

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

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## Endoluminal Therapies for Barrett's Esophagus and Dysplasia

Gregory Ginsberg, MD  
Physician  
Director, Endoscopic Services  
Hospital of the University of Pennsylvania

### G&H What is Barrett's esophagus and what is its clinical significance?

**GG** Barrett's esophagus is a condition wherein the normal squamous mucosa of the esophagus has been replaced by specialized intestinal metaplasia. This is thought to be in response to chronic acid injury to the esophagus. This condition is macroscopically recognizable at endoscopy, but is confirmed with biopsies demonstrating a histopathology of glandular epithelium with goblet cells.

Barrett's esophagus is associated with an increased risk of developing esophageal adenocarcinoma, the cancer type with the fastest increasing incidence rates in the United States. In progressing from the precursor condition to cancer, a gradation of changes occurs known as dysplasia. Surveillance is indicated for patients with Barrett's esophagus; tissue sampling is employed to detect the development of dysplasia and carcinoma.

### G&H What is the risk of patients with Barrett's esophagus developing cancer, and how is this risk monitored?

**GG** Advanced carcinoma is uniformly fatal, and so it is important to try to identify patients with precancerous or early cancerous lesions that are curable. The standard practice has been for patients with high-grade dysplasia to undergo operative esophagectomy. This approach was based on older surgical data showing that among patients with long-segment Barrett's esophagus with high-grade dysplasia based on endoscopy, approximately 30–50%

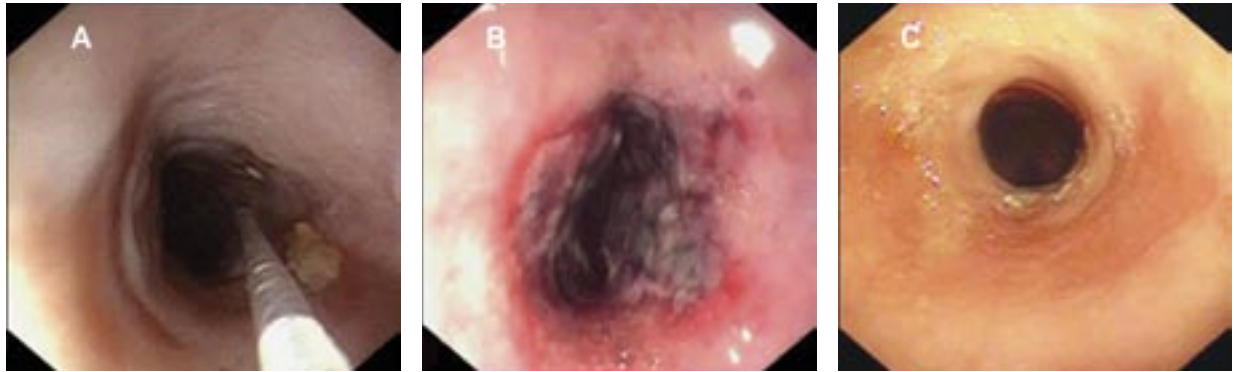
had carcinoma detected within the resected specimen. However, modern endoscopic inspection and biopsy techniques markedly reduce the risk of unrecognized carcinoma developing. In addition, studies measuring the risk of carcinoma among patients with high-grade dysplasia who undergo observational management, remaining on acid suppression therapy, have found that 16–30% develop apparent carcinoma over 7–8 years.

Most Barrett's esophagus-associated cancers are diagnosed at the index endoscopy. For all the others, we do not currently have the ability to predict which patients are likely to develop cancer. However, through surveillance and early detection, while the disease remains limited to the mucosa, cures can be achieved by eradicating the mucosal-based disease with endoluminal therapies. This is particularly attractive for older patients and those with comorbidities that make operative esophagectomy a less attractive option

### G&H What are the different kinds of endoluminal therapies currently being used?

**GG** Endoluminal therapies fall into two broad categories: ablation and resection. Ablation techniques include contact and noncontact thermal therapies. The contact thermal therapies include multipolar electrocautery devices, as well as radiofrequency (Stellartech Research Coagulation System, Barrx). Noncontact thermal therapies include laser and argon plasma beam coagulation. Photodynamic therapy (PDT) is a laser light-mediated means to achieve cytotoxic mucosal ablation. Lastly, cryotherapy has been recently described for Barrett's esophagus ablation as well.

In addition to the ablative approaches, there is wide-area endoscopic mucosal resection and endoscopic submucosal dissection. The major advantage of endoscopic mucosal resection over ablation therapies is that the resected specimen is available for the pathologist, who can confirm or refute the presence of high-grade dysplasia or carcinoma, and offer pathologic prognostic predictors, such as the presence or absence of cancer, the degree of differentiation, the presence or absence of lymphovascular invasion, and the deep and lateral margins.



**Figure 1.** Long-segment Barrett's esophagus with multifocal high-grade dysplasia with bare fiber cylindrical diffuser catheter for photodynamic therapy light application (A); at 48 hours (B) and 3 months (C) after photodynamic therapy.

All of these various approaches are only effective in achieving resquamation in the presence of an acid-free environment. Patients must be acid controlled either with pharmacotherapies, specifically proton pump inhibitors, or an antireflux procedure, most often a Nissen fundoplication.

**G&H** What considerations are needed when deciding which technique to use?

**GG** In general, my approach is to use multimodal endoluminal therapy with a combination of these techniques. Different treatments can be selected based on the characteristics of individual patients. For example, patients who have Barrett's esophagus with focal nodularity should be treated with endoscopic mucosal resection first so that the presence of invasive carcinoma can be determined. Long-segment Barrett's esophagus with high-grade dysplasia might best be treated with PDT because it treats a length of tubular esophagus in a relatively uniform circumferential manner. Contact and noncontact thermal therapies may be best applied in focal residual Barrett's esophagus after endoscopic mucosal resection or PDT. Radiofrequency was only recently cleared for the ablation of nondysplastic Barrett's esophagus and its efficacy in limiting dysplasia remains promising but as yet unproven.

PDT is approved by the US Food and Drug Administration for the treatment of Barrett's esophagus and high-grade dysplasia based on the PHOBAR-II trial, published in *Gastrointestinal Endoscopy* by Overholt and colleagues. There remains limited experience with wide application of this technique. It is important to be aware that ineffective therapy may lead to unrecognized cancer progression despite careful surveillance and efforts to eradicate disease.

**G&H** How does PDT work?

**GG** PDT employs the systemic administration of a photosensitizing agent that is selectively retained by Barrett's mucosa, which is then exposed under endoscopic guidance to laser light of a specific wavelength (Figure 1). This light triggers a photochemical reaction that results in selective cell death. With this technique, the drug dose and light dose are predetermined in order to enhance efficacy.

**G&H** What are potential concerns with using PDT for Barrett's esophagus?

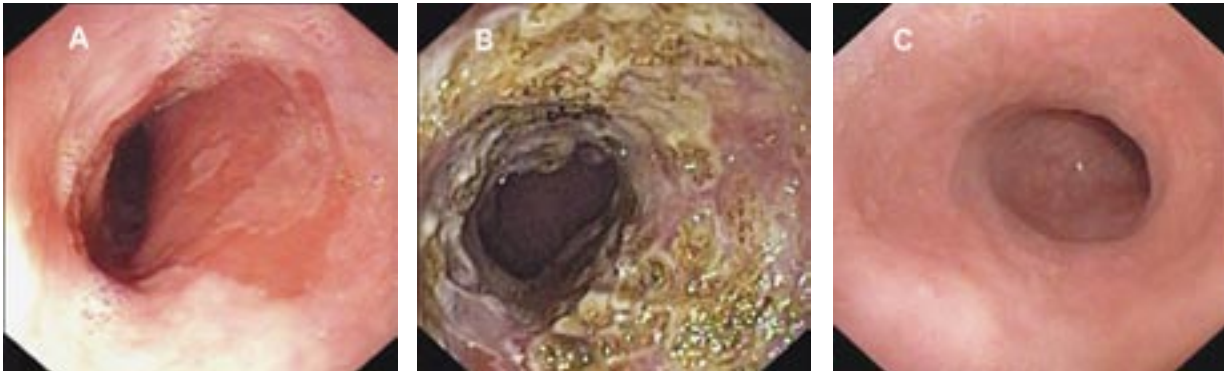
**GG** A concern with endoluminal ablation therapy is the condition referred to as "buried" Barrett's esophagus, in which ablation therapy promotes regeneration of surface squamous epithelium, but does not completely eradicate all subsurface Barrett's metaplasia, and foci of "buried" specialized intestinal metaplasia persist. As such, the macroscopically recognizable marker for surveillance has been eliminated, but the potentially precancerous condition persists beneath a normal-appearing mucosal surface. Skin photosensitivity to natural sunlight may persist for up to 4–6 weeks after PDT. Esophageal stricture may occur in up to 20–30% of patients treated with PDT. Experience and improved techniques are minimizing these risks.

**G&H** Is this situation a concern with endoscopic mucosal resection?

**GG** The possibility of "buried" Barrett's esophagus appears to be less of a concern with endoscopic mucosal resection because the tissue is resected down to the muscle layer. When wide-area endoscopic mucosal resection encompasses more than 50–75% of the circumference the risk of stricture formation is increased.

**G&H** How does argon plasma beam coagulation work?

**GG** Argon plasma beam coagulation uses a probe that directs electrically charged argon plasma to the mucosal



**Figure 2.** Short-segment Barrett's esophagus with high-grade dysplasia (A) treated with argon plasma beam coagulation ablation (B) and at 3-month follow-up (C).

surface, allowing for a relatively well-controlled depth of coagulative necrosis as well as the ability to “paint” reasonably wide areas during a single session (Figure 2).

While this technique has proved challenging in the confines of the tubular esophagus, in most cases it has replaced thermal laser therapy as it is safer and easier to use and is now fairly well established. Contact and non-contact coagulation therapies generally achieve a less uniform ablation and are best applied for spot treatment of focal residual Barrett's esophagus adjunctive to PDT and/or endoluminal resection.

**G&H** Could you describe radiofrequency ablation?

**GG** The radiofrequency ablation technique involves a balloon-tipped catheter with a multipolar series of electrical plates on the surface extending circumferentially and up to 3 cm in length. A momentary application of radiofrequency energy achieves coagulative necrosis in a fairly uniform manner circumferentially and to a preprogrammed depth of tissue. Preliminary data suggest that this technique is safe and effective for the ablation of nondysplastic Barrett's esophagus.

**G&H** What is the benefit of having a predetermined depth?

**GG** The idea behind developing a technique to work at a predetermined depth is to reliably destroy the pluripotent stem cell in the basement membrane of the mucosa while avoiding injury to the muscularis propria layer and thus retard stricture formation. When the cancerous or precancerous tissue is destroyed and the remaining environment is acid free, normal squamous mucosa returns.

**G&H** In what situations would cryotherapy be used?

**GG** The use of cryotherapy in Barrett's esophagus has been reported within the past 6 months. Investigators at Walter Reed Medical Center have reported on a through-the-scope probe that can deliver liquid nitrogen to the surface, freezing the tissue and resulting in tissue destruction to a relatively uniform depth. Because cryotherapy is a noncontact technique (in this way like argon plasma beam coagulation) it can be used to treat broad areas of the surface in a single session.

**G&H** What is the status of endoluminal therapies in terms of their broad application for the treatment of Barrett's esophagus?

**GG** As we acquire experience and long-term data, these techniques will gradually enter more expanded practice. At the present time, they should be limited to specialty centers, until evidence supports their adoption in broader practice.

**Suggested Reading**

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