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Review Article

Endoscopic therapy for Barrett's esophagus

Nicholas J. Shaheen

Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

Abstract

Barrett's esophagus (BE) is the precursor lesion to esophageal adenocarcinoma. This cancer has undergone a rapid increase in incidence in Western societies in the last 30 years. Current practices seek to lower the risk of death from this cancer by performing screening upper endoscopy on those with chronic reflux symptoms, and then surveillance upper endoscopy on those found to have BE at periodic intervals. While this approach is intuitively appealing, no data substantiate a decreased cancer risk with these practices, and substantial issues limit the effectiveness of this approach. This article outlines the current approaches to BE, their shortcomings, and presents data supporting the use of endoscopic therapy for subjects with BE and dysplasia. A significant and growing literature supports the use of endoscopic therapy in BE, and this approach, combined with improved risk stratification, may improve our care of subjects with BE.

Key words

Gastroesophageal reflux, barrett's esophagus, dysplasia, surveillance endoscopy, radiofrequency ablation

Background and Epidemiology

In stark contrast to the recent progress in other solid tumors, incidence and death rates from esophageal adenocarcinoma continue to rise at a rapid pace. There has been a 300–500% increase in the incidence of esophageal adenocarcinoma from the 1970s to the 1990s[1] and a near-parallel increase in mortality [Figure 1], underscoring the need for new and effective prevention and treatment strategies for this lethal cancer.

Esophageal adenocarcinoma is thought to develop through a series of metaplastic, then dysplastic, changes of the esophageal mucosa.[2] Chronic gastroesophageal reflux (GERD) precipitates a metaplastic change from the normal squamous epithelium to a more acid-resistant columnar histology.[3] When this columnar epithelium contains goblet cells, it is termed *specialized* or *intestinalized metaplasia*. When endoscopically evident, columnar metaplasia with goblet cells found in the esophagus is termed *Barrett's esophagus* (BE).[4]

BE is an extremely common condition present in approximately 10% of subjects with chronic GERD.[5] Since 10–20% of adult Americans have at least weekly symptoms of GERD, the number of cases of BE in the USA is thought to be >2 million subjects.[2,6,7] Many subjects who have BE are never diagnosed as having the condition. Once present, BE does not generally spontaneously regress; barring an intervention, the patient will have BE for life.

Most subjects harboring BE will not progress to esophageal carcinoma. However, in a proportion (0.5%/year) of these subjects, the metaplastic tissue will undergo a series of dysplastic steps from low-grade dysplasia (LGD) to high-grade dysplasia (HGD),[8] culminating in the development of esophageal adenocarcinoma.[9,10]

Given the poor prognosis of cancer diagnosed at the point of symptoms, current interest and effort is directed primarily toward early detection.[11] Current strategies for prevention of esophageal adenocarcinoma focus on endoscopic screening, with endoscopic surveillance for patients in which Barrett's epithelium has been detected.[12] In the approach most commonly used by gastroenterologists in the USA, subjects with chronic heartburn are offered screening upper endoscopy to assess the presence of BE. Patients found on endoscopy to harbor BE are then enrolled in endoscopic surveillance programs consisting

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Address for correspondence:
Dr. Nicholas Shaheen, MD, MPH, CB #7080, 724 Burnett-Womack Building, University of North Carolina, Chapel Hill, NC 27599-7080, USA.
E-mail: nicholas_shaheen@med.unc.edu

of periodic endoscopy at fixed intervals that depend on the presence or absence of epithelial dysplasia.[4] In the current American College of Gastroenterology guidelines [Table 1], subjects with BE and no dysplasia undergo endoscopy with biopsy every 3 years. Subjects with BE and LGD are to have a single follow-up endoscopy at 6 months, then yearly thereafter. Subjects with BE and HGD have three options: Esophagectomy, endoscopic ablative therapy, or intensive endoscopic surveillance (initially at 3-month intervals for at least a year).

Endoscopic Surveillance is an Inefficient, Cost-ineffective Practice

Although intuitively logical, surveillance endoscopy for subjects with BE has several shortcomings. Most importantly, no direct evidence demonstrates the practice to be effective in preventing death from adenocarcinoma. While cohort studies demonstrate that subjects with cancers detected as part of screening and surveillance programs present with earlier stage disease and less nodal involvement, such data are subject to lead-time and length bias.[12-14] Surveillance endoscopy is also an expensive procedure (with a cost of $2000 or more in some centers). Because the yield of any given procedure is low, cost-effectiveness studies of endoscopic surveillance in BE suggest the practice is cost-ineffective, associated with hundreds of thousands of dollars per life-year saved.[15] This cost does not include the substantial indirect costs borne by the patient, including absence from work for both the patient and an accompanying individual to care for the patient after the procedure. Also, because endoscopy must be repeated periodically, a patient diagnosed at age 40 may be subjected to 15–20 such exams during his/her lifetime. In addition, interpretation of serial histological specimens is highly subjective, and misclassification of degrees of dysplasia is commonplace.[16,17] Progression to cancer between endoscopies is possible, and intervention after the development of HGD or cancer is not assured of being effective. The usual intervention for progressors, esophagectomy, can be a morbid procedure, with significant perioperative morbidity and mortality.[18] The psychological stress associated with these examinations is not well described, but appears substantial.[19,20] Although endoscopists heavily endorse and perform surveillance endoscopy, cancer rates continue to increase in the USA.[21,22]

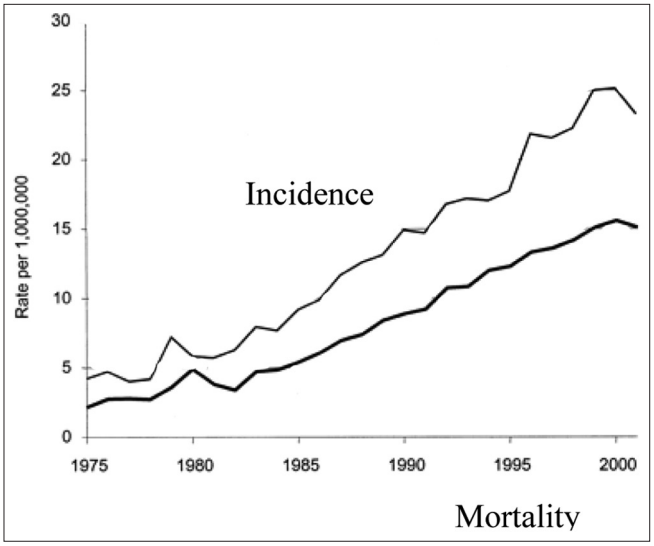

Figure 1: Incidence (top curve) and mortality (lower) from esophageal adenocarcinoma (data from Pohl H *et al.*, J Natl Cancer 2005;97:147.)

Endoscopic Ablation: A Rapidly Evolving Alternative to Esophagectomy in Barrett's Esophagus

Esophagectomy is a morbid and sometimes mortal surgical procedure. The morbidity rate of the procedure is as high as 50% in some series: Patients may suffer postoperative pneumonia, wound dehiscence and infection, and bleeding, among other complications.[23] While mortality rates in select high volume centers are low, nationwide 30-day mortality rates after esophagectomy are >10% and are strongly associated with the operator's surgical volume.[18] Esophagectomy can be further complicated by the fact that esophageal adenocarcinoma presents relatively late in life. In most series, subjects with incident adenocarcinoma are near or above 70 years of age, at which age many patients have comorbid conditions such as heart disease or pulmonary conditions that complicate or even preclude surgical intervention.[24,25]

Because of these difficulties, centers specializing in endoscopy sought to develop techniques for endoscopic ablation, designed to lead to eradication of BE, in the hope that destruction of the precancerous tissue would lead to reduced cancer risk. All endoscopic ablative therapies for BE rely on the same seminal observation: Destruction of BE tissue in an acidic

Table 1: American college of gastroenterology is a proper noun and should be capitalized

Dysplasia	Documentation	Follow-up
None	Two EGDs with biopsy within 1 year	Endoscopy every 3 years
Low grade	• Highest grade on repeat EGD • with biposies within 6 months • Expert pathologist confirmation	1 year interval until no dysplasia × 2
High grade	• Mucosal irregularity • Repear EGD with biopsies to rule out EAC • within 3 months • Expert pathologist confirmation	ER • Continued 3 month surveliance or intervention based on results and patient

*EGD: Esophagogastroduodenoscopy, ER: Endoscopic resection, EAC: Esophageal adenocarcinoma

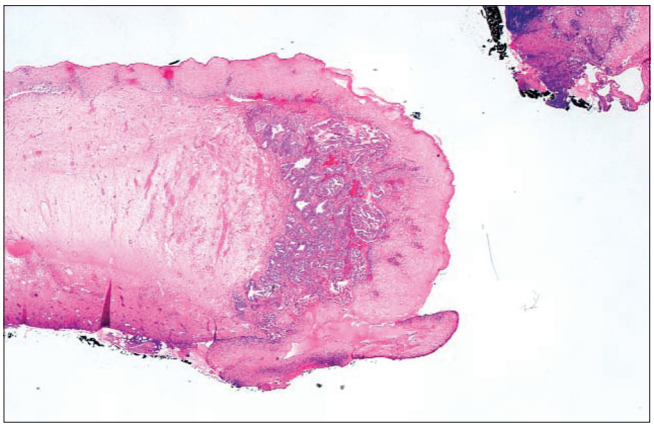

Figure 2: "Buried Glands," courtesy of John Goldblum, MD

milieu generally leads to the regeneration of squamous, not columnar tissue.[26] Therefore, an ablative therapy, coupled with vigorous acid suppression with proton pump inhibitors, often results in reversion of BE to squamous tissue. This regenerated squamous epithelium, termed *neosquamous epithelium*, appears to have the characteristics of normal squamous tissue.

Early attempts at endoscopic ablative therapies suffered from several shortcomings which limited their utility. Methods like electrocoagulation or argon plasma coagulation required mucosal contact with a small probe to induce tissue damage.[26,27] The prolonged procedure times necessary to treat subjects with long segments of disease limited the appeal of such approaches. Other therapies, such as photodynamic therapy, or YAG laser destruction, proved unreliable and sometimes caused deep tissue injury.[28,29] Because deep circumferential tissue injury commonly results in esophageal stricture, such approaches were limited by the high incidence of strictures (as high as 36% in subjects undergoing photodynamic therapy who required two treatments).[30] Perforation is a recognized, but infrequent, complication of all ablative therapies. Conversely, undertreatment of the tissue could result in a situation known as "buried glands" [Figure 2], where a seemingly normal veneer of neosquamous epithelium in an ablated area hides the underlying residual BE, which can no longer be identified by the endoscope. Adenocarcinoma developing in such concealed BE has been reported.[31] Also, subjects undergoing photodynamic therapy were at high risk for photosensitivity due to sunlight exposure, requiring them to stay inside for weeks following therapy.[28]

How Effective is Ablative Therapy for Barrett's esophagus?

Multiple studies have attempted to describe the utility of ablative therapy using different treatment modalities. Older modalities, such as multipolar electrocoagulation and argon plasma coagulation, were demonstrated to lead to some ingrowth of neosquamous epithelium; however, complete reversion of long segments of BE was difficult and time consuming, owing to the small surface area treated with a single application of the device and the variability in the energy delivered based on probe placement and other factors.[26,27,32-36]

Photodynamic therapy is able to treat much longer segments of BE.[28,37-40] Most data with this technology show that dysplasia may be downstaged, but that a large proportion of subjects treated with photodynamic therapy (PDT) are left with at least some residual metaplastic tissue. With respect to cancer prevention, Overholt and colleagues demonstrated that subjects with HGD undergoing PDT had an approximately 50% decrease in the incidence of adenocarcinoma compared to untreated controls (28% vs. 13%, $P<0.05$).[30] However, in that study, the stricture rate in the PDT group was 36% overall and increased as the number of sessions of PDT required increased. PDT strictures may be densely fibrotic and resistant to dilation, and 11% of subjects who developed a stricture in this trial required more than 10 dilations before resolution of the dysphagia. Additionally, only 52% of the treated subjects had complete endoscopic and histological remission of the disease.

Radiofrequency ablation also has the capability of treating long segments of BE. Multiple cohort studies of subjects with non-dysplastic BE show that high rates of complete reversion of neosquamous epithelium are attainable with this modality.[41,42] While rates of complete reversion to neosquamous epithelium may be slightly lower in dysplastic BE, rates of complete reversion for LGD and HGD of greater than 90% and 80%, respectively, have been reported.[43] The side effect profile of Radio frequency ablation Radio frequency ablation (RFA) appears superior to that of PDT. While almost all subjects experience some chest pain after therapy, these symptoms are manageable with oral analgesics on an outpatient basis in the vast majority of subjects. The reported stricture rate in series of RFA varies between 0 and 7%, and these strictures are generally easily amenable to dilatation.[41,44] Because of the high rate of reversion to neosquamous epithelium, the relatively low rate of stricturing, the lack of photosensitivity, and the reduced cost associated with RFA compared to PDT, RFA has gained popularity as a favored modality for BE ablation.

Endoscopic cryotherapy with liquid nitrogen (CSA Medical, Baltimore, MD, USA) has been demonstrated in preliminary data to induce reversion to neosquamous epithelium.[45,46] The safety profile and efficacy in cancer prevention are currently not well described. Head-to-head comparisons of RFA with other forms of ablation do not currently exist. However, comparison of data from the randomized controlled trial of PDT by Overholt *et al.* with these results, as well as assessment of previous trial data from other forms of ablation, demonstrates that RFA compares favorably with competing strategies, being both more effective and as well or better tolerated.[27,30,35,47] Although a relatively nascent technology, durability data are encouraging, with little or no reversion to BE at a mean of 30 months after treatment.[48]

Advanced Imaging in Barrett's Esophagus

Several techniques have shown promise in increasing the yield of upper endoscopy for detecting dysplasia in the setting of BE. These include vital staining, autofluorescence, confocal microscopy, optical coherence tomography, and narrow band imaging.[49-52] Because our current standard of care, random biopsies with surveillance endoscopy, only hits dysplasia by chance, any modality that might increase yield by targeting biopsies would be a welcome addition to the armamentarium.

Multiple modalities have been suggested. Narrow band imaging with or without the addition of magnification endoscopy may improve on our current ability to detect dysplasia. A recent meta-analysis of narrow band imaging in conjunction with magnification endoscopy demonstrated a 96% sensitivity and a 94% specificity for the diagnosis of HGD.[53] Various endoscopic confocal endoscopy technologies are also under development and may allow for real-time identification of dysplasia. If these areas can be identified during endoscopy, they may be treated during that procedure, streamlining care of the patient with BE and cutting costs. Currently, no imaging modalities beyond white light endoscopy and narrow-band imaging have gained wide usage, although several modalities have been reported to have promising results. Importantly, any new modality used will need to provide reproducible, interpretable images that increase the yield of screening and surveillance examinations, a standard not easily met.[54]

Risk Stratification in Barrett's esophagus

Our current screening and surveillance efforts are hampered by inadequate risk stratification – we do not know who of the large group with GERD symptoms will have BE and who among the large group of BE patients will develop cancer. Additionally, we know that 40% or so of those who develop esophageal adenocarcinoma will not have significant pre-existing GERD symptoms. Therefore, we have been largely frustrated in making headway with this disease.

One hope for the future is improved risk stratification. If biomarkers could be developed which could tell us who among those with BE would be most likely to progress to cancer, we could focus efforts on that subgroup and avert waste of resources. Our only currently used biomarker, the degree of dysplasia in biopsies, is poorly sensitive and specific. Although no biomarkers beyond this are currently commonly used, efforts to develop such markers are progressing in multiple centers.

So, How to Manage the Patient with Barrett's esophagus?

After considering the efficacy of ablative therapy, the risks of the ablation procedures, and the natural history of untreated BE, it is possible to draw some conclusions about the care of subjects with BE. First, given the high rate of success, the low rates of complication, and the encouraging data on reduction of cancer risk, ablative therapy seems to be an appropriate and effective alternative to either intensive endoscopic surveillance or surgical esophagectomy for the subject with HGD. Such subjects are at prohibitively high risk of progression to cancer to advocate watchful waiting as a standard approach, and two randomized controlled trials now substantiate ablative therapy as a superior approach to intensive endoscopic surveillance in such patients. Esophagectomy is a procedure associated with considerable morbidity; major complication rates in excess of 50% have been reported, and clinically significant mortality rates are seen as well, especially in low-volume centers.[18] While no head-to-head comparison of the two management strategies is available, comparison of outcomes of cohorts treated with each modality demonstrates similar cancer-specific and all-cause mortality rates between surgical and endoscopic management with ablative therapy.[55] For that reason, ablative therapy should be considered a viable treatment option for all subjects with HGD. However, this should only be undertaken in the absence of mucosal abnormalities, which should be removed by endoscopic mucosal resection prior to considering ablation.

Is ablation appropriate for LGD? Because of the absence of direct data substantiating a decrease in cancer risk in subjects with LGD, we do not currently know whether ablative therapy is superior to endoscopic surveillance in this patient population. Our understanding of progression rates in LGD is incomplete, with heterogeneity in the literature and some groups reporting high rates of progression. Some indirect data suggest that ablation could be helpful, including high rates of complete reversion to neosquamous epithelium, as well as cost-effectiveness modeling.[56] Given the inconclusive nature of the data on ablation in LGD, a shared decision-making model is especially important for physicians and patients contemplating ablation for LGD.

In subjects with non-dysplastic disease, risks of progression are lower still. Similar to the situation with LGD, evidence supporting any endoscopic intervention is indirect. High rates of durable regression can be obtained, but the impact of these rates on long-term cancer risk is not known. Decision analysis modeling again suggests that the intervention may be cost-effective.[56] Given the large numbers of subjects with non-dysplastic disease and the accumulated data substantiating a low risk of progression in this lesion, routine ablative therapy in all subjects with non-dysplastic disease seems unduly aggressive with our currently available data. As translational scientists work toward better risk stratification in subjects with BE, a subgroup of subjects at higher risk for progression in this pool may be identified, increasing the value of the intervention and decreasing the number of patients with BE requiring therapy.

Conclusions

Ablative therapy for BE has led to a wave of enthusiasm amongst endoscopists. Newer modalities are able to treat large areas of disease and are associated with high rates of complete reversion to squamous epithelium. The impact of these methods on the subsequent risk of cancer is less well understood; however, some direct and indirect data support the idea that ablation is associated with a substantial reduction in cancer risk in the dysplastic population. Of the currently available technologies, radiofrequency ablation appears to be associated with the highest rate of reversion to squamous epithelium and has a favorable side effect profile when compared to photodynamic therapy. Some data also support durability of this reversion.

Who to treat? With respect to HGD, ablation appears to be superior to intensive endoscopic surveillance with respect to cancer incidence. While no study directly compares esophagectomy to ablative therapy, the less-invasive nature of the latter, combined with the high success rates in epithelial reversion, argues that ablation is a reasonable alternative to surgery. In the settings of LGD and non-dysplastic disease, no direct data substantiate a decreased risk of cancer and the rationale for ablation involves a surrogate marker – the removal of BE should presumably result in diminished cancer risk. The benefit of this intervention should be greater in LGD than in non-dysplastic BE, at least to the extent at which the risk of cancer is higher in LGD. However, cancer risk in LGD is unclear at the present time. Until such time that several key variables are better described and more data are available, the utility in non-dysplastic disease will be incompletely understood, and the decision to treat in these settings will require a shared decision-making model.

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