Expanded endoscopic techniques improve esophageal lesion characterization and treatment options for early-stage neoplasia.

Endoscopic Therapy of Neoplasia Related to Barrett’s Esophagus and Endoscopic Palliation of Esophageal Cancer
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Background: Barrett’s esophagus (BE) is the most important identifiable risk factor for the progression to esophageal adenocarcinoma.

Methods: This article reviews the current endoscopic therapies for BE with high-grade dysplasia and intramucosal cancer and briefly discusses the endoscopic palliation of advanced esophageal cancer.

Results: The diagnosis of low-grade or high-grade dysplasia (HGD) is based on several cytologic criteria that suggest neoplastic transformation of the columnar epithelium. HGD and carcinoma in situ are regarded as equivalent. The presence of dysplasia, particularly HGD, is also a risk factor for synchronous and metachronous adenocarcinoma. Dysplasia is a marker of adenocarcinoma and also has been shown to be the preinvasive lesion. Esophagectomy has been the conventional treatment for T1 esophageal cancer and, although debated, is an appropriate option in some patients with HGD due to the presence of occult cancer in over one-third of patients.

Conclusions: Endoscopic ablative modalities (eg, photodynamic therapy and cryoablation) and endoscopic resection techniques (eg, endoscopic mucosal resection) have demonstrated promising results. The significant morbidity and mortality of esophagectomy makes endoscopic treatment an attractive potential option.

Introduction
Barrett’s esophagus (BE) is the replacement of the stratified squamous esophageal epithelium with various types of columnar epithelia and is thought to result from chronic gastroesophageal reflux.1 BE is the most important identifiable risk factor for progression to esophageal adenocarcinoma, one of the cancers with the fastest rising incidence and a 5-year survival rate of approximately 10% to 15%.2-6 In BE, the squamocolumnar junction is proximal to the esophagogastric junction (proximal end of gastric folds). The American College of Gastroenterology has defined BE as a “change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by biopsy.”7 Prospective studies have documented the progression from BE to low- and high-grade dysplasia and eventually to invasive adenocarcinoma.8,9 There is poor interobserver agreement among experienced pathologists for the diagnosis of low-grade dysplasia (< 50%
interobserver agreement) and high-grade dysplasia (85% interobserver agreement). Interobserver reproducibility was substantial at the ends of the spectrum (BE and high-grade dysplasia/esophageal adenocarcinoma). Both intraobserver and interobserver variation improved overall after the application of a modified grading system that was developed at a consensus conference.\textsuperscript{10,11}

This review focuses on the endoscopic therapies for BE with high-grade dysplasia and intramucosal cancer and briefly discusses the endoscopic palliation of advanced esophageal cancer.

**Endoscopic Characteristics of BE**

BE is arbitrarily divided into short- and long-segment BE on the basis of the length of the esophageal intestinal metaplasia: < 3 cm and ≥ 3 cm, respectively.\textsuperscript{12,13} Long-segment BE has been shown to be a risk factor for cancer and for recurrence of neoplasia with endoscopic therapy.\textsuperscript{14} The Prague circumferential and maximal length (C & M) criteria were developed to standardize the endoscopic grading of BE as opposed to the use of subjective terms such as long, short, or ultrashort.\textsuperscript{12} The Prague C & M criteria uses the C value as the circumferential extent and the M value as maximal extent of BE above the gastroesophageal junction in centimeters. Validated by 29 expert endoscopists from 14 countries,\textsuperscript{15} the Prague criteria have helped to quantify BE in a uniform manner and provide an objective measure to evaluate endoscopic therapies for BE. Endoscopically visible lesions (Fig 1) associated with high-grade dysplasia have a higher risk for harboring cancer than flat areas of dysplasia have.\textsuperscript{16-18} Protruded, raised, or depressed lesions are at higher risk for submucosal invasion than flat areas. Endoscopic resection (ER) provides an opportunity to accurately stage the depth of visible lesions in BE.\textsuperscript{14,19}

**Pathological Classification**

Esophageal neoplasia is classified according to the internationally accepted Vienna classification\textsuperscript{19}: category 1: no dysplasia; category 2: indefinite for dysplasia; category 3: low-grade intraepithelial neoplasia/dysplasia; category 4: high-grade intraepithelial neoplasia/dysplasia; category 5: invasive epithelial neoplasia; category 5.1: invasion into the lamina propria (also referred to as intramucosal cancer); and category 5.2: submucosal cancer. Dysplasia is defined as neoplastic epithelium that remains confined within the basement membrane of the epithelial surface within which it arose. The diagnosis of low- or high-grade dysplasia is based on several cytologic criteria that suggest neoplastic transformation of the columnar epithelium.\textsuperscript{11,20} High-grade dysplasia and carcinoma in situ are regarded as equivalent. The presence of dysplasia, particularly high-grade (Fig 2), is also a risk factor for synchronous and metachronous adenocarcinoma. Dysplasia not only is a marker of adenocarcinoma, but also has been shown in prospective studies to be the preinvasive lesion.\textsuperscript{8,21,22}

Duplication of the muscularis mucosa is a characteristic finding in BE, but it can pose difficulty in proper staging of superficial esophageal adenocarcinomas. Pathologists need to be aware of this distinctive anatomy of BE to accurately stage adenocarcinomas, particularly to avoid mistaking a thickened muscularis mucosa for muscularis propria.

The terminology and classification of early esophageal cancers have evolved and are outlined in the 2010 TNM staging system of the American Joint Committee on Cancer (AJCC).\textsuperscript{23} In the intramucosal cancer category, neoplastic cells have penetrated through the basement membrane and are further subdivided based on their depth of invasion. A tumor limited to the epithelial layer is defined as m1, which corresponds to the Tis stage in the AJCC system. Lesions identi-
fied as m2 and m3 are more invasive and comprise the T1a category (Fig 3). An m2 lesion invades the lamina propria, while an m3 lesion invades into but not through the muscularis mucosa. The submucosal carcinoma tumor, staged T1b by the AJCC, invades beyond the muscularis mucosa into the submucosa but not into the muscularis propria.

Subdivisions have also been categorized within the submucosal carcinoma category. Lesions that have penetrated the shallowest third of the submucosa are identified as sm1, those that have penetrated the intermediate third are sm2, and those in the deepest third are sm3. These subdivisions are important since deeper lesions are associated with higher rates of lymph node involvement. Ancona et al24 reported that the rates of lymph node metastasis were 0% for T1m1 (mucosal) lesions and 28% in T1sm1 lesions. Compared with T1sm2/3 lesions, T1sm1 carcinomas have a lower rate of lymph node metastasis.24,25 In addition to the depth of invasion, factors that predict lymph node involvement in early esophageal cancer are angiolymphatic and neural invasion as well as histologic grade.25

Role of Endoscopic Ultrasound in Staging Early Esophageal Neoplasia

Endoscopic ultrasound is an accurate technique for locoregional staging of esophageal cancer (Fig 4). It is less accurate for detecting submucosal invasion (T1a vs T1b) in patients with high-grade dysplasia and intramucosal cancer and does not have a significant affect on the management of intramucosal cancer. In addition, accuracy is influenced by the experience of the endosonographer.26,27 However, endoscopic ultrasound with fine needle aspiration can diagnose malignant adenopathy in the setting of high-grade dysplasia or intramucosal cancer and help identify patients who are not eligible for endoscopic therapy.15 When lymph node involvement is present, the patient should be referred for esophagectomy. The utility of endoscopic ultrasound in flat high-grade dysplasia is questionable28 but is usually helpful in patients with endoscopically visible lesions. To improve accuracy, some studies have evaluated high-frequency endoscopic ultrasound with miniprobes. However, results have shown that while this may improve the accuracy of T staging, the accuracy of N staging may be inferior because the visualization is more superficial. Finally, differentiating mucosal lesions (T1a) from lesions invading into the submucosa (T1b) is more difficult in BE than in the squamous esophagus due to factors such as associated inflammation in BE, duplication of the muscularis mucosa, and hiatal hernia.7,29

Treatment Options for High-Grade Dysplasia and T1 Esophageal Cancer

Esophagectomy is the conventional treatment for T1 esophageal cancer and, although debated, is an appropriate option in some patients with high-grade dysplasia due to the presence of occult cancer in over a third of patients.30 Alternative modalities have been increasingly studied, and promising results for patients with T1 cancers have been reported with endoscopic ablative modalities in particular, including photodynamic therapy (PDT) and endoscopic mucosal resection (EMR).14,19 Endoscopic treatment is a particularly appealing modality, given the significant morbidity and mortality associated with esophagectomy.

Esophagectomy is generally preferred for lesions that invade the submucosa (T1b), given the higher rates of lymph node metastasis associated with these lesions. The rationale for esophagectomy in high-grade dysplasia is both prevention and cure of occult cancer. Patients with high-grade dysplasia are at a higher risk for progressing to esophageal adenocarcinoma than are patients with nondysplastic BE or low-grade dysplasia. Based on retrospective studies, the rate of cancer in patients who were undergoing esophagectomy for prophylactic treatment of high-grade dysplasia varies from 0% to 73%; among 23 studies, the pooled average was 39.9% in the 441 patients who underwent esophagectomy for high-grade...
Prospective studies with rigorous endoscopic criteria for ER have reported lower rates of occult submucosal invasive disease. Among patients with high-grade dysplasia and intramucosal cancer undergoing complete endoscopic mucosal resection in the setting of BE, the rate of occult submucosal invasive cancer was 4%. Therefore, the incidence of invasive cancer in this population is likely much lower that the 40% rate previously reported. As the morbidity of esophagectomy is high, even in high-volume centers, it is now reserved for T1b lesions (submucosal invasion), node-positive cancers, and T1a cancers where endoscopic therapy has failed.

### Endoscopic Therapies for BE

Endoscopic therapies include tissue-acquiring modalities such as focal ER (Fig 5), complete Barrett’s eradication endoscopic mucosal resection (CBE-EMR; Fig 6), and endoscopic submucosal dissection. Tissue-acquiring modalities are important to pathologically stage a visible lesion in the setting of high-grade dysplasia and for the treatment of known intramucosal cancer. While ablative therapies such as photodynamic therapy (PDT), radiofrequency ablation (RFA), and cryotherapy accomplish tissue destruction and permit treatment of larger areas, they do not provide a specimen for histopathological evaluation. To date, the longest experience of ablative therapies has been with PDT.

Endoscopic ultrasound does not accurately differentiate between a T1a tumor (intramucosal cancer) and a T1b tumor (submucosal invasion). Obtaining a pathology specimen with diagnostic ER (Fig 7) accurately differentiates between these lesions. ER is an endoscopic approach in which the neoplastic epithelium is excised, providing an accurate histologic diagnosis and T stage with the potential of being curative for mucosal lesions. ER has been applied not only to BE with high-grade dysplasia but also to intramucosal cancer (Fig 8) in which the risk of lymph node involvement or hematogenous dissemination is low enough to justify a relatively conservative approach compared with esophagectomy. It is important to differentiate between the presence of intramucosal cancer (confined to the mucosa), which has a low nodal metastasis risk, from cancer with invasion into the submucosa, which is associated with
a higher nodal metastasis risk and generally requires multimodality therapy. Interobserver agreement for a diagnosis of dysplasia was significantly improved with analysis of ER specimens than with conventional biopsies. In addition, submucosa was present in up to 88% of ER specimens but in only 1% of biopsy samples, and the presence of muscularis mucosae was observed in only 58% of biopsy specimens. The histologic examination of ER specimens can also assess the degree of angiolymphatic invasion, an important risk factor for the presence of lymph node metastasis. Other studies have shown that final staging by ER modifies the previous diagnosis (Figs 9 and 10) in up to 48% of cases and dramatically changes the clinical management of these patients. The demonstration of tumor-negative margins in ER samples directly correlates with the absence of residual tumor at esophagectomy.

In a review of 742 ER specimens, carcinomas infiltrating the submucosal layer were rare (sm1: 7.5%; sm2: 3.7%; sm3: 4.8%), as were those invading lymph vessels (3.5%), and there were none with venous invasion. In that study, 75% of patients had an R0 resection. Several studies have demonstrated the efficacy and safety of ER. Complete ER was achieved in 91% of the focal lesions, in 86% of cases treated under the (stepwise) radical ER protocol, and in 100% for escape treatment after RFA. In BE neoplasia, ER is considered appropriate for lesions limited to the superficial mucosa (M1 and M2 tumors having low rates of lymph node metastasis, < 3%). While there...
is less consensus with regard to lesions that extend to the muscularis mucosa (T1m3 tumors, Fig 3), most centers consider this an accepted indication for endoscopic treatment. Some groups have suggested that ER may be appropriate for lesions that penetrate into the superficial submucosal layer (sm1 tumors with submucosal penetration < 500 microns). ER may be an adequate treatment option in selected T1sm1 lesions with good histologic grade and the absence of angiolymphatic invasion and also in patients who are high-risk surgical candidates.24,25,52 Larger prospective studies are required before recommending ER for all T1sm1 lesions.

Two ER techniques have been well studied and are in common use. They involve using either a plastic cap mounted on the endoscope tip or a modified band ligation device to facilitate targeted piecemeal resection.

**Cap Technique**

With this technique, the target area is marked with the tip of a snare and coagulation current. Submucosal injection of a fluid, which may be saline or diluted epinephrine (1:100,000), creates a submucosal cushion to minimize the risk of perforation. A transparent cap with a distal ridge that allows positioning of a crescent-shaped ER snare is attached to the tip of the endoscope. The lesion is sucked into the cap, thus creating a pseudopolyp and captured by forcefully closing the snare. The lesion is then removed using electrocoagulation. Using a large-caliber flexible cap (with an outer diameter of 18 mm), lesions with a diameter of more than 2 cm can be removed en bloc.

**Multiband Mucosectomy**

Multiband mucosectomy (MBM) is a technically easy and relatively safe ER technique (Fig 11). This “suck-band-ligate” technique uses a modified variceal band ligator and involves placing bands over the mucosa to create pseudopolyps (Fig 12); these can be resected with a snare that can be passed alongside the banding device. Up to six consecutive resections can be performed without prior submucosal lifting. The muscle layer does not get sucked into the band (pseudopolyp), and therefore resection can be safely performed without creating a submucosal cushion. A large area can be resected piecemeal, taking care to overlap the margins of each resection by 1 to 2 mm to avoid residual areas of mucosa between resections. The advantages of this technique are that it does not require submucosal injection, it permits multiple resections without removing the endoscope using the same snare, and it is technically easier to perform. A multiband mucosectomy device is now commercially available (Duette, Cook Medical, Limerick, Ireland).

In a prospective randomized study, 100 consecutive ERs were performed in 72 patients with early-stage esophageal cancer.42 Fifty of these resections utilized a “suck-band-ligate” device without prior submucosal injection, and 50 used the cap technique after a submucosal lift. No significant differences were observed between the two groups with regard to the maximum diameters, calculated area of the resected specimens, or complication rate. A multicenter randomized controlled trial compared the cap and MBM techniques and found that procedure times and costs were significantly reduced with the MBM technique.37 No significant differences were seen in the amount of specimen resected.

**Evolving ER Techniques: Combination ER and Ablative Therapy**

A drawback of ER monotherapy is the high recurrence rate within a 5-year follow-up. Endoscopic ablative therapy with PDT or RFA permits treatment of the whole Barrett’s segment, which may permit treatment.
of larger lesions and may be associated with a lower recurrence rate. Because of the risk for recurrence, patients treated with ER require regular endoscopic follow-up to detect recurrent lesions. In most reports, patients were followed every 3 months during the first year and annually thereafter.

In practice, focal ER of visible lesions is effectively and safely combined with ablative modalities to eradicate the BE mucosa. A prospective study that included 279 patients receiving ER, 55 receiving PDT, and 13 receiving both provided a 5-year follow-up after ER and PDT of BE with high-grade dysplasia. A complete response was achieved in 96.6%. Surgery was necessary in 3.7% after endoscopic therapy failed. Metachronous lesions developed in 21.5% but were endoscopically managed. No patients died of esophageal adenocarcinoma or procedure-related complications, and 56 died of concomitant disease. The calculated 5-year survival rate was 84%. Larger lesion diameter (> 2 cm), long-segment BE, piecemeal resection, lack of adjunctive ablative therapy, multifocal neoplasia, and the presence of residual dysplasia are among the risk factors associated with recurrence following ER. This study showed that endoscopic therapy was effective and safe, with an excellent long-term survival rate. The identified risk factors help stratify patients who are at risk for recurrence and require intensive follow-up. Lower-risk lesions (protruded and flat lesions), a lesion diameter up to 20 mm that is limited to the mucosa, and well-to moderately well-differentiated tumors predict a successful outcome with endoscopic therapy.

Complications of ER
ER does have risks and should be performed by gastroenterologists with appropriate training. Acute bleeding occurs in about 3% of patients and delayed bleeding in 2%, but they were endoscopically managed in most studies (Fig 13). Esophageal stricture occurred in 37% to 48% of patients (stepwise radical resection), and patients treated for focal lesions or in escape treatment showed no stenosis. Stricture formation are common if large areas (> 3 cm length or > 50% of the circumference) of Barrett’s mucosa are resected. The reported incidence of perforation is 0% to 5%. Adequate acid suppression following ER is important to ensure complete wound healing with neosquamous epithelium and also to minimize scarring and potentially reduce the rate of stricture formation. Most centers use high-dose proton pump inhibitors for 4 to 6 weeks after ER.

Complete Barrett’s Eradication Endoscopic Mucosal Resection
The goal of this therapy (CBE-EMR, Fig 6) is the resection of all Barrett’s epithelium, with the curative intent of eliminating high-grade dysplasia and intramucosal cancer and reducing the risk of metachronous lesions. Chennat et al conducted a retrospective study of 49 patients with histologically confirmed BE and high-grade dysplasia or intramucosal cancer. The mean number of sessions per patient was 2.1 and the mean BE segment length was 3.2 cm. Surveillance biopsies showed normal squamous epithelium in 97% of patients. No perforations or uncontrollable bleeding occurred. About 37% patients developed symptomatic esophageal stricture and all were managed endoscopically. The high rate of stricture with CBE-EMR should be considered carefully; patients should be counseled and considered for endoscopic ablation after focal endoscopic mucosal resection of visible lesions. Although expertise might vary from site to site and patient characteristics need to be taken into account, ER and endoscopic ablation are established therapies for BE-related high-grade dysplasia and intramucosal cancer. Esophagectomy is reserved for...
cases with submucosal invasion (T1b) or with evidence of lymph node metastasis, or for those in whom endoscopic therapy is unsuccessful.

**Endoscopic Ablative Therapies of BE**

As noted earlier, ablative therapies permit tissue destruction without providing a histologic specimen for accurate diagnosis and staging. Ablative therapies are well suited for “flat” areas of BE dysplasia. Any nodularity or mucosal irregularity within the BE segment is best evaluated with ER that provides a histologic specimen for accurate diagnosis and T staging. Ablative modalities are not the primary treatment of esophageal adenocarcinoma, including T1a lesions. In patients with intramucosal esophageal adenocarcinoma treated with ER, ablative modalities serve an adjunct to eradicate the background BE.

**Radiofrequency Ablation**

The first use of a balloon-based bipolar electrode for complete ablation of esophageal epithelium in the human esophagus was described in 2004. Since then, more than 40 studies have been published regarding the use of RFA for the treatment of BE with or without dysplasia and early esophageal carcinoma. RFA is the preferred ablative modality in many centers due to the larger amount of observational data compared with newer modalities, as well as its ease of use, greater standardization, and greater familiarity with endoscopists.

Its commonly used mode employs energy emitted from a controlled radiofrequency source (HALO® or HALO™, BÂRRX Medical Inc, Sunnyvale, CA). The HALO® is used for circumferential ablation (Fig 14), and the HALO™ is intended for a more focal targeted ablation (Fig 15). The use of HALO® involves a sizing balloon catheter that is introduced into the esophagus and measures esophageal width, followed by an appropriately sized RFA balloon catheter. For the treatment of Barrett’s-related dysplasia, the controller of the RFA source is preset to deliver energy of 12 J/cm², which causes complete destruction of the mucosa, but without injury to the submucosa. The RFA balloon is 3 cm long and consists of 60 narrowly spaced electrode rings in a bipolar fashion. After the esophageal diameter is measured by the sizing balloon, the RFA balloon catheter is introduced in the esophagus and placed in its position. The balloon is then inflated and the RFA source releases energy circumferentially on the esophageal surface for 300 milliseconds. In another form, a more targeted and focal ablation may be carried out using the HALO™ catheter, which does not require a sizing catheter. The HALO™ is a square-shaped catheter with the same electrodes on its external surface, which is attached to the tip of the endoscope. It allows the focal ablation of small areas of residual Barrett’s epithelium.

After thermal dose-escalation animal testing and pre-esophagectomy human experiments, the first larger clinical evaluation of RFA included BE patients without dysplasia in a study by Sharma et al on the ablation of intestinal metaplasia. This multicenter trial demonstrated a 70% complete remission of BE in the circumferential balloon-treated group at 1 year of follow-up, without evidence of subsequent stricture formation or buried BE among 4,306 evaluated biopsy fragments. A subsequent study reported 98% complete remission of intestinal metaplasia following stepwise circumferential therapy with additional focal ablative therapy of remaining BE. In the only multicenter, randomized, and sham-controlled trial conducted to date, 127 patients with prior diagnosis of dysplastic BE (63 high-grade dysplasia and 64 low-grade dysplasia) were randomized in a 2:1 ratio to receive either RFA or a sham endoscopic procedure (control group). After a 1-year follow-up, all measured primary and secondary outcomes showed significant differences favoring the treatment group: progression rate, progression

![Fig 14. — The HALO® used for circumferential ablation.](image)

![Fig 15. — The HALO™ intended for a more focal targeted ablation.](image)
rate to cancer, complete regression of intestinal meta
plasia, complete regression of low-grade dysplasia, and
complete regression of high-grade dysplasia. A
systematic review of nine observational studies involv-
ing 429 patients and at least 12 months of follow-up
was recently published. After analysis, complete
eradication of intestinal metaplasia was achieved in
46% to 100% of patients and complete regression of
neoplasia in 46% to 100%.

RFA is associated with the fewest complications
since it involves a limited depth of injury, although
stricture formation occurs in approximately 6% in pro-
spective series. A patient with a straight esoph-
geal segment without strictures is ideal for this mo-
dality. Patients with a tortuous esophagus may fare
better with a treatment such as PDT, which can be
applied more readily in this situation. RFA has also
been studied in patients who failed PDT. Fourteen
patients with residual high-grade dysplasia follow-
ing aminolevulinic acid or Photofrin PDT underwent
RFA and/or rescue ER. An overall complete revers-
al of dysplasia was achieved in 86%, and the rate
of strictures was 7%. Although preliminary, this
study suggests RFA with rescue ER may be effective
for eradication of high-grade dysplasia in patients in
whom PDT has failed.

Photodynamic Therapy
PDT is a minimally invasive treatment of solid tumors
that uses a photosensitizing drug (photosensitizer)
and laser light. It has been approved for use to treat
BE with dysplasia. The photosensitizer accumulates
in the tumoral tissue. Once a specific wavelength of
light is endoscopically applied with a laser, the treat-
ment works by a mechanism of free oxygen radical
production. This generation of free radicals results
in ischemic necrosis of tumor cells.

A prospective randomized study showed a signifi-
cant difference for the study group treated with PDT
and omeprazole compared with the group treated
with omeprazole only regarding the ablation of high-
grade dysplasia (77% vs 39%; \( P = .004 \)) and the re-
currence of neoplasia (15% vs 29%; \( P = .027 \)). The
patients followed a maximum of three PDT sessions at
intervals of at least 3 months. The treatment was well
tolerated and was associated with a median survival of
60.5 months. The technique might be used in elderly
patients and/or in those with significant comorbidities.
Overholt et al retrospectively studied a cohort of
103 patients who had varying degrees of BE with
dysplasia and intramucosal cancer who were treated
with PDT. With a median follow-up of 50 months, the
intent-to-treat success rates for eradication of dysplas-
tic epithelium were 92.9% for the low-grade dysplasia
group, 77.5% for the high-grade dysplasia group, and
44.4% for the intramucosal cancer group.

Due to several limitations associated with this
therapy, clinicians have shown increased interest in
newer ablative treatment modalities. One limitation is
the additional time required from both the patient and
the provider for the administration of the photosen-
sitizing agents prior to endoscopic therapy. Another
is the systemic distribution of the photosensitizing
agents that requires patients to avoid direct sunlight
and wear full protective clothing (eg, sunglasses, wide-
brim hats, long-sleeved shirts) for several weeks to
prevent sunburn, which could be significant. Also,
patients can develop esophageal strictures following
prior ablative treatments. Overholt et al reported
cases of adenocarcinoma that arose from buried Bar-
rett's glands following PDT.

Cryoablation Therapy
Endoscopic spray cryotherapy is a relatively new ab-
latived modality for the treatment of gastrointestinal
diseases. Endoscopic spray cryotherapy using liquid
nitrogen is a novel method of destruction of BE tissue
and has been studied extensively. It uses a visu-
ally directed, noncontact method that directly exposes
the Barrett's mucosa to liquid nitrogen at −196°C at
low pressure (2 to 3 psi) via a disposable 7F spray

catheter that is introduced in the working channel of
a regular endoscope. A modified orogastric decom-
pression tube is placed to vent excess nitrogen gas
from the esophagus and stomach. The esophageal
mucosa is exposed to the liquid nitrogen for 10 to 20
seconds and then allowed to thaw for approximately
1 minute. The freeze/thaw cycles are repeated 3 to
4 times per session. The session is repeated in 6 to 8
weeks if needed. The intracellular and extracellular
ice crystals that are formed during the freeze cycle
have an abrasive action and disrupt the integrity of
dysplastic cell membranes. Two mechanisms of cell
death then occur: (1) an immediate cellular lysis at
the coldest site of direct ablation and (2) induction of
inflammatory apoptosis by cryoinjury in areas more
peripheral to the therapy that are initially damaged
but not initially destroyed.

Several trials have shown cryotherapy as a safe
and effective tool. Short-term results are promising,
with eradication of intestinal metaplasia in 46% to 78%
of cases and of dysplasia between 79% and 87% of
cases. Johnston et al published a pilot study in
2005 suggesting that cryospray ablation is effective in
dowgrading dysplasia and promoting the regenera-
tion of normal squamous epithelium in areas of BE.
In this single-center study, serial cryospray ablation
sessions were performed at monthly intervals on 11
patients with metaplasia and/or dysplasia. Complete
histologic eradication of BE was noted in 78% of the
patients. Dumot et al performed a nonrandomized
prospective cohort trial that included 30 patients with
either high-grade dysplasia or intramucosal cancer undergoing cryospray ablation. Results were promising: 68% of those with high-grade dysplasia and 80% of those with intramucosal cancer had elimination of cancer or downgrading of high-grade dysplasia. Shaheen et al. retrospectively assessed 98 patients with BE and high-grade dysplasia, the largest cohort to date. Of the 60 enrolled subjects completing all cryospray ablation treatments with a mean of four treatments, 58 (97%) had complete eradication of high-grade dysplasia at a mean follow-up of 10.5 months.

The technique has been in use at our institute for the last several years and has been employed to ablate residual Barrett’s epithelium after definitive chemoradiation of esophageal adenocarcinoma. After complete clinical response of esophageal adenocarcinoma to chemoradiation therapy, cryoablation reduced the median length of persistent BE and resulted in histologic downgrading in 14 patients. Among 10 patients with high-grade dysplasia, 2 were reduced to low-grade dysplasia, 6 to BE with no dysplasia, and 2 to no BE. Among 4 patients with low-grade dysplasia, 3 were reduced to BE with no dysplasia and 1 to no BE. No major complications have been reported except for a gastric perforation in 1 patient with Marfan syndrome. This therapy is now contraindicated in patients with limited distensibility of the stomach.

**Palliation of Dysphagia in Advanced Esophageal Cancer**

Palliation of dysphagia related to esophageal cancer may be accomplished with esophageal dilation, stent placement, or other ablative modalities. Dilation provides temporary relief and needs to be repeated frequently. Ablative modalities such as PDT, neodymium-doped yttrium aluminum garnet laser (Nd:YAG), and cryoablation have been tried but not shown to be consistently effective or safe in this situation. In this article we focus primarily on the role of self-expanding metal stents (SEMS) in the palliation of malignant dysphagia.

**Ablative Therapies for Malignant Dysphagia**

In a prospective randomized trial involving 236 patients, PDT and laser therapy had similar efficacy in terms of dysphagia relief, although there was a trend toward a better response with PDT for tumors located in the upper two-thirds of the esophagus. PDT was associated with esophageal strictures and photosensitivity (19%) that may persist for 6 weeks but with fewer perforations than with the Nd:YAG laser (1% vs 7%). Chest pain and worsening dysphagia are common after PDT and usually resolve over several weeks. With the widespread availability of newer SEMS, PDT is rarely used for the palliation of malignant dysphagia. Cryospray ablation is another noncontact therapy that uses supercooling to cause cryonecrosis and has been used to palliate esophageal cancer.

**Esophageal Stents**

Endoscopic stent placement is used to palliate dysphagia in patients with locally unresectable or advanced metastatic esophageal cancer, in those with poor functional status and weight loss, or in those with locally recurrent disease. Stents may also be used as a bridge to surgery during neoadjuvant chemoradiation. The location of disease within the esophagus is an important factor, given that expandable metal stents are more effective for upper rather than distal lesions.

This discussion focuses only on SEMS as plastic stents are rarely used in this situation.

SEMS are composed of a variety of metal alloys such as nitinol, and they are available in several lengths and diameters. Metal stents are available in three varieties: uncovered, partially covered, and fully covered. Covered stents resist tumor ingrowth, but they have a higher migration rate, especially when fully covered. Partially covered stents are uncovered at their ends, allowing the stent to embed in the tissue and thus prevent migration. Fully covered stents offer the advantage of potentially being removable, but they are associated with an increased risk of migration. Uncovered stents are less likely to migrate but are subject to tumor ingrowth and resultant obstruction. In addition, some stents have an antireflux valve to prevent esophageal reflux in patients with stents placed across the gastroesophageal junction.

Stents can be used as a bridge to surgery for esophageal cancer. Brown et al. reported on 32 patients with dysphagia related to esophageal adenocarcinoma who underwent SEMS placement prior to neoadjuvant therapy. Initial stent placement was successful in all patients, and mean dysphagia scores improved significantly; however, stent migration occurred in 8 patients. Twenty of the 32 patients subsequently underwent esophagogastrectomy. Stents were removed in 5 of these 20 patients prior to surgery, while the stents in the remaining 15 patients were removed with the resected specimen. No surgical complications were attributed to stent placement. Gastrointestinal SEMS can be placed under endoscopic guidance without the aid of fluoroscopy. Initial stricture dilation is generally recommended, and the diameter of the stent to be deployed should not be greater than 2 mm of the estimated stricture diameter. The length of the stenosis must be accurately measured and a stent chosen that is at least 4 cm longer than the stricture. Placement can be accomplished endoscopically by visualization and documentation of distances measured from the incisors to the proximal margin of the tumor, followed by stent placement.
under endoscopic visualization. At our institute, we investigated dysphagia response, stent migration, and adverse events, with small-caliber (≤ 16 mm body diameter) covered SEMS for malignant dysphagia in a cohort of 31 patients. Small-caliber SEMS were placed under direct endoscopic visualization without fluoroscopic assistance. The overall migration rate was 35%, and the dysphagia score improved significantly in 97% of patients.

Patients with large, bulky, mid and proximal esophageal tumors should be evaluated for possible tracheal compression. Imaging such as CT scans should be reviewed to determine if tracheal compression is present. Such patients may benefit from airway stent placement prior to esophageal stent placement. During the placement of stents, the endoscopist should be prepared for the possibility of tracheal compression and the need for endotracheal intubation and emergent stent removal if stridor develops. Balloon dilatation prior to stent deployment at the level of the stricture could indicate airway compromise. After deployment, the SEMS expands against the stenosis, and this anchors the stent and helps prevent stent migration. For stent placement in the very distal esophagus, it is important to avoid leaving an excessive length of stent within the stomach to prevent contact with the opposite gastric wall, which could result in obstruction and/or ulceration.

Following stent placement, patients should be advised to consume a soft mechanical diet to avoid food impaction. In addition, if an open stent (non-anti-reflux) is placed across the esophagogastric junction, then strict anti-reflux precautions and high-dose proton pump inhibitors are needed. Greater than 95% of patients undergoing stent placement for malignant esophageal obstruction are able to tolerate a liquid diet.84-86

In patients with malignant dysphagia in the presence of a tracheoesophageal fistula, SEMS restored luminal patency in about 98% and sealed the fistula in 70% to 100% of patients.87,88 However, subsequent tumor ingrowth is common, and many patients require additional interventions for recurrent dysphagia or complications related to the stent, such as migration.86 A meta-analysis that included 40 trials and 2,542 patients found that SEMS insertion is safer and more effective than rigid plastic tube insertion.89 This review also found that SEMS insertion provided more rapid palliation of dysphagia compared with brachytherapy, but the difference gradually diminished over time.

Complications of SEMS Placement

In a survey that included 212 endoscopists who had placed a total of 434 SEMS,90 the overall rate of intra- or post-procedural technical complications was 5.4%. The complications included misplacement (0.3%), failed expansion (3.9%), failed deployment (0.8%), and migration (0.3%). The overall rate of intra- or post-procedural clinical complications was 14.7%, including chest pain (12.2%), perforation (0.6%), bleeding (0.6%), and death (1.4%). Delayed technical complications occurring in 18.1% included overgrowth/ingrowth (11.3%) and migration (6.8%). Delayed clinical complications occurred in 26.9%, including gastroesophageal reflux disease (3.7%), recurrent dysphagia (8.2%), tracheoesophageal fistula (2.8%), bleeding (3.9%), perforation (0.8%), and death within 30 days that was not related to immediate stent placement (7.4%).

Conclusions

In the last decade, significant advances have developed in the endoscopic management of Barrett’s esophagus (BE)-related neoplasia. Endoscopic resection and ablative modalities have become the standard of care in the management of high-grade dysplasia and intramucosal cancer in patients with BE. Further refinements and modifications in these techniques and devices can be expected over the next decade. Endoscopic submucosal dissection is a promising new en bloc resection technique that is widely used in Asia and Europe and is being studied in North America. The accurate pathological staging provided by endoscopic resection has resulted in a better selection of patients for esophagectomy. The safety and efficacy of endoscopic radiofrequency ablation have been demonstrated in several studies, and this therapy is now used in many countries in the management of BE dysplasia. A multimodality endoscopic approach involving endoscopic resection for visible lesions and ablative therapy for eradication of the BE is the widely accepted approach in the management of BE-related neoplasia. The significant improvements in the design of self-expanding metal stents may improve the quality of life of patients with severe malignant dysphagia.

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