DECEMBER 2016
VOL. 16, ISSUE 7

IU Health Physicians

ADVANCED praxis CME

A JOURNAL OF CURRENT TRENDS IN MEDICINE FROM IU HEALTH PHYSICIANS, A PARTNERSHIP OF IU SCHOOL OF MEDICINE AND INDIANA UNIVERSITY HEALTH

CASE MANAGEMENT Endoscopic Diagnosis, Treatment, and Surveillance of Barrett's Esophagus

A 60-year-old, overweight (body mass index = 29), white male with a 30-pack-year tobacco history complains to his primary physician of symptoms of gastroesophageal reflux disease (GERD) that have persisted for more than five years. Until recently, his "heartburn" was relatively well controlled with over-the-counter agents, including a proton pump inhibitor (PPI; esomeprazole magnesium, 40 mg twice-daily), but it has now become more troublesome. (*continued on page 2*)

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OBJECTIVES
After reading this article, the reader should be able to:

- Describe the link between a) gastroesophageal reflux disease and Barrett's esophagus (BE), and b) BE and esophageal adenocarcinoma.
- Identify the endoscopic findings suggestive of BE.
- Discuss the limitations of BE screening.
- Summarize the role of endoscopy for the evaluation, treatment, and surveillance of BE and esophageal adenocarcinoma.
- Compare and contrast the endoscopic ablative therapies used in the management of BE.

Date of original release: December 2016
Date of expiration: December 2017

COMMERCIAL SUPPORT
This CME activity does not have any commercial support.

Given the duration of symptoms and diminishing response to treatment, the physician recommends esophagogastroduodenoscopy (EGD). The examination reveals salmon-colored mucosa extending 6 cm above the junction of the esophagus and stomach *(Figure 1)* together with an area of nodularity in the lower esophagus, both findings suspicious for Barrett's esophagus (BE). A biopsy is performed, confirming the diagnosis and identifying high-grade dysplasia in the nodular region. The patient is referred to Indiana University Health for management.

Overview of Barrett's Esophagus

An estimated six percent of US adults have BE,[1] a condition in which metaplastic columnar mucosa replaces the stratified esophageal squamous epithelium.[2] Metaplasia is often a response to chronic inflammation, with GERD linked to a 10 to 15 percent risk. Other risk factors for BE include hiatal hernia, age >50 years, male gender, white race, cigarette smoking, family history, and central obesity.

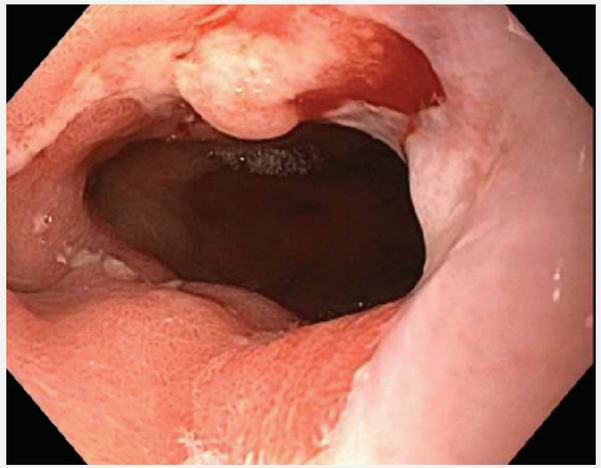
"The diagnosis of BE is suggested when endoscopy reveals columnar mucosa—which is salmon-colored and coarse, in contrast to the pearly white, glossy esophageal squamous mucosa—extending above the gastroesophageal junction and lining the distal esophagus," explains William Kessler, MD, associate professor of clinical medicine at Indiana University School of Medicine and gastroenterologist at IU Health. "The diagnosis is confirmed when biopsy specimens of the columnar mucosa show specialized intestinal metaplasia with its characteristic goblet cells."

Esophageal Adenocarcinoma and BE Screening

BE is a precursor to most cases of esophageal adenocarcinoma, a tumor that has increased in incidence more than seven-fold over the past several decades and is highly lethal, with five-year survival rates less than 18 percent.[3,4] In the United States, an estimated 17,000 new cases of esophageal adenocarcinoma will be diagnosed in 2016, and 16,000 people are expected to die from the disease.[5]

Figure 1. Characteristic appearance of BE

Salmon-colored mucosa and mild nodularity.



The metaplastic Barrett mucosa causes no additional symptoms, and the condition is typically discovered during endoscopy performed to evaluate GERD symptoms.[2] Patients with long-segment BE (≥3 cm) generally have severe GERD with erosive esophagitis and are at higher risk for malignancy as compared with short-segment BE (<3 cm). Short-segment BE is far more common, however, and affected individuals often have no symptoms of GERD. Consequently, current screening programs for BE, which require a history of GERD,* have only a limited impact on esophageal adenocarcinoma mortality in the general population. In fact, an estimated 95 percent of patients presenting with this form of cancer do not have a previous diagnosis of BE.[6]

Endoscopic Evaluation, Treatment, and Surveillance

Endoscopic Mucosal Resection

Longitudinal studies have shown that most cases of BE do not progress beyond nondysplastic intestinal metaplasia or transient low-grade dysplasia.[8,9] Yet when progression to high-grade dysplasia occurs, the risk of esophageal cancer may exceed 10 percent per patient-year,[10] thus justifying intervention in all individuals with BE. Endoscopic mucosal resection (EMR) involves the creation of a pseudopolyp and the use of a snare to remove Barrett's metaplasia down to the submucosa, which provides large tissue specimens that can be used to assess the lateral extension and depth of any neoplastic involvement and the adequacy of the resection. The snare is the recommended diagnostic and therapeutic endoscopic tool for nodular BE.

EMR has value for both diagnosis and staging and as a therapeutic procedure for removing Barrett's epithelium with and without neoplasia, according to Hala Fatima, MD, associate professor of clinical medicine at IU School of Medicine and gastroenterologist at IU Health. With regard to the former, a study comparing preoperative EMR findings with subsequent histologic examination of esophagectomy specimens for 25 patients with BE and high-grade dysplasia or adenocarcinoma found perfect agreement in tumor staging by EMR and surgery.[11] EMR is potentially curative for small, well-differentiated esophageal cancers that are limited to the mucosa *(T1a; Table 1)*, thereby avoiding the need for surgery.

"Endoscopic ultrasonography, an imaging modality for gastrointestinal cancer staging, may be added to determine the depth of cancer invasion and whether an entire lesion has been removed," Dr. Fatima adds.

Because of the high frequency of lymph node metastases in tumors involving the submucosa *(T1b; Table 1)*, endoscopic therapy is generally not considered definitive, and surgery is required.

TABLE 1. ESOPHAGEAL CANCER STAGING — PRIMARY TUMOR [19]

T0	No evidence of primary tumor
T_{is}	High-grade dysplasia
T1	Tumor invasion of lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invasion of lamina propria or muscularis mucosae
T1b	Tumor invasion of submucosa
T2	Tumor invasion of muscularis propria
T3	Tumor invasion of adventitia
T4	Tumor invasion of adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures (e.g., aorta, vertebra body, trachea)

**The American College of Gastroenterology recommends consideration of endoscopic screening for BE in men with chronic (>5 years) and/or frequent (weekly or more) GERD symptoms and ≥2 risk factors for BE. When BE is suspected, at least eight random biopsies are obtained whenever possible to maximize the yield of intestinal metaplasia on histology.[7]*

The patient undergoes repeat EGD with EMR of the area of nodularity *(Figure 2)*. Pathology from this 2 cm area reveals BE with high-grade dysplasia, no evidence of cancer, and no evidence of dysplasia at the cauterized margins *(Figure 3)*.

Endoscopic Ablative Therapy

At IU Health, most patients undergoing EMR for nodular lesions are subsequently treated with endoscopic ablative therapy, which uses radiofrequency or thermal energy to destroy any remaining Barrett's epithelium or esophageal cancer cells.

"Three to four rounds of ablative therapy separated by eight-week intervals are usually needed, although there is significant interpatient variability," says Dr. Kessler. "As is true for EMR, these are outpatient procedures performed under sedation. Patients go home on liquid pain medication, consume a liquid diet for 48 hours, and eat a soft diet for the next week."

Figure 2. BE pre-EMR

Pseudopolyp created with a band ligator.

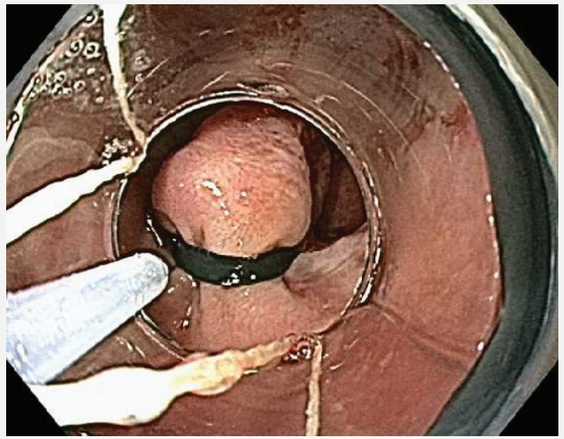
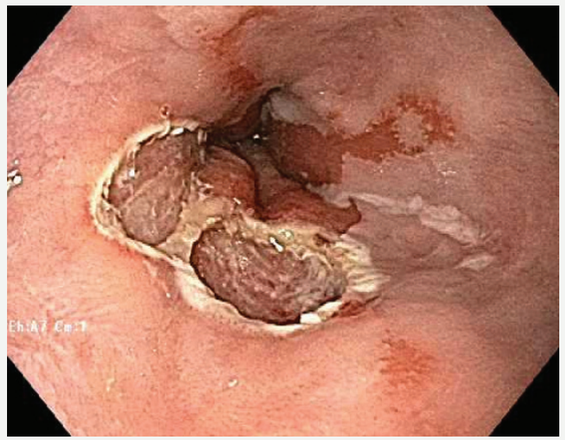


Figure 3. BE post-EMR

Defect after completion of the procedure.



"Daily PPIs must be taken for life to control acid exposure, and patients are advised to avoid GERD triggers, such as chocolate, caffeine, and alcohol, and to discontinue tobacco use if they are smokers," Dr. Fatima continues.

Radiofrequency ablation (RFA). IU Health gastroenterologists use RFA for most patients with BE because the technique has the most supporting evidence[12-14] and is technically straightforward. RFA provides high-frequency alternating current to the mucosa with the aim of ablating neoplastic cells to allow regrowth of normal squamous mucosa. Complete eradication of high-grade dysplasia has been reported in 80 to 100 percent of RFA-treated patients.[12,14,15]

Cryotherapy. Cryotherapy using liquid nitrogen freezes the BE tissue to a temperature of -175° C, fracturing cell membranes and denaturing proteins *(Figure 4)*. Initially, the treatment effect is minimal, but within days, the tissue sloughs off, ideally healing with neosquamous epithelium.[16] A review of the literature shows cryotherapy successfully eradicates high-grade dysplasia in 87 to 96 percent of patients.[17]

"IU Health gastroenterologists use cryotherapy after two or three unsuccessful attempts at radiofrequency ablation or in patients with deeper or poorly differentiated adenocarcinomas who are not candidates for surgery," says Dr. Fatima.

Argon plasma coagulation (APC). APC is a contact-free ablation method that is applied longitudinally or circumferentially. Sixteen-year follow-up of patients with BE treated with APC found sustained complete endoscopic eradication in 50 percent and partial eradication in 35 percent.[18] IU Health gastroenterologists use APC for patients who do not respond adequately to either RFA or cryotherapy.

The side effects associated with the three endoscopic ablative therapies are similar and include a low rate of stricture formation and, rarely, esophageal perforation.

"IU Health gastroenterologists use cryotherapy after two or three unsuccessful attempts at radiofrequency ablation or in patients with deeper or poorly differentiated adenocarcinomas who are not candidates for surgery," says Dr. Fatima.

Figure 4. BE immediately post-cryotherapy

Frozen esophagus.

The patient returns to IU Health eight weeks after EMR for four sessions of endoscopic ablative therapy that includes both RFA and cryotherapy. After the fourth treatment, no residual BE is identified on extensive mapping biopsies. The patient is scheduled for a repeat EGD every six months for the first year followed by annual endoscopy thereafter for lifelong surveillance.

"Mapping endoscopic biopsy, which involves four-quadrant biopsies every 1 cm for the entire length of the treatment area, is performed at each surveillance visit," Dr. Kessler describes. "Endoscopic ablative therapy eradicates BE and dysplasia in the vast majority of patients, but unless all metaplastic cells are destroyed, the mucosa may heal with an overlying layer of neosquamous epithelium that buries metaplasia in the lamina propria, where it is hidden from the endoscopist's view."

Although the frequency with which "buried metaplasia" occurs is unknown, it underscores the importance of ongoing surveillance to detect incipient signs of disease recurrence.

"IU Health has two nurses dedicated to the care of patients with BE, and they work closely with these individuals to ensure they return for their scheduled follow-up visits," says Dr. Fatima. "Nonetheless, most of our patients are extremely adherent to the surveillance regimen, recognizing that timely repeat ablative interventions can avoid the need for life-altering surgery."

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William Kessler, MD

Gastroenterologist, IU Health

Associate Professor of Clinical Medicine, IU School of Medicine

wkessle1@iuhealth.org

Dr. Kessler received his medical degree from the Loyola University Stritch School of Medicine in Chicago, IL and did his residency in internal medicine and completed a fellowship in gastroenterology and hepatology at IU School of Medicine. His clinical interests are focused on the diagnosis and treatment of GERD and BE and colorectal cancer screening.

Dr. Kessler is a fellow of the American College of Gastroenterology and co-investigator for four ongoing clinical trials at IU School of Medicine. He is the author of several peer-reviewed journal articles and serves as a reviewer for the journal *Diseases of the Esophagus*.

Hala Fatima, MD

Gastroenterologist, IU Health

Associate Professor of Clinical Medicine, IU School of Medicine

hfatima@iuhealth.org

Dr. Fatima received her medical degree from the Aga Khan University in Karachi, Pakistan and did her residency in internal medicine and completed a fellowship in clinical gastroenterology at IU School of Medicine. Her clinical interests are focused on BE surveillance and treatment, management of early esophageal cancer, luminal gastroenterology, colorectal cancer screening, and large polyp resection.

Dr. Fatima is a member of the American College of Gastroenterology and the recipient of an endoscopic research award from the American Society of Gastrointestinal Endoscopy. She is the author of several peer-reviewed journal articles and has lectured extensively in the United States and internationally.

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340 West Tenth Street, FS 5100
Indianapolis, IN 46202

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Dr. William Kessler, featured physician: wkessle1@iuhealth.org

Dr. Hala Fatima, featured physician: hfatima@iuhealth.org

Kara Anderson, publisher of *Advanced Praxis*: advancedpraxis@iuhealth.org