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REVIEW

Controversies in Barrett Esophagus

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Abstract

Barrett esophagus develops when metaplastic columnar epithelium predisposed to develop adenocarcinoma replaces esophageal squamous epithelium damaged by gastroesophageal reflux disease. Although several types of columnar metaplasia have been described in Barrett esophagus, intestinal metaplasia with goblet cells currently is required for a definitive diagnosis in the United States. Studies indicate that the risk of adenocarcinoma for patients with nondysplastic Barrett esophagus is only 0.12% to 0.38% per year, which is substantially lower than previous studies had suggested. Nevertheless, the incidence of esophageal adenocarcinoma continues to rise at an alarming rate. Regular endoscopic surveillance for dysplasia is the currently recommended cancer prevention strategy for Barrett esophagus, but a high-quality study has found no benefit of surveillance in preventing deaths from esophageal cancer. Medical societies currently recommend endoscopic screening for Barrett esophagus in patients with multiple risk factors for esophageal adenocarcinoma, including chronic gastroesophageal reflux disease, age of 50 years or older, male sex, white race, hiatal hernia, and intra-abdominal body fat distribution. However, because the goal of screening is to identify patients with Barrett esophagus who will benefit from endoscopic surveillance and because such surveillance may not be beneficial, the rationale for screening might be made on the basis of faulty assumptions. Endoscopic ablation of dysplastic Barrett metaplasia has been reported to prevent its progression to cancer, but the efficacy of endoscopic eradication of nondysplastic Barrett metaplasia as a cancer preventive procedure is highly questionable. This review discusses some of these controversies that affect the physicians and surgeons who treat patients with Barrett esophagus. Studies relevant to controversial issues in Barrett esophagus were identified using PubMed and relevant search terms, including *Barrett esophagus*, *ablation*, *dysplasia*, *radiofrequency ablation*, and *endoscopic mucosal resection*.

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Studies suggest that 2% to 7% of adults in Western countries have Barrett esophagus, the condition in which a metaplastic columnar epithelium predisposed to malignancy replaces the stratified squamous epithelium that normally lines the distal esophagus.[1,2] Barrett esophagus and its underlying condition, gastroesophageal reflux disease (GERD), are the major risk factors for esophageal adenocarcinoma, a tumor whose frequency has increased more than 7-fold during the past several decades in the United States.[3,4] The history of Barrett esophagus has been one of persistent controversy and disagreement among experts regarding the pathogenesis, the management, and even the definition of this common disorder.[5] The recent availability of endoscopic techniques for eradicating Barrett metaplasia has intensified some of these debates. This review highlights some of the key current controversies confronted by the physicians and surgeons who treat patients with Barrett esophagus. To identify relevant articles, we performed a literature search of PubMed for reports published between 1990 and December 2013 using the keywords *Barrett esophagus*, *ablation*, *radiofrequency ablation*, *dysplasia*, and *endoscopic mucosal resection*. Reports were reviewed by both authors to identify those relevant to the controversies chosen for discussion in this article.

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CONTROVERSY 1: THE DEFINITION OF BARRETT ESOPHAGUS—ARE GOBLET CELLS REQUIRED FOR THE DIAGNOSIS?

Barrett esophagus develops as a consequence of GERD, which damages the squamous epithelium of the distal esophagus while stimulating healing through columnar metaplasia rather than through the regeneration of more squamous cells.[4] Endoscopically, the metaplastic columnar epithelium has a characteristic salmon-pink color and coarse texture that are readily distinguished from the pale, glossy appearance of the esophageal squamous epithelium (Figure 1). Authorities generally agree that the diagnosis of Barrett esophagus requires the following: (1) the endoscopic finding that columnar epithelium extends above the gastroesophageal junction (GEJ) to line the distal

ARTICLE HIGHLIGHTS

- US medical societies require intestinal metaplasia with goblet cells in esophageal biopsy specimens as a diagnostic criterion for Barrett esophagus.
- The risk of esophageal adenocarcinoma for patients with nondysplastic Barrett esophagus ranges from 0.12% to 0.38% per year.
- Endoscopic screening for Barrett esophagus is recommended currently for patients with multiple risk factors for esophageal adenocarcinoma, including chronic gastrointestinal reflux disease, age of 50 years or older, male sex, white race, hiatal hernia, elevated body mass index, intra-abdominal body fat distribution, nocturnal reflux symptoms, and tobacco use.
- Despite the lack of proof that endoscopic surveillance for Barrett esophagus reduces mortality from esophageal cancer or is cost-effective, we still recommend the regular endoscopic surveillance for patients with Barrett esophagus endorsed by the gastroenterology societies.
- Radiofrequency ablation of high-grade dysplasia in Barrett esophagus has been reported to prevent its progression to cancer in a randomized controlled trial.
- Major issues that must be resolved before recommending radiofrequency ablation to treat nondysplastic Barrett esophagus include the importance of subsquamous intestinal metaplasia and the frequency and extent with which Barrett metaplasia recurs after eradication.
- Ongoing research that might help to address some of these controversies includes investigations on the use of molecular markers, advanced endoscopic imaging techniques, and risk stratification models to quantify cancer risk for individual patients with Barrett esophagus.

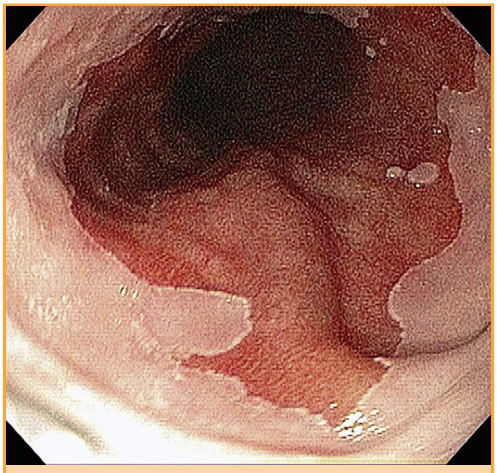

FIGURE 1. Endoscopic image of Barrett esophagus showing salmon-pink–colored mucosa in the distal esophagus extending up from the gastroesophageal junction.

esophagus and (2) the histologic finding of columnar metaplasia in esophageal biopsy specimens. However, authorities disagree on the type of columnar metaplasia that establishes the diagnosis of Barrett esophagus. Specifically, they disagree about whether the finding of goblet cells is a requisite diagnostic criterion.[6]

Goblet cells, normally found in the intestines, usually can be identified readily by their characteristic histologic features in biopsy specimens stained with hematoxylin-eosin (Figure 2). In biopsy specimens of the esophagus or stomach, the goblet cell is a marker for intestinal metaplasia.[7] In Barrett esophagus, intestinal metaplasia with goblet cells has been called *specialized intestinal metaplasia* or *specialized columnar epithelium*. Early studies on Barrett esophagus established that specialized intestinal metaplasia is the esophageal epithelial type usually associated with adenocarcinoma, and, for the past several decades, most studies on Barrett esophagus have used specialized intestinal metaplasia as an entry criterion.[6] Thus, most of what is known about cancer risk in Barrett esophagus is on the basis of studies that included patients with intestinal metaplasia either primarily or exclusively.

Cardiac epithelium, which has traditionally been considered the normal lining of the most proximal portion of the stomach (the gastric cardia), is almost exclusively composed of mucus-secreting, gastric foveolar–type cells without goblet cells. Cardiac epithelium can also be found in the esophagus, and observations suggest that cardiac epithelium might not be a normal type of epithelium but rather an abnormal, metaplastic epithelium acquired as a consequence of GERD.[8,9] Although lacking the goblet cells of specialized intestinal metaplasia, cardiac epithelium nevertheless expresses molecular markers of intestinal differentiation (eg, villin and CDX2).[10] Thus, cardiac epithelium can be considered "intestinalized" even without goblet cells. Furthermore, cardiac epithelium exhibits

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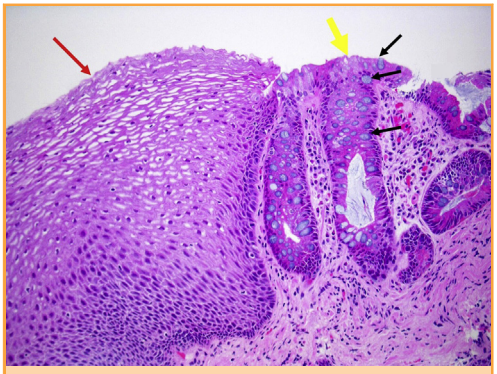

FIGURE 2. Histopathologic analysis of Barrett esophagus. Normal squamous epithelium is seen on the left (red arrow). Barrett intestinal-type columnar metaplasia is seen on the right (yellow arrow). Note the prominent goblet cells in the Barrett metaplasia (black arrows) (hematoxylin-eosin and Alcian blue; original magnification ×200). Image courtesy of Shelby Melton, MD.

genetic abnormalities similar to those found in specialized intestinal metaplasia; thus, cardiac epithelium might be predisposed to malignancy despite its lack of goblet cells.[11] Indeed, even in specialized intestinal metaplasia, the highly differentiated goblet cell seems an unlikely candidate to be the malignant cell of origin.

The British Society of Gastroenterology considers esophageal cardiac epithelium to be a form of Barrett esophagus.[12,13] In support of this contention, one study identified predominantly cardiac epithelium near the margins of small, endoscopically removed esophageal adenocarcinomas.[14] This observation suggested that the tumors might have arisen from cardiac epithelium rather than from intestinal metaplasia. Another study that followed up 712 patients with a columnar-lined esophagus for a median of 12 years found a similar rate of cancer development for patients with cardiac epithelium and those with intestinal metaplasia in their esophageal biopsy specimens.[15] However, other studies have not documented a high cancer risk for patients with cardiac epithelium. In one study of patients who had biopsy specimens taken from their columnar-lined esophagus and who were then followed up for a mean of approximately 5 years, progression to dysplasia or cancer occurred in 16 of 178 patients whose biopsy specimens revealed intestinal metaplasia (with goblet cells), but no such progression occurred in 118 patients whose biopsy specimens revealed only cardiac epithelium.[16] In a population-based study of 8522 patients from Northern Ireland who had a columnar-lined esophagus, the risk of esophageal cancer for those with intestinal metaplasia was 0.38% per year, whereas the risk for patients with cardiac epithelium was only 0.07% per year.[17] Thus, it is not clear whether cardiac epithelium has a strong malignant predisposition.

The question of whether patients who have only cardiac epithelium lining the distal esophagus have Barrett esophagus is primarily a semantic issue. Norman Barrett did not mention either intestinal metaplasia or cardiac epithelium in his original report of the condition that now bears his name.[18] In response to the controversy regarding the importance of cardiac epithelium, the authors of the recent medical position statement on Barrett esophagus from the American Gastroenterological Association (AGA) made a distinction between the conceptual definition of Barrett esophagus and its diagnostic criteria.[6] They argued that Barrett esophagus is considered a medical condition rather than a histologic curiosity solely because of the cancer risk. Therefore, they defined Barrett esophagus conceptually as "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus." The authors also wrote, "Presently, intestinal metaplasia [with goblet cells] is required for the diagnosis of Barrett's esophagus because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy." That statement remains valid to date, and the AGA, the American Society of Gastrointestinal Endoscopy (ASGE), and the American College of Gastroenterology (ACG) all agree that intestinal metaplasia with goblet cells is a requisite diagnostic criterion for Barrett esophagus.[6,19,20]

CONTROVERSY 2: DOES ENDOSCOPIC SURVEILLANCE OF PATIENTS WITH BARRETT ESOPHAGUS PREVENT DEATHS FROM ESOPHAGEAL CANCER AND SHOULD ENDOSCOPIC SURVEILLANCE BE PERFORMED?

Adenocarcinomas in Barrett esophagus are believed to evolve through a series of genetic

and epigenetic alterations that accumulate in the metaplastic cells during a span of years, endowing them with progressive growth advantages that culminate in malignancy. Some of these premalignant genetic alterations can cause morphologic changes in the tissue that pathologists can appreciate as dysplasia.[21] Dysplasia in Barrett esophagus is widely regarded as the immediate precursor of adenocarcinoma, and studies have documented that surgical or endoscopic removal of the dysplastic tissue can prevent its progression to cancer.[6] These observations are the basis for using endoscopic surveillance as a cancer preventive strategy for patients with Barrett esophagus, with the rationale that this endoscopy will detect dysplasia, which can then be treated to prevent its malignant progression. Despite this plausible rationale, however, there is no proof (in the form of a randomized trial) that endoscopic surveillance prevents deaths from esophageal cancer in Barrett esophagus.

High-quality studies have found that the risk of esophageal cancer for patients with nondysplastic Barrett esophagus ranges from 0.12% to 0.38% per year, a risk considerably lower than had been estimated in previous reports.[17,22-24] Another study suggests that the risk of cancer in nondysplastic Barrett esophagus is not static, as had been assumed, but rather decreases over time.[25] This multicenter study included 1401 patients with nondysplastic Barrett esophagus who were followed up for a median duration of 5 years. In those patients whose first endoscopy revealed nondysplastic Barrett esophagus, the annual rate of cancer development was 0.32%. The cancer risk then decreased with every subsequent endoscopy revealing nondysplastic Barrett esophagus, and for patients who had 5 endoscopies without dysplasia, the annual cancer risk was only 0.11%. With such a low incidence of cancer, which seems to decrease over time, the logistics of performing a definitive randomized trial to document the benefit of endoscopic surveillance for patients with nondysplastic Barrett esophagus are daunting. Such a study would require large numbers of patients to be followed up for many years. One large randomized controlled trial that evaluated surveillance endoscopy in Barrett esophagus is ongoing in the United Kingdom, but results are not expected for a number of years.[26]

To date, the only direct evidence supporting the practice of endoscopic surveillance has come from observational studies reporting that patients whose Barrett esophagus cancers are diagnosed during surveillance endoscopy have earlier-stage tumors and better survival than those whose cancers are discovered when they seek medical attention for symptoms such as dysphagia and weight loss.[27,28] However, these studies are not definitive because they are highly susceptible to biases that might exaggerate the benefits of surveillance, including biases of lead time, length time, and the inclusion of healthy volunteers.[29] The efficacy of endoscopic surveillance for Barrett esophagus has also been addressed using computer modeling. These studies have concluded that surveillance can be cost-effective under certain circumstances, but these studies also are not definitive because they rely on multiple assumptions.[30-33] Faced with a marked increase in the frequency of esophageal adenocarcinoma and noting the plausible rationale for surveillance with nondefinitive studies suggesting its potential benefit, gastroenterology societies, including the AGA, ASGE, and ACG, have decided to endorse regular endoscopic surveillance for patients with Barrett esophagus despite the lack of a definitive supporting evidence base.[6,12,19,20]

A number of reports have documented that patients with Barrett esophagus can develop incurable esophageal cancers despite their adherence to a program of regular endoscopic surveillance,[34] and a recent community-based, case-control study has seriously challenged the efficacy of surveillance endoscopy for cancer prevention.[35] In this study, the investigators identified 38 members of a large health plan who had died of esophageal adenocarcinoma and who were known to have had Barrett esophagus for at least 6 months before the diagnosis of cancer. The frequency of having a surveillance endoscopy within 3 years before the index date in these cases was compared with that of 101 living control health plan members with Barrett esophagus who were matched for age, sex, and duration of follow-up. If endoscopic surveillance were effective in preventing deaths from esophageal cancer, then the controls would be expected to have had a higher frequency of surveillance endoscopy than the cases. Surprisingly, the investigators found that the cases

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and controls had nearly identical frequencies of endoscopic surveillance (55% and 60% for cases and controls, respectively) and that surveillance was not associated with a decreased risk of death from esophageal adenocarcinoma (adjusted odds ratio, 0.99; 95% CI, 0.36-2.75). Although this study cannot exclude a small benefit for endoscopic surveillance, the findings suggest that, if surveillance has any benefit at all, it is substantially smaller than had been assumed for many years.

In summary, more recent studies have found that the risk of cancer for patients with nondysplastic Barrett esophagus is substantially lower than previous studies had suggested and that the low risk decreases further over time. These observations, combined with the case-control study reporting no benefit of endoscopic surveillance, seriously challenge the wisdom of current societal recommendations for surveillance in patients with nondysplastic Barrett esophagus. Unfortunately, the incidence of esophageal adenocarcinoma in Western countries continues to increase at an alarming rate. It is clear that better methods are needed to improve risk stratification for patients with Barrett esophagus to prevent deaths from esophageal cancer. Investigators are exploring a number of modalities that might improve risk stratification, including advanced endoscopic imaging techniques, such as chromoendoscopy, autofluorescence endoscopy, narrow band imaging, optical coherence tomography, and confocal laser endomicroscopy.[36-39] Molecular markers, including abnormalities in p53 and abnormal cellular DNA content detected by flow cytometry, have been associated with cancer progression in Barrett esophagus.[40,41] Cytogenetic abnormalities can be detected by fluorescence in situ hybridization, and panels of biomarkers that can identify multiple abnormalities in DNA content, gene expression, and DNA methylation have shown promise for risk stratification.[41-43] In addition, risk stratification models that incorporate a number of clinical, histologic, or molecular features have been explored.[44,45] Currently, however, none of these modalities has been proven to provide sufficient clinical information to justify its routine application in clinical practice. Despite the many limitations of surveillance endoscopy, it is the current standard of care recommended by gastroenterology societies and should continue to be offered to patients with Barrett esophagus for now.

CONTROVERSY 3: WHO SHOULD BE SCREENED TO IDENTIFY BARRETT ESOPHAGUS?

Until recently, endoscopic screening for Barrett esophagus was suggested for nearly all patients with chronic GERD symptoms. Today, however, the most recent guidelines from the AGA, ASGE, ACG, and the American College of Physicians (ACP) recommend such endoscopic screening only for patients who have at least one risk factor for esophageal adenocarcinoma in addition to chronic GERD, including age of 50 years or older, male sex, white race, hiatal hernia, elevated body mass index, intra-abdominal body fat distribution, nocturnal reflux symptoms, and tobacco use.[6,19,20,46,47] Nevertheless, it is the GERD symptoms that trigger the consideration for screening, and this symptom requirement undoubtedly limits the utility of the proposed screening strategies because many patients with Barrett esophagus have no GERD symptoms. Indeed, approximately 50% of patients with short-segment Barrett esophagus (Barrett metaplasia extending <3 cm up the distal esophagus) deny GERD symptoms,[2] and studies of patients with esophageal adenocarcinoma have found that approximately 40% report no history of prior GERD symptoms.[48,49] Furthermore, although it has been assumed widely that most esophageal adenocarcinomas arise from Barrett metaplasia, it is conceivable that this assumption is incorrect and that these tumors arise from other glandular elements in the esophagus or gastric cardia. Irrespective of the underlying reason, it is clear that present screening programs have not been effective in stemming the increasing incidence of esophageal adenocarcinoma, and less than 5% of patients found to have an esophageal adenocarcinoma have a prior diagnosis of Barrett esophagus.[3,50]

Endoscopic screening for Barrett esophagus is an expensive practice. Several cost-effectiveness studies addressing this issue have found that screening GERD patients could be cost-effective under certain circumstances, assuming that the patients screened were those at highest risk (eg, 50-year-old white men with GERD).[31,51] It has been estimated that if men

older than 40 years with long-standing GERD were screened with endoscopy and that GERD elevated the risk of adenocarcinoma 20-fold, then approximately 1400 endoscopies would need to be performed to detect one case of adenocarcinoma.[49] Of course, a key assumption underlying these cost-effectiveness studies is that the identification of Barrett esophagus by screening will result in benefit, an assumption that has not been established in any definitive study.

The primary goal of screening individuals with GERD symptoms is to identify patients with Barrett esophagus who then will benefit from surveillance. For decades, it has been assumed that endoscopic surveillance of Barrett esophagus prevents deaths from esophageal adenocarcinoma. As discussed in the previous section, however, it is not at all clear that endoscopic surveillance benefits patients with Barrett esophagus. Consequently, the practice of screening for Barrett esophagus may be made on the basis of fundamentally flawed premises. After all, what would be the point of screening for a disease that has no specific treatment and for which surveillance is not effective in preventing complications? Considering the alarming increase in the frequency of esophageal adenocarcinoma and the lack of definitive data regarding the benefits of screening and surveillance, we currently suggest adherence to the guideline recommended by the gastroenterology societies and the ACP that screening should be performed for patients who have at least one risk factor for esophageal adenocarcinoma in addition to chronic GERD. Nevertheless, we suggest that the societies should consider the challenges we raise to the premise for screening and surveillance in future revisions of their guidelines.

CONTROVERSY 4: WHICH PATIENTS WITH BARRETT ESOPHAGUS SHOULD BE TREATED WITH ENDOSCOPIC ERADICATION THERAPY (AND HOW WELL DOES IT WORK)?

High-Grade Dysplasia

In contrast to the relatively low risk of malignancy for patients with nondysplastic Barrett metaplasia, the risk of progression to cancer with high-grade dysplasia is considered high enough to warrant intervention.[6] Reported rates of cancer progression with high-grade dysplasia have varied widely (from 4% to 63% per year), perhaps due to substantial differences among studies in their patient populations, the frequency of associated endoscopically visible lesions, and the rigor with which prevalent cancers were excluded.[52-54] A meta-analysis on this issue calculated the annual rate of cancer progression with high-grade dysplasia at approximately 6% per year, but considerably higher rates have been described in randomized trials of endoscopic therapies.[53,55,56]

Until recently, when endoscopic screening or surveillance revealed high-grade dysplasia in Barrett esophagus, the standard treatment was esophagectomy, a procedure associated with considerable morbidity and mortality. In recent years, endoscopic techniques have been developed to ablate or resect dysplastic Barrett mucosa with far less morbidity than esophagectomy and with virtually no mortality.[57] *Endoscopic ablation techniques* deliver thermal or photochemical energy to the esophageal mucosa with the intent of destroying the Barrett metaplasia, and ablation techniques do not provide a tissue specimen for histologic analysis.[56,58] Barrett metaplasia also can be removed by endoscopic mucosal resection (EMR), in which large segments of esophageal mucosa and submucosa are resected with a diathermic snare, and submitted for histologic examination.[6,59] Endoscopic mucosal resection can be therapeutic (because it removes neoplastic mucosa), and EMR provides invaluable information regarding the depth of tumor involvement (T stage).

Uncontrolled studies suggest that the frequency of metachronous neoplasia can be reduced if all of the Barrett mucosa is eradicated, not just the dysplastic areas.[60] Today, the term *endoscopic eradication therapy* is used to describe the use of one or any combination of endoscopic modalities with the specific goal of completely eradicating all of the Barrett metaplasia, both dysplastic and nondysplastic. Although endoscopic treatments cannot cure neoplasms that have metastasized to regional lymph nodes, such nodes are present in only 1% to 2% of patients with mucosal neoplasms (including intramucosal adenocarcinoma) in Barrett esophagus; therefore, endoscopic treatment is deemed appropriate.[61]

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Well-studied endoscopic ablation techniques for Barrett esophagus include radiofrequency ablation (RFA), which uses radiofrequency energy to inflict a thermal injury that destroys the metaplastic mucosa, and photodynamic therapy (PDT), a laser-based technique that destroys the mucosa with photochemical energy. Randomized controlled trials have found that endoscopic ablation of dysplastic Barrett esophagus with PDT or RFA can prevent the progression to cancer.[55,56,62] Although these 2 ablative techniques have not been compared head to head in a randomized trial, RFA appears to achieve comparable to superior rates of dysplasia eradication and cancer prevention with greater ease of administration and substantially fewer serious adverse effects than PDT. Consequently, RFA has become the preferred procedure for endoscopic ablation, and both the AGA and ASGE now recommend endoscopic eradication therapy as the procedure of choice for the treatment of most patients with high-grade dysplasia in Barrett esophagus.[6,20]

Low-Grade Dysplasia

Studies on the management of low-grade dysplasia in Barrett esophagus are confounded by difficulties in establishing the diagnosis, and study results are often contradictory. The scoring of dysplasia is based largely on subjective histologic criteria, and a number of studies have found only fair to poor agreement among pathologists for the diagnosis of low-grade dysplasia.[63-65] In a Dutch study in which 2 expert pathologists reviewed pathology slides for 147 patients who had low-grade dysplasia diagnosed at community hospitals, the experts confirmed the diagnosis in only 15% of cases.[64] For those 15%, however, the cumulative risk of neoplastic progression was an alarming 85% at 109 months. In contrast, a recent US study of 210 patients with low-grade dysplasia followed up for a mean of 6.2 years described a rate of progression to high-grade dysplasia or cancer of only 1.83% per year.[65] Faced with such contradictory data, gastroenterology societies recommend either a program of more intensive endoscopic surveillance or endoscopic ablation for patients with the diagnosis of low-grade dysplasia confirmed by at least 2 expert gastrointestinal pathologists.[6,20]

Nondysplastic Barrett Metaplasia

Noting the success of RFA in safely eradicating Barrett metaplasia and in preventing the progression from dysplasia to cancer, some authorities have proposed that the use of RFA should not be restricted to patients with dysplasia in Barrett esophagus.[66] Rather, they contend that RFA should be offered to all patients with dysplastic or nondysplastic Barrett esophagus. They argue that Barrett metaplasia can be neoplastic even if it does not manifest the histologic features of dysplasia, that the efficacy of endoscopic surveillance as a cancer prevention strategy is dubious, and that the safety and efficacy of RFA have been established in high-quality studies on the treatment of dysplasia. Some even have proposed that the standard practice of routinely removing polyps found during colonoscopy is intellectually identical to ablating nondysplastic Barrett esophagus and that the current practice of limiting RFA only to Barrett esophagus with dysplasia would be like limiting colonoscopic polypectomy only to polyps that are large or clearly malignant.[67]

Proponents of using RFA to eradicate nondysplastic Barrett metaplasia assume that the procedure will prevent esophageal cancer, but that assumption is questionable. The efficacy of RFA for preventing cancer in nondysplastic Barrett esophagus has not been established in long-term follow-up of randomized trials but instead has been inferred from the results of the aforementioned randomized trial of RFA for the treatment of dysplasia and from studies that found that RFA can eliminate endoscopically visible evidence of Barrett metaplasia in most patients for up to 5 years.[55,68] Unfortunately, 2 unresolved issues call into question the assumption that the elimination of visible evidence of Barrett metaplasia by RFA means that the cancer risk has been eliminated: (1) the importance of subsquamous intestinal metaplasia (SSIM) and (2) the frequency with which Barrett metaplasia recurs after initial complete eradication.

Subsquamous Intestinal Metaplasia

Another area of contention relates to the frequency and importance of SSIM. After RFA of Barrett metaplasia, patients are treated with proton pump inhibitors to prevent acid reflux so that the ablated mucosa can be reepithelialized

by new (neo)squamous epithelium. Biopsy specimens of the neosquamous lining sometimes reveal metaplastic glands located under the epithelium in the lamina propria.[69] This SSIM (which also has been called *buried metaplasia*, *buried glands*, or *buried Barrett*) is hidden from the endoscopist and generally is discovered only when the endoscopist takes a biopsy specimen of neosquamous epithelium that happens (by chance) to overlie the buried glands. The frequency with which SSIM progresses to malignancy is not clear, but there are numerous reports of cancers developing in this condition.[70]

Generally, SSIM has been assumed to develop as the result of incomplete endoscopic ablation procedures that destroy only a superficial layer of Barrett mucosa while leaving a viable, deeper layer of glands to be buried by an overgrowth of neosquamous epithelium.[69] Some have proposed that SSIM develops not as a result of ablation procedures but rather as a consequence of extensive biopsy sampling of Barrett mucosa during surveillance endoscopy, with neosquamous epithelium growing over intestinal metaplasia in the biopsy sites.[71] However, more recent reports suggest that, with or without endoscopic ablation, most patients with Barrett esophagus have foci of SSIM.[72]

Reported rates of detection of SSIM, with or without prior ablation, have varied widely (from 0% to 98%).[69,73] This enormous disparity among studies probably is the result of 2 confounding factors: (1) inadequate depths of esophageal biopsy samples and (2) differences among studies in the location of esophageal biopsy samples. Typically, SSIM is found in the subepithelial lamina propria, which often is beyond the depth achieved by endoscopic biopsy specimens.[74] A systematic review on the frequency of SSIM after endoscopic ablation procedures found SSIM reported in 14.2% of patients treated with PDT and in 0.9% of patients after RFA, but the authors cautioned that those estimates were suspect because they were made on the basis of reports that did not provide crucial information on the adequacy of biopsy samples for SSIM evaluation.[69] Although one study concluded that approximately 80% of esophageal biopsy samples are adequate to evaluate for SSIM, others have refuted this contention convincingly by finding adequate sampling depth for SSIM in only 4% to 37% of esophageal biopsy specimens.[74-76] Thus, it appears that most endoscopic pinch biopsy specimens are not adequate to evaluate for SSIM, and estimates of SSIM frequency on the basis of such biopsy specimens are likely to be underestimates.

The EMR specimens are larger and, usually, deeper than typical endoscopic pinch biopsy specimens. In one study of 47 patients who had EMR performed to eradicate dysplasia in Barrett esophagus, SSIM was found in 13 (28%), none of whom had undergone prior ablation procedures.[73] The SSIM, which revealed dysplasia in 10 of those 13 patients, always was located within 6 mm of the junction with Barrett epithelium. Two studies from the Netherlands found no SSIM in EMR specimens of neosquamous epithelium after RFA for a combined total of 44 patients, but those specimens were taken more than 10 mm proximal to the junction with Barrett epithelium.[76,77] Another recent study of 110 patients with neoplastic Barrett esophagus sampled by EMR found SSIM in EMR specimens that crossed the junction between squamous and Barrett epithelium in 108 of the 110 patients (98%), none of whom had undergone prior endoscopic ablation.[72] In all cases, the SSIM was located within 10 mm of the junction with Barrett epithelium. Thus, studies that sample the esophagus proximal to this level are unlikely to reveal SSIM.

Although the mechanism underlying the development of SSIM remains unclear and its precise frequency remains disputed, it appears that many if not most patients with Barrett esophagus have SSIM in the area adjacent to the junction between squamous and Barrett epithelium, even in the absence of prior ablation procedures. How often ablation procedures cause new SSIM to develop, the effect of ablation on preexisting SSIM, and the risk of cancer associated with SSIM are not clear. With all these uncertainties, patients cannot be reassured that the eradication of surface metaplasia by RFA has eliminated their cancer risk.

Recurrent Barrett Metaplasia

Three previous studies that followed up patients who had complete eradication of Barrett metaplasia by RFA found low rates of recurrent metaplasia ranging from 0% to 9%.[68,78,79]

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Some more recent studies have described considerably higher recurrence rates. For example, Vaccaro et al[80] followed up 47 patients who had complete eradication of intestinal metaplasia by RFA for 5 to 38 months, during which they found recurrent metaplasia in 15 (32%). In this study, the investigators routinely took 4 biopsy specimens from columnar epithelium at the GEJ, just distal to the neosquamocolumnar junction. Four patients (9%) had dysplasia found in their recurrent metaplasia, all in biopsy specimens from the GEJ. Another study of 229 patients from 3 different academic medical centers who had endoscopic therapy (RFA with or without EMR) with complete eradication of intestinal metaplasia found that 20% had recurrent metaplasia at 1 year and 33% had a recurrence at 2 years.[81] In this study, biopsy specimens were obtained from both the tubular esophagus and the GEJ; 18 patients had recurrence in the tubular esophagus alone, 17 had recurrence at the GEJ alone, and 2 had recurrence in both the tubular esophagus and GEJ. The recurrent metaplasia was not neoplastic in most cases, but neoplasia was found in 22% of the patients with recurrences (3% cancer, 11% high-grade dysplasia, and 8% low-grade dysplasia).

A meta-analysis of more than 3800 patients treated with RFA found that complete eradication of intestinal metaplasia was achieved overall in 78% of patients, usually after 2 or 3 RFA treatment sessions, with wide variations among centers in reported success rates (range, 36%-94%).[58] Complete eradication of dysplasia was achieved in 91% of cases (range, 74%-97%). Esophageal stricture was the most common adverse event, reported in 5% of patients (95% CI, 3%-7%). Among 6 studies that addressed the durability of RFA, 3 included biopsies of the GEJ and cardia, and 3 focused on the tubular esophagus alone. Among studies that included at least 1 year of follow-up after complete eradication of intestinal metaplasia, the metaplasia recurred in 13% of patients overall (95% CI, 9%-18%), and 0.7% eventually progressed to esophageal adenocarcinoma. The investigators noted wide variations among centers in reported recurrence rates for intestinal metaplasia and dysplasia.

The reasons for the wide variations among studies in the reported recurrence rate for intestinal metaplasia are not clear but might be due to variability among different centers in treatment protocols (eg, whether or not gastric folds at the GEJ are ablated routinely), lengths of follow-up, and the indication for ablative therapy (eg, dysplastic vs nondysplastic Barrett esophagus). In addition, there is substantial variability among centers in their follow-up biopsy protocols, including the number of biopsy specimens taken from the tubular esophagus and whether biopsy specimens are taken routinely at the GEJ. It is also possible that some so-called recurrences might not be recurrences at all but rather residual small islands of Barrett metaplasia in the tubular esophagus or at the GEJ that were overlooked or not sampled on previous endoscopies. The long-term cancer risk associated with recurrent Barrett metaplasia is unclear and will remain so for some time because RFA is a relatively new procedure and long-term follow-up studies are not yet available. Although it seems unlikely that a tiny focus of metaplasia has the same malignant potential as a long segment of untreated Barrett metaplasia, recurrences after RFA for dysplastic Barrett frequently involve dysplasia, suggesting that they still have substantial cancer risk.

If RFA for nondysplastic Barrett esophagus is considered intellectually the same as removing all polyps discovered during colonoscopy,[67] then one might argue that recurrence of intestinal metaplasia after RFA is no different than recurrence of colorectal polyps after polypectomy. Regular surveillance colonoscopy is advised for patients who have adenomatous colon polyps removed precisely because those polyps are expected to recur frequently. During surveillance colonoscopy, however, recurrent polyps are visible lesions that can be removed immediately. After RFA for Barrett esophagus, recurrent intestinal metaplasia at the GEJ usually is not visible and is detected only as the result of biopsy sampling.[80] Thus, patients with recurrent metaplasia in those biopsy samples would require another endoscopy to administer more RFA and perhaps another endoscopy after that to document eradication of the recurrent metaplasia. The cost and logistics of such a practice rapidly could become unmanageable.

With unanswered questions regarding the frequency and importance of SSIM and recurrent Barrett metaplasia, the wisdom of

recommending RFA for cancer prevention for nondysplastic Barrett esophagus is questionable. When considering this option, clinicians should appreciate that (1) RFA generally requires several endoscopic procedures to achieve complete eradication of Barrett metaplasia, entailing considerable cost and inconvenience; (2) RFA is complicated by esophageal stricturing in approximately 5% of cases; (3) the efficacy of RFA in reducing the already low rate of cancer development for patients with nondysplastic Barrett esophagus is not established; (4) SSIM can occur after RFA, and the significance and risk of this entity is unclear, with some cases of subsquamous dysplasia and cancer reported; and (5) metaplasia recurs frequently after RFA and, therefore, (6) RFA does not obviate endoscopic surveillance.[82]

One recent study used a decision analytic Markov model to explore the cost-effectiveness of RFA for hypothetical cohorts of 50-year-old men who had Barrett esophagus with and without dysplasia.[83] Within reasonable parameters, RFA for Barrett esophagus with dysplasia was cost-effective, whereas RFA for nondysplastic Barrett esophagus was not cost-effective and was prohibitively expensive from a policy perspective. In its recent medical position statement, the AGA Institute concluded, "Endoscopic eradication therapy is not suggested for the general population of patients with Barrett's esophagus in the absence of dysplasia."[84] At this time, we believe that available data strongly support the use of endoscopic eradication therapy for most patients with high-grade dysplasia in Barrett esophagus. For patients with confirmed low-grade dysplasia, we believe that endoscopic eradication and more intensive endoscopic surveillance are both reasonable management strategies, but we generally favor endoscopic eradication. We do not recommend the use of endoscopic ablation for the general population of patients with nondysplastic Barrett esophagus.

CONCLUSION

Barrett esophagus is a common disorder that continues to spark discussion and debate at medical conferences and in the literature. At this time, intestinal metaplasia in esophageal biopsy samples is required for the diagnosis because the risk of cancer in the absence of intestinal metaplasia is extremely low. Screening for Barrett esophagus and surveillance endoscopy remain the standard of care, despite the results of recent studies that call into question the efficacy of these practices. Recent data describing relatively high recurrence rates for intestinal metaplasia and dysplasia after apparently successful endoscopic eradication therapy suggest that patients should remain in surveillance endoscopy programs after endoscopic therapy of Barrett esophagus. Endoscopic ablation therapy for nondysplastic Barrett esophagus will likely remain a source of controversy for some time to come because of unresolved issues regarding cost and recurrence rates and the lack of long-term outcome data.

Abbreviations and Acronyms: **ACG** = American College of Gastroenterology; **ACP** = American College of Physicians; **AGA** = American Gastroenterological Association; **ASGE** = American Society of Gastrointestinal Endoscopy; **EMR** = endoscopic mucosal resection; **GEJ** = gastroesophageal junction; **GERD** = gastroesophageal reflux disease; **PDT** = photodynamic therapy; **RFA** = radiofrequency ablation; **SSIM** = subsquamous intestinal metaplasia

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REFERENCES

1. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology*. 2005;129(6):1825-1831.
2. Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology*. 2003;125(6):1670-1677.
3. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev*. 2010;19(6):1468-1470.
4. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. *JAMA*. 2013;310(6):627-636.
5. Spechler SJ, Fitzgerald RC, Prasad GA, Wang KK. History, molecular mechanisms, and endoscopic treatment of Barrett's esophagus. *Gastroenterology*. 2010;138(3):854-869.
6. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology*. 2011;140(3):e18-e52.
7. Spechler SJ. Barrett's esophagus: is the goblet half empty? *Clin Gastroenterol Hepatol*. 2012;10(11):1237-1238.
8. Chandrasoma P. Pathophysiology of Barrett's esophagus. *Semin Thorac Cardiovasc Surg*. 1997;9(3):270-278.
9. Chandrasoma PT. Histologic definition of gastro-esophageal reflux disease. *Curr Opin Gastroenterol*. 2013;29(4):460-467.
10. Hahn HP, Blount PL, Ayub K, et al. Intestinal differentiation in metaplastic, nongoblet columnar epithelium in the esophagus. *Am J Surg Pathol*. 2009;33(7):1006-1015.

11. Liu W, Hahn H, Odze RD, Goyal RK. Metaplastic esophageal columnar epithelium without goblet cells shows DNA content abnormalities similar to goblet cell-containing epithelium. *Am J Gastroenterol*. 2009;104(4):816-824.
12. Watson A, Heading RC, Shepherd N. *Guidelines for the Diagnosis and Management of Barrett's Columnar-Lined Oesophagus: A Report of the Working Party of the British Society of Gastroenterology*. London, England: British Society of Gastroenterology; August 2005. www.bsg.org.uk. Accessed August 26, 2013.
13. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut*. 2014;63(1):7-42.
14. Takubo K, Aida J, Naomoto Y, et al. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. *Hum Pathol*. 2009;40(1):65-74.
15. Kelty CJ, Gough MD, Van Wyk Q, Stephenson TJ, Ackroyd R. Barrett's oesophagus: intestinal metaplasia is not essential for cancer risk. *Scand J Gastroenterol*. 2007;42(11):1271-1274.
16. Westerhoff M, Hovan L, Lee C, Hart J. Effects of dropping the requirement for goblet cells from the diagnosis of Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2012;10(11):1232-1236.
17. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst*. 2011;103(13):1049-1057.
18. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg*. 1950;38(150):175-182.
19. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2008;103(3):788-797.
20. Evans JA, Early DS, Fukami N, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc*. 2012;76(6):1087-1094.
21. Spechler SJ. Dysplasia in Barrett's esophagus: limitations of current management strategies. *Am J Gastroenterol*. 2005;100(4):927-935.
22. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut*. 2012;61(7):970-976.
23. Wani S, Falk G, Hall M, et al. Patients with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2011;9(3):220-227.
24. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med*. 2011;365(15):1375-1383.
25. Gaddam S, Singh M, Balasubramanian G, et al. Persistence of nondysplastic Barrett's esophagus identifies patients at lower risk for esophageal adenocarcinoma: results from a large multicenter cohort. *Gastroenterology*. 2013;145(3):548-553.
26. Jankowski J, Barr H. Improving surveillance for Barrett's oesophagus: AspECT and BOSS trials provide an evidence base. *BMJ*. 2006;332(7556):1512.
27. Fountoulakis A, Zafirellis KD, Dolan K, Dexter SP, Martin IG, Sue-Ling HM. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. *Br J Surg*. 2004;91(8):997-1003.
28. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology*. 2002;122(3):633-640.
29. Shaheen NJ, Provenzale D, Sandler RS. Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma: a review of the evidence. *Am J Gastroenterol*. 2002;97(6):1319-1327.
30. Sonnenberg A, Soni A, Sampliner RE. Medical decision analysis of endoscopic surveillance of Barrett's oesophagus to prevent oesophageal adenocarcinoma. *Aliment Pharmacol Ther*. 2002;16(1):41-50.
31. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. *Ann Intern Med*. 2003;138(3):176-186.
32. Gerson LB, Groeneveld PW, Triadafilopoulos G. Cost-effectiveness model of endoscopic screening and surveillance in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2004;2(10):868-879.
33. Hur C, Nishioka NS, Gazelle GS. Cost-effectiveness of aspirin chemoprevention for Barrett's esophagus. *J Natl Cancer Inst*. 2004;96(4):316-325.
34. Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. *J Thorac Cardiovasc Surg*. 1994;108(5):813-821.
35. Corley DA, Mehtani K, Quesenberry C, Zhao W, de Boer J, Weiss NS. Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas. *Gastroenterology*. 2013;145(2):312-319.
36. Longcroft-Wheaton G, Duku M, Mead R, Poller D, Bhandari P. Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in patients with Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2010;8(10):843-847.
37. Curvers WL, van Vilsteren FG, Baak LC, et al. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicenter, randomized, cross-over study in general practice. *Gastrointest Endosc*. 2011;73(2):195-203.
38. Sharma P, Hawes RH, Bansal A, et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's oesophagus: a prospective, international, randomised controlled trial. *Gut*. 2013;62(1):15-21.
39. Canto MI, Anandasabapathy S, Brugge W, et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). *Gastrointest Endosc*. 2014;79(2):211-221.
40. Kastelein F, Biermann K, Steyerberg EW, et al. Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. *Gut*. 2013;62(12):1676-1683.
41. Fritcher EG, Brankley SM, Kipp BR, et al. A comparison of conventional cytology, DNA ploidy analysis, and fluorescence in situ hybridization for the detection of dysplasia and adenocarcinoma in patients with Barrett's esophagus. *Hum Pathol*. 2008;39(8):1128-1135.
42. Alvi MA, Liu X, O'Donovan M, et al. DNA methylation as an adjunct to histopathology to detect prevalent, inconspicuous dysplasia and early-stage neoplasia in Barrett's esophagus. *Clin Cancer Res*. 2013;19(4):878-888.
43. Jin Z, Cheng Y, Gu W, et al. A multicenter, double-blinded validation study of methylation biomarkers for progression prediction in Barrett's esophagus. *Cancer Res*. 2009;69(10):4112-4115.
44. Rubenstein JH, Morgenstern H, Appelman H, et al. Prediction of Barrett's esophagus among men. *Am J Gastroenterol*. 2013;108(3):353-362.
45. Bird-Lieberman EL, Dunn JM, Coleman HG, et al. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus. *Gastroenterology*. 2012;143(4):927-935.
46. Shaheen NJ, Weinberg DS, Denberg TD, Chou R, Qaseem A, Shekelle P. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. *Ann Intern Med*. 2012;157(11):808-816.
47. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308-328.
48. Chak A, Faulx A, Eng C, et al. Gastroesophageal reflux symptoms in patients with adenocarcinoma of the esophagus or cardia. *Cancer*. 2006;107(9):2160-2166.
49. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340(11):825-831.
50. Dulai GS, Guha S, Kahn KL, Gornbein J, Weinstein WM. Preoperative prevalence of Barrett's esophagus in esophageal

adenocarcinoma: a systematic review. *Gastroenterology*. 2002; 122(1):26-33.
51. Rubenstein JH, Inadomi JM, Brill JV, Eisen GM. Cost utility of screening for Barrett's esophagus with esophageal capsule endoscopy versus conventional upper endoscopy. *Clin Gastroenterol Hepatol*. 2007;5(3):312-318.
52. Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology*. 1989;96(5 pt 1):1249-1256.
53. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc*. 2008;67(3):394-398.
54. Verbeek RE, van Oijen MG, ten Kate FJ, et al. Surveillance and follow-up strategies in patients with high-grade dysplasia in Barrett's esophagus: a Dutch population-based study. *Am J Gastroenterol*. 2012;107(4):534-542.
55. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009; 360(22):2277-2288.
56. Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. *Gastrointest Endosc*. 2005;62(4):488-498.
57. Dunbar KB. Endoscopic eradication therapy for mucosal neoplasia in Barrett's esophagus. *Curr Opin Gastroenterol*. 2013;29(4):446-453.
58. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for barrett's esophagus: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(10):1245-1255.
59. Alvarez Herrero L, Pouw RE, van Vilsteren FG, et al. Safety and efficacy of multiband mucosectomy in 1060 resections in Barrett's esophagus. *Endoscopy*. 2011;43(3):177-183.
60. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut*. 2008; 57(9):1200-1206.
61. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol*. 2012;107(6):850-862.
62. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. *Gastrointest Endosc*. 2007;66(3):460-468.
63. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol*. 2001;32(4):368-378.
64. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol*. 2010;105(7):1523-1530.
65. Wani S, Falk GW, Post J, et al. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology*. 2011;141(4):1179-1186.
66. Fleischer DE, Odze R, Overholt BF, et al. The case for endoscopic treatment of non-dysplastic and low-grade dysplastic Barrett's esophagus. *Dig Dis Sci*. 2010;55(7):1918-1931.
67. El-Serag HB, Graham DY. Routine polypectomy for colorectal polyps and ablation for Barrett's esophagus are intellectually the same. *Gastroenterology*. 2011;140(2):386-388.
68. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy*. 2010;42(10): 781-789.
69. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. *Am J Gastroenterol*. 2011;106(11):1899-1908.
70. Titi M, Overhiser A, Ulusarac O, et al. Development of subsquamous high-grade dysplasia and adenocarcinoma after successful radiofrequency ablation of Barrett's esophagus. *Gastroenterology*. 2012;143(3):564-566.
71. Bronner MP, Overholt BF, Taylor SL, et al. Squamous overgrowth is not a safety concern for photodynamic therapy for Barrett's esophagus with high-grade dysplasia. *Gastroenterology*. 2009;136(1):56-64.
72. Anders M, Lucks Y, El-Masry MA, et al. Subsquamous extension of intestinal metaplasia is detected in 98% of cases of neoplastic Barrett's esophagus [published online July 23, 2013]. *Clin Gastroenterol Hepatol*. http://dx.doi.org/10.1016/j.cgh.2013.07.013.
73. Chennat J, Ross AS, Konda VJ, et al. Advanced pathology under squamous epithelium on initial EMR specimens in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: implications for surveillance and endotherapy management. *Gastrointest Endosc*. 2009;70(3):417-421.
74. Gupta N, Mathur SC, Dumot JA, et al. Adequacy of esophageal squamous mucosa specimens obtained during endoscopy: are standard biopsies sufficient for postablation surveillance in Barrett's esophagus? *Gastrointest Endosc*. 2012;75(1):11-18.
75. Shaheen NJ, Peery AF, Overholt BF, et al. Biopsy depth after radiofrequency ablation of dysplastic Barrett's esophagus. *Gastrointest Endosc*. 2010;72(3):490-496.
76. Pouw RE, Gondrie JJ, Rygiel AM, et al. Properties of the neosquamous epithelium after radiofrequency ablation of Barrett's esophagus containing neoplasia. *Am J Gastroenterol*. 2009; 104(6):1366-1373.
77. Phoa KN, Pouw RE, van Vilsteren FG, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. *Gastroenterology*. 2013;145(1):96-104.
78. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology*. 2011;141(2):460-468.
79. Gondrie JJ, Pouw RE, Sondermeijer CM, et al. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. *Endoscopy*. 2008; 40(5):370-379.
80. Vaccaro BJ, Gonzalez S, Poneros JM, et al. Detection of intestinal metaplasia after successful eradication of Barrett's esophagus with radiofrequency ablation. *Dig Dis Sci*. 2011;56(7): 1996-2000.
81. Gupta M, Iyer PG, Lutzke L, et al. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US multicenter consortium. *Gastroenterology*. 2013;145(1): 79-86.
82. Spechler SJ. Barrett's esophagus without dysplasia: wait or ablate? *Dig Dis Sci*. 2011;56(7):1926-1928.
83. Hur C, Choi SE, Rubenstein JH, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. *Gastroenterology*. 2012;143(3):567-575.
84. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011;140(3):1084-1091.