Diagnosis and management of Barrett's esophagus for the endoscopist

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Abstract: In Barrett's esophagus, the stratified squamous epithelium lining the esophagus is replaced by specialized intestinal-type columnar epithelium. The prevalence of Barrett's esophagus has ranged from 0.9% to 4.5%. The rate of progression from Barrett's esophagus to esophageal adenocarcinoma is 0.5% per patient-year. Proton-pump inhibitors are the mainstay of symptom control in Barrett's patients. Nondysplastic Barrett's and Barrett's with low-grade dysplasia (LGD) are typically managed by periodic surveillance. Radiofrequency ablation is being evaluated as a modality for managing nondysplastic Barrett's and Barrett's with LGD. The options for the management of Barrett's patients with high-grade dysplasia (HGD) include endoscopic therapy, surgery, and intensive surveillance until biopsy reveals adenocarcinoma. Endoscopic therapy involves endoscopic mucosal resection (EMR) and ablation. More aggressive techniques such as endoscopic submucosal dissection and larger segment endoscopic mucosal resection are under study. In this review, we discuss the diagnosis and management of Barrett's esophagus. The recommendations from the major gastroenterologic societies and the current and investigational endoscopic modalities for the management of Barrett's esophagus with and without dysplasia are reviewed.

Keywords: Barrett esophagus, endoscopic surgical procedures, esophageal neoplasms

Introduction

Barrett's esophagus is a condition in which the stratified squamous epithelium lining the esophagus is replaced by specialized intestinal-type columnar epithelium. The presence of goblet cells is the key pathologic feature establishing intestinal metaplasia. Chronic gastroesophageal reflux disease (GERD) damages the esophageal mucosa. One Barrett's hypothesis is that the damaged squamous cells are replaced by columnar cells during the healing process [Shaheen and Richter, 2009; Spechler, 2002]. This is known as intestinal metaplasia. Barrett's esophagus is considered to follow a progression from intestinal metaplasia to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally to esophageal adenocarcinoma in a subset of patients. Barrett's esophagus is usually found in middle-aged adults. According to a retrospective study of 2100 patients undergoing upper endoscopy, the prevalence is higher among Whites (6.1%) as compared with Hispanics (1.7%) and African Americans (1.6%) [Abrams *et al.* 2008]. The male-to-female ratio is 2 : 1 [Cook *et al.* 2005].

The prevalence of Barrett's has ranged from 0.9% to 4.5% [Hirota *et al.* 1999; Cameron *et al.* 1990]. A study from Sweden estimated that Barrett's esophagus was present in 1.6% of the general population [Ronkainen *et al.* 2005]. In two studies of 136 and 170 patients with nondysplastic Barrett's esophagus, followed for approximately 4 years, the rate of progression to adenocarcinoma was 0.5% per patient-year [O'Connor *et al.* 1999; Drewitz *et al.* 1997]. This is the risk that is usually quoted to patients diagnosed with Barrett's esophagus. In a study, the incidence of cancer in those with LGD was 0.6% per year [Sharma *et al.* 2006]. In another study of 75 Barrett's patients with HGD, 12 (16%) developed cancer over a mean follow-up period of 7.3 years [Schnell *et al.* 2001]. In another study of 15 patients with HGD, 4 (27%) progressed to adenocarcinoma between 17 and 35 months of follow up [Weston *et al.* 2000]. In this review, we discuss the diagnosis, imaging, and management of Barrett's esophagus highlighting current and prospective endoscopic therapies.

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Diagnosis

Two criteria, one endoscopic and one histologic, need to be satisfied for the diagnosis of Barrett's esophagus. Upper endoscopy should demonstrate displacement of the squamocolumnar junction proximal to the gastroesophageal junction (GEJ). The stratified squamous epithelium lining the esophagus is a pale pearly color, while the columnar epithelium is salmon colored. The junction of these two epithelia is called the Z-line. The GEJ is the location at which the esophagus meets the stomach. This can be identified as the level of the most proximal extent of the gastric folds. In the normal state, the Z-line coincides with the GEJ. In Barrett's esophagus, the Z-line is displaced proximally relative to the GEJ (Figure 1).

On the pathologic examination, intestinal metaplasia can be identified by the presence of goblet cells on biopsy of the esophageal mucosa. In a study of biopsies obtained from Barrett's esophagus, three types of columnar epithelium, cardiac-type mucosa, fundic-type mucosa, and intestinal metaplasia, were detected [Paull *et al.* 1976]. The neoplastic risk of cardiac- and fundic-type mucosa is not known [Sharma *et al.* 2004]. When intestinal metaplasia is not found on biopsy specimens from salmon-colored mucosa in the esophagus, it is termed endoscopically suspected Barrett's esophagus. Conversely, the significance of intestinal metaplasia in biopsy specimens from the GEJ in the absence of endoscopically suspected Barrett's esophagus is unknown in terms of risk of progression to cancer.

There is significant interobserver variation among pathologists in the diagnosis of Barrett's esophagus with dysplasia/cancer. The finding of Barrett's esophagus with dysplasia should be confirmed by an expert GI pathologist. In one study, the interobserver agreement among pathologists was only fair for LGD ($\kappa = 0.32$), while it is moderate for HGD/carcinoma ($\kappa = 0.65$) [Montgomery *et al.* 2001]. Another study showed a good interobserver agreement among two GI pathologists for HGD and esophageal adenocarcinoma (EAC) [Ormsby *et al.* 2002]. When two GI pathologists agree on the diagnosis of LGD, there is increased risk of progression from LGD to HGD or carcinoma [Skacel *et al.* 2000].

Advanced imaging in Barrett's esophagus

Standard endoscopic imaging is useful for the detection of grossly visible lesions but may be less sensitive for the detection of early or subtle mucosal changes. Newer imaging techniques are being studied in hopes of improving the identification of dysplasia and cancer arising in Barrett's mucosa.

Narrow band imaging

Narrow band imaging (NBI) is a high-resolution endoscopic technique that enhances the fine structure of the mucosal surface (Figure 2). The principle underlying the use of NBI is that the depth of penetration of light is directly proportional to its wavelength, which means the longer the wavelength of light, the deeper the penetration. The blue light used in NBI allows optimal

Figure 1. High resolution endoscopic image from a 49 year-old man with Barrett's esophagus. The Barrett's segment measured 2 cm, consistent with short segment Barrett's esophagus.

Figure 2. High resolution endoscopic image of a 49 year-old man with Barrett's esophagus with narrow band imaging. Compared to Figure 1, the Barrett's mucosa is more prominent and more easily visualized.

superficial imaging [Kara *et al.* 2006]. The blue light is also absorbed by hemoglobin, allowing visualization of the superficial vasculature. In a study which evaluated 200 mucosal areas in 63 patients with Barrett's, a regular mucosal and vascular pattern and flat mucosa (i.e. without any villi or pits) were significantly associated with intestinal metaplasia, while all areas with high-grade intraepithelial neoplasm exhibited at least irregular mucosal patterns, irregular vascular patterns, or abnormal blood vessels [Kara *et al.* 2006].

Chromoendoscopy

Chromoendoscopy involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy [Fennerty, 1994]. Chromoendoscopy with methylene blue has been studied in Barrett's patients. The technique of dye application, experience of the investigators, and patient populations has varied by study. A meta-analysis of nine such studies showed that staining with methylene blue did not significantly increase the detection of specialized intestinal metaplasia and dysplasia compared with random biopsies [Ngamruengphong *et al.* 2009].

Optical coherence tomography

Optical coherence tomography (OCT) is similar in principle to ultrasonography but uses light waves rather than acoustical waves. It uses back-scattering of light to obtain cross-sectional images of tissue. A prospective study of 33 patients with Barrett's showed a sensitivity of 68% and a specificity of 82% for detection of dysplasia [Isenberg *et al.* 2005]. OCT is not currently in use in clinical practice outside of the research setting.

Laser confocal microscopy

This technique allows subsurface analysis of the intestinal mucosa and *in-vivo* histology during the endoscopic procedure. In a study of 63 patients using laser confocal microscopy, Barrett's esophagus and associated neoplasia could be predicted with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively [Kiesslich *et al.* 2006]. This is a newer technique requiring significant operator expertise in the use of the probe and in the interpretation of the real-time microscopic detail. Confocal microscopy is being evaluated in the research setting.

Management of nondysplastic Barrett's esophagus

Conservative management is recommended for patients with Barrett's esophagus without evidence of dysplasia or cancer. It involves symptom control and periodic endoscopic surveillance to exclude progressive disease. Lifestyle modifications can be helpful to increase esophageal acid clearance and decrease the incidence of reflux events. Patients with sleep disturbance due to heartburn at night may benefit from elevation of the head of the bed and allowing 3 hours between meals and recumbency. Body mass index (BMI) is associated with symptoms of gastroesophageal reflux disease in both normal-weight and overweight women. Moderate weight gain among persons of normal weight may cause or exacerbate symptoms of reflux [Hampel *et al.* 2005]. Avoiding certain foods can help control symptoms. Citrus fruits, carbonated beverages, tomatoes, onions and spicy foods may be acidic or irritative. Fatty food, caffeinated beverages, chocolate and mint may predispose to gastric reflux [Kahrilas, 2008]. Although there is physiologic evidence that exposure to tobacco, alcohol, chocolate and high-fat meals decreases lower esophageal sphincter pressure, evidence of the efficacy of dietary modification in controlling reflux symptoms is lacking [Kaltenbach *et al.* 2006]. Many clinicians advise avoiding tobacco and alcohol, though there is no definitive proof supporting an improvement in GERD symptoms after cessation [Kaltenbach *et al.* 2006].

Acid suppressing medications are the mainstay of therapy for reflux symptoms. Proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) can be used to decrease stomach acid secretion. The goal is to keep the stomach pH above 4 to decrease erosive esophagitis and to provide symptom relief [Vaezi and Richter, 1996]. More complete esophagitis healing and heartburn relief is observed with PPIs versus H2RAs and occurs nearly twice as fast [Chiba, 1997]. A large meta-analysis of 136 randomized, controlled trials involving 35,978 patients with esophagitis showed that using twice the standard dose of a PPI was associated with modest benefit; about 25 patients need to be treated with the double-dose PPI for one patient to benefit [Khan *et al.* 2007]. In a study of normal subjects, the effect of adding H2RA to twice-daily PPI therapy was studied. It showed that bedtime ranitidine was more effective than bedtime

omeprazole on residual nocturnal acid secretion in patients receiving omeprazole twice daily [Peghini *et al.* 1998]. However, subsequent studies have failed to reproduce the benefit of H2RA added to twice-daily PPI therapy in suppressing nocturnal acid breakthrough [Fackler *et al.* 2002]. Many clinicians recommend twice-daily PPI therapy for Barrett's patients.

It is not clear whether aggressive treatment of reflux prevents progression. There is indirect evidence that acid exposure increases proliferation and decrease apoptosis in Barrett's esophagus [Souza *et al.* 2002]. In an observational study of 236 VA patients with Barrett's esophagus, patients who had received a prescription for PPIs were found to be at a lower risk for progression to dysplasia as compared with patients with no therapy or treatment with H2RAs (hazards ratio 0.25). Furthermore, among those on PPIs, a longer duration of use was associated with less frequent occurrence of dysplasia [El-Serag *et al.* 2004]. Although often assumed, the hypothesis that acid suppression prevents progression has not been borne out by clinical trial data.

Radiofrequency ablation is a rapidly evolving therapeutic modality for Barrett's esophagus.

In a study, 70 patients with nondysplastic Barrett's esophagus were treated with endoscopic balloon-based radiofrequency ablation (HALO³⁶⁰ System, BARRX Medical, Inc., Sunnyvale, CA). Follow-up esophagogastroduodenoscopy with biopsies were performed at 1, 3, 6, and 12 months. In 70% of patients, all biopsy specimens were negative for Barrett's esophagus at 12 months [Sharma *et al.* 2007]. At 30 months after additional focal ablative therapy, biopsy specimens were negative in 60 out of 61 available patients [Fleischer *et al.* 2008]. There were no strictures and no buried glandular mucosa. In a similar study, at 6 months, 29/49 (59%) patients had complete ablation with normal squamous epithelium. At 12 months, 25/27 (93%) patients had no evidence of Barrett's mucosa on biopsies [Velanovich, 2009]. Concerns with endoscopic ablative therapies, including radiofrequency ablation (RFA), include stricture formation and development of postablation buried Barrett's metaplasia, which could progress to dysplasia. Although RFA has been shown to be effective in the treatment of dysplastic Barrett's esophagus, its use in nondysplastic Barrett's is currently investigational.

Surveillance guidelines from the three gastroenterologic societies are summarized in Table 1.

Table 1. Guidelines for management of Barrett's esophagus.

	ACG [Wang and Sampliner, 2008]	ASGE [Hirota <i>et al.</i> 2006]	AGA [Sharma <i>et al.</i> 2004]
Nondysplastic Barrett's esophagus	Two upper endoscopies with biopsy within 1 year and follow up with endoscopy every 3 years	Two upper endoscopies with biopsy within 1 year and follow up with endoscopy every 3 years	Assess within 1 year and if no dysplasia, defer for 5 years or until cancer therapy is not possible or life expectancy is limited
Barrett's esophagus with LGD	Two upper endoscopies with biopsy within 6 months. Follow-up endoscopy every year until dysplasia is absent on two subsequent examinations	Follow up after 6 months with concentrated biopsies in area of dysplasia; follow up every 12 months thereafter if dysplasia persists	Assess in 1 year and re-examine every year if dysplasia is confirmed by two pathologists (if there is disagreement about the presence of dysplasia then re-examine in 2 years)
Barrett's esophagus with HGD	Repeat EGD with biopsy within 3 months. Follow up with EMR in case of any mucosal irregularity; then intensive endoscopic surveillance every 3 months or an intervention, such as esophagectomy or ablation, in the case of flat mucosa	Patients can choose to have surgery or endoscopic therapy; follow up patients who choose surveillance every 3 months for 1 year with several large biopsies every 1 cm; after 1 year without cancer detection, surveillance duration can be lengthened, provided dysplastic changes are absent on two subsequent examinations	Patients should be treated with surgical resection or endoscopic therapy; surveillance can be offered provided follow up with endoscopy is every 3 months with a minimum of eight biopsies every 2 cm along the esophagus

ACG, American College of Gastroenterology; ASGE, American Society of Gastrointestinal Endoscopy; AGA, American Gastroenterological Association; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection.

The American College of Gastroenterology (ACG) and American Society of Gastrointestinal Endoscopy (ASGE) recommend two esophageal examinations within 1 year of the diagnosis of Barrett's esophagus with four quadrant biopsies taken from the Barrett's mucosa at 2 cm intervals. Follow-up endoscopy should be performed every 3 years [Wang and Sampliner, 2008; Hirota *et al.* 2006].

Management of Barrett's esophagus with low-grade dysplasia

Patients with Barrett's esophagus with LGD are usually managed conservatively. After the diagnosis of LGD, repeat endoscopy should be performed in 6 months to exclude the presence of higher-grade dysplasia. The ACG recommends follow-up endoscopy every year until dysplasia is absent on two subsequent examinations [Wang and Sampliner, 2008]. The American Gastroenterological Association (AGA) also recommends yearly follow-up endoscopy but includes a caveat that if there is disagreement about the presence of dysplasia then the patient should be re-examined in 2 years (Table 1) [Sharma *et al.* 2004]. Symptoms of GERD, if present, should be managed with conservative measures and antisecretory therapy.

Management of Barrett's esophagus with high-grade dysplasia

A high degree of interobserver variability is seen in the histological diagnosis of Barrett's esophagus with HGD, and the diagnosis should be confirmed by an expert gastrointestinal pathologist [Montgomery *et al.* 2001]. The options for management of patients with HGD are endoscopic therapy, surgery, or intensive surveillance until biopsy reveals adenocarcinoma. The Seattle biopsy protocol, with biopsies from all visible abnormalities and random four-quadrant biopsies every 1 cm starting from the top of the gastric folds up to the squamocolumnar junction, is superior to random biopsies or 2-cm biopsies in detecting early cancers arising in Barrett's esophagus with HGD. In a study of 45 patients with Barrett's with HGD, the 2-cm protocol (four-quadrant biopsies every 2 cm) missed 50% of cancers that were detected by a 1-cm protocol in Barrett's segments 2 cm or more without visible lesions [Reid *et al.* 2000]. According to Vienna classification, there are five categories of esophageal neoplasia (Table 2) [Schlemper *et al.* 2000].

Endoscopic mucosal resection

The Japanese Society for Gastrointestinal Endoscopy (JSGE) has described criteria for Barrett's with HGD suitable for endoscopic mucosal resection (EMR) [Ell *et al.* 2000; Takeshita *et al.* 1997]. Criteria included (1) a diameter of less than or equal to 2 cm; (2) involvement of less than one-third of the circumference of the esophageal wall; and (3) limitation to the mucosa. Patients diagnosed with HGD may be considered for repeat endoscopy and protocol biopsy, with or without EMR at a referral center to confirm the diagnosis and to rule-out synchronous lesions.

With EMR, the dysplastic epithelium is removed endoscopically. This allows for histologic examination, which is not possible with the ablative therapies. EMR, by resecting larger areas, may detect a focus of cancer missed by conventional biopsy. Studies have demonstrated that EMR is safe and effective for the treatment of superficial lesions [Vieth *et al.* 2004; Ell *et al.* 2000; Nijhawan and Wang, 2000].

Some EMR techniques involve initial submucosal injection. Following injection, the lesion is aspirated into a transparent cap and resected with a snare [Inoue *et al.* 1993]. Lesions up to 2 cm in size may be resectable using this approach. An alternative is to use a band-and-snare method in which the target lesion is banded using a specialized EMR device. Following banding the lesion is resected using a snare [Fleischer *et al.* 1996]. In a prospective randomized trial, no significant differences were observed between these two techniques with regard to the maximum diameter or calculated area of the resected specimens [May *et al.* 2003].

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) has been applied in the management of gastric

Table 2. Vienna classification of esophageal neoplasia.

Category	Description
Category 1	No dysplasia
Category 2	Indefinite for dysplasia
Category 3	Low-grade intraepithelial neoplasia
Category 4	High-grade intraepithelial neoplasia
Category 5	Invasive epithelial neoplasia
5.1	Intramucosal cancer
5.2	Submucosal cancer

and esophageal tumors. In this approach, after submucosal injection an initial incision is made with a standard needle knife. Electrosurgical current is applied using the insulation-tipped (IT) knife to complete the incision around the lesion. The IT knife is then used to dissect the submucosa. In a study of 24 patients with GEJ tumors, all of the lesions were removed *en bloc* [Yoshinaga *et al.* 2008]. Subsequent management depends on the presence of cancer cells in the lateral and vertical margin of the resected lesion. ESD has not been widely utilized in the United States.

Large segment mucosal resection

More aggressive mucosal resection techniques have been studied in animal models. Widespread EMR (WEMR) has been studied for lesions larger than 2 cm. It is still in the pre-clinical trial stage and has been reported in a swine model. A submucosal cushion is raised with injection. A needle knife is then used to strip the mucosa distally and the mucosa is then resected with a snare. Partial or circumferential resection of the mucosa can be performed. Risk of stricture formation is high with circumferential resection when more than three-quarters of the circumference of the mucosa is resected [Yoshida *et al.* 1995]. *En bloc* esophageal mucosectomy (EEM) enables a concentric column of mucosa to be resected in a piecemeal fashion. Concentric resection could decrease sampling error and permit *in-situ* evaluation. Unsamplable dysplastic or neoplastic tissue adjacent to the biopsy site could be completely resected. The procedure was well tolerated in a swine model but to date has not been evaluated in a human clinical trial [Willingham *et al.* 2009].

Endoscopic ablative therapies

With ablative therapies, dysplastic or neoplastic epithelium is ablated using thermal, radiofrequency or photochemical energy. Ablated metaplastic epithelium is replaced by a neosquamous layer. Multiple ablative modalities have been examined including potassium titanyl phosphate (KTP) laser (neodymium-doped yttrium aluminium garnet (Nd:TAG) laser directed through a KTP crystal), argon plasma coagulation (APC), Nd:YAG laser, photodynamic therapy (PDT), and more recently RFA and cryoablation. There are two major concerns with ablative modalities. (1) No pathologic specimens are generated for histologic examination. (2) There may be progression of buried Barrett's

metaplasia or dysplasia under the neosquamous layer. A case report has described development of an adenocarcinoma beneath regenerated squamous epithelium postablation [Van Laethem *et al.* 2000].

Radiofrequency ablation

RFA (The HALO device, BÂRRX Medical, Sunnyvale, California) has been tested in randomized clinical trials in Barrett's esophagus with dysplasia [Shaheen *et al.* 2009; Ganz *et al.* 2008]. With RFA, a cylindrical balloon is inflated to bring electrodes in contact with the esophageal mucosa. Focal areas may be treated with an RFA pad [Sharma *et al.* 2009]. A multicenter randomized sham controlled clinical trial of 127 patients with dysplastic Barrett's esophagus was performed. In patients with LGD, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group. Among patients with HGD, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group. Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group. Patients in the ablation group had less disease progression and fewer cancers. In addition to ablative therapy, these patients also underwent intensive endoscopic surveillance [Shaheen *et al.* 2009]. Adverse effects included chest pain, upper gastrointestinal bleeding in one patient and esophageal stricture in five patients. All five stricture patients underwent successful endoscopic dilatation (mean, 2.6 sessions). In another uncontrolled study of 142 Barrett's esophagus patients with HGD, histologic complete response, defined as no evidence of HGD on biopsy specimen, was observed in 90.2% patients. Adverse events included a stricture in an asymptomatic patient not requiring dilation [Ganz *et al.* 2008].

Photodynamic therapy

PDT uses a photosensitizing drug to sensitize the tissue to light. Delivery of light to the sensitized tissue leads to destruction of the cells. The two photosensitizers which have been studied in the past include porfimer sodium and 5-aminolevulinic acid (5-ALA). In a randomized trial of porfimer sodium with PPI versus PPI alone in 208 patients with HGD, complete ablation of HGD was seen in 77% of patients in phototherapy plus PPI group versus 39% of

patients in PPI only group [Overholt *et al.* 2005]. A Mayo clinic study of 199 Barrett's patients with HGD reported that 129 patients (65%) were treated with PDT and 70 (35%) with esophagectomy. Overall mortality in the PDT group was 9% (11/129) and in the surgery group was 8.5% (6/70) over a median follow-up period of 59 ± 2.7 months for the PDT group and 61 ± 5.8 months for the surgery group [Prasad *et al.* 2007]. Esophageal stricture may be seen in approximately one-third of patients following PDT. PDT is currently being replaced by newer ablative modalities with less risk of procedural complications.

Cryotherapy

Cryotherapy destroys biological tissue through a variety of methods. Rapid freezing causes failure of cellular metabolism due to stress on lipids and proteins. Continued freezing produces extracellular ice, creating a hyperosmotic extracellular environment and drawing fluid from cells [Baust and Gage, 2005; Gage and Baust, 1998]. The CryoSpray Ablation System (CSA) (CSA Medical, Inc., Baltimore, Maryland, USA) uses low-pressure liquid nitrogen spray delivered through a 7-Fr catheter passed through the working channel of a standard upper endoscope [Dumot and Greenwald, 2008]. In a study of 11 Barrett's patients, including five with LGD and one with HGD, patients underwent a mean of 4.2 sessions (range 1–8 sessions) of cryotherapy. In this pilot study, nine of the 11 patients (78%) had complete histologic reversal of Barrett's esophagus, with no dysplasia found at a 6-month follow up. No significant complications occurred and the treatment was well tolerated. Only two patients reported symptoms in 46 treatments. These included mild solid food dysphagia and chest discomfort, which resolved within 48 hours with one patient requiring analgesia [Johnston *et al.* 2005].

Surgical esophagectomy

In Barrett's patients with HGD, there is an increased risk of occult malignancy which supports arguments for surgical esophagectomy in this setting. In a series of 23 Barrett's patients with HGD who underwent surgical esophagectomy, occult adenocarcinoma was found in 35% (8/23) of surgical specimens [Mirnezami *et al.* 2009]. Another study reported occult adenocarcinoma in 39 out of 85 patients (41%) who had undergone esophagectomy for Barrett's with HGD [Edwards *et al.* 1996]. Prior to the

development of endoscopic therapies, esophagectomy was the only modality of treatment available for HGD and EAC. Esophagectomy is definitive and requires no further surveillance as it removes the entire tissue at risk for development of cancer. However, there is considerable postsurgical morbidity and mortality. The mortality associated with esophagectomy is inversely related to the number of esophagectomies performed. In a Dutch study, based on the number of esophagectomies a year, hospitals were classified as low-volume centers (1–10 resections a year), medium-volume centers (11–20 resections a year) and high-volume centers (>50 resections a year). Hospital mortality at these centers was 12.1%, 7.5% and 4.9%, respectively [Van Lanschot *et al.* 2001]. The average hospital stay after esophagectomy is 10–14 days. The immediate complications include pneumonia, anastomotic leak, wound infection, arrhythmia and heart failure. Long-term complications include dysphagia, weight loss, gastroesophageal reflux, cough and dumping which may impair health-related quality of life [Viklund *et al.* 2006].

Intensive surveillance endoscopy

With this approach, patients with HGD undergo surveillance endoscopy every 3–6 months to evaluate for progression to EAC. Treatment, including endoscopic therapy or surgery, is offered when cancer is detected. In a report of 75 HGD patients who underwent intensive endoscopic surveillance, 12 developed EAC at the end of 7.3 years of surveillance. Eleven of the 12 patients were cured after they underwent surgery or ablative therapy while the 12th patient was lost to follow up and had unresectable tumor when he returned [Schnell *et al.* 2001]. In another report, 15 patients with unifocal HGD underwent intensive surveillance endoscopy. Four patients developed EAC at the end of 37 months of follow up, with one patient progressing to metastatic disease [Weston *et al.* 2000]. With the development of lower-risk endoscopic interventions, intensive surveillance may become less common given the risk of progressive disease.

Management of Barrett's esophagus with intramucosal carcinoma

According to the AJCC TNM classification system, T1 is the tumor which invades lamina propria (T1a) or submucosa (T1b). Barrett's with intramucosal carcinoma is classified as T1a [Greene, 2002]. Another classification system divides mucosal tumors into three types based

Table 3. Guidelines for management of intramucosal carcinoma of esophagus.

	National Comprehensive Cancer Network (NCCN) [Ajani <i>et al.</i> 2008]	European Society for Medical Oncology (ESMO) [Stahl and Oliveira, 2009]
Intramucosal carcinoma of esophagus (Tis and T1a)	Endoscopic mucosal resection or ablation or esophagectomy	Surgery is the treatment of choice in early cancer. Endoscopic mucosal resection is under investigation

on the depth of invasion [Shimada *et al.* 2006; Endo *et al.* 2000]. M1 lesions are limited to the epithelial layer (corresponds to carcinoma *in situ*). M2 lesions invade the lamina propria (corresponds to T1a). M3 lesions invade into but not through the muscularis mucosa (corresponds to T1a). Lesions invading the submucosa are further divided into Sm1, Sm2, and Sm3, which penetrate the proximal, intermediate, and deeper one-third of the submucosa, respectively.

In a study of 120 patients with pathologically proven HGD ($n=13$) or T1-adenocarcinoma ($n=107$), only one of the 79 T1m1-3/sm1 tumors (1%) showed lymph node metastases as compared with 18 out of 41 T1sm2-3 tumors (44%) [Westerterp *et al.* 2005]. In another study of 90 patients with resected T1 adenocarcinoma of esophagus, lymph node metastases were present in 12% of patients with intramucosal invasion and 44% patients with submucosal invasion. Endoscopic therapy is not indicated in patients with lymph node metastases. M1 and M2 lesions are not associated with lymph node metastases and hence may be amenable to endoscopic treatment [Liu *et al.* 2005; Westerterp *et al.* 2005]. M3 lesions with evidence of lymphatic invasion are most likely to harbor lymph node metastases [Eguchi *et al.* 2006]. Esophagectomy with therapeutic lymphadenectomy may be the preferred approach in these patients.

Endoscopic ultrasound (EUS) and computed tomography (CT) can be used for staging of EAC. EUS is used for locoregional staging while CT may demonstrate distant metastases. EMR can also be used for staging purposes. Esophageal specimens obtained by EMR had better interobserver agreement regarding neoplasia compared with biopsy specimens [Mino-Kenudson *et al.* 2007]. The guidelines about lesions suitable for EMR, described above for HGD, also apply for superficial EAC [Ell *et al.* 2000; Takeshita *et al.* 1997]. Histological evaluation of EMR specimens provides information about the depth of invasion of the

tumor, which may predict local lymph node metastases [Buskens *et al.* 2004].

The options available for endoscopic treatment are EMR and endoscopic ablation with PDT, RFA, or cryoablation (Table 3). Focal removal of HGD and intramucosal carcinoma (IMCA) by EMR without removing the remaining nondysplastic Barrett's epithelium can result in high rate of metachronous neoplasia of up to 35% [May *et al.* 2002]. Ablation of the remaining Barrett's mucosa can significantly reduce the rate of metachronous neoplasia or recurrence [Pech *et al.* 2008]. In a prospective study of 100 Barrett's patients with mucosal carcinoma, complete local remission was achieved in 99 of the 100 patients after 1.9 months (range 1–18 months) and a maximum of three resections. During a mean follow-up period of 36.7 months, recurrent or metachronous carcinomas were found in 11% of the patients, but successful repeat treatment with endoscopic resection was possible in all of these cases [Ell *et al.* 2007]. Studies using PDT for superficial carcinoma have had a small sample size. In a study of 37 patients with early adenocarcinoma treated with PDT, all patients achieved a complete response during a median follow-up period of 37 months; however there were 10 recurrences [Pech *et al.* 2005]. There have been no trial data reported for RFA in patients with intramucosal carcinoma. EMR coupled with ablative therapy may provide a superior means of managing high-risk Barrett's lesions and is being actively studied in a multi-institution setting. If endoscopic therapy is selected, focal resection of HGD and IMCA lesions by serial EMRs followed by endoscopic ablation of the nondysplastic Barrett's mucosa should be considered.

Conclusion

Barrett's esophagus affects a large number of patients with progression thought to occur in 0.5% of individuals per patient-year. Medical therapy can manage reflux symptoms but has not been proven to decrease progression. Endoscopic therapy may enable less-morbid management for

Barrett's lesions with dysplasia. The role for ablation in Barrett's patients without dysplasia is being examined in a multicenter setting. More aggressive mucosal resections have been reported in animal studies and are being evaluated in referral centers. As data becomes available, comprehensive management for Barrett's esophagus will likely involve multiple modalities with surveillance, ablation, mucosal resection, and esophagectomy being indicated in well defined subgroups. A multidisciplinary approach to the management of esophageal lesions may emerge where patients are offered cross-specialty tailored therapy for Barrett's related dysplasia and neoplasia.

Conflict of interest statement

None declared.

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