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American Gastroenterological Association Technical Review on the Management of Barrett's Esophagus

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American Gastroenterological Association Institute Process for Development of Technical Reviews

The aim of evidence-based medicine is to improve the quality of health care by integrating the best research evidence with clinical expertise and patient values. Evidence-based clinical guidelines are sets of recommendations intended to assist health care providers and patients in selecting the best management for common clinical situations while accounting for patient-specific circumstances. In addition to providing optimal, patient-centered care and improved outcomes, guidelines can reduce practice variability, identify gaps in evidence, enhance efficiency of resource use, and facilitate development of outcome and performance measures.

The American Gastroenterological Association Institute (AGAI) Medical Position Statement Procedure Manual, released in 2007, endorses the 2003 version of the US Preventive Services Task Force system to grade strength of recommendations. Although an excellent standard for producing recommendations regarding preventive services, the US Preventive Services Task Force has limitations when used to assess interventions that are not based on

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prevention. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (<http://www.gradeworkinggroup.org/index.htm>) has been adopted by several national and international societies and was constructed to address the shortcomings of existing grading systems, including the US Preventive Services Task Force system. GRADE separates quality of evidence from the strength of recommendation to ensure that the magnitude of benefits and harms is assessed as rigorously as the efficacy of interventions. With regard to strength of recommendations, GRADE has 2 categories: strong and weak (Table 1). Strong recommendations are meant to signify interventions that should be received by most individuals with a particular condition and can be adopted as policy in most circumstances. Weak recommendations require individualized scrutiny of the evidence and policy making would require substantial debate and involvement from multiple stakeholders. The classification requires consideration of 4 factors: quality of evidence, uncertainty about the balance between desirable and undesirable effects, variability in values and preferences, and uncertainty about whether the intervention represents a wise use of resources (Table 2). Of importance to our current health care debate is that interventions receiving a strong recommendation may be targets for development of performance measures.

Quality of evidence is assessed on a 4-point scale: high, moderate, low, and very low. Instead of being classified strictly on the basis of study design (ie, randomized, controlled clinical trials automatically receiving “high” quality marks), these levels reflect the likelihood that further research would change our confidence in the estimate of the beneficial effect of a particular intervention. Five factors that determine quality include study limitations, inconsistency of results between studies, indirectness (generalizability) of results, imprecision, and publication bias. For this reason, randomized, controlled clinical trials that have methodological flaws may be downgraded, whereas well-done observational studies that have large effect sizes (ie, relative risk [RR] >2–5 or <0.5–0.2) may be upgraded.

AGAI Procedure for Construction of Technical Reviews

The AGAI Clinical Practice and Quality Management Committee (CPQMC) chooses a topic by consensus discussion, votes after reviewing a list of potential topics derived from AGAI member recommendations, and develops the specific questions the guideline will answer. The CPQMC committee chair, with support of AGA staff, then contacts the AGAI clinical counsel chair and requests the input of the counsel for authorship and external reviewers.

Authors are selected and write a technical review (TR), which is an evidence-based document that provides the basis for clinical practice recommendations. For each of the specific questions raised by the CPQMC, authors conduct an independent systematic review of the literature using published guidelines (PRISMA). Articles selected for inclusion in the TR are based on a priori inclusion and exclusion criteria agreed on by all authors. Data extraction is shared among TR authors, and the individual study and summary results are reviewed and approved by all authors. The search terms for each topic included in the TR are included in the Appendix. It is not the function of the TR to provide a summary estimate for each variable included in the review. For this reason, results are summarized in the text of the TR and not subjected to a formal meta-analysis. The draft TR is compiled by the lead author and approved by all authors before submission for publication.

A medical position panel composed of the TR authors, additional content experts, practicing gastroenterologists, other specialists (eg, surgeon, pathologist), a patient representative, a payer representative, and American Gastroenterological Association staff meet through a series of face-to-face and telephone meetings to construct the medical position statement,

which is based on the TR but also reflects these discussions by the medical position panel. The medical position panel approves the medical position statement, after which this document and the TR are reviewed by the CPQMC. Based on the vote of the committee, a recommendation is submitted to the AGAI Governing Board, which provides final approval. When approval is granted, the medical position statement is published in *GASTROENTEROLOGY* and is also posted on the American Gastroenterological Association web site.

The objectives of the AGAI TR on the management of patients with Barrett's esophagus were to evaluate diagnostic and management strategies for patients at risk for or diagnosed with Barrett's esophagus. Specifically, 10 broad questions were developed by interaction among the authors, the AGAI, the Clinical Practice and Quality Management Committee, and representatives from the AGAI Council. The questions were designed to encapsulate the major management issues leading to consultations for Barrett's esophagus and esophageal adenocarcinoma in clinical practice in 2010. For each question, a comprehensive literature search was conducted, pertinent evidence reviewed, and a summary of relevant data produced. The conclusions of this review were based on the best available evidence or, in the absence of quality evidence, the expert opinion of the authors of the TR.

What Is the Definition of Barrett's Esophagus? What Landmark Identifies the Gastroesophageal Junction? What Epithelial Type Is Required for the Diagnosis of Barrett's Esophagus? Should Endoscopists Measure the Extent of Barrett's Metaplasia?

Authorities generally have defined Barrett's esophagus conceptually as the condition in which metaplastic columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus.¹⁻⁴ Unfortunately, this deceptively simple conceptual definition does not translate readily into clinically useful diagnostic criteria for 2 major reasons. (1) There are no universally accepted, precise, and validated landmarks that delimit the distal extent of the esophagus (ie, that identify the gastroesophageal junction [GEJ]). If it cannot be determined precisely where the esophagus ends and the stomach begins, then it may not be possible to ascertain the type of epithelium that lines the most distal esophagus. (2) There is no way to verify that gastric-type columnar epithelia found in the distal esophagus are metaplastic. These 2 factors become major confounders when attempting to establish a diagnosis of Barrett's esophagus for patients with only short segments of esophageal columnar epithelium.

What Landmark Identifies the Gastroesophageal Junction?—The diagnosis of Barrett's esophagus can be suspected when, during endoscopic examination, columnar epithelium (which has a characteristic endoscopic appearance) is observed to extend above the GEJ into the esophagus. Of course, this diagnostic suspicion is based on the assumption that the endoscopist can identify the GEJ. Few studies have addressed specifically the issue of how to localize the GEJ, and even those that have the accuracy of the criteria used cannot be assessed meaningfully in the absence of a validated landmark (ie, a gold standard).

Western endoscopists generally identify the GEJ as the most proximal extent of the gastric folds, a landmark first proposed in 1987 in a report of a small and methodologically flawed study.⁵ The location of the proximal extent of the gastric folds is affected by respiration, gut motor activity, and the degree of distention of the esophagus and stomach, all of which can change from moment to moment. Endoscopists in Asia often use the distal extent of the palisade vessels, which are fine longitudinal veins located in the lamina propria of the distal esophagus, as their landmark for the GEJ.^{6,7} The palisade vessels can be obscured by esophagitis, their level of termination can be irregular and difficult to localize with precision, and conceptually it is not clear why the distal end of the palisade vessels should

be considered the end of the esophagus. Thus, the scientific validity of the 2 most widely used landmarks for the GEJ is dubious.

The issue of the “best” landmark for the GEJ is likely to remain controversial indefinitely because, ultimately, the choice of any such landmark will be arbitrary. The majority of published studies on Barrett's esophagus conducted over the past 20 years have used the proximal extent of the gastric folds as the landmark for the GEJ and, in the absence of compelling data for the use of alternative markers, we presently recommend the continued use of this landmark despite its shortcomings.

What Epithelial Type Is Required for a Diagnosis of Barrett's Esophagus?—

Barrett's esophagus is judged to develop through the process of metaplasia in which one adult cell type replaces another. For reasons that are not clear, Barrett's metaplasia is predisposed to cancer development. Three types of columnar epithelia have been described in Barrett's esophagus: (1) a gastric fundic-type epithelium that has mucus-secreting cells, parietal cells, and chief cells; (2) a cardia-type (also known as junctional-type) epithelium composed almost exclusively of mucus-secreting cells; and (3) an intestinal-type epithelium (sometimes called specialized columnar epithelium or specialized intestinal metaplasia) that contains prominent goblet cells.⁸ The fundic- and cardia-type epithelia in Barrett's esophagus can be morphologically indistinguishable from columnar epithelia found in the stomach.

If biopsy specimens of suspected Barrett's esophagus reveal only fundic- and cardia-type epithelia, then it can be difficult to establish that those epithelial types are metaplastic because (1) biopsy sampling error can result in inadvertent biopsy of the stomach instead of the esophagus, especially when only short segments of columnar epithelium appear to extend above the GEJ, and (2) some authorities have argued that the normal distal esophagus can have short segments of a gastric-type columnar lining.⁹ With no precise landmark for the GEJ, it is difficult to support or refute that contention. If biopsy specimens of suspected Barrett's esophagus reveal intestinal-type epithelium, in contrast, then there is little doubt that the epithelium is abnormal and metaplastic. This finding does not obviate the issue of biopsy sampling error, however, because intestinal metaplasia is common in the stomach that is chronically infected with *Helicobacter pylori*.¹⁰

Intestinal-type epithelium can be readily identified by the pathologist and, unlike the gastric-type epithelia, intestinal-type epithelium is clearly abnormal when located in the esophagus. Furthermore, early reports suggested that the intestinal-type epithelium in Barrett's esophagus was the one predisposed to malignancy. For those reasons, practical more than scientific or conceptual, investigators and clinicians adopted the policy of requiring the demonstration of intestinal metaplasia in esophageal biopsy specimens as a sine qua non for the diagnosis of Barrett's esophagus. However, recent findings have challenged the validity of that practice. There are data to suggest that cardia-type epithelium may not be normal, but rather may be a metaplastic lining that develops as a consequence of chronic gastroesophageal reflux disease (GERD).¹¹

Histochemical and genetic studies of cardia-type epithelium have revealed molecular abnormalities, similar to those found in specialized intestinal metaplasia, that may predispose to cancer development.^{12,13} Recent clinical studies also suggest that cardia-type epithelium has malignant potential. In one such study of 141 patients who underwent endoscopic mucosal resection (EMR) for small esophageal adenocarcinomas, 71% had cardia-type epithelium, not intestinal metaplasia, found adjacent to the cancer, and 57% had no intestinal metaplasia whatsoever found in the EMR specimen.¹⁴

The columnar-lined esophagus has clinical importance only because it predisposes to the development of esophageal cancer. The debate about whether patients who have only cardia-type epithelium lining the distal esophagus have “Barrett's esophagus” is primarily a semantic issue. The key unanswered clinical question for those patients is this: What is the risk of developing esophageal cancer? The great majority of studies on the risk of cancer in Barrett's esophagus have included patients with specialized intestinal metaplasia either primarily or exclusively.¹⁵ Although recent data suggest that cardia-type epithelium may well predispose to malignancy, the magnitude of that risk is not yet clear. A reasonable estimate of cancer risk is needed to make rational management decisions for patients with Barrett's esophagus, and no such estimate is available for patients who have only cardia-type epithelium in their columnar-lined esophagus.

Despite reasonable arguments supporting the concept that Barrett's esophagus might be defined by the presence of cardia-type as well as by intestinal-type epithelium in the esophagus, there are substantial practical reasons for not adopting this definition into clinical practice at this time. The inclusion of patients with cardia-type epithelium under the rubric of “Barrett's esophagus” would substantially increase the number of patients with that disorder, which would substantially increase treatment costs. The benefits of surveillance and treatment programs for Barrett's esophagus are debated, even for patients with intestinal metaplasia, whose cancer risk is far better defined. The likelihood of finding intestinal-type epithelium in Barrett's esophagus varies directly with the extent of the esophageal columnar lining, and the issue of whether to consider cardia-type epithelium a marker for Barrett's esophagus usually concerns only patients with short segments of esophageal columnar epithelium (generally segments considerably less than 3 cm in extent). The clinical benefit of biopsy sampling for patients with such short segments of esophageal columnar epithelium has not been established.

What Is the Definition of Barrett's Esophagus?—Any definition of Barrett's esophagus necessarily will have an arbitrary component. If Barrett's esophagus is to be considered a medical condition rather than merely an anatomic curiosity, then it should have clinical importance. The columnar-lined esophagus has clinical importance only if it predisposes to esophageal cancer. Therefore, we believe that Barrett's esophagus can be defined 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. Presently, intestinal metaplasia is the only one of the 3 types of esophageal columnar epithelia described that clearly predisposes to malignancy; therefore, we suggest that the term “Barrett's esophagus” presently should be used only for patients who have intestinal metaplasia in the esophagus. Circumstantial evidence suggests that cardia-type epithelium also may be predisposed to cancer development, but presently that predisposition has not been established and there are insufficient data to make meaningful recommendations regarding the management of patients who have a columnar-lined esophagus with cardia-type epithelium alone. If future studies establish a malignant predisposition for cardia-type epithelium, then those patients also can be considered to have Barrett's esophagus by our proposed definition. For now, however, only patients with intestinal-type columnar metaplasia in the esophagus are known to have an increased cancer risk, and only those patients meet our criteria for the diagnosis of Barrett's esophagus.

Should Endoscopists Measure the Extent of Barrett's Metaplasia?—Barrett's esophagus has been categorized as long segment (when the metaplastic epithelium extends at least 3 cm above the GEJ) or short segment (when there is <3 cm of metaplastic epithelium lining the esophagus).¹⁶ Another more recently proposed system for categorizing Barrett's esophagus, the Prague C and M criteria, identifies both the circumferential extent

(C) and the maximum extent (M) of Barrett's metaplasia.¹⁷ One study has shown excellent interobserver agreement among endoscopists using the Prague C and M criteria when columnar epithelium extends at least 1 cm above the GEJ but poor agreement for shorter segments of esophageal columnar lining.¹⁷

There may be clinical value in measuring the extent of Barrett's metaplasia visualized during endoscopic examination (ie, the distance between the GEJ and the squamocolumnar junction in the esophagus). Data suggest that the likelihood of finding intestinal metaplasia in the columnar-lined esophagus and the magnitude of the cancer risk vary directly with the extent of the metaplastic lining (see the following text). For patients found to have dysplasia in Barrett's esophagus, furthermore, the extent of metaplasia is a factor that may influence the choice among the therapeutic options (see the following text). Therefore, we advocate the use of a system, like the Prague C and M criteria, that provides information on the extent of Barrett's metaplasia. However, the clinical benefit of using any proposed endoscopic system for classifying Barrett's esophagus has not been established by formal investigation and, presently, patients with any extent of intestinal metaplasia are managed similarly.

What Is the Risk of Esophageal Cancer for the General Population of Patients With Barrett's Esophagus?

A number of older reports linking Barrett's esophagus to esophageal adenocarcinoma described an inordinately high incidence of cancer, in the range of 20 to 40 per 1000 person-years (2%–4% per year).^{18–20} A variety of confounding factors, including selection bias, the inclusion of prevalent cancers, and publication bias, may have contributed to the overestimation of cancer risk in those studies.¹⁵ Subsequent reports of larger series generally have described a substantially lower cancer risk for patients with Barrett's esophagus, but even some modern reports describe very high cancer incidence rates.²¹ National health statistics cannot be used to estimate cancer risk because the denominator (ie, the total number of persons with Barrett's esophagus in the general population) is not known. Nevertheless, a reasonable estimate of the incidence of cancer in Barrett's esophagus is needed to formulate rational management strategies for patients with this condition.

A number of systematic reviews of studies on the incidence of cancer in patients with Barrett's esophagus have been published.^{15,22–24} A recent review described outcomes for 47 studies that met inclusion criteria from an initial search that yielded 7780 publications from MEDLINE and EMBASE databases (years 1950–2006).²⁴ The overall estimate of cancer incidence was based on 209 cancers discovered in 11,279 patients with Barrett's esophagus who were followed up for 47,496 person-years. The average incidence of cancer was 6.1 per 1000 person-years, but this estimate may have been spuriously high because it included patients in whom cancer was discovered within the first year after the diagnosis of Barrett's esophagus. Such patients likely had prevalent cancers that were missed on their initial endoscopic examinations. After adjusting the results to exclude those patients, the incidence of cancer was 5.3 per 1000 person-years (0.5% per year), an estimate well aligned with the results of prior systematic reviews.

Among 4 studies published since the aforementioned systematic review was a report of a cohort of 502 patients with Barrett's esophagus from Leeds in the United Kingdom.²⁵ The annual incidence of cancer among patients who had Barrett's esophagus with specialized intestinal metaplasia was 16 per 1000 person-years (1.6% per year). Another single-center cohort from Birmingham in the United Kingdom calculated an incidence of 3.1 per 1000 person-years (0.3% per year) based on 3 cancers diagnosed among 188 patients with Barrett's esophagus.²⁶ A third study from the United Kingdom reported statistics from a multicenter national registry involving 738 patients with a combined follow-up of 3697 years. The overall annual incidence of esophageal adenocarcinoma was 0.5% (95%

confidence interval [CI], 0.3–0.8).²⁷ Finally, an endoscopic and pathology-based database in Spain was retrospectively examined to calculate a cancer risk in patients with Barrett's esophagus of 5.2 per 1000 person-years (0.5% per year).²⁸

The risk of cancer in Barrett's esophagus appears to vary with the extent of esophageal metaplasia; therefore, patients with long-segment disease may have a higher incidence of adenocarcinoma than those with short-segment Barrett's esophagus.²³ In the aforementioned Spanish cohort, for example, the annual risk of esophageal adenocarcinoma was 0.57% for patients with long-segment Barrett's esophagus compared with only 0.26% for patients with short-segment disease.²⁸ The risk of cancer development also is lower in women than in men with Barrett's esophagus (4.5 vs 10.2 cancers per 1000 person-years).²⁴

The precise risk of cancer in Barrett's esophagus remains unclear. Reported estimates of cancer risk continue to vary widely, and it is not clear how biases, statistical aberrations, and regional differences in incidence rates contribute to the disparities among the published reports. Methodologically, larger studies (ie, 500 or more person-years of observation) report lower cancer incidence rates than smaller studies, as do studies that represent population-based as opposed to referral-based cohorts.²⁴ Estimates of cancer risk also are likely to be affected by the proportion of patients with short-segment Barrett's esophagus and women in the cohort. With these limitations in mind, most modern systematic reviews and large series suggest that the annual incidence of cancer for the general population of patients with Barrett's esophagus is approximately 0.5% per year. For patients with dysplasia in Barrett's epithelium, the risk of cancer is substantially higher (see the following text).

Does Barrett's Esophagus Affect Life Expectancy? How Does a Diagnosis of Barrett's Esophagus Affect Quality of Life?

Does Barrett's Esophagus Affect Life Expectancy?—A review of the literature reveals some contradictory results for studies assessing the impact of a diagnosis of Barrett's esophagus on life expectancy. In a population-based study in Northern Ireland, Anderson et al compared mortality rates for subjects with Barrett's esophagus with those for age- and sex-matched subjects in the general population. The investigators found no significant differences in overall mortality rates between the 2 groups.²⁹ Although deaths from esophageal cancer were more common in the group with Barrett's esophagus, the total frequency of such deaths was so low that it had little effect on overall mortality. Another study that compared survival for subjects with Barrett's esophagus with survival for 2 control groups (the general population and patients with Schatzki's rings) also found no difference in life expectancy among the groups.³⁰ In contrast, Moayyedi et al in the United Kingdom found increased mortality for subjects who had Barrett's esophagus diagnosed at 4 hospitals in Leicestershire compared with age- and sex-matched subjects in the general population.³¹ Interestingly, however, the excess mortality in the patients with Barrett's esophagus was primarily due to extraesophageal diseases such as bronchopneumonia and ischemic heart disease. In another large population-based study in which survival for a cohort of 1677 patients with Barrett's esophagus was compared with an age- and sex-matched cohort of 13,416 individuals in the general population, Solaymani-Dodaran et al found that the patients with Barrett's esophagus had a 37% increase in mortality.³² Approximately 45% of the excess mortality in the patients with Barrett's esophagus was due to esophageal cancer, whereas 55% was due to extraesophageal disorders such as cardiovascular disease. The excess deaths from cardiovascular problems may be related to the association of Barrett's esophagus with obesity, which also is a risk factor for cardiovascular disease.

Despite the somewhat disparate findings of these studies on survival for patients with Barrett's esophagus, several conclusions are warranted. First, even though deaths from

esophageal adenocarcinoma are more common in patients with Barrett's esophagus than in individuals without that condition, adenocarcinoma remains an uncommon cause of mortality in patients with Barrett's esophagus nevertheless.^{33,34} Furthermore, because this cancer generally occurs later in life,³⁵ the impact of such a death on the mean survival of the cohort is lessened, because deaths due to extraesophageal diseases such as cardiovascular disorders are far more common and therefore drive overall mortality rates. It also appears that mortality due to cardiovascular disease may be increased in patients with Barrett's esophagus, perhaps because of the association of the disorder with obesity.

How Does a Diagnosis of Barrett's Esophagus Affect Quality of Life?—

Numerous studies have attempted to quantify the quality of life in patients with Barrett's esophagus, but those studies are limited in several important ways. First, they lump all subjects with prevalent disease into a single category and compare that group with controls such as subjects who have GERD without Barrett's esophagus or the general population. It is likely that the quality of life for patients with Barrett's esophagus varies with a number of important factors, such as disease duration and the number of surveillance endoscopies performed, that are not accounted for in such studies. Second, the studies generally use a convenience sample of subjects with Barrett's esophagus attending outpatient clinics or endoscopy units at tertiary care centers. The impact of the disease on such subjects may be very different from that on the general population of individuals with Barrett's esophagus. For instance, one might expect subjects attending repeated endoscopic surveillance sessions to be more concerned about their risk of developing adenocarcinoma than those who forego such measures. Finally, there is no validated, disease-specific, widely accepted quality-of-life measure for Barrett's esophagus. Investigators have used generic quality-of-life measures as well as organ-specific measures and tools developed specifically for GERD populations. Those tools may fail to capture important domains of quality of life for subjects with Barrett's esophagus.

With these limitations in mind, a systematic review found 25 articles in the English-language literature that provide quantitative assessments of quality of life or financial and psychological burdens of disease for subjects with Barrett's esophagus.³⁶ Five studies assessed patients using the generic quality-of-life measure 36-Item Short Form Health Survey (SF-36),³⁷ 3 studies used Quality of Life in Reflux and Dyspepsia (QOLRAD),³⁸ and 2 studies used Gastrointestinal Quality of Life Index.³⁹ Four studies evaluated utility measures in patients with Barrett's esophagus. Utilities rate the desirability of living with a given disease state on a scale of 0 to 1, where a rating of 1 indicates essentially no decrease in the desirability of life and 0 indicates a quality of life so undesirable it is equal to death. Eight studies did not use traditional quality-of-life instruments but quantitatively assessed impact (psychological, financial, social, and so on) or burden of disease by other measures. Of these 25 studies, 9 included patients with Barrett's esophagus as a subset of patients with GERD symptoms or a priori compared patients with Barrett's esophagus with patients with GERD. The remaining 16 studies included only patients with Barrett's esophagus.

On balance, these studies show that a diagnosis of Barrett's esophagus has a substantial negative impact on quality of life. All reported cohorts showed lower SF-36 scores in subjects with Barrett's esophagus compared with the population norms. Studies using organ-specific measures such as QOLRAD and Gastrointestinal Quality of Life Index also showed diminished quality of life in subjects with Barrett's esophagus compared with the population norms. One study found similar QOLRAD scores in patients with Barrett's esophagus and patients with GERD. Whereas both groups reported substantial GERD symptoms, it is possible that a major component of the decrease in quality of life experienced by the patients with Barrett's esophagus was due to their GERD symptoms. Attempts to quantify quality of life in Barrett's esophagus using health state utilities have repeatedly shown diminished

utility for life with this condition. The negative impact on utility varies with the degree of dysplasia in Barrett's epithelium and has been reported to be as low as 0.77 for patients with high-grade dysplasia.⁴⁰

Although subjects with Barrett's esophagus are consistently found to have a poorer quality of life than the general population, it is unclear to what extent this is attributable to anxiety regarding cancer risk, discomfort due to GERD symptoms, or other factors. Patients with Barrett's esophagus appear to greatly overestimate their cancer risk, and this overestimation is associated with an increase in their utilization of health care.⁴¹ In addition to this psychological distress, patients with Barrett's esophagus face higher individual costs for life insurance and may be unable to obtain health insurance.⁴²

In summary, by generic and organ-specific quality-of-life measures, subjects with Barrett's esophagus repeatedly have been shown to have substantially lower scores than population norms. Subjects with Barrett's esophagus consistently report their utility of living with the disease lower than without it, and the decrease in utility correlates with the degree of dysplasia in Barrett's epithelium. A diagnosis of Barrett's esophagus appears to cause psychological stress and may be associated with substantial, but incompletely understood, additional costs such as increased life and health insurance premiums.

Who Is at Risk for Barrett's Esophagus? Who Should Be Screened for Barrett's Esophagus?

Who Is at Risk for Barrett's Esophagus?—A systematic review of original literature on the epidemiology of Barrett's esophagus shows that most published studies describe hospital-based or endoscopy clinic-based cohorts; relatively few describe large population-based cohorts. It is important to consider this potential bias when assessing those epidemiologic studies, which have identified a number of risk factors for Barrett's esophagus. Selected risk factors are reviewed briefly in the following text.

It is not clear when Barrett's esophagus develops, but most recognized cases are diagnosed in the sixth decade of life or later.^{43,44} Although the utilization of endoscopy (and hence the chance of finding Barrett's esophagus) is higher in older subjects, cohort studies suggest that, as age increases, so does the likelihood that a subject with GERD symptoms will have Barrett's esophagus.⁴³ Whether the condition results from a single catastrophic insult to the esophageal mucosa, which may be more likely to occur in older subjects, or whether Barrett's esophagus is the cumulative result of years of reflux-induced damage is not clear. Longitudinal studies, which have found that the extent of Barrett's metaplasia does not increase with time (at least in subjects on therapy), provide some support for the concept that the condition develops all at once.⁴⁵

There is a male predominance for Barrett's esophagus, as there is for esophageal adenocarcinoma. In case-control and cohort studies, the risk of Barrett's esophagus among men with GERD symptoms is 1.5- to 3-fold higher than that of women.^{44,46–48} A recent meta-analysis of cohort studies comprising consecutively enrolled subjects with Barrett's esophagus shows a case mix of men and women of approximately 2:1.⁴⁹ Whether this male preponderance is the result of differences between men and women in hormonal effects on the esophagus, body fat distribution, or other as-yet unidentified factors is not clear.

Most cohort studies show that the majority of subjects with Barrett's esophagus are white.⁴⁸ Because most of these studies are clinic or hospital based, some of the apparent ethnic predisposition may be biased by the underlying demographics of the patients who attend those facilities. Several studies have attempted to quantify how the proportion of subjects with heartburn who have Barrett's esophagus varies among different ethnic groups. Abrams

et al found that, among subjects who underwent endoscopy at their institution, white subjects were approximately 4 times as likely to have Barrett's esophagus as Hispanic or black subjects.⁴³ Similarly, a cohort study of subjects presenting for screening colonoscopy who were invited to undergo upper endoscopy found that white subjects were more likely to have Barrett's esophagus than black subjects.⁵⁰ In a community-based study, Corley et al found that the incidence of Barrett's esophagus in non-Hispanic white subjects was more than 6 times greater than that in black subjects.⁴⁸ In contrast, Eloubeidi et al did not find race to be a predictor of Barrett's esophagus in a Veterans Administration population.⁵¹ If there are significant differences in the prevalence of Barrett's esophagus between white and black subjects, they are not likely the result of differences in the underlying prevalence of GERD, because the distribution of heartburn symptoms appears to be similar between those 2 groups.⁵² However, limited studies suggest that both GERD and Barrett's esophagus are far less common in Asian patients than in white subjects.⁵³

GERD is strongly associated with Barrett's esophagus. Case-control studies suggest that subjects with heartburn are 6 to 10 times more likely to have Barrett's esophagus than those without heartburn. Furthermore, there appears to be a dose-response relationship in that subjects with more frequent or chronic GERD symptoms are more likely to have Barrett's esophagus.^{51,54-57} Hiatal hernia also is associated with the presence of Barrett's esophagus.^{46,55} However, the relationship between GERD symptom severity and Barrett's esophagus is not as strong.⁵¹

Cohort and case-control studies assessing esophageal acid exposure in subjects who have GERD with and without Barrett's esophagus showed that those with Barrett's esophagus have, on average, greater acid exposure than those without and that the extent of Barrett's metaplasia correlates directly with the duration of esophageal acid exposure.⁵⁵ Increased bile reflux (as estimated by a system that measures esophageal exposure to bilirubin) also has been documented in subjects with Barrett's esophagus,^{46,58} but the role of components of refluxate other than acid in the development of the condition remains controversial.

A high body mass index and an intra-abdominal distribution of body fat have been shown to be strong risk factors for Barrett's esophagus. Patients with Barrett's esophagus have, on average, a higher body mass index than either patients with GERD without Barrett's esophagus or general population controls.⁵⁹⁻⁶¹ Interestingly, the distribution of body fat may be the key to this association. For any given body mass index, subjects with higher amounts of intra-abdominal obesity, manifest either radiographically or by increased waist-to-hip ratio measures, appear to have an increased risk of Barrett's esophagus.^{59,60,62} In fact, in a recent analysis of body anthropometry in subjects with Barrett's esophagus, body mass index was no longer an independent predictor of the disorder once waist-to-hip ratio was factored.⁶² Whether the increased risk associated with intra-abdominal obesity is due to mechanical or hormonal factors or a consequence of yet-undescribed factors is not known.

Alcohol and smoking are not nearly as strongly associated with Barrett's esophagus as they are with squamous cell cancer of the esophagus, and studies on the association of these habits with Barrett's esophagus have yielded inconsistent results. In a population-based study, Ronkainen et al showed that subjects who used tobacco or alcohol were approximately 3 times as likely to have Barrett's esophagus as subjects who did not.⁶³ Other studies have found an association between either smoking⁴⁴ or alcohol⁶⁴ and Barrett's esophagus, whereas a number of investigations have not.⁶⁵⁻⁶⁷ In fact, recent data suggest that consumption of wine actually may protect against Barrett's esophagus.^{65,66} High vegetable and fruit intake appear to diminish the risk of Barrett's esophagus, although the mechanism is not known.^{68,69}

In summary, well-established risk factors for Barrett's esophagus include advanced age, male sex, white ethnicity, GERD, hiatal hernia, elevated body mass index, and a predominantly intra-abdominal distribution of body fat. Moderate consumption of wine and a diet high in fruits and vegetables may protect against the disorder.

Who Should Be Screened for Barrett's Esophagus?—Despite the considerable published data available on risk factors for Barrett's esophagus, few attempts have been made to apply this information systematically in the design of guidelines on who to screen for the condition. Furthermore, despite the dearth of studies showing clinical benefit resulting from endoscopic screening for Barrett's esophagus, the practice remains widespread among clinicians in the United States.⁷⁰ Professional organizations are divided on whether to recommend endoscopic screening for Barrett's esophagus, however, with some suggesting that the practice may be appropriate⁷¹ and others not endorsing it routinely.^{72,73}

Most recommendations on screening for Barrett's esophagus have focused on subjects with chronic GERD symptoms, because GERD was one of the first and strongest risk factors for Barrett's esophagus identified and because chronic esophageal inflammation due to GERD has been thought to contribute to esophageal carcinogenesis. Several cohort and case-control studies suggest that endoscopic screening and surveillance for Barrett's esophagus can have beneficial effects.^{74,75} Subjects who have esophageal adenocarcinoma discovered as the result of an endoscopic screening or surveillance program for Barrett's esophagus present with earlier-stage tumors, are less likely to have lymph node involvement, and have better short-term life expectancies than patients who present with symptoms of esophageal cancer such as dysphagia and weight loss. Cost-effectiveness analyses suggest that endoscopic screening may be cost-effective if certain predefined clinical parameters are met.^{76,77}

Although these data may seem compelling, several conceptual and logistical difficulties diminish the utility of screening endoscopy as it is currently practiced in the United States. First and foremost, approximately 40% of subjects who have adenocarcinoma of the esophagus report no history of chronic GERD symptoms.⁷⁸ Using GERD symptoms as an entrance criterion to endoscopic screening programs immediately excludes those subjects, decreasing by almost one-half our ability either to prevent the cancer or to detect it at an early, presymptomatic stage. Second, even among subjects with GERD symptoms, the risk of adenocarcinoma is very low in absolute terms. Studies show that up to 40% of the adult US population experience GERD symptoms on a monthly basis and 20% on a weekly basis.⁷⁹ Although the incidence of adenocarcinoma of the esophagus has increased 6-fold in the past 3 decades,⁸⁰ fewer than 10,000 Americans develop esophageal adenocarcinoma each year, representing a minute fraction of the total number of individuals with GERD symptoms. Even among patients with Barrett's esophagus, cohort studies show that more than 90% never develop esophageal adenocarcinoma.⁸¹ Therefore, the vast majority of individuals who undergo endoscopic screening for Barrett's esophagus based on the presence of GERD symptoms will not benefit from the procedure.

There also are substantial problems with the execution of various facets of endoscopic screening and surveillance programs that diminish their effectiveness. These include difficulties in the endoscopic recognition of important lesions,⁸² the random nature of esophageal biopsy sampling that is subject to considerable sampling error,⁸³ and disagreement among pathologists in the histologic interpretation of the esophageal biopsy specimens.⁸⁴ Finally, endoscopic examinations are expensive, especially after factoring in costs not only for the endoscopy but also for the tissue acquisition and interpretation.

No direct evidence substantiates the utility of endoscopic screening for Barrett's esophagus, and substantial confounding factors such as lead time and length bias compromise the validity of the observational studies, suggesting that the practice is beneficial.⁸⁵ Therefore, inadequate evidence exists to endorse endoscopic screening for Barrett's esophagus based solely on the presence of GERD symptoms, and decisions on when to recommend endoscopic screening should continue to be individualized. It is incumbent on the practitioner to ensure that patients who elect to undergo endoscopic screening for Barrett's esophagus understand not only the putative advantages of the procedure but also the substantial shortcomings and possible negative effects, which include the expense and risks of the endoscopy and of the invasive procedures that might be recommended to treat lesions found by endoscopy as well as the potential adverse impact on quality of life (see the following text). Whether the development of new endoscopic technologies that are more sensitive, less expensive, and easier to perform or the availability of improved endoscopic treatments for Barrett's esophagus eventually will tip the scales in favor of screening is not yet known.

What Is the Natural History of Dysplasia in Barrett's Esophagus?

During the process of carcinogenesis in Barrett's esophagus, some of the genetic alterations that endow cells with growth advantages (eg, activation of oncogenes, inactivation of tumor suppressor genes) also cause morphologic changes in the tissue that the pathologist recognizes as dysplasia (also called intraepithelial neoplasia). Thus, dysplasia can be viewed as the histologic expression of genetic alterations that favor unregulated cell growth.⁸⁶ Dysplasia can be categorized as low grade or high grade depending on the degree of histologic abnormalities. Pathologists can have difficulty distinguishing low-grade dysplasia in Barrett's esophagus from reactive changes caused by reflux esophagitis; consequently, interobserver agreement for the diagnosis of low-grade dysplasia may be poor.

Dysplasia in Barrett's esophagus sometimes causes no endoscopically apparent abnormalities, and dysplasia can be patchy both in its extent and severity. These factors contribute to the substantial problem of biopsy sampling error in identifying dysplasia. Endoscopists traditionally have used a 4-quadrant biopsy sampling system (which is essentially a random sampling technique) to find dysplasia in Barrett's esophagus, and it is clear that this system can miss areas of dysplasia and even cancer. In series of patients who underwent esophagectomies because endoscopic examination revealed high-grade dysplasia in Barrett's esophagus, for example, a number of studies have found that invasive cancer is present in 30% to 40% of the resected esophagi.⁸⁷ However, a recent critical review of those studies suggests that 13% is a more accurate estimate of the frequency of invasive cancer in this situation, and when a careful endoscopic examination excludes all visible lesions, the frequency of finding invasive cancer at esophagectomy is only 3%.⁸⁸

A meta-analysis published in 2008 focused on the incidence of esophageal adenocarcinoma in patients with high-grade dysplasia in Barrett's esophagus.⁸⁹ The literature search of MEDLINE and associated sources yielded 3843 citations, of which 196 were deemed potentially relevant; on complete review, however, only 4 articles met the inclusion criteria for the study (ie, study patients had histologically confirmed Barrett's esophagus with high-grade dysplasia, no prevalent cancer, and no ablative or surgical therapy). The crude incidence of esophageal adenocarcinoma among patients with high-grade dysplasia was 55.7 per 1000 person-years (5.6% per year). Using different weighting algorithms, the incidence increased to 65.8 per 1000 person-years (6.6% per year) with 95% CIs of 49.9 to 84.6 (Poisson) or 49.7 to 81.8 (binomial) per 1000 person-years of observation.

The incidence of cancer in patients who have low-grade dysplasia in Barrett's esophagus is especially poorly defined. Some studies have found a risk of cancer no greater than that for

the entire population of patients with Barrett's esophagus,⁹⁰⁻⁹² whereas others have observed considerably higher rates.^{84,93} One reason for these disparities may be the poor interobserver correlation among pathologists in the diagnosis of low-grade dysplasia.⁹⁴ This possibility is supported by the observation that, among patients whose diagnosis of low-grade dysplasia is confirmed by 2 or more pathologists, the incidence of cancer is substantially higher than that for patients whose pathologists disagree on the diagnosis.^{84,93} The "extent" of low-grade dysplasia defined as the proportion of crypts that exhibit dysplastic changes has been suggested to improve the ability to discern which patients are at greater risk for development of cancer.⁹⁵

Another unresolved issue is whether dysplasia can regress or whether the inability to demonstrate dysplasia on follow-up endoscopic examinations is merely the result of biopsy sampling error. In one of the largest multicenter longitudinal studies, 42% of patients initially diagnosed with low-grade dysplasia had no dysplasia found on subsequent endoscopic examinations and an additional 32% had low-grade dysplasia found only intermittently during their course of surveillance.⁹² In this study, the calculated incidence of esophageal adenocarcinoma among patients with low-grade dysplasia was 0.6% per year (95% CI, 0-2%), a rate of cancer development similar to that reported for the general population of patients with Barrett's esophagus. On the other hand, 3 patients in whom cancer developed did not have dysplasia diagnosed during prior endoscopic surveillance examinations. It is not clear whether those cancers developed *de novo*, without first manifesting dysplasia, or whether the preceding dysplasia merely was missed due to biopsy sampling error. Other reports also have described the apparent regression of dysplasia in the absence of ablation.²²

Does Endoscopic Surveillance Improve Survival for Patients With Barrett's Esophagus?

Endoscopic surveillance has been proposed for patients with Barrett's esophagus with the unproved assumption that the practice will reduce deaths from esophageal adenocarcinoma and thereby prolong survival. Societal guidelines generally have recommended endoscopic surveillance for patients with Barrett's esophagus at intervals that vary with grade of dysplasia found in the metaplastic epithelium. Intervals of 3 to 5 years have been suggested for patients who have no dysplasia, 6 to 12 months for those found to have low-grade dysplasia, and every 3 months for patients with high-grade dysplasia who receive no invasive therapy.⁷²

During endoscopic surveillance, the endoscopist attempts to identify esophageal neoplasia in an early, curable stage, usually in the form of dysplasia. To find dysplasia, endoscopists generally have relied on a systematic, 4-quadrant biopsy sampling technique designed with the intent of maximizing the chance for identifying an inconspicuous lesion that may be randomly distributed throughout the Barrett's epithelium. The "Seattle protocol" calls for obtaining such 4-quadrant biopsy specimens at intervals of every 1 to 2 cm throughout the columnar-lined esophagus. In addition, areas of mucosal irregularity (eg, nodules, masses, ulceration), which are especially likely to be associated with dysplasia, are sampled separately.

A prospective study showed a significant increase in the number of cases of high-grade dysplasia and invasive cancer detected after institution of a rigorous endoscopic surveillance protocol like the one described previously.⁹⁶ In the community, however, surveillance often is not performed in this rigorous manner. A retrospective study of endoscopic and pathology reports from 15 hospitals in The Netherlands revealed that adherence to the Seattle protocol was good (79%) for cases in which Barrett's metaplasia involved only up to 5 cm of the distal esophagus but diminished with increasing extent of metaplasia to the point that there was only 30% adherence among cases with metaplasia involving 10 to 15 cm of the

esophagus.⁹⁷ An American study using a large pathology database maintained by Caris Diagnostics identified 2245 patients who had esophageal biopsy specimens taken for evaluation of Barrett's esophagus and who had endoscopy reports that documented the extent of esophageal columnar lining.⁹⁸ Overall, adherence to the Seattle protocol was found in only 51% of cases. As in the previous study, adherence to the protocol varied inversely with the extent of Barrett's metaplasia. In addition, failure to adhere to the protocol was associated with a significantly decreased rate of detecting dysplasia (summary odds ratio, 0.53; 95% CI, 0.35–0.82). These studies suggest that, although adherence to recommended surveillance procedures is associated with higher rates of detection of dysplasia, many practicing gastroenterologists do not adhere to those guidelines and adherence appears to be poorest for the population at highest risk for development of cancer (ie, patients with extensive Barrett's metaplasia).

Streitz et al studied 77 patients who they treated for esophageal adenocarcinoma to explore whether prior endoscopic surveillance was associated with better survival (Table 3).⁹⁹ In 19 patients, the cancers were found during surveillance endoscopies performed because Barrett's esophagus had been discovered 8 to 120 months earlier (median, 24 months). The remaining 58 patients presented to the hospital with symptoms of esophageal cancer, and Barrett's esophagus was first diagnosed when their tumors were resected. Compared with the latter patients, the patients whose tumors were discovered during endoscopic surveillance had cancers in significantly lower stages and had a significantly better 5-year actuarial survival rate (62% vs 20%). It should be noted that 9 patients in the surveillance group had esophagectomy performed for carcinoma in situ or high-grade dysplasia, although 2 of these had invasive carcinoma found in the resected specimen.

Peters et al reported the results of a similar study comparing outcomes for 17 patients who had esophagectomy performed for high-grade dysplasia or adenocarcinoma discovered during endoscopic surveillance with those for 35 patients who had esophagectomy for adenocarcinomas discovered outside a surveillance program.¹⁰⁰ Although the endoscopic surveillance protocol was not standardized, all 17 patients had a diagnosis of Barrett's esophagus without cancer established at least 6 months before esophagectomy. Five of the 9 patients who underwent resection for high-grade dysplasia were found to have invasive cancer in the resected specimen. As in the previous study, the patients whose tumors were discovered during surveillance had cancers in significantly lower stages and longer survivals.

In another single-center experience, Van Sandick et al also compared outcomes for patients with adenocarcinoma of the esophagus or esophagogastric junction discovered in and outside endoscopic surveillance programs.⁷⁵ The 16 patients in the surveillance group were known to have had Barrett's esophagus for a median duration of 42 months, and they had been under endoscopic surveillance for intervals ranging from 2 months to 2.5 years (median, 10 months). Five of those 16 patients had esophagectomy for high-grade dysplasia; 1 was found to have invasive cancer, 2 were found to have intramucosal carcinoma, and 2 had only high-grade dysplasia found in the resected esophagus. Compared with the 54 patients whose tumors were discovered outside a surveillance program, the pathologic stage of cancer was significantly lower for patients in the surveillance group, and their 2-year survival was significantly better (85.9% vs 43.3%; $P = .0029$). Surveillance was associated with significantly longer survival even when patients with a preoperative diagnosis of high-grade dysplasia (without cancer) were excluded from the analysis.

Fountoulakis et al studied a cohort of consecutive patients who underwent esophagectomy for high-grade dysplasia or adenocarcinoma in Barrett's esophagus, comparing the survival of those whose neoplasms were discovered in and outside a standardized endoscopic

surveillance program.¹⁰¹ The surveillance group included 17 patients who had at least one endoscopy performed at least 6 months after their first diagnosis of Barrett's esophagus, whereas the no-surveillance group comprised 74 patients who first presented to the hospital with adenocarcinoma. Overall survival was significantly longer for patients in the surveillance group, with 1- and 3- year survival rates for the surveillance and no-surveillance groups of 88% versus 67% and 80% versus 31%, respectively.

Using the Northern California Kaiser Permanente cancer registry, Corley et al studied outcomes for 589 patients with adenocarcinoma of the esophagus or gastric cardia diagnosed from 1990 to 1998.⁷⁴ Among only 23 patients who were known to have had Barrett's esophagus for at least 6 months before the cancer was diagnosed, 15 had their tumors discovered during surveillance endoscopy, whereas 8 had their cancers detected during endoscopy performed because of cancer symptoms. As in the single-center observational studies discussed previously, the patients whose tumors were discovered during surveillance had cancers at significantly lower stages and had significantly better 2-year survival compared with the patients whose tumors were discovered because they were symptomatic (73.3% vs 12.5%; $P = .02$).

Cooper et al studied a cohort of 1633 patients in the Surveillance, Epidemiology and End Results (SEER) database who had adenocarcinoma of the esophagus or gastric cardia.¹⁰² Through linkage with Medicare claims data, the investigators were able to identify those who had endoscopy performed more than 1 year before the cancer was diagnosed. A record of prior endoscopy was found in only 9.7% of the patients, and only 3.7% had Barrett's esophagus identified at least 1 year before the diagnosis of cancer. However, a prior diagnosis of Barrett's esophagus was associated with a lower cancer stage and a higher probability of treatment by esophagectomy. The median survival for patients with esophageal adenocarcinoma who had a prior endoscopy was 7 months, compared with only 5 months for those who had no prior endoscopy ($P < .01$). The association between prior endoscopy and prolonged survival remained significant even after adjusting for age at diagnosis, sex, race, and number of comorbidities using Cox proportional hazards modeling (relative hazards, 0.73; 95% CI, 0.57–0.93).

A more recent analysis of the SEER-Medicare data conducted by Cooper et al included 2754 patients with a new diagnosis of esophageal adenocarcinoma.¹⁰³ Having an endoscopy performed 3 years to 6 months before the diagnosis of cancer was associated with an improvement in median survival from 7 months (for patients with no prior endoscopy) to 11 months, yielding a significant reduction in the hazard ratio for death. Additional independent factors associated with improved survival included a prior diagnosis of Barrett's esophagus and receipt of therapy, including surgery, radiation, or chemotherapy. Of note, however, only 11.5% of the patients with cancer were found to have had a prior endoscopy, and Barrett's esophagus was identified in only 8.1% of patients before their diagnosis of cancer.

In a case-control study using the Veterans Affairs database, Kearney et al found that a group of 245 patients who had GERD and adenocarcinoma of the esophagus or gastric cardia were significantly less likely to have undergone endoscopy in the 1 to 8 years before the index date than 980 control subjects (matched by age, sex, and race) who had GERD without cancer (adjusted odds ratio, 0.66; 95% CI, 0.45–0.96).¹⁰⁴ Furthermore, a dose effect was noted whereby endoscopy performed 2 to 4 years before the index date was more protective against cancer death than endoscopy performed more than 4 years before that date.

Countering these positive results is a retrospective, controlled, cohort study by Rubenstein et al that used the Veterans Affairs national administrative databases to identify 155 subjects who had GERD associated with adenocarcinoma of the esophagus or esophagogastric

junction.¹⁰⁵ Although the 25 patients who had endoscopy performed 1 to 5 years before their diagnosis of cancer had tumors in a lower stage than the 130 patients who had no endoscopy during that same period, there was no significant difference in survival between the 2 groups (adjusted hazard ratio, 0.93; 95% CI, 0.58–1.50). Analysis of a subset of subjects for whom complete endoscopic and histopathologic data were available revealed that patients who had endoscopic surveillance performed according to guidelines proposed by the American College of Gastroenterology had better survival than those who did not. After adjustment for potential confounders, however, the improvement in survival did not achieve statistical significance. This study highlights the potential for lead- and length-time biases that can exaggerate the benefits of surveillance programs in observational studies.

In summary, the evidence to support endoscopic surveillance as a means to improve survival for patients who develop neoplasia in Barrett's esophagus relies on administrative data that have been examined retrospectively. The preponderance of this evidence suggests that endoscopic surveillance can reduce mortality from esophageal adenocarcinoma through the early detection of treatable cancers. However, such observational studies are prone to a number of biases, such as lead- and length-time biases, that could well exaggerate the benefits of surveillance programs. It remains unclear whether endoscopic surveillance is beneficial at all; consequently, it is not possible to make meaningful recommendations regarding the optimal intervals between endoscopic procedures or the optimal surveillance biopsy procedures.

Can Biomarkers Be Used to Confirm the Histologic Diagnosis of Dysplasia? Can Biomarkers Be Used Instead of Dysplasia for Risk Stratification in Barrett's Esophagus?

Can Biomarkers Be Used to Confirm the Histologic Diagnosis of Dysplasia?—

Presently, cancer risk stratification for patients with Barrett's esophagus is based primarily on the histologic finding of dysplasia. However, dysplasia is a very imperfect predictor of cancer risk for a number of reasons, including poor interobserver agreement among pathologists in distinguishing dysplasia from reactive epithelial changes (caused by reflux esophagitis) and in grading the severity of dysplastic change.^{84,106,107} Immunostaining for p53 has been proposed as an adjunct to the diagnosis of dysplasia, but the utility of this technique is limited by confounding factors such as high rates of false-positive staining and staining characteristics that vary with the type of p53 antibody used.¹⁰⁸ Immunostaining for α -methylacyl-CoA racemase (AMACR) and for a panel of biomarkers that includes β -catenin, cyclin D1, and p53 also has shown promise in preliminary studies for distinguishing dysplasia from reactive changes and for distinguishing among grades of dysplasia.^{109–111} In contrast to those promising reports, a study that attempted to correlate grades of dysplasia with messenger RNA expression levels for a panel of 10 genes believed to contribute to carcinogenesis in Barrett's esophagus found that the utility of the panel was severely limited by significant interpatient and inpatient variations in gene expression levels.¹¹² At this time, data supporting the use of biomarkers to confirm the histologic diagnosis of dysplasia must be considered preliminary, and biomarkers cannot yet be recommended for this purpose for routine clinical practice.

Can Biomarkers Be Used Instead of Dysplasia for Risk Stratification in Barrett's Esophagus?—A number of biomarkers other than the histologic finding of dysplasia have been proposed to predict the risk of neoplastic progression and, hence, the need for endoscopic surveillance or more invasive treatments in patients with Barrett's esophagus. In general, these putative biomarkers reflect DNA abnormalities, acquired during the process of carcinogenesis, that either endow the cells with growth advantages directly or favor the development of growth-promoting mutations. Most of the proposed biomarkers for Barrett's esophagus have been evaluated in cross-sectional studies only, and no biomarker

yet has been validated in prospective, controlled clinical trials. However, some biomarkers have been evaluated in studies in which biopsy specimens of Barrett's metaplasia were collected in a prospective systematic fashion, but the biomarker analyses were performed retrospectively. Promising biomarkers that have been so evaluated include aneuploidy/tetraploidy, 17p loss of heterozygosity (LOH), and several multiple biomarker panels.

Aneuploidy/tetraploidy: Genomic instability, which predisposes to the development of cancer-causing mutations, can be manifested by gains or losses in parts of chromosomes, a condition called aneuploidy. Aneuploidy can be detected in fresh frozen tissues by flow cytometry and in esophageal brushings or paraffin-embedded tissues by fluorescence in situ hybridization. Several reports suggest that flow cytometric evidence of aneuploidy and/or increased tetraploidy (specimens in which the fraction of cells with 4 sets of chromosomes exceeds 6%) can predict neoplastic progression in Barrett's esophagus more accurately than the histologic grade of dysplasia.^{113–115}

One study found that the 5-year cumulative incidence of cancer was 4% for patients with Barrett's esophagus who had biopsy specimens showing no dysplasia, indefinite dysplasia, or low-grade dysplasia (95% CI, 1.6–9.0).¹¹³ If the flow cytometry in those same cases was normal, then the 5-year incidence of cancer was 0% (95% CI, 0–4.7); if the flow cytometry showed aneuploidy or increased tetraploidy, then the 5-year incidence of cancer was 28% (95% CI, 12.0–55.0). Thus, the results of flow cytometry provided more useful predictive information on cancer than the histologic finding of no to low-grade dysplasia. For patients with high-grade dysplasia, however, flow cytometry added little additional predictive information. These findings were confirmed in a subsequent study by the same investigators.¹¹⁴ The aforementioned studies suggest that aneuploidy or increased tetraploidy might be used to predict the risk of cancer in patients who have Barrett's esophagus with no dysplasia or only low-grade dysplasia. However, those studies detected aneuploidy/tetraploidy by flow cytometry performed on frozen tissue specimens. Esophageal biopsy specimens rarely are frozen in clinical practice, and high-quality flow cytometry may not be widely available in clinical centers. These factors may have hindered the adoption of aneuploidy/tetraploidy as a clinical biomarker for neoplastic progression in Barrett's esophagus. In small studies, aneuploidy/tetraploidy detected by automated image cytometry and fluorescence in situ hybridization, techniques that might be more feasible for routine clinical practice, have been found to predict neoplastic progression in Barrett's esophagus.^{116,117} These preliminary findings require validation in high-quality prospective studies before the tests can be recommended for routine clinical application.

17p LOH: LOH for chromosome 17p, which harbors the *p53* gene, also has shown promise as a biomarker for neoplastic progression in Barrett's esophagus. In one study of patients with Barrett's esophagus whose biopsy specimens showed changes ranging from no dysplasia to high-grade dysplasia, the 3-year cumulative incidence of cancer was 38% (95% CI, 26.0–54.0) for those with 17p LOH compared with only 3.3% (95% CI, 1.4–8.0) for those with 2 intact 17p alleles.¹¹⁸ In the subset of patients who had no dysplasia, indefinite dysplasia, or low-grade dysplasia, furthermore, 17p LOH was a significant predictor of progression to high-grade dysplasia (RR, 3.6; 95% CI, 1.3–10). Other studies by the same group of investigators confirm these findings.¹¹⁹

In the aforementioned studies, 17p LOH was detected using a labor-intensive technique in which cells that were purified by flow cytometry were then subjected to whole-genome amplification followed by genotypic analyses for LOH. More recently, cross-sectional studies have shown promising results using simpler fluorescence in situ hybridization analyses for 17p LOH on biopsy and brush cytology specimens of Barrett's esophagus.^{120–123} However, one study that compared the techniques head to head found that

fluorescence in situ hybridization had a lower sensitivity for detecting 17p LOH than the flow cytometric approach.¹²¹

Biomarker panels: Numerous genetic abnormalities are acquired in variable sequences during the process of carcinogenesis in Barrett's esophagus. Therefore, it is not surprising that combinations of biomarkers in panels may be better at predicting the risk of neoplastic progression than individual biomarkers. For example, one study found that patients with Barrett's esophagus who had 3 biomarker abnormalities (aneuploidy/tetraploidy, 17p LOH, and 9p LOH) in their esophageal biopsy specimens had an 80% incidence of cancer within 6 years, whereas those who had none of those abnormalities had an incidence of cancer of only 12% at 10 years.¹¹⁹ Compared with the latter group, the RR of cancer progression for patients with an abnormal biomarker panel was 38.7 (95% CI, 10.8–138.5).

A gene methylation-based biomarker panel also has shown promise for predicting development of cancer in Barrett's esophagus. Promoter methylation is a process that can silence the expression of a number of genes, including cancer-preventing tumor suppressor genes. A study that evaluated methylation of a number of tumor suppressor genes in biopsy specimens of Barrett's esophagus found that methylation of p16, RUNX3, and HPP1 was associated with a significantly increased risk of progression to high-grade dysplasia or cancer.¹²⁴ The investigators generated a mathematical model for predicting neoplastic progression in Barrett's esophagus that used the results of their methylation-based biomarker panel (that included the aforementioned tumor suppressor genes), the patient's age, and the extent of Barrett's metaplasia. When applied in a retrospective longitudinal fashion to a cohort of patients with Barrett's esophagus, this prediction model was able to identify patients destined to progress to high-grade dysplasia or cancer as early as 2 years before neoplasia was recognized. Another more recent study has confirmed the ability of a methylation-based biomarker panel to predict neoplastic progression in Barrett's esophagus.¹²⁵

In summary, a number of individual biomarkers and panels of biomarkers have been proposed to predict the risk of neoplastic progression for patients with Barrett's esophagus. To date, however, none of these has been validated in prospective, controlled clinical trials. Available data on aneuploidy/tetraploidy and 17p LOH suggest that these biomarkers are no better than the histologic finding of high-grade dysplasia for predicting progression of cancer in Barrett's esophagus. However, aneuploidy/tetraploidy, 17p LOH, and methylation-based biomarker panels may be superior to histology alone for risk stratifying those patients with Barrett's esophagus whose initial biopsy specimens show no dysplasia, indefinite dysplasia, or low-grade dysplasia. In certain circumstances, therefore, those biomarkers could be used in combination with histology for risk stratification. Current data suggest that the identification of aneuploidy by flow cytometry or the identification of 17p LOH by the combination of flow cytometry, whole-genome amplification, and genotypic analysis are the best available biomarker techniques. Thus, the routine clinical use of biomarkers instead of dysplasia for risk stratification in Barrett's esophagus cannot be recommended at this time. Nevertheless, it seems likely that the results of biomarker validation studies will be available in the near future and that biomarkers eventually will be used to determine which patients with Barrett's esophagus will benefit from endoscopic surveillance or ablative techniques.

Should Chromoendoscopy or “Electronic Chromoendoscopy” Be Used to Enhance the Detection of Metaplasia and Dysplasia in Barrett's Esophagus?

The Seattle biopsy protocol for endoscopic surveillance in Barrett's esophagus, which involves 4-quadrant biopsy sampling of every 1 to 2 cm of the columnar-lined esophagus, is time consuming, labor intensive, costly, and subject to considerable sampling error. A number of alternative endoscopic techniques have been proposed to enhance the detection of

intestinal metaplasia and dysplasia in the esophagus. The ultimate goals for these advanced imaging techniques are to improve the endoscopic detection of curable neoplasia in Barrett's esophagus while reducing procedure time, expense, and sampling error.

Modern videoendoscopes use a charge-coupled device, which has a surface composed of photosensitive elements (pixels). In high-resolution endoscopes, the charge-coupled device has a large number of pixels (600,000 to 1,000,000) that provide detailed images of the mucosal surface. High-resolution endoscopy can be combined with magnification devices that enlarge the video image up to 150 $\times$.^{126–128} High-definition television systems, which can generate up to 1080 scanning lines on a screen, enable the projection of a high-quality image onto a large screen for ease of viewing.¹²⁹ Compared with standard endoscopy, high-resolution endoscopy appears to have higher sensitivity for detecting early neoplastic lesions in Barrett's esophagus.^{130,131} Indeed, it is not clear that the image enhancement techniques discussed in the following text add important information beyond that available by careful white light inspection of the esophagus using high-resolution endoscopy.

Chromoendoscopy involves the application of chemical agents (eg, Lugol's solution, methylene blue, indigo carmine, and acetic acid) that highlight various features of the esophageal mucosa in an attempt to improve the detection of abnormalities.^{132–140} Lugol's solution, which is taken up by esophageal squamous cells that contain glycogen, has been used to highlight the squamocolumnar junction and as an aid for identifying residual islands of Barrett's metaplasia (which are not stained by Lugol's solution) after endoscopic eradication therapy.¹⁴¹ Reports on the use of methylene blue, which is absorbed by intestinal-type epithelium that is not dysplastic, have described variable results. In a prospective, randomized, crossover trial that compared methylene blue-directed biopsy with standard 4-quadrant biopsy in 48 patients with Barrett's esophagus, the techniques were found to be similar for the detection of intestinal metaplasia and dysplasia, although the mean number of biopsies required to detect those conditions was significantly lower with methylene blue staining.¹³⁵ In contrast, another randomized crossover study found that the 4-quadrant biopsy technique detected dysplasia significantly more often than the methylene blue-directed biopsy technique.¹³⁶ A recent meta-analysis of 9 studies that included 450 total patients found that methylene blue staining and 4-quadrant biopsy techniques have similar rates for detecting intestinal metaplasia and dysplasia.¹⁴⁰ Further decreasing enthusiasm for methylene blue staining is a study documenting that the technique causes DNA damage in Barrett's epithelium.¹⁴²

Different mucosal pit patterns in columnar epithelia can be recognized by combining magnification endoscopy with the mucosal application of indigo carmine dye or acetic acid. Using acetic acid, Guelrud et al described 4 pit patterns in Barrett's epithelium (round, reticular, villous, and ridged) and found that the ridged and villous patterns were associated with intestinal metaplasia.¹⁴¹ Sharma et al studied 80 patients with Barrett's esophagus using indigo carmine and found that the ridged/villous mucosal pattern had high sensitivity (97%) and reasonable specificity (76%) for intestinal metaplasia.¹³⁸ In addition, all of 6 patients with high-grade dysplasia were found to have a distorted or irregular glandular pattern. However, a prospective, randomized, crossover study of 28 patients found that indigo carmine chromoendoscopy did not increase the sensitivity for detecting early neoplasia in Barrett's esophagus beyond that of high-resolution white light endoscopy.¹³¹

“Electronic chromoendoscopy” can be achieved by techniques such as narrow band imaging (NBI), which uses spectral narrow-band optical filters to highlight vascular patterns on the mucosal surface, or by optimal band imaging and I-scan, which use a postprocessing technology to highlight contrast between squamous and columnar epithelia.¹⁴³ In a preliminary study of 24 patients with high-grade dysplasia or early cancer in Barrett's

esophagus, optimal band imaging was found to detect neoplasia with a sensitivity of 87% but with a positive predictive value of only 37%.¹⁴⁴ Some single-center studies have attempted to correlate the magnified NBI appearance of the mucosal glandular and vascular patterns with the presence of metaplasia and dysplasia.^{145,146} In one such prospective study of magnification NBI in 51 patients with Barrett's esophagus, a ridge/villous pattern predicted the presence of intestinal metaplasia with a sensitivity of 93.5% and a specificity of 86.7%, whereas an irregular/distorted pattern predicted high-grade dysplasia with a sensitivity and specificity of 100% and 98.7%, respectively.¹⁴⁵ The magnified NBI images could not distinguish low-grade dysplasia from nondysplastic tissue, however. In another study, Kara et al showed that areas of high-grade dysplasia in Barrett's esophagus had at least one of 3 abnormal patterns by NBI: (1) an irregular/disrupted mucosal pattern, (2) an irregular vascular pattern, and (3) abnormal blood vessels.¹⁴⁶ A randomized crossover trial that compared chromoendoscopy and NBI in 28 patients found no significant difference between the 2 techniques for the detection of high-grade dysplasia and early cancer (93% vs 86% sensitivity), and neither technique was superior to high-resolution white light endoscopy in that regard.¹³¹ In another study, endoscopists were asked to identify dysplasia in still images of Barrett's epithelium taken during magnification endoscopy. The yield for identifying dysplasia in images taken with high-resolution white light endoscopy was 86%, and prediction rates did not increase significantly with the addition of either chromoendoscopy or NBI.¹⁴⁷

Two recent reports describe prospective studies that have compared the diagnostic yield of NBI (nonmagnified) with that of white light endoscopy.^{148,149} In one study of 65 patients who were known to have dysplasia in Barrett's esophagus, standard-resolution white light endoscopy was performed first, followed by NBI performed by another endoscopist who used NBI to detect and obtain biopsy specimens from areas suspicious for dysplasia.¹⁴⁸ The lesions initially detected by standard endoscopy were then disclosed and biopsy was performed; finally, random 4-quadrant biopsy specimens were taken throughout the columnar-lined esophagus. NBI was found to identify more patients with dysplasia than standard-resolution white light endoscopy with random biopsy sampling (57% vs 43%; $P < .001$). NBI also found higher grades of dysplasia significantly more often than standard endoscopy (18% higher grade with NBI than with standard vs 0% higher grade with standard than with NBI; $P < .001$). In a multicenter, randomized, crossover trial comparing NBI-targeted biopsies with high-resolution white light endoscopy and 4-quadrant biopsies in 123 patients with Barrett's esophagus, there were no significant differences between the 2 techniques in the frequency of detecting intestinal metaplasia (85% for each technique) and dysplasia (71% for NBI vs 55% for white light endoscopy; $P = .15$).¹⁴⁹ However, significantly fewer biopsies were required to establish a diagnosis with NBI (3.6 vs 7.6 per procedure; $P < .0001$).

Chromoendoscopy for Barrett's esophagus is time consuming, fraught with technical problems (eg, achieving uniform dye application), potentially hazardous (in the case of methylene blue), poorly standardized (regarding the interpretation of mucosal patterns), and subject to considerable interobserver variability. Studies comparing chromoendoscopy with standard-resolution endoscopy have had contradictory findings, and studies have not established any diagnostic advantage for chromoendoscopy beyond that which can be achieved by high-resolution white light endoscopy. Consequently, we do not advocate the routine use of chromoendoscopy in Barrett's esophagus. Electronic chromoendoscopy techniques such as NBI are less time consuming and technically easier to perform than chromoendoscopy but are still subject to problems of poor standardization and interobserver variability. The studies discussed previously suggest that NBI may be superior to standard-resolution white light endoscopy for detecting esophageal metaplasia and dysplasia, but

studies so far have not established a convincing advantage for NBI over high-resolution white light endoscopy.

We conclude that endoscopic surveillance is best performed with careful inspection of the columnar-lined esophagus using high-resolution white light endoscopy, with biopsy sampling of any lesions or suspicious areas so identified followed by 4-quadrant biopsy sampling of the Barrett's metaplasia. The use of NBI or similar electronic chromoendoscopy techniques cannot be advocated or discouraged at this time.

Should Advanced Endoscopic Imaging Techniques Such as Autofluorescence Imaging, Confocal Laser Endomicroscopy, Diffuse Reflectance and Light Scattering Spectroscopy, and Optical Coherence Tomography Be Used to Enhance the Detection of Metaplasia and Dysplasia in Barrett's Esophagus?

Cells contain endogenous fluorophores (eg, reduced nicotinamide adenine dinucleotide, porphyrins) that can absorb endoscopically delivered laser light and re-emit it as fluorescent light with distinctive spectroscopic characteristics. Autofluorescence imaging (AFI) exploits this phenomenon to highlight abnormal areas in Barrett's esophagus that can be targeted for biopsy sampling.^{150–152} AFI attempts to distinguish normal from neoplastic epithelia based on differences in their fluorescence spectra. An initial feasibility study found that AFI was a sensitive test that improved the rate of detecting high-grade dysplasia but with poor specificity that resulted in a positive predictive value of only 50%.¹⁵⁰

In a multicenter study of 84 patients, Curvers et al explored the diagnostic potential of “tri-modal imaging” in which the esophagus is first inspected by high-resolution white light endoscopy, followed by AFI to rapidly highlight abnormal areas not detected by white light, followed by NBI to confirm the abnormality of areas highlighted by AFI.¹⁵² High-resolution white light endoscopy identified 16 patients with neoplasia, all of whom were also identified by AFI. In addition, AFI detected 11 patients with early neoplasia who were not identified by white light endoscopy. In total, AFI identified 102 abnormalities that were not seen by white light endoscopy, but with poor specificity resulting in a false-positive rate for neoplasia detection of 81%. That false-positive rate was reduced to 26% by NBI examination. However, multi-modality imaging also missed neoplasia in 3 patients (10%) for whom the condition was detected only by random 4-quadrant biopsies.

Confocal laser endomicroscopy involves examination of the gut mucosa using endoscopically delivered laser light, which is reflected back through a pinhole onto sensors that relay the signals to a computer, which translates the information into a cross-sectional microscopic image of the mucosa.^{153–158} Magnifications even beyond 1000× can be achieved with confocal laser endomicroscopy, allowing for real-time microscopic analysis of mucosal crypt architecture and capillaries. The use of this system with ultra-high magnifications (450× and 1125×) to evaluate individual cellular and subcellular structures has been called “endocytoscopy.”^{159,160}

Initial reports on confocal laser endomicroscopy from a single center, using a confocal laser endomicroscopy device integrated into the tip of a conventional videoendoscope, described excellent accuracy rates (85%–94%) for the detection of high-grade dysplasia in patients with Barrett's esophagus, most of whom had abnormalities seen by white light endoscopy.^{153,156} Another group used a probe-based confocal laser endomicroscopy device to study patients who had Barrett's esophagus without visible lesions and observed that the finding of fused glands identified advanced neoplasia with a sensitivity of 80% and with good interobserver agreement, as evidenced by a κ value of 0.6.¹⁵⁴ In an ex vivo study of 166 biopsy specimens from 16 patients, the positive and negative predictive values of endocytoscopy for high-grade dysplasia/early cancer were found to be 44% and 83%,

respectively.¹⁶⁰ At 1125× magnification, however, adequate assessment of endocytoscopy images was not possible in 22% of the target areas.

Both diffuse reflectance spectroscopy and light scattering spectroscopy have been used to study Barrett's esophagus. Diffuse reflectance spectroscopy analyzes light that has been scattered multiple times within the tissue before it is detected by the sensing device, whereas light scattering spectroscopy analyzes light that is scattered back to the sensing device after undergoing only a single scattering event. Algorithms have been developed to use the spectroscopic information so collected to distinguish nonneoplastic and neoplastic regions in Barrett's esophagus.^{161–163} Using the diffuse reflectance spectra collected from 16 patients, one diagnostic algorithm was able to distinguish high-grade dysplasia from low-grade dysplasia and nondysplastic tissue in Barrett's esophagus with a sensitivity of 86% and a specificity of 100%.¹⁶¹ The sensitivity and specificity for separating any grade of dysplasia from no dysplasia were 79% and 88%, respectively. Using light scattering spectroscopy data for 76 sites in 13 patients with Barrett's esophagus, Wallace et al found that a diagnostic algorithm based on nuclear enlargement had a sensitivity and specificity of 90% in distinguishing dysplastic from nondysplastic tissue.¹⁶³

Optical coherence tomography uses near-infrared light to provide high-resolution cross-sectional imaging of the esophageal mucosa.¹⁶⁴ The technique is similar in principle to endosonography, but image formation in optical coherence tomography depends on variations in the reflectance of light (rather than ultrasonic waves) from different tissue layers.^{165–168} In an initial study of 121 patients with Barrett's esophagus, objective image criteria for Barrett's metaplasia (without dysplasia) were formulated on the basis of data obtained from 166 optical coherence tomography images that had corresponding biopsy specimens.¹⁶⁶ Data from this training set were validated using 122 optical coherence tomography images that were obtained prospectively. The optical coherence tomography criteria so developed were found to have a sensitivity and specificity of 97% and 92%, respectively, for the identification of Barrett's metaplasia.

The studies discussed previously describe some promising preliminary results for the advanced imaging techniques in the detection of esophageal metaplasia and dysplasia. To date, however, these advanced techniques have not been shown to provide additional clinical information (beyond that available by high-resolution white light endoscopy) sufficient to warrant their routine application in clinical practice.

Should Proton Pump Inhibitors Be Used for Chemoprevention in Barrett's Esophagus? Should Nonsteroidal Anti-inflammatory Drugs Be Used for Chemoprevention in Barrett's Esophagus?

Should Proton Pump Inhibitors Be Used for Chemoprevention in Barrett's Esophagus?—Chemoprevention involves the use of a pharmacologic agent to prevent the development of cancer.¹⁶⁹ Whereas the process of carcinogenesis in Barrett's esophagus may span decades, studies on potential chemopreventive agents generally have evaluated the effects of those agents on surrogate markers for cancer development, such as dysplasia, rather than on the development of cancer itself. The validity of using such surrogate end points is not clear. Furthermore, although a number of agents have been proposed for chemoprevention in Barrett's esophagus, only one has been evaluated in prospective, randomized, controlled clinical trials. Based on available data, the most promising chemopreventive agents for this condition appear to be the proton pump inhibitors (PPIs) and the nonsteroidal anti-inflammatory drugs (NSAIDs).

The evidence to support potent acid suppression with PPIs as a chemopreventive strategy in Barrett's esophagus is largely indirect. In certain ex vivo and in vitro model systems, for

example, acid has been shown to damage DNA and to induce proliferative and antiapoptotic effects.^{170–173} By inference, therefore, gastric acid inhibition should be beneficial. A number of observational studies have found an inverse correlation between long-term use of PPIs and the incidence of dysplasia and adenocarcinoma in patients with Barrett's esophagus.^{174–177} Some prospective clinical studies have shown that PPI therapy is associated with a decrease in proliferation markers, a potentially cancer-protective effect, in biopsy specimens of Barrett's metaplasia.^{178–180} Unfortunately, prospective clinical studies have yet to prove that PPI therapy can prevent the development of dysplasia and its progression in Barrett's esophagus.

PPI therapy also has effects that, conceivably, might promote the development of cancer in Barrett's esophagus. For example, use of PPIs often is associated with an increase in the serum levels of gastrin, a hormone that has been shown to increase proliferation in Barrett's epithelium. Epidemiologic studies that have attempted to seek a cancer-promoting effect for PPIs have encountered the problem of confounding by indication, because long-term PPI therapy often is prescribed to treat GERD, which is a risk factor for esophageal adenocarcinoma. Thus, an association between PPIs and cancer may have nothing to do with the PPI, but rather may result from the underlying GERD for which the PPI is prescribed. Using the large general practitioners research database in the United Kingdom, for example, Garcia Rodriguez et al found that patients who were treated with acid suppression for an "esophageal indication" such as GERD had a significantly increased risk of developing esophageal adenocarcinoma (odds ratio, 5.42; 95% CI, 3.13–9.39).¹⁸¹ In contrast, for patients who were treated with acid suppression for a "gastroduodenal indication" such as peptic ulcer disease, there was no significantly increased risk of adenocarcinoma (odds ratio, 1.74; 95% CI, 0.90–3.34). The lack of an association with cancer in patients taking PPIs for gastroduodenal disease suggests that the positive association in the patients with esophageal disease resulted from confounding by indication. In other words, it was likely the GERD, not the GERD treatment, that increased the incidence of cancer. Other studies on this issue also have not found a significant association between esophageal adenocarcinoma and the use of antisecretory agents per se.^{182,183}

In summary, available circumstantial evidence supports the use of PPIs as a chemopreventive strategy in patients with Barrett's esophagus. Few would argue the need for PPIs to control GERD symptoms and to heal reflux esophagitis for these patients. However, insufficient data are available to support the practice of prescribing PPIs in dosages higher than those needed to eliminate the symptoms and endoscopic signs of GERD or, for patients with no such symptoms and signs, in dosages higher than those recommended as conventional for the treatment of GERD. Similarly, insufficient data are available to support the practice of using esophageal pH monitoring to titrate PPI dosing so as to normalize esophageal acid exposure for patients with Barrett's esophagus.

Should Nonsteroidal Anti-Inflammatory Drugs Be Used for Chemoprevention in Barrett's Esophagus?—Multiple lines of evidence suggest that aspirin and other NSAIDs protect against esophageal adenocarcinoma. There are data to suggest that NSAIDs exert their antitumor effects both through the inhibition of cyclooxygenase-2 and through actions independent of cyclooxygenase inhibition.^{184,185} In vitro studies have shown that NSAIDs can decrease cellular proliferation, increase apoptosis, and interfere with angiogenesis, effects that would be expected to prevent cancer formation.^{186–189} In animal models of GERD, NSAIDs have been found to decrease the development of Barrett's esophagus and esophageal adenocarcinoma.^{190–192} In addition, decreased proliferation has been documented in biopsy specimens of Barrett's epithelium taken from patients who were treated with rofecoxib, a cyclooxygenase-2 selective NSAID.¹⁹³ Irrespective of the

underlying mechanism, ample experimental data suggest that NSAIDs may be effective chemopreventive agents for patients with Barrett's esophagus.

A number of epidemiologic studies also have supported the use of aspirin and other NSAIDs as chemopreventive agents in Barrett's esophagus. A meta-analysis of such studies by Corley et al found that the use of NSAIDs was associated with a 33% reduction in the risk of developing esophageal adenocarcinoma (odds ratio, 0.67; 95% CI, 0.51–0.87), and both aspirin and nonaspirin NSAIDs appeared to be equally effective in this regard.¹⁹⁴ More recent studies on this issue have yielded contradictory results, however. A questionnaire-based study that included approximately 300,000 members of AARP found no significant association between esophageal adenocarcinoma and the use of aspirin (1.00; 95% CI, 0.73–1.37) or nonaspirin NSAIDs (0.90; 95% CI, 0.69–1.17).¹⁹⁵ In contrast, Vaughn et al prospectively studied a cohort of 350 patients with Barrett's esophagus followed up for 20,770 person-months and found that, compared with those who never used NSAIDs, current users of NSAIDs had a significantly decreased risk of esophageal adenocarcinoma (hazard ratio, 0.20; 95% CI, 0.10–0.41).¹⁹⁶ Finally, Heath et al randomized 100 patients who had either low- or high-grade dysplasia in Barrett's esophagus to receive either the cyclooxygenase-2 selective NSAID celecoxib 200 mg twice daily (49 patients) or placebo (51 patients). After 48 weeks of treatment, there was no significant difference between the 2 groups in the proportion of esophageal biopsy specimens showing dysplasia or cancer.¹⁹⁷ However, this study had a number of limitations (eg, the use of dysplasia as the primary outcome, the use of a low dose of celecoxib) that may have affected the outcome.

Limited data suggest that biomarkers might have a role in identifying those patients with Barrett's esophagus who are most likely to benefit from chemopreventive therapies. For patients with Barrett's esophagus with DNA content abnormalities, 17p LOH, and/or 9p LOH in their esophageal biopsy specimens, for example, one study found that the use of NSAIDs was associated with a significant reduction in the risk of esophageal adenocarcinoma at 6 and 10 years of follow-up.¹¹⁹ In contrast, no beneficial effect of NSAIDs was seen in those patients whose biopsy specimens had none of those abnormalities.

NSAIDs clearly have substantial potential for toxicity, including serious gastrointestinal and cardiovascular side effects, and it is not clear whether the potential cancer-preventive effects warrant those risks. Even use of low-dose aspirin has been associated with serious bleeding complications. A meta-analysis of randomized controlled trials comparing low-dose aspirin (75–325 mg) and placebo for cardiovascular prophylaxis found that the absolute annual increase in risk attributable to aspirin was only 0.13% (95% CI, 0.08–0.20) for major bleeding, 0.12% (95% CI, 0.07–0.19) for major gastrointestinal bleeding, and 0.03% (95% CI, 0.01–0.08) for intracranial bleeding.¹⁹⁸ Thus, the overall risk of using low-dose aspirin is small. Moreover, patients included in that meta-analysis were not receiving concomitant PPI therapy, which has been shown to reduce the risk of gastrointestinal bleeding with low-dose aspirin by a factor of 2 to 9.^{199,200} Typically, the diagnosis of Barrett's esophagus is made in men older than 50 years of age and, as discussed previously, those patients may be at increased risk for cardiovascular disease. Low-dose aspirin has been shown to be beneficial for primary cardiovascular events in men older than 50 years of age who are at risk for developing coronary artery disease.^{201,202} Thus, low-dose aspirin has the potential to prevent cardiovascular events as well as esophageal cancer.

In summary, most available reports suggest that aspirin and other NSAIDs protect against the development of cancer in Barrett's esophagus, but definitive studies are lacking. Presently, we believe that it is appropriate to consider the prescription of low-dose aspirin for patients with Barrett's esophagus who also have risk factors for cardiovascular disease.

Whereas patients will already be taking a PPI, the risks of aspirin causing serious gastrointestinal toxicity in average-risk individuals should be minimal. A large, prospective, randomized clinical trial in the United Kingdom is investigating the chemopreventive effects of PPIs alone and in combination with aspirin (AspECT), and the results of that study are eagerly awaited.²⁰³

Should Antireflux Surgery Be Advised to Prevent Cancer in Barrett's Esophagus?

For many patients with Barrett's esophagus, PPI therapy eliminates GERD symptoms, but esophageal acid exposure remains abnormal nevertheless.^{204–206} In one study of 48 patients with Barrett's esophagus who had been rendered asymptomatic by PPI treatment, for example, 50% had persistently abnormal acid exposure documented by esophageal pH monitoring.²⁰⁶ Even if PPIs normalize acid reflux, the reflux of nonacidic gastric material persists and, conceivably, bile and other noxious agents in that refluxed material might contribute to carcinogenesis in Barrett's esophagus. As noted previously, furthermore, PPIs themselves have effects that, in theory, might promote development of cancer (eg, elevated serum gastrin levels, bacterial colonization of the stomach). For all these reasons, it has been proposed that fundoplication, which is designed to eliminate gastroesophageal reflux, might be more effective than antisecretory therapy for preventing cancer in Barrett's esophagus.²⁰⁷

A number of observational studies have described fewer cases of dysplasia and cancer developing in patients with Barrett's esophagus who had antireflux surgery than in those who had received medical treatment.^{208–210} Those studies generally have been small and subject to numerous biases that might inflate the benefits of surgical therapy. Higher-quality studies have not found that antireflux surgery is superior to medical therapy for prevention of cancer in Barrett's esophagus.

During 10 to 13 years of follow-up for patients (many of whom had Barrett's esophagus) who had participated in a randomized trial of medical and surgical therapies for GERD, 4 of 165 patients (2.4%) in the medical group and 1 of 82 (1.2%) in the surgical group developed an esophageal adenocarcinoma.²¹¹ The difference between the treatment groups in the incidence of this malignancy was not statistically significant but, with such a low observed rate of cancer development, the study did not have sufficient statistical power to detect a small cancer-protective effect for fundoplication.

Two studies using large patient databases^{212,213} and 3 meta-analyses^{22,214,215} also have found no significant cancer-preventive effect for antireflux surgery. In one meta-analysis, Chang et al initially found that the incidence of esophageal adenocarcinoma in Barrett's esophagus was significantly lower in surgically treated patients (2.8 [95% CI, 1.2–5.3] per 1000 patient-years) than in medically treated patients (6.3 [95% CI, 3.6–10.1]; $P = .034$).²² However, the investigators found that there was significant heterogeneity in the cancer incidence rates reported in case series compared with the higher-quality controlled studies ($P = .014$). In the controlled studies, there were no significant differences in cancer incidence rates between surgically and medically treated patients (4.8 [1.7–11.1] vs 6.5 [2.6–13.8] per 1000 patient-years, respectively; $P = .32$). The authors concluded that evidence suggesting that surgery reduced the risk of cancer in Barrett's esophagus was driven largely by uncontrolled studies.

In summary, there is no convincing evidence that antireflux surgery is more effective than medical therapy for prevention of cancer in Barrett's esophagus. We conclude that antireflux surgery should not be advised with the rationale that the procedure will prevent esophageal cancer.

What Is the Role for EMR in Barrett's Esophagus? Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus Without Dysplasia? Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus With Low-Grade Dysplasia? Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus With High-Grade Dysplasia or Intramucosal Carcinoma?

What Is the Role for EMR in Barrett's Esophagus?—In EMR, a diathermic snare or endoscopic knife is used to remove Barrett's metaplasia down to the submucosa, providing large tissue specimens that can be used to assess the depth of any neoplastic involvement and the adequacy of the resection. Thus, EMR has potential value as both a diagnostic/staging procedure and as a therapeutic procedure for removing Barrett's epithelium with and without neoplasia.

In surgical series of patients who have undergone esophagectomy for the treatment of high-grade dysplasia or intramucosal adenocarcinoma in Barrett's esophagus, lymph node metastases have been described in 0% to 7%.^{216–220} For patients whose tumors extend into the submucosa, however, the frequency of lymph node metastases often exceeds 20%.^{216,217,220} For this reason, endoscopic therapy generally is not considered definitive for patients with neoplasms that involve the submucosa. When considering endoscopic eradication therapy for neoplasia in Barrett's esophagus, therefore, accurate T staging is essential. Although endoscopic ultrasonography (EUS) is considered the most accurate imaging modality for the T staging of gastrointestinal cancers, standard EUS accurately predicts the depth of invasion for early esophageal cancers in only 50% to 60% of cases.²²¹ Even high-frequency probe EUS is inadequate in this situation, as evidenced by one study of 9 patients who underwent esophagectomy for early neoplasia in Barrett's esophagus in whom preoperative T staging by high-frequency probe EUS was found to be accurate in only 4 cases.²²²

In a study of 40 patients with neoplasia in Barrett's esophagus who had EMR performed after endoscopic biopsy and EUS, histologic review of the EMR specimen revealed intramucosal carcinoma in 24% of patients with an EUS/biopsy diagnosis of high-grade dysplasia and invasive cancer in 40% of patients with an EUS/biopsy diagnosis of intramucosal carcinoma.²²³ In a study in which preoperative EMR findings were compared with subsequent histologic examination of esophagectomy specimens for 25 patients with high-grade dysplasia or adenocarcinoma in Barrett's esophagus, there was perfect agreement in T staging by EMR and esophagectomy.²²⁴ These studies show that EMR can be considered a valuable diagnostic/staging procedure for identifying submucosal invasion that might not be apparent by less invasive techniques such as mucosal biopsy and EUS.

In addition to its role in staging neoplasms in Barrett's esophagus, EMR also has been used to eradicate Barrett's epithelium, high-grade dysplasia, and early Barrett's cancers. Cohort studies have found that EMR can achieve complete eradication of Barrett's epithelium in 75% to 100% of cases and complete eradication of dysplasia in 86% to 100% of cases.^{225–232} At this time, there are no published randomized trials comparing EMR with other endoscopic therapies for the eradication of Barrett's epithelium.

Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus Without Dysplasia?—Endoscopic eradication therapy for Barrett's esophagus includes EMR and/or the endoscopic ablative techniques, which use thermal, photochemical, or radiofrequency energy to destroy the Barrett's epithelium without providing a tissue specimen. Following ablation or EMR, patients are prescribed antireflux therapy (usually PPIs) so that the eradicated esophageal mucosa heals with the growth of new squamous epithelium (also called neo-squamous epithelium). Endoscopic ablation for Barrett's esophagus was first described in 1992, and early feasibility studies were conducted

in patients with nondysplastic Barrett's esophagus. Presently, endoscopic therapies are being used primarily to treat patients with dysplasia and early adenocarcinoma in Barrett's esophagus.

The earliest studies of endoscopic ablative therapy used lasers to destroy nondysplastic Barrett's epithelium. Since then, the techniques that have been studied most extensively for the eradication of Barrett's esophagus without dysplasia include multi-polar electrocoagulation (MPEC), argon plasma coagulation (APC), and radiofrequency ablation (RFA).^{233–243} Most reports of such studies describe case series, and there is considerable heterogeneity among those studies regarding the primary end points (eg, complete eradication, partial eradication, percentage regression of Barrett's metaplasia), the duration of follow-up, and the postablation surveillance protocols.

For MPEC, several prospective case series have described the complete eradication of nondysplastic Barrett's epithelium in 65% to 100% of cases. In a study involving only 14 patients, Montes et al reported a complete eradication rate of 100% during a mean follow-up of 21.6 months.²³³ In contrast, another study of 58 patients followed up for 6 months found a complete eradication rate of only 78%.²³⁴

For APC, the complete eradication of nondysplastic Barrett's esophagus has been described in 36% to 100% of cases, with recurrences found in up to 66% of the treated patients. In a cohort of 70 patients treated with APC and followed up for a median of 51 months, Madisch et al reported a complete eradication rate of 98%, with a recurrence rate of 12%.²³⁷ In contrast, another study of 25 patients treated with APC noted an initial complete eradication rate of only 84% and found a recurrence rate of 66% during a median follow-up period of 30 months.²³⁸ Manner et al used high-power (90 W) APC to treat 51 patients who had Barrett's esophagus without dysplasia.²⁴³ Nine of the 51 patients (18%) experienced transient side effects, including chest pain, fever, and odynophagia. Five patients (10%) had a major complication, including hemorrhage (2 patients), esophageal stricture (2 patients), and esophageal perforation (1 patient). During a mean follow-up of 14 months, complete eradication of Barrett's epithelium was achieved in 37 of the 48 patients (77%) who had follow-up examinations.

Bright et al randomized 40 patients with Barrett's esophagus who had undergone antireflux surgery to receive either APC or endoscopic surveillance without ablative therapy.²⁴⁰ During a median follow-up period of 68 months, complete eradication of Barrett's epithelium was achieved in 40% of patients treated with APC compared with 20% in the surveillance group. One patient treated with APC was found to have progression to low-grade dysplasia, whereas 2 patients in the surveillance group developed low-grade dysplasia and another 2 progressed to high-grade dysplasia during the same period of follow-up.

Two randomized trials have compared MPEC and APC for the treatment of Barrett's esophagus without dysplasia. In a study of 35 such patients followed up for 2 years, Sharma et al found no significant differences in the percentage of complete eradication for 16 patients treated with MPEC (75% complete eradication) compared with 19 patients treated with APC (63% complete eradication; $P = .49$).²³⁵ Both techniques required multiple treatment sessions (4 for MPEC vs 3 for APC; not significant), and no factors were identified that could be used to predict complete eradication. The other randomized trial involved 52 patients and also found no significant differences between the treatment groups in the percentage of complete eradication (81% for MPEC vs 65% for APC; $P = .21$).²³⁶

In another comparative trial, 68 patients who had Barrett's esophagus without dysplasia were randomized to receive treatment with either APC or photodynamic therapy (PDT) using 5-aminolevulinic acid as the photosensitizer. During a median follow-up period of 12 months,

complete eradication was noted in 97% of patients in the APC group compared with only 50% of patients who received PDT ($P < .0001$).²³⁹

RFA therapy uses a balloon-based circumferential array of closely spaced electrodes to deliver radiofrequency energy to the esophageal mucosa. This system was designed with the intent of inflicting a uniform circumferential thermal injury with depth that is controlled by a generator, which can vary the power, density, and duration of the energy applied. In one study of 70 patients who had Barrett's esophagus without dysplasia, RFA resulted in apparent complete eradication of Barrett's epithelium in 69% of patients at 12 months.²⁴¹ Noting the problem of frequent incomplete eradication, the RFA manufacturer introduced a smaller, endoscope-mounted, radiofrequency catheter ablation device to be used for the focal ablation of metaplasia that remains behind after treatment with the circumferential system. In a 30-month follow-up study of the same cohort described in the aforementioned report, use of the focal ablative device resulted in the complete eradication of Barrett's epithelium in 97% of the patients.²⁴²

The reports described previously establish that endoscopic ablative therapies can eradicate nondysplastic Barrett's epithelium in the short-term for the majority of patients. However, those reports do not establish the benefit of that eradication. Some reports describe a high rate of recurrent metaplasia, and it is not clear that any ablative procedure provides long-term protection from esophageal cancer. A recent cost-utility analysis suggests that ablation of nondysplastic Barrett's epithelium could be a preferred management strategy if the procedure eliminates the need for long-term endoscopic surveillance, with its attendant risks and expense.²⁴⁴ However, in the absence of long-term studies showing efficacy, it is not clear that surveillance should be discontinued after ablation therapy. Consequently, it is not clear that the potential benefit of ablation in reducing the small risk of cancer for patients who have Barrett's esophagus without dysplasia warrants the risks and substantial expense of the ablative procedures.

Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus With Low-Grade Dysplasia?—Few studies have focused exclusively on the efficacy of endoscopic eradication for patients with low-grade dysplasia in Barrett's esophagus. Rather, such patients commonly have been included as a subgroup in eradication trials that have involved primarily patients without dysplasia or patients with high-grade dysplasia, a feature that can confound the interpretation of study results. Overall, eradication rates for low-grade dysplasia have ranged from 35% to 100%, with a similar range for recurrence rates.

One study that used APC to ablate dysplastic Barrett's epithelium found complete eradication of low-grade dysplasia in all of 19 patients followed up for a median of 12 months.²⁴⁵ Using PDT with 5-aminolevulinic acid, Ackroyd et al completely eradicated low-grade dysplasia in all of 40 patients during a mean follow-up of 53 months.²⁴⁶ Another study using PDT, this time with sodium porfimer ($n = 14$), found complete eradication of low-grade dysplasia in 13 of 14 patients (93%) followed up for a mean of 50.7 months.²⁴⁷ A randomized trial that compared the efficacies of APC and PDT (with porfimer sodium) for treating low-grade dysplasia found substantially lower rates of complete eradication (62% with APC vs. 77% with PDT), with no significant difference between the 2 treatment groups in the frequency of complete eradication.²⁴⁸ In a recent single-center study that used RFA to treat 39 patients with low-grade dysplasia, complete eradication of dysplasia was achieved in 95%, and 87% had complete eradication of Barrett's metaplasia during a median follow-up of 24 months.²⁴⁹

Recently, Shaheen et al reported the results of a multicenter, prospective, randomized, sham-controlled trial on endoscopic eradication that included 64 patients with low-grade dysplasia in Barrett's esophagus who were randomized to receive either RFA (42 patients) or a sham procedure (22 patients).²⁵⁰ At 12 months, complete eradication of low-grade dysplasia was achieved in 90% of patients in the RFA group compared with 23% in the sham group ($P < .001$). Complete eradication of Barrett's metaplasia was achieved in 81% and 4% of the RFA and sham groups, respectively ($P < .001$). During the trial period, however, there was no significant difference between the RFA and sham treatment groups in the percentage of patients who had progression from low-grade to high-grade dysplasia (5% in the RFA group and 14% in the sham group; $P = .33$), and no patient with low-grade dysplasia in either group progressed to cancer.

The conclusions that can be drawn from studies on endoscopic eradication therapy for low-grade dysplasia are similar to those for the eradication of nondysplastic Barrett's esophagus discussed previously. Available reports establish that ablative therapies can eradicate low-grade dysplasia in the short-term for the majority of patients, but the reports do not establish the benefit of that eradication. Difficulties in verifying a diagnosis of low-grade dysplasia (see the previous text) and uncertainty regarding its natural history further confound the situation. In the absence of long-term studies showing efficacy, it is not clear that the potential benefit of ablation in reducing cancer risk for patients who have Barrett's esophagus with low-grade dysplasia warrants the risks and substantial expense of the ablative procedures.

Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus With High-Grade Dysplasia or Intramucosal Carcinoma?—

In a recent study of 39 patients with neoplasia in Barrett's esophagus (25 high-grade dysplasia, 14 early cancers), sequential EMR (mean of 3 sessions) resulted in complete eradication of neoplasia in all patients and complete eradication of Barrett's epithelium in 89%, with no recurrences observed during a median follow-up of 11 months.²⁵¹ The largest reported experience with EMR as the primary technique to eradicate high-grade dysplasia and early cancer in Barrett's esophagus involved 349 patients followed up for a mean of 63.6 months.²³² The early complete eradication rate for neoplasia was 97%, but metachronous neoplasms subsequently developed in 21.5% of patients; 85% of those patients received further endoscopic eradication therapy and achieved a second complete remission. Risk factors for metachronous neoplasms identified in this study included piecemeal resection of the lesion (RR, 2.4; 95% CI, 1.13–4.89), long-segment Barrett's esophagus (RR, 1.9; 95% CI, 1.06–3.3), no use of mucosal ablative therapies after EMR (RR, 2.5; 95% CI, 1.52–3.85), time until complete remission achieved greater than 10 months (RR, 0.3; 95% CI, 0.12–0.75), and multifocal neoplasia (RR, 2.1; 95% CI, 1.16–3.9).

For the treatment of high-grade dysplasia in Barrett's esophagus, PDT was the first endoscopic ablative modality to be evaluated in a randomized controlled trial. In that trial, 208 patients with high-grade dysplasia were randomized either to the control group, which received treatment with omeprazole alone, or to the group that received treatment with PDT (using porfimer sodium as the sensitizing agent) plus omeprazole. In the initial report of this study, when the duration of follow-up was 2 years, the primary goal of complete eradication of high-grade dysplasia was achieved in 77% of patients in the PDT group compared with 39% of patients in the control group ($P < .0001$).²⁵² In a subsequent follow-up study of those patients at 5 years, intention-to-treat analyses showed that PDT was significantly more effective than omeprazole alone for eradicating high-grade dysplasia (77% [106/138] vs 39% [27/70]; $P < .0001$) and that PDT-treated patients were less likely to progress to cancer (15% vs 29%; $P = .027$), although the trial was not designed specifically to test this outcome.²⁵³ In addition to this randomized controlled trial, a number of small uncontrolled

studies of PDT (using 5-aminolevulinic acid as the sensitizing agent) for the treatment of high-grade dysplasia or early cancer in Barrett's esophagus have found complete eradication rates ranging from 77% to 100%.^{254,255}

Reports of uncontrolled studies have described promising results for RFA for patients with high-grade dysplasia in Barrett's esophagus. In a single-center study in which 24 patients with high-grade dysplasia were treated with RFA and followed up for up to 24 months, complete eradication of dysplasia and intestinal metaplasia was found in 79% and 67% of patients, respectively.²⁴⁹ A multicenter registry of 142 patients with high-grade dysplasia treated with RFA therapy described complete eradication of dysplasia and intestinal metaplasia in 90% and 54% of patients, respectively.²⁵⁶

The previously mentioned prospective, sham-controlled trial of RFA by Shaheen et al included 63 patients with high-grade dysplasia in Barrett's esophagus who were randomized to receive either RFA (42 patients) or a sham procedure (21 patients).²⁵⁰ At 12 months, after an average of 3.5 endoscopic sessions, complete eradication of high-grade dysplasia was achieved in 81% of patients in the RFA group compared with 19% in the sham group ($P < .01$). Complete eradication of Barrett's metaplasia was achieved in 74% and 0% of the RFA and sham groups, respectively ($P < .001$). Furthermore, 4 patients in the sham group progressed to cancer compared with only 1 in the RFA group ($P = .04$).

Reports of small studies have described the use of cryotherapy and APC to eradicate high-grade dysplasia and early cancer in Barrett's esophagus.^{257,258} In a prospective trial that used CryoSpray in 31 patients (26 with high-grade dysplasia, 5 with early cancer), complete eradication of neoplasia and intestinal metaplasia was achieved at 12 months in 23% and 1% of patients, respectively.²⁵⁸ Although these results may seem unimpressive, it should be noted that 27% of the patients had previous unsuccessful attempts at endoscopic eradication with other modalities. Attwood et al used APC in 29 patients with high-grade dysplasia and reported complete eradication of dysplasia and intestinal metaplasia in 86% and 76% of patients, respectively.²⁵⁹ However, 4 patients developed cancer during a 37-month follow-up period.

Most of the studies discussed previously on endoscopic ablation of neoplasia in Barrett's esophagus have evaluated the results of a single ablative technique performed without EMR. However, an emerging concept in the endoscopic management of neoplasia in Barrett's esophagus is that endoscopic eradication may be best effected by first removing visible abnormalities with EMR, which provides invaluable staging information as well as therapy, followed by the ablation of all remaining Barrett's metaplasia. In the aforementioned study by Pech et al on endoscopic eradication therapy for patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus, metachronous neoplasms were detected during follow-up in 30% of 137 patients treated with EMR alone, whereas metachronous neoplasms were found in only 17% of 200 patients who were treated with EMR followed by ablation with APC or PDT.²³² In a recent multicenter European trial, 23 patients with neoplasia in Barrett's esophagus (7 with high-grade dysplasia, 16 with early cancer) had EMR followed by RFA.²⁶⁰ At a median follow-up of 22 months, complete eradication of neoplasia and intestinal metaplasia was achieved in 95% and 88% of patients, respectively.

Major complications of endoscopic eradication therapy for Barrett's esophagus include esophageal stricture formation, bleeding, and perforation. Minor complications include transient chest pain, fever, and odynophagia. After PDT and RFA, esophageal stricture development has been reported in up to 36% and 6% of patients, respectively.^{250,258} After EMR, esophageal stricture formation has been observed primarily in patients treated with circumferential resections that were aimed at eliminating all Barrett's epithelium.^{227,229}

Rates of bleeding with the various modalities have varied from 0 to 10%, and perforations are uncommon.

Although a number of studies describe complete elimination of all Barrett's epithelium after endoscopic eradication therapy, this claim is suspect because it is based on endoscopic appearance and on random biopsy sampling techniques. These practices do not eliminate the possibility that the eradication procedure caused squamous epithelium to grow over foci of Barrett's epithelium (so-called "buried" metaplasia), which may retain malignant potential. Buried metaplasia easily can be missed as the result of biopsy sampling error, and superficial biopsy specimens of squamous epithelium that do not provide at least some lamina propria are not informative for buried metaplasia. Indeed, without resecting the esophagus and examining its full thickness histologically, it is virtually impossible to exclude the presence of buried metaplasia. A recent systematic review found that buried metaplasia was associated with dysplasia or cancer in the buried glands in 0 to 30% of patients in studies on endoscopic eradication therapy.²⁶¹

One recent study suggests that the risk of buried metaplasia following eradication therapy may be exaggerated, because buried metaplasia can be found with similar frequency in patients who are treated with PPIs alone (without endoscopic ablation). Bronner et al examined biopsy specimens of esophageal squamous epithelium taken during the previously mentioned randomized trial of PDT for patients with high-grade dysplasia in Barrett's esophagus.²⁶² After reviewing 33,658 esophageal biopsy specimens, the investigators found no significant difference in the frequency of squamous overgrowth (buried metaplasia) between the group treated with PDT (39 of 132 patients; 30%) and the group that received omeprazole alone (22 of 67 patients; 33%; $P > .05$). Furthermore, the highest grade of neoplasia per endoscopy was not found exclusively in the buried metaplasia in any patient. Apparently, squamous epithelium frequently grows over metaplastic glands in patients who are treated with PPIs, perhaps as a consequence of the extensive esophageal biopsy procedures used during endoscopic surveillance.

Whether or not the risk of buried metaplasia after ablation is exaggerated, it is clear that cancer can develop in some patients who are treated with endoscopic eradication therapy. A recent systematic review and meta-analysis found 43 reported cases of esophageal cancer that occurred in patients who had undergone endoscopic ablation for Barrett's esophagus without dysplasia (4 of 1457 cases), low-grade dysplasia (2 of 239 cases), or high-grade dysplasia (37 of 611 cases).²⁶³ Those data were used to calculate weighted-average incidence rates for cancer development after endoscopic ablation therapy as follows: 1.63 cancers per 1000 patient-years (95% CI, 0.07–3.34) for Barrett's esophagus without dysplasia, 1.58 cancers per 1000 patient-years (95% CI, 0.66–3.84) for low-grade dysplasia, and 16.76 cancers per 1000 patient-years (95% CI, 10.6–22.9) for high-grade dysplasia.

In summary, large, prospective, randomized trials have established that endoscopic ablation therapy with PDT and RFA is superior to treatment with PPIs alone for preventing the progression from high-grade dysplasia to cancer in Barrett's esophagus. Compared with PDT with porfimer sodium, RFA appears to have a better safety profile and is easier to administer. Large, nonrandomized, and uncontrolled cohort studies have shown excellent long-term survival rates for carefully selected patients with high-grade dysplasia and early cancer who are treated with EMR. Recurrent or metachronous cancers occur frequently in those patients, however, especially if the residual Barrett's epithelium is not ablated. Nevertheless, the recurrent cancers usually are amenable to further endoscopic eradication therapy.

It remains unclear whether the excellent results for endoscopic eradication therapy reported by the few expert centers that have studied those techniques can be reproduced in the community. The durability of the eradication therapy, the frequency and importance of buried metaplasia, and the long-term efficacy of ablation therapy for cancer prevention remain unsettled issues. With those caveats, we conclude that endoscopic eradication therapy is a reasonable therapeutic option for patients with high-grade dysplasia in Barrett's esophagus, especially in those for whom advanced age or comorbid illness renders esophagectomy inordinately hazardous (see the following text). If endoscopic eradication therapy is to be used, we recommend that any visible abnormalities should be removed by EMR, which provides invaluable staging information as well as therapy, followed by the ablation of all remaining Barrett's metaplasia.

Is Esophagectomy Still a Reasonable Option for Patients Who Have High-Grade Dysplasia in Barrett's Esophagus?

For decades, esophagectomy had been the traditional treatment recommended for patients with high-grade dysplasia in Barrett's esophagus.⁸⁶ For those patients, esophagectomy definitively eliminated all of the esophagus lined by Barrett's epithelium (dysplastic and nondysplastic) and, unlike modern endoscopic therapies, allowed for the removal of associated lymph nodes that could harbor metastases. Unfortunately, esophagectomy also could be associated with substantial rates of mortality and long-term morbidity. In some series of patients with esophageal cancer treated by esophagectomy, the operative mortality rate exceeded 20%. Indeed, the burgeoning interest in endoscopic eradication therapy for dysplasia in Barrett's esophagus has been fueled largely by the perception that esophagectomy has unacceptably high rates of mortality and long-term morbidity (Table 3).

A number of studies have shown that mortality rates for esophagectomy are inversely related to the frequency with which the operation is performed at any given medical center.²⁶⁴ In a study of data from the Dutch National Medical Registry, for example, the mortality rates for esophagectomy were 12.1%, 7.5%, and 4.9% at centers performing 1 to 10, 11 to 20, and >50 esophagectomies per year, respectively.²⁶⁵ Other reports have described esophagectomy mortality rates for high- and low-volume medical centers of 2.5% and 15.4%,²⁶⁶ 2.7% and 16%,²⁶⁷ 3.4% and 17.3%,²⁶⁸ 4.8% and 16%,²⁶⁹ and 8.4% and 20.3%,²⁷⁰ respectively. Therefore, one way to reduce the mortality from esophagectomy is to have the operation performed by an experienced surgeon who practices in a center that has a high volume for esophagectomy.

Estimated mortality rates for esophagectomy have been based largely on series of patients who had the operation performed for the treatment of symptomatic esophageal cancers.⁸⁶ Such patients are often elderly and debilitated by the dysphagia and anorexia that often accompany such advanced esophageal tumors. In addition to patients with adenocarcinoma in Barrett's esophagus, furthermore, those series often have included patients with squamous cell carcinoma of the esophagus, many of whom have had severe comorbid illnesses caused by the cigarette smoking and alcoholism associated with that tumor. One would anticipate substantially lower mortality rates for esophagectomy performed to treat dysplasia or early cancer in younger and otherwise healthy patients with Barrett's esophagus. In support of this notion, reports of a number of modern small series have described excellent survival rates when esophagectomy is performed primarily or exclusively for such patients (Table 4).^{271–300} Most of those studies have found no operative mortality, and none have described a mortality rate that exceeds 3.3%.

Esophagectomy can cause distressing symptoms such as dysphagia, early satiety, loss of appetite, and fatigue, which can seriously impair quality of life. Most studies that have addressed specifically the issue of quality of life after esophagectomy have included

primarily patients who had the operation because of advanced esophageal cancer, and the results of such studies may not be applicable to patients who undergo esophagectomy for asymptomatic neoplasia in Barrett's esophagus. Virtually all studies that have assessed quality of life in the immediate postoperative period have found that quality of life declines significantly immediately after esophagectomy.³⁰¹ However, most,^{302–305} but not all,^{306,307} long-term studies also have found that the quality of life returns to or even exceeds baseline levels by 3 months to 2 years after esophagectomy. Other studies that have assessed long-term function, years after esophagectomy, have found that the patients' quality of life scores are similar to those of control subjects in the general population.^{308–310}

Two studies have focused on quality of life primarily in patients who underwent esophagectomy for high-grade dysplasia or early cancer in Barrett's esophagus. One study of 34 such patients found that SF-36 results obtained at a mean follow-up of 46 months after esophagectomy were equal to or better than those of a healthy control population.²⁷⁹ The other study included 36 patients who had esophagectomy for high-grade dysplasia or intramucosal carcinoma and who were followed up for a mean duration of 4.9 years. Similar to the previous study, SF-36 scores for the patients were similar to those of age- and sex-matched control subjects.²⁷⁸

Although esophagectomy generally is considered the most definitive of the therapeutic options for patients with dysplasia in Barrett's esophagus, new columnar metaplasia (cardia type and intestinal type) develops frequently in the esophageal remnant in patients who have had esophagectomy with esophagogastrostomy, presumably as a consequence of the reflux esophagitis that often accompanies this procedure.^{311–315} Conceivably, those patients might be at risk for developing adenocarcinoma in the neo-metaplastic epithelium, and there are rare case reports of such an occurrence.^{316–318} Nevertheless, the risk of carcinogenesis in the Barrett's epithelium that develops after esophagectomy appears to be very small.

In summary, esophagectomy for high-grade dysplasia in Barrett's esophagus definitively removes all of the esophagus at increased risk for malignancy (unlike limited EMR and endoscopic ablation), provides a specimen that can be examined for evidence of invasion (unlike endoscopic ablation), and obviates the concern that local lymph nodes might contain metastases (unlike EMR and ablation). When performed in otherwise healthy individuals with dysplasia in Barrett's esophagus, the mortality rate for the operation is substantially less than 5%, and the long-term quality of life after esophagectomy is good in most cases. Thus, the option of esophagectomy still warrants serious consideration, especially for younger and otherwise fit patients who have high-grade dysplasia in Barrett's esophagus.

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Appendix

Search Algorithms Used in Systematic Reviews

What Is the Definition of Barrett's Esophagus? What Landmark Identifies the Gastroesophageal Junction? What Epithelial Type Is Required for the

Diagnosis of Barrett's Esophagus? Should Endoscopists Measure the Extent of Barrett's Metaplasia?

To identify relevant papers on the definition of Barrett's esophagus and the interrelated topics of identification of the gastroesophageal junction, histologic evaluation of esophageal biopsy samples for a determination of epithelial type, and measurement of the extent of Barrett's metaplasia, the text words "Barrett esophagus" were combined with the medical subject heading (MeSH) search terms "definition," "epithelium," "gastroesophageal junction," "esophagogastric junction," "diagnosis" (limited to title and abstract only), "extent," or "length." Relevant papers were selected from a yield of 1236.

What Is the Risk of Esophageal Cancer for the General Population of Patients With Barrett's Esophagus? What Is the Natural History of Dysplasia in Barrett's Esophagus?

To identify relevant papers on the progression and regression of patients with Barrett's esophagus with regard to dysplasia and esophageal adenocarcinoma, the search keywords "Barrett esophagus" or Barrett metaplasia" or "Barrett's mucosa" or "Barrett's epithelium" were combined with MeSH search terms "dysplasia" or "esophageal cancer" or "esophageal neoplasm." Relevant papers were selected from a yield of 305,425 references.

Does Barrett's Esophagus Affect Life Expectancy? How Does a Diagnosis of Barrett's Esophagus Affect Quality of Life?

To identify relevant papers on the impact of a diagnosis of Barrett's esophagus on life expectancy, the search keywords "Barrett esophagus" or Barrett's oesophagus" or "Barrett metaplasia" or "Barrett's mucosa" or "Barrett's epithelium" were combined with search keywords "life expectancy" or "mortality." Relevant papers were selected from a yield of 525 papers. Bibliographies of relevant articles were reviewed for additional pertinent manuscripts not encapsulated by the search. Reported data were retrospective cohort and case-control data reporting mortality. To define relevant papers on quality of life, we used the MeSH search terms "Barrett esophagus" and "quality of life" as well as the terms "Barrett's esophagus," "Barrett esophagus," "Barrett's," and "intestinal metaplasia" combined with the terms "quality of life," "QoL," "HRQoL," "SF-36," "QOLRAD," "GIQLI," "burden," and "economic impact." We also searched the MeSH search term "GERD" with the MeSH search term "quality of life" in addition to the term "Barrett's esophagus." Appropriate manuscripts were selected from 102 papers. We subsequently assessed the bibliographies of all identified relevant articles to identify data missed on the initial literature search. Reported studies were cohort studies, case series, or clinical trials.

Who Is at Risk for Barrett's Esophagus? Who Should Be Screened for Barrett's Esophagus?

To identify relevant papers on risk factors for Barrett's esophagus, the search keywords "Barrett esophagus" or Barrett's oesophagus" or "Barrett metaplasia" or "Barrett's mucosa" or "Barrett's epithelium" were combined with search keywords "risk factor" and "prevalence." Relevant papers were selected from 1932 citations. Regarding who should be screened for Barrett's esophagus, the search keywords "Barrett esophagus" or Barrett's oesophagus" or "Barrett metaplasia" or "Barrett's mucosa" or "Barrett's epithelium" were combined with the MeSH search term "screening." From 4597 citations, case-control studies, cohort data, and cross-sectional studies were retrieved. We subsequently assessed

the bibliographies of all identified relevant articles to identify data missed on the initial literature search.

Does Endoscopic Surveillance Improve Survival for Patients With Barrett's Esophagus?

To identify relevant papers on the role of endoscopic surveillance on mortality from esophageal adenocarcinoma, the keywords “Barrett esophagus” or “esophageal” and “adenocarcinoma” were combined with MeSH search terms “mass screening” or “early detection of cancer” or “surveillance” or “endoscopy.” Relevant papers were selected from a yield of 3250 references.

Can Biomarkers Be Used to Confirm the Histologic Diagnosis of Dysplasia? Can Biomarkers Be Used Instead of Dysplasia for Risk Stratification in Barrett's Esophagus?

To identify relevant papers on the role of biomarkers for confirming a diagnosis of dysplasia and for risk stratification in Barrett's esophagus, the text words “Barrett esophagus” were combined with the MeSH search terms “biomarker,” “molecular,” “mutation,” “deletion,” “heterozygosity,” “gene,” or “genetic.” Relevant papers were selected from a yield of 608.

Should Chromoendoscopy or “Electronic Chromoendoscopy” Be Used to Enhance the Detection of Metaplasia and Dysplasia in Barrett's Esophagus?

To identify relevant papers on the role of chromoendoscopy and related techniques for the yield of Barrett's esophagus and dysplasia, the following keywords and MeSH search terms were used: “Barrett esophagus” and “chromoendoscopy” or “electronic chromoendoscopy” or “narrow band imaging” or “FICE” or “NBI.” Relevant papers were selected from a yield of 109 references.

Should Advanced Endoscopic Imaging Techniques Such as Autofluorescence Imaging, Confocal Laser Endomicroscopy, Diffuse Reflectance and Light Scattering Spectroscopy, and Optical Coherence Tomography Be Used to Enhance the Detection of Metaplasia and Dysplasia in Barrett's Esophagus?

To identify relevant papers on the role of spectroscopy, autofluorescence, confocal endomicroscopy, and related techniques for the yield of Barrett's esophagus and dysplasia, the following keywords and MeSH search terms were used: “Barrett esophagus” and (“adenocarcinoma” or “dysplasia” or “metaplasia”) and (“advanced imaging” or “optical coherence” or “spectroscopy” or “reflectance” or “endomicroscopy” or “endoscopic imaging” or “imaging”). Relevant papers were selected from a yield of 1551 references.

Should Proton Pump Inhibitors Be Used for Chemoprevention in Barrett's Esophagus? Should Nonsteroidal Anti-inflammatory Drugs Be Used for Chemoprevention in Barrett's Esophagus?

To identify relevant papers on the role of proton pump inhibitors and nonsteroidal anti-inflammatory drugs for chemoprevention in Barrett's esophagus, the text words "Barrett esophagus" were combined with the MeSH search terms "proton pump inhibitor," "PPI," "nonsteroidal anti-inflammatory drugs," or "NSAID." Relevant papers were selected from a yield of 391.

Should Antireflux Surgery Be Advised to Prevent Cancer in Barrett's Esophagus?

To identify relevant papers on the role of antireflux surgery for cancer prevention in Barrett's esophagus, the text words "Barrett esophagus" were combined with the MeSH search terms "fundoplication," "antireflux surgery," or "cancer risk." Relevant papers were selected from a yield of 1214.

What Is the Role for EMR in Barrett's Esophagus? Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus Without Dysplasia? Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus With Low-Grade Dysplasia? Should Endoscopic Eradication Be Used to Treat Patients Who Have Barrett's Esophagus With High-Grade Dysplasia or Intramucosal Carcinoma?

To identify relevant papers on the role of endoscopic therapies on the treatment of Barrett's esophagus, dysplasia, and esophageal adenocarcinoma, the following keywords and MeSH search terms were used: "Barrett esophagus" and ("adenocarcinoma" or "dysplasia") and ("endoscopic mucosal resection" OR "ablation" OR "endoscop*" OR "therap*"). Relevant papers were selected from a yield of 382 references.

Is Esophagectomy Still a Reasonable Option for Patients Who Have High-Grade Dysplasia in Barrett's Esophagus?

To identify relevant papers on the role of esophagectomy for patients with high-grade dysplasia in Barrett's esophagus, the text words "Barrett esophagus" were combined with the MeSH search terms "esophagectomy," "resection," or "dysplasia." Relevant papers were selected from a yield of 1516.

Abbreviations used in this paper

AFI	autofluorescence imaging
AGAI	American Gastroenterological Association Institute
APC	argon plasma coagulation
CI	confidence interval

CPQMC	Clinical Practice and Quality Management Committee
EMR	endoscopic mucosal resection
EUS	endoscopic ultrasonography
GEJ	gastroesophageal junction
GERD	gastroesophageal reflux disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LOH	loss of heterozygosity
PEC	multi-polar electrocoagulation
NBI	narrow band imaging
PDT	photodynamic therapy
PPI	proton pump inhibitor
QOLRAD	Quality of Life in Reflux and Dyspepsia
RFA	radiofrequency ablation
RR	relative risk
SEER	Surveillance, Epidemiology and End Results
SF-36	36-Item Short Form Health Survey
TR	technical review

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