must be achievable and sustainable. There have been limited studies on the effect of inadequate acid suppression among endoluminal therapy failures. The most effective means of establishing adequate acid suppression has not been established. The implications of non-acid reflux remain unclear.

Lesion characteristics that must be taken into consideration include the length and configuration of the BE-involved segment, unifocal or multifocal distribution of HGD or EMC on biopsy forceps tissue sampling, and the presence of mucosal irregularities. These characteristics enable the well-equipped therapeutic endoscopist to individualise therapy. Programmatic tissue-sampling techniques should be employed to include biopsies from all mucosal irregularities and the four quadrants at 1–2-cm intervals from the involved segment pre- and post-therapy. While the use of vital staining to detect focal areas of dysplasia within the BE-involved segment has been disappointing for most, emerging light and computer-enhanced imaging may be useful to discriminate focal areas of residual SIM at post-treatment surveillance. EUS can accurately predict the suitability of lesions for endoscopic therapy and should be part of the case-selection process.

Endoscopic resection is well suited to mucosal irregularities (e.g. focal nodules) that harbour HGD or EMC, and for limited tongues of short-segment BE or SIM at the oesophagogastric junction. Endoscopic resection is a safe and effective technique for curative resection of focal HGD and EMC in the luminal digestive tract. The endoscopic resection specimen also provides: (1) a more accurate histopathological interpretation; (2) confirmation of the depth of invasion; (3) assessment of the degree of differentiation; (4) the presence or absence of lymphovascular invasion; and (5) the completeness of resection. For these reasons, when feasible, endoscopic resection maintains an advantage over ablative therapies alone.

Endoscopic resection is not practical for more expansive oesophageal SIM, or when HGD and EMC are detected on random forceps biopsy sampling. Ablative therapies better serve when these more expansive and indistinct characteristics are present, and adjunctively after endoscopic resection of mucosal irregularities. RFA is fast becoming the favoured technique for thermal oesophageal mucosal ablation. The safety, efficacy, cost, and ease of use of RFA compare favourably to probe-based thermal therapies and PDT.

Patients considering endoscopic therapy as an alternative to surgery for BE with HGD/EMC must understand that this approach remains developmental. They must be willing to commit to multiple sessions to achieve complete eradication, intensive surveillance in the immediate post-treatment period, and life-long surveillance thereafter. Patients must be willing to remain on acid-suppression therapy to ensure and preserve successful endoluminal eradication. They must be willing to accept a small but ill-defined risk of developing invasive carcinoma during or after eradication therapy, and that eradication therapy may fail. It is the physician’s duty to make the patient a fully informed decision-maker with respect to these considerations.
SUMMARY

Endoscopic eradication therapy for BE with HGD/EMC is evolving. For many patients, endoscopic therapy will provide a safe, effective, minimally invasive alternative to oesophagectomy as first-line management. Careful patient selection will be essential to prevent misapplications of endoscopic therapy. Vigilant post-treatment surveillance will be required to detect residual/recurrent and metachronous carcinoma at a curable stage. Endoscopic therapy in patients with BE with HGD/EMC should be individually tailored on the basis of the characteristics of the involved segment. To maximise the favourable outcome of endoscopic therapy, the therapeutic gastrointestinal endoscopist will require a well-equipped ‘tool-box’ and proficiency with EUS, enhanced imaging, endoscopic resection, and broad-field ablation techniques. A respect for potential treatment-related complications must ensure that the cure is not more harmful than the disease. Long-term follow-up and comparisons to observation, surgery, and chemoradiotherapy are all reasonable, as are comparisons of single and multimodal endoscopic therapies.

Practice points

- Barrett’s oesophagus with HGD/EMC may be safely and effectively treated non-operatively
- careful patient selection is integral to successful therapy
- a variety of tools and techniques is being applied for endoluminal eradication of BE with HGD/EMC
- endoluminal resection enhances accuracy of diagnosis and staging treatment strategies should be individualised
- endoluminal resection and/or thermal and non-thermal ablation therapies serve as unimodal or multimodal therapies
- the ideal goal of endoluminal therapy should be complete eradication of all Barrett’s mucosa to reduce the risk of recurrent or metachronous lesions
- the optimal approach remains to be developed
- for the time being, endoluminal eradication therapy should be relegated to dedicated centres
- patients must be willing to undergo multiple treatment sessions, and embrace life-long endoscopic surveillance and acid-suppression therapy

Research agenda

- improvements in dysplasia detection by enhanced endoscopic imaging for image guided intervention
- long-term follow-up of patients treated with endoscopic therapy for cancer detection and mortality
- comparisons of incremental endoluminal resection versus ablation techniques versus combined therapies
- comparisons of endoluminal eradication to operative oesophagectomy
REFERENCES


86. Bhat Y, Bensinger C & Ginsberg GG. Endoluminal resection with the Duette multi-band mucosectomy system is safe, efficacious, and enhances diagnosis and staging in highly dysplastic Barrett’s. Gastrointest Endosc 2008; 67(5): AB188.
90. Ginsberg GG, Furth EE, Ginsberg JK et al. Multi-modal endoluminal eradication therapy for specialized intestinal metaplasia of the esophagus and the esophagogastric junction with high-grade dysplasia and/or intramucosal carcinoma. Gastrointest Endosc 2007; 65: AB154.