

A Critical Review of the Diagnosis and Management of Barrett's Esophagus: The AGA Chicago Workshop

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Background & Aims: The diagnosis and management of Barrett's esophagus (BE) are controversial. We conducted a critical review of the literature in BE to provide guidance on clinically relevant issues. **Methods:** A multidisciplinary group of 18 participants evaluated the strength and the grade of evidence for 42 statements pertaining to the diagnosis, screening, surveillance, and treatment of BE. Each member anonymously voted to accept or reject statements based on the strength of evidence and his own expert opinion. **Results:** There was strong consensus on most statements for acceptance or rejection. Members rejected statements that screening for BE has been shown to improve mortality from adenocarcinoma or to be cost-effective. Contrary to published clinical guidelines, they did not feel that screening should be recommended for adults over age 50, regardless of age or duration of heartburn. Members were divided on whether surveillance prolongs survival, although the majority agreed that it detects curable neoplasia and can be cost-effective in selected patients. The majority did not feel that acid-reduction therapy reduces the risk of esophageal adenocarcinoma but did agree that nonsteroidal antiinflammatory drugs are associated with a cancer risk reduction and are of promising (but unproven) value. Participants rejected the notion that mucosal ablation with acid suppression prevents adenocarcinoma in BE but agreed that this may be an appropriate strategy in a subgroup of patients with high-grade dysplasia. **Conclusions:** Based on this review of BE, the opinions of workshop members on issues pertaining to screening and surveillance are at variance with published clinical guidelines.

interest.^{1,2} Since its first description in the 1950s, the definition of BE has undergone modifications that include the inclusion of histologic findings.^{3,4} Controversy surrounds the management of patients with BE, including whether screening or surveillance for the lesion is justified and regarding the role of acid suppression, antireflux surgery, and ablative therapies.

There are no in-depth, published, systematic reviews of the optimal approaches to the diagnosis and management of patients with BE. Given the controversies involving this lesion, a workshop was convened to evaluate critically the current data related to BE and to provide an in-depth analysis of clinical issues associated with this disorder. The American Gastroenterological Association (AGA) Barrett's Esophagus Workshop was held on February 1–3, 2003, in Chicago, Illinois. The workshop was sponsored by the AGA Clinical Practice Section with the support of the AGA Council. This workshop conducted a critical review of the literature pertaining to the diagnosis, screening, surveillance, and treatment of BE. Rather than proposing guidelines and recommendations or arriving at a consensus, the aim of this workshop was to evaluate and grade the current evidence to provide clinicians information and guidance on important practical clinical issues as well as to identify areas requiring further study. The workshop was specifically designed to provide details as to how the workshop group graded clinically relevant statements to provide readers an hon-

The increasing incidence of esophageal adenocarcinoma and the recognition of Barrett's esophagus (BE) as its premalignant precursor have sparked much

Table 1. Grading Scheme for Working Subgroups

Category	Nature of evidence
I	Evidence obtained from at least 1 well-designed, randomized, controlled trial
II	Evidence obtained from well-designed cohort or case-controlled studies
III	Evidence obtained from case series, case reports, or flawed clinical trials
IV	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
V	Insufficient evidence to form an opinion

Category	Level of Subgroup support for statement
A	There is good evidence to support the statement
B	There is fair evidence to support the statement
C	There is poor evidence to support the statement, but recommendations may be made on other grounds
D	There is fair evidence to reject the statement
E	There is good evidence to reject the statement

NOTE. Grading scheme for working subgroups, adapted from Dent et al.⁵

est appraisal of the degree of divergence of expert opinion.

Workshop Methodology

The workshop format was modeled closely after the “Genval” evidence-based appraisal of gastroesophageal reflux disease.⁵ The workshop comprised 18 physicians (15 gastroenterologists, 2 surgeons, 1 pathologist) from 4 countries. All participants had an established basic or clinical research interest in the epidemiology, diagnosis, or treatment of BE and/or expertise in an evidence-based review process. The material was divided into 4 content areas, each with a designated leader: definition and diagnosis, screening, surveillance, and treatment. The 4 section leaders and chairmen developed 42 clinically relevant statements, which formed the basis for the workshop discussions. Prior to the meeting, each of the participants performed a literature review for 3 or 4 of the statements assigned to them.

The workshop was conducted in 3 segments. First, each of the 4 content leaders provided a state-of-the-art overview for their assigned area, which served as a framework for subsequent discussions. Second, in 4 working groups conducted simultaneously (comprised of a content leader and 3 content experts), each content expert reviewed the evidence for 3 or 4 statements. After each statement, the group discussed the evidence presented, graded the strength of this evidence, and assigned the statement a consensus numerical grade for the “Nature of the Evidence” and a “Grade of Recommendation” (Table 1).⁵ The subgroup “acceptance” or “rejection” for a statement was based on group consensus after review of the

data and open discussion. There were no predetermined criteria for distinguishing “fair” or “good” evidence. In the third segment, all 18 members of the workshop reassembled, reviewed the subgroup summaries, and further discussed each topic. After each discussion, including the subgroup’s assessment of the strength of the evidence as well as their recommendation, each member anonymously voted his “Level of Support” for the statement (Table 2).⁵

The evidence grading used in this workshop reflects the use of evidence in evaluating the study design, study execution, consistency of treatment effects, and allowance of nonrandomized designs, case series, or modeling studies in which these may have been the appropriate methods. This is especially true for BE, given the lack of randomized controlled or prospective trials in screening, surveillance, or treatment.

This report includes the reviews by the group leaders, followed by voting and discussion for a series of statements relevant to the diagnosis, screening, surveillance, and treatment of BE. Each section starts with a brief overview of the topic. The outcome of voting for the statement in each of the 4 different topic sessions is provided in Tables 3–6. The raw vote tallies are provided to highlight those areas in which there is a high degree of consensus or disagreement for acceptance or rejection.

Barrett’s Esophagus: Definition and Diagnosis

The definition of BE has evolved over the last 3 decades. Suggested definitions have included the direct observation of “extensive columnar metaplasia” in 1975⁶; a combination of endoscopic, histologic, and manometric criteria in 1987⁷; and, more recently, a combination of endoscopic and histologic criteria consisting of an abnormal appearing distal esophageal lining (endoscopic BE) with histologic evidence of esophageal intestinal metaplasia (confirmed/histologic BE).⁴ An optimal, practical definition of BE requires clear, accepted, reproducible, and clinically relevant criteria with evidence of an increased risk of esophageal adenocarcinoma in those with the lesion. With appropriate training, endoscopic criteria

Table 2. Group Grading Scheme for Level of Support for Each Statement

A	Accept recommendation completely
B	Accept recommendation with some reservations
C	Accept recommendation with major reservations
D	Reject recommendation with reservations
E	Reject recommendation completely

NOTE. Group grading scheme for level of support for each statement is adapted from Dent et al.⁵

Table 3. Diagnosis of Barrett's Esophagus

Statement number	Nature of evidence	Subgroup support	Group grading (%)				
			Accept completely	Accept with some reservation	Accept with major reservation	Reject with reservation	Reject completely
1. Esophageal intestinal metaplasia documented by histology is a prerequisite criterion for the diagnosis of BE	IV	C	28	44	16	6	6
2. Special stains (such as alcian blue, PAS, and others) are necessary for the histologic diagnosis of BE	V	D	6	—	—	72	22
3. Markers such as cytokeratin staining distinguish intestinal metaplasia of the esophagus from intestinal metaplasia of the stomach	III	D	—	11	39	44	6
4. The working definition of BE is displacement of the squamocolumnar junction proximal to the gastroesophageal junction	III	B	39	50	—	11	—
5. Endoscopy with multiple systematic biopsies is needed to establish the diagnosis of BE	III	A	83	11	6	—	—
6. Long-segment (>3 cm) and short-segment (<3 cm) BE are distinct clinical entities	III	D	—	—	6	55	39
7. The proximal margin of the gastric folds is a reliable endoscopic marker for the gastroesophageal junction	IV	C	—	78	22	—	—
8. The use of techniques such as chromoendoscopy, magnification endoscopy, light-induced fluorescent endoscopy, and spectroscopy currently is of unproven utility for the detection of intestinal metaplasia or dysplasia	III	A	39	50	11	—	—
9. The normal appearing and normally located squamocolumnar junction should not be biopsied	IV	C	78	22	—	—	—
10. A patient with a columnar-lined distal esophagus without confirmed intestinal metaplasia on biopsy requires a follow-up endoscopy	III	C	17	33	22	22	6

NOTE. See Tables 1 and 2 for grading schemes.

for BE are fairly reproducible⁸; however, diagnostic inconsistencies occur.⁹ In addition, both gastroenterologists and pathologists often fail to document adequately the diagnostic criteria for BE.^{10,11} The clinical importance of the definition of BE is that it should identify a lesion documented to be at risk of esophageal adenocarcinoma. There is evidence that BE may not be the precursor for all esophageal adenocarcinomas.¹² This may be due in some cases to the cancer having obliterated the BE from which it arose^{13–15} or to difficulty in distinguishing esophageal adenocarcinoma from true cardiac adenocarcinoma. A uniform definition of BE will enable clinicians to discuss the same entity and researchers to enroll comparable patients across studies.

Statement 1: Esophageal Intestinal Metaplasia Documented by Histology Is a Prerequisite Criterion for the Diagnosis of BE

The discussion focused on the lack of direct evidence linking intestinal metaplasia to esophageal adenocarcinoma. Although the vast majority of esophageal and

gastroesophageal adenocarcinomas are accompanied by intestinal metaplasia,^{16–20} all 3 types of columnar epithelium—cardiac-type mucosa, fundic-type mucosa, and intestinal metaplasia—can be detected in the columnar lined esophagus.²¹ Retrospective studies of esophagectomy specimens from patients with BE consistently demonstrate intestinal metaplasia and dysplasia both adjacent to and remote from adenocarcinoma.^{16–20} Although it is difficult to prove that it is the intestinal metaplasia alone that predisposes to neoplastic progression, the workshop participants agreed that the identification of dysplastic epithelium arising in cardiac-type or fundic-type mucosa in the absence of coexisting intestinal metaplasia appears to be uncommon. However, the neoplastic risk of cardiac- and fundic-type mucosa is not known.

Statement 2: Special Stains (Such as Alcian Blue, PAS, and Others) Are Necessary for the Histologic Diagnosis of BE

The group observed that, if intestinal metaplasia is required for the diagnosis of BE, then the

Table 4. Screening for Barrett's Esophagus

Statement number	Nature of evidence	Subgroup support	Group grading (%)				
			Accept completely	Accept with some reservation	Accept with major reservation	Reject with reservation	Reject completely
11. Endoscopic screening for Barrett's esophagus and dysplasia has been shown to improve mortality from esophageal adenocarcinoma	V	E	—	—	6	39	55
12. Endoscopic screening for Barrett's esophagus and dysplasia has been shown to be cost-effective	IV	C	—	—	22	50	28
13. Routine endoscopic screening for the detection of Barrett's esophagus should be recommended for all adults ≥ 50 years of age	V	D	—	—	—	44	56
14. A high-risk group for the development of BE can be identified	II	A	39	39	17	—	5
15. This group will benefit from screening endoscopy	V	D	6	6	11	55	22
16. Endoscopic screening for BE and dysplasia should be performed in all adults ≥ 50 years of age with heartburn	V	E	—	—	—	39	61
17. Endoscopic screening for BE and dysplasia should be performed in all adults ≥ 50 years of age with >5 – 10 years of heartburn	IV	D	—	—	17	78	5
18. Endoscopic screening for BE and dysplasia should be performed in all white adults ≥ 50 years of age with >5 – 10 years of heartburn	IV	D	—	—	17	72	11
19. Standard endoscopy with biopsy currently is the most reliable means of establishing a diagnosis of BE	III	A	78	17	5	—	—
20. Unsedated small-caliber endoscopy and biopsy is an alternative approach for the screening of BE	III	B	6	11	50	27	6
21. The results of nonendoscopic methods of diagnosis such as brush or balloon cytology are of proven value in the screening of BE	V	D	6	—	—	39	55

NOTE. See Tables 1 and 2 for grading schemes.

accurate recognition of intestinal metaplasia in a biopsy sample is critical for establishing the correct diagnosis. Goblet cells stain intensely blue with the Alcian blue (AB) portion of the AB/PAS stain because of the presence of acid mucins.^{22–26} The AB/PAS stain can help to avoid “over interpretation” of pseudogoblet cells (i.e., distended foveolar-type cells that stain for PAS but do not contain AB-positive acid mucins) as true goblet cells. In a study by Alikhan et al.,²⁷ gastric metaplasia without intestinal metaplasia was diagnosed as BE in 38% of cases by general pathologists in community practice, emphasizing that overdiagnosis of BE is common. The workshop concluded that, in most cases of BE, intestinal metaplasia can be identified easily on standard stained sections; hence, special stains such as AB/PAS are not required routinely for histologic diagnosis. In select cases, particularly those in which goblet cells are rare or prominent “pseudogoblet cells” are present, the working group felt that AB/PAS can help to confirm the diagnosis and avoid overdiagnosis of intestinal metaplasia.

Statement 3: Markers Such as Cytokeratin Staining Distinguish Intestinal Metaplasia of the Esophagus From Intestinal Metaplasia of the Stomach

Intestinal metaplasia can arise in the most proximal aspect of the stomach (cardia intestinal metaplasia), a condition that may be difficult to distinguish from short-segment BE (SSBE).²⁸ If the etiology and/or risk of progression to dysplasia/adenocarcinoma were similar in these 2 conditions, it would not be important to distinguish cardia intestinal metaplasia from SSBE. The members reviewed recent evidence that suggests that these are distinct diseases with different etiologies and risks of neoplastic progression.²⁹ Proponents for the use of CK staining reviewed studies that found a pattern of cytokeratin (CK) 7 and 20 immunoreactivity in both long-segment BE (LSBE) and SSBE that was not found in intestinal metaplasia of gastric origin, including cardia intestinal metaplasia.^{30,31} BE was characterized by superficial and deep CK7 immunoreactivity and superficial band-like CK20 staining in the areas of intestinal meta-

Table 5. Surveillance of Barrett's Esophagus

Statement number	Nature of evidence	Subgroup support	Group grading (%)				
			Accept completely	Accept with some reservation	Accept with major reservation	Reject with reservation	Reject completely
22. Endoscopic surveillance in patients with Barrett's esophagus has been shown to prolong survival	III	B	—	28	22	44	6
23. Endoscopic surveillance in selected patients with BE can be cost-effective	NA	B	—	39	39	22	—
24. Endoscopic surveillance detects curable neoplasia in patients with BE	III	B	39	44	17	—	—
25. Endoscopic surveillance should be limited to patients with BE with dysplasia	III	D	—	11	6	44	39
26. Patients with short- and long-segment BE should have the same surveillance	V	C	6	27	61	6	—
27. Endoscopy with multiple systematic biopsies is needed for the detection of dysplasia or adenocarcinoma for the surveillance of BE	II	A	72	28	—	—	—
28. The use of flow cytometry or biomarkers (such as p53 and p16 mutations) is promising and merits further clinical research	II	A	72	16	6	—	6
29. The distinction between focal and diffuse high-grade dysplasia in BE has important clinical implications	V	C	—	—	67	33	—
30. After antireflux surgery, patients with BE should have the same endoscopic surveillance as medically treated patients	II	A	94	—	6	—	—
31. Intensive endoscopic surveillance is an appropriate strategy in a subgroup of patients with high-grade dysplasia in BE	II	B	33	61	6	—	—

NOTE. See Tables 1 and 2 for grading schemes.

plasia (so-called "Barrett's CK7/20 pattern"). Intestinal metaplasia of gastric origin did not have this CK7/20 staining pattern. Other members argued that, although some studies support these observations,^{32,33} others report discrepant results.^{34–36}

Statement 4: The Working Definition of BE Is Displacement of the Squamocolumnar Junction Proximal to the Gastroesophageal Junction With the Presence of Intestinal Metaplasia

The goal for defining BE is the creation of a standardized method for identification of this esophageal adenocarcinoma risk factor to facilitate recognition by endoscopists, treatment by clinicians, and optimal research.^{37,38} The majority of the workshop participants agreed that the proposed definition is practical because it combines the primary endoscopic and histologic features that are most commonly associated with cancer risk.³⁹ A few felt that endoscopic recognition of distal esophageal columnar tissue alone (without intestinal metaplasia) may be sufficient for a diagnosis of BE.

The group felt that identification of landmarks at the time of endoscopy was crucial. Endoscopic criteria for the recognition of a columnar lined distal esophagus include the proximal displacement of the squamocolumnar junc-

tion (z-line) relative to the gastroesophageal junction. Endoscopic localization of the gastroesophageal junction and measurement of z-line displacement is moderately reproducible, with mild to substantial variation in measured segment lengths between examinations.⁹ The group felt that this definition represents the best metric currently available. The definition's histologic requirement is the presence of intestinal metaplasia. Most members agreed that this definition has good consensus and approximates the definitions propounded in recent expert reviews and published in society guidelines^{4,40}; however, some questioned whether the presence of intestinal metaplasia is required for a diagnosis of BE.

Statement 5: Endoscopy With Multiple Systematic Biopsies Is Needed to Establish the Diagnosis of BE

The group felt that the diagnosis of BE requires direct visual examination of the esophagus with endoscopy, and there was some discussion regarding nonendoscopic methods such as radiologic studies or clinical risk factor scoring systems that may increase the proportion of persons identified with BE. However, these nonendoscopic methods were felt to have insufficient predictive value.^{41,42} The diagnosis of esophageal intestinal metaplasia requires multiple directed biopsies of the esopha-

Table 6. Treatment of Barrett's Esophagus

Statement number	Nature of evidence	Subgroup support	Group grading (%)				
			Accept completely	Accept with some reservation	Accept with major reservation	Reject with reservation	Reject completely
32. Acid suppressive therapy has been shown to improve symptoms and to heal and prevent relapse of erosive esophagitis in patients with BE	III	B	22	78	—	—	—
33. Patients with long segment (≥ 3 cm circumferentially) BE have high levels of nocturnal esophageal acid exposure	II	A	55	45	—	—	—
34. These patients should be treated with twice daily PPI therapy	III	D	—	—	5	78	17
35. Normalization of esophageal acid exposure by acid suppression reduces the risk for development of esophageal adenocarcinoma	V	D	—	—	11	50	39
36. Epidemiologic studies show a significant risk reduction in esophageal adenocarcinoma in aspirin/NSAID users	II	A	72	28	—	—	—
37. The use of aspirin/NSAID therapy as a chemopreventative agent for risk reduction in patients with BE is promising but of unproven value	II	A	61	33	6	—	—
38. Among patients with BE, the reported short- and long-term control of reflux symptoms after antireflux surgery varies widely	II	A	67	33	—	—	—
39. In patients with BE, antireflux surgery has not proven to have a major effect against the development of esophageal adenocarcinoma	III	A	83	17	—	—	—
40. Mucosal ablation in conjunction with intensive acid suppression or antireflux surgery leads to partial or complete replacement of metaplastic columnar epithelium by squamous mucosa	I	A	61	22	17	—	—
41. Mucosal ablation with intensive acid suppression or antireflux surgery prevents adenocarcinoma in patients with BE without dysplasia	IV	E	6	—	—	—	94
42. Mucosal ablative techniques (including mucosal resection) are appropriate strategies in a subgroup of patients with high-grade dysplasia in BE	I	A	28	44	28	—	—

NOTE. See Tables 1 and 2 for grading schemes.

geal columnar mucosa because intestinal metaplasia is not uniformly distributed.⁴³ The workshop recognized pitfalls of current biopsy techniques. It was discussed that, even among patients with long segments of esophageal columnar metaplasia, over 20% may not have intestinal metaplasia detected on a single set of endoscopic biopsies.^{9,43,44} Multiple biopsies, therefore, should be obtained within a suspected segment of esophageal columnar mucosa,⁴³ and, although not formally voted on, most members would use a 4-quadrant biopsy protocol every 2 cm.

Statement 6: Long-Segment (≥ 3 cm) and Short-Segment (< 3 cm) BE Are Distinct Clinical Entities

Esophageal intestinal metaplasia appears to represent a continuum. Prior classification of BE into short- and long-segment metaplasia was arbitrary and not clinically valid. The workshop felt that BE classification

schemes should reflect important differences in risk factors or in neoplastic progression rates. Longer segments of BE are associated in some studies with increasing severity of gastroesophageal reflux disease and more advanced age.^{45–47} There also are trends for increasing cancer risk with longer segments^{48–50}; however, there is no evidence that a risk gradient may be demarcated at a particular segment length. Intestinal metaplasia identified on biopsy of a normal appearing gastroesophageal junction appears to be a distinct entity from either short- or long-segment BE^{29,51} (see details in statement 9).

Statement 7: The Proximal Margin of the Gastric Folds Is a Reliable Endoscopic Marker for the Gastroesophageal Junction

All workshop members were in agreement that a reliable endoscopic determination of the gastroesophageal junction (GEJ) is needed to make a diagnosis of BE and to record the length of columnar epithelium in the

esophagus. A widely used endoscopic marker of the GEJ is the proximal margin of the gastric folds.^{52–54} Other markers of the GEJ include the level at which the tubular esophagus meets the wider, sac-like stomach⁵⁵ and the pinch at the end of the tubular esophagus.²⁸ Given its widespread use by experts in the field, the group uniformly favored using the proximal margin of the gastric folds to identify the GEJ but recognized that there are scant data that validate it.^{56,57} No studies have compared the upper margin of the gastric folds with other markers, such as the level at which the tubular esophagus meets the wider, sac-like stomach. However, the group agreed that this still represented the best landmark recognized at endoscopy.

Statement 8: The Use of Techniques Such as Chromoendoscopy, Magnification Endoscopy, Light-Induced Fluorescence Endoscopy, and Spectroscopy Currently Is of Unproven Utility for the Detection of Intestinal Metaplasia or Dysplasia

The group discussion focused on the limitations of standard endoscopy for the identification of BE. Routine video endoscopy without biopsy and histologic evaluation cannot distinguish intestinal metaplasia, from fundic or cardiac epithelium. Furthermore, the presence and grade of dysplasia cannot be determined by routine endoscopy. Data were presented concerning nonbiopsy endoscopic methods that are currently under evaluation to identify intestinal metaplasia and dysplasia.⁵⁸ One of these techniques is chromoendoscopy, which uses a dye such as methylene blue to selectively stain intestinal metaplasia and to distinguish areas of high-grade dysplasia.⁵⁹ Magnification endoscopy with instruments that provide $\times 35$ – 115 enlargement enhance surface mucosal detail and may help identify intestinal metaplasia and dysplasia.⁶⁰ Recent data regarding the use of light-induced fluorescence endoscopy and light-scattering spectroscopy were also reviewed by the group.^{58,61,62} The workshop participants agreed that these techniques currently are of unproven utility for the detection of intestinal metaplasia or dysplasia, and further validation and evaluation of their effectiveness is necessary before they are applicable to routine clinical practice.

Statement 9: The Normal Appearing and Normally Located Squamocolumnar Junction Should Not Be Biopsied

Biopsy specimens taken just distal to a normal appearing and normally located squamocolumnar junction, with no visible esophageal columnar segment, may show intestinal metaplasia at the cardia (i.e., proximal stomach), which is unrelated to reflux symptoms (see

statement 6).⁵⁵ Although dysplasia or early cardia adenocarcinomas are found in a few cases of cardia intestinal metaplasia, longitudinal studies to determine the cancer risk in patients with cardia intestinal metaplasia are not available.^{55,63–65} In addition, although the prevalence of cardia intestinal metaplasia ($>15\%$) is much higher than the prevalence of BE, cardia adenocarcinoma is less common than esophageal adenocarcinoma (2 of 100,000 vs. 2–4 of 100,000/year).^{1,55,63,66} Therefore, the absolute cancer risk of an individual with cardia intestinal metaplasia is much lower than in BE. The group felt that no current evidence supports screening for cardia intestinal metaplasia by taking biopsy specimens from the normal squamocolumnar junction.

Statement 10: A Patient With a Columnar-Lined Distal Esophagus Without Confirmed Intestinal Metaplasia on Biopsy Requires a Follow-up Endoscopy

The discussion for the above statement was similar to that for statements 1 and 5. Intestinal metaplasia is more often found when endoscopy shows a long rather than a short (<3 cm) extent of columnar lining.^{67–71} More than 20% of patients without confirmation of intestinal metaplasia endoscopy with systematic biopsies are found to have intestinal metaplasia on later endoscopy^{44,71} because of sampling error or interim development of intestinal metaplasia after the first examination. The workshop agreed that clinicians should consider repeat endoscopy with systemic biopsies in patients with substantial lengths of columnar lining in the distal esophagus without confirmed intestinal metaplasia on initial biopsies, but the specifics of the timing and frequency of the follow-up endoscopy were not discussed. However, there was wide variance in voting among workshop members on this statement, reflecting their uncertainty and the need for further studies on this topic.

Barrett's Esophagus: Screening

The goal of a screening program should be to detect neoplasia or lesions at risk of developing neoplasia, allowing intervention or surveillance that leads to improved outcomes such as a reduced incidence of cancer or cancer deaths. Recent guidelines in support of screening for BE⁴ have been endorsed by other gastrointestinal societies and are commonly followed in clinical practice. However, others disagree with these guidelines because they do not address important issues such as who, when, how, and how often to screen and, most importantly, why to screen for BE.⁷²

The prevalence of BE may be relatively high in the general population, but the majority of people remains

undiagnosed, as suggested by autopsy studies.^{73,74} Recent studies of patients referred for screening sigmoidoscopy or colonoscopy who agreed to undergo upper endoscopy demonstrated BE in 10%–25% of these patients.^{75,76} Patients with chronic gastroesophageal reflux disease (GERD) are believed to be at increased risk for the development of BE,^{77–79} and the prevalence of BE is higher in white males, begging the question of whether screening should be restricted to this higher risk subgroup.⁸⁰ Recent data suggest that the risk of dysplasia increases 3.3% a year in patients with BE, suggesting a significant risk of clinically important neoplastic lesions within Barrett's occurs later in life.⁸¹ These data suggest the possibility that screening could be deferred until a certain age (e.g., age 50 years or greater) is reached.

A final question is whether screening for BE is cost-effective and will improve health-related outcomes. Screening implies that patients with BE will enter surveillance programs for the detection of neoplasia. Although data from 2 large cohorts indicate that the incidence of cancer in BE is only 0.4%–0.5%/year,⁸² data pooled from large BE surveillance programs in the United States indicate that the combined incidence of cancer and high-grade dysplasia is 1.3%/yr.⁸³ Depending on the natural history of high-grade dysplasia, these data suggest that screening and subsequent surveillance could be cost-effective.^{84–86}

Statement 11: Endoscopic Screening for BE and Dysplasia Has Been Shown to Improve Mortality From Esophageal Adenocarcinoma

The group reviewed substantial theoretical concerns that mitigate against screening for BE and neoplasia in the general population with reflux symptoms. Among these are the high prevalence of reflux symptoms,⁸⁷ the low incidence of neoplasia,⁴ and the relatively high costs of endoscopy. Some studies have shown that subjects with BE have the same age-adjusted life expectancy as unaffected comparator groups or the general population, and no decrease in disease-related mortality has been documented in those who are undergoing surveillance.^{88–90} Furthermore, studies demonstrate that up to 40% of patients with esophageal adenocarcinoma do not experience frequent reflux symptoms and therefore would not be detected through screening programs targeted to patients only with reflux symptoms.^{12,91,92} The consensus of workshop members was that screening for BE and dysplasia has not been demonstrated to improve mortality from esophageal adenocarcinoma.

Statement 12: Endoscopic Screening for BE and Dysplasia Has Been Shown to Be Cost-Effective

The group discussed the few clinical studies that address the cost-effectiveness of screening for BE and dysplasia. A retrospective analysis of a Swedish case-control study estimated the number of endoscopies needed to identify patients with esophageal or gastric cardia adenocarcinoma among patients with various risk factors for neoplasia.⁹³ Because the absolute risk of esophageal adenocarcinoma is low even in the subgroup with severe reflux symptoms and obesity, it was concluded that screening was not justified among the general population with reflux symptoms.

Results of several mathematical models that assess the cost-effectiveness and cost utility of endoscopic screening of subjects with GERD for BE and neoplasia were evaluated. A recent model demonstrated that screening 50-year-old men with GERD symptoms could be cost-effective if certain assumptions were met regarding disease prevalence and utility.⁹⁴ This study demonstrated that a 1-time screening endoscopy had a cost-effectiveness ratio of \$10,000 per additional quality-adjusted life-year of survival gained if follow-up endoscopies were performed only in BE patients with dysplasia. Likewise, a model by Soni et al. found that, under certain assumptions (which may be difficult to achieve), a 1-time screening examination could be cost-effective compared with no screening, resulting in a cost of \$24,700 per quality-adjusted life-year saved.⁹⁵ Although these provocative models are useful for hypothesis generation, the majority of the group felt that, in the absence of definitive clinical studies, this statement should be rejected.

Statement 13: Routine Endoscopic Screening for the Detection of BE Should Be Recommended for all Adults ≥50 Years of Age

The discussion for the above statement highlighted the lack of data regarding the prevalence and natural history of BE in the general population. If BE is highly prevalent in the asymptomatic population, the risk of progression to esophageal adenocarcinoma in these populations must be low, given the low absolute number of cases of this cancer.⁷² Endoscopic screening of the asymptomatic population for BE should only be considered if there is a means to identify subsets of patients through risk-stratification who have an increased prevalence of BE or an increased risk of neoplastic progression. Some recent studies demonstrate that the prevalence of BE in certain asymptomatic cohorts may be higher than previously thought.^{74,75} The group nevertheless was

unanimous that screening of unselected 50-year-old adults for BE should not be undertaken.

Statement 14: A High-Risk Group for the Development of BE Can Be Identified

Multiple risk factors for BE have been identified. These include longer duration and increased frequency of GERD symptoms, male gender, and white race.^{90,96–99} Alcohol or tobacco use and obesity have been found to be risk factors in some studies.⁹⁷ Hiatal hernia has been demonstrated to be a risk factor, and hernia size is correlated with the length of BE.^{97,98,100} There was near unanimous group consensus that, within the general population, a subgroup at high risk for BE can be identified.

Statement 15: This Group Will Benefit From Screening Endoscopy (See Statement 14)

As discussed in statements 11, 12, and 13, there is controversy as to whether screening for BE will be beneficial even in high-risk subgroups. Because of unanswered questions regarding the optimal risk stratification to identify high risk groups, the cost-effectiveness of screening, and the lack of proven benefit of endoscopic surveillance in patients in whom BE is identified, the majority of the group rejected the contention that any identified group will benefit from screening endoscopy.

Statement 16: Endoscopic Screening for BE and Dysplasia Should Be Performed in all Adults \geq 50 Years of Age With Heartburn

Approximately 1 in 5 adults has heartburn at least once per week, 5% of whom have BE.¹⁰¹ However, 40% or more of patients with esophageal adenocarcinoma have minimal or no reflux symptoms.¹² Thus, the workshop realized that the pool of patients with BE at risk for esophageal carcinoma *without symptoms of heartburn* may be as large as that with heartburn and that current evidence does not support endoscopic screening for BE in all adults \geq 50 years of age with heartburn.

In considering the potential benefits of 1-time endoscopic screening for BE in patients with long-term heartburn symptoms, the group felt that deleterious consequences of screening should be considered. The presence of erosive esophagitis at the time of screening may mask underlying BE, and biopsies near eroded areas may lead to overdiagnosis of dysplasia. The members also felt that the potential impact of false-positive diagnoses of BE with attendant generation of patient anxiety, unnecessary follow-up examinations, and difficulty obtaining life and other insurance are unintended harms of screening that must be considered.

Statement 17: Endoscopic Screening for BE and Dysplasia Should Be Performed in all Adults \geq 50 Years of Age With \geq 5–10 Years of Heartburn

The above statement adds *duration* of heartburn to the question of screening. There is evidence that the duration of heartburn increases the likelihood of finding BE.⁷⁹ However, it was felt by the majority of the group that recommending screening endoscopy dependent on the duration of heartburn could not be justified based on available data.

Statement 18: Endoscopic Screening for BE and Dysplasia Should Be Performed in all Whites \geq 50 Years of Age With \geq 5–10 Years of Heartburn

Based on data from the U.S. Census Bureau, whites account for 75% of United States residents—approximately 45 million whites over age 50 years.¹⁰² The annual incidence of BE-associated esophageal adenocarcinoma in whites is approximately 5 of 100,000, occurring predominantly in males.² Although much has been made of the fact that the incidence of esophageal adenocarcinoma is increased in white males, there are other gastrointestinal cancers in other ethnic groups in the United States for which the incidence is even higher: Esophageal squamous cancer in black men is approximately 10 of 100,000, and gastric cancer in U.S. Asian men is 14 of 100,000.² Other discussions were similar as for statements 14–17. The majority felt that there was fair evidence to reject this proposition, namely, that the additional stratification to whites with heartburn could not be justified based on available data.

Statement 19: Standard Endoscopy With Biopsy Currently Is the Most Reliable Means of Establishing a Diagnosis of BE

For the purposes of screening for BE, the group unanimously accepted this statement, although noting that there are limitations of the current techniques of endoscopy and biopsy for the diagnosis of BE¹⁰³ (also see statement 5).

Statement 20: Unsedated Small Caliber Endoscopy and Biopsy Is an Alternative Approach for the Screening of BE

The group noted that unsedated upper endoscopy using small caliber instruments is feasible, acceptable, and accurate when compared with conventional sedated endoscopy^{104,105} and offers potential advantages of decreased sedation-related complications and costs. However, limited information is available on unsedated en-

doscopy in the evaluation of BE, and there are no studies examining its utility in screening. Furthermore, the group did discuss in detail whether unsedated endoscopy will meet with patient acceptance in the United States, given the cultural preference for sedation and the variable acceptance and tolerability of unsedated endoscopy in published trials. Although there is little evidence comparing unsedated small caliber endoscopy with conventional endoscopy for the diagnosis of BE, the group nonetheless accepted the statement that this technique was an acceptable alternative approach for the screening of BE.

Statement 21: The Results of Nonendoscopic Methods of Diagnosis Such as Brush or Balloon Cytology Are of Proven Value in the Screening of BE

Almost all workshop members felt that current nonendoscopic methods are of unproven value in the screening of BE. Given the previous “acceptance” by the workshop that BE requires both endoscopic and histologic abnormalities for accurate diagnosis (see statement 4), nonendoscopic methods have fundamental limitation as a diagnostic test for BE because most do not allow visualization of the esophagus. To date, no studies have evaluated the utility of nonendoscopic techniques such as balloon or brush cytology in screening for BE. Studies of nonendoscopic devices in the *surveillance* of patients with BE suggest that they have a reasonable yield of columnar cells, but the yield of goblet cells is only 33%–67%.^{106,107}

Barrett’s Esophagus: Surveillance

Endoscopic surveillance for patients with BE is recommended to identify curable neoplasia and is based on a number of assumptions: (1) In the absence of surveillance, patients with BE have decreased survival because of deaths from esophageal adenocarcinoma; (2) surveillance of patients with BE reliably detects curable neoplasia (dysplasia or early cancer); and (3) treatment of esophageal neoplasia detected by surveillance prolongs survival. There is scant evidence that BE decreases survival, and studies have not found a difference in overall survival between patients with BE compared with appropriately matched individuals in the general population.⁸⁸ These studies were composed predominantly of older patients who may have died of comorbid illnesses before succumbing to undiagnosed esophageal adenocarcinoma,^{89,108} and it is possible that a long-term study of younger patients with BE would show a reduction in life expectancy. It is controversial whether treatment of esophageal neoplasms detected by surveillance results in

prolonged survival.⁸³ Again, retrospective studies have shown that esophageal cancers detected in patients with BE who are undergoing endoscopic surveillance are associated with longer survival than those diagnosed during evaluation of cancer symptoms, but these studies are susceptible to a number of biases that may inflate the apparent benefits of surveillance.^{109–112} Investigators have used computer-assisted cost-effectiveness models to estimate the relative costs and benefits of various surveillance strategies in patients with BE. Such models provide a range of possible outcomes that vary according to changes in baseline assumptions and provide comparisons of the costs to the health care system and providers for the differences in length and quality of life afforded by various surveillance strategies.

Statement 22: Endoscopic Surveillance in Patients With BE Has Been Shown to Prolong Survival

There was a lot of discussion on the currently available case series and population-based studies and the potential biases in their results. The group acknowledged that there are no prospective randomized studies that have tested the efficacy of surveillance in preventing esophageal adenocarcinoma or its cancer-related death in patients with BE. However, there are a few uncontrolled studies that suggest that, among patients with esophageal adenocarcinoma, survival is higher in those who had been undergoing endoscopic surveillance.^{83,112,114} The outcomes of these studies may have been influenced by selection bias, lead-time bias, and length bias.¹¹⁵ Because patients were not prospectively assigned to different follow-up strategies, patients with a good or poor prognosis may have been unequally assigned to follow-up with and without surveillance endoscopy, respectively (*selection bias*). The seemingly longer survival from esophageal adenocarcinoma in patients undergoing surveillance endoscopy may reflect an earlier detection of incurable cancer in the preclinical stage without any true improvement in the overall survival length or change in the natural history (*lead-time bias*). Patients with slow growing cancers tend to have longer survival, independent of the benefit conferred by surveillance programs (*length bias*). Other studies have suggested that only a minority of patients with BE are willing or suitable to be enrolled in a surveillance program and that the majority of such patients die from causes other than esophageal adenocarcinoma.^{108,110}

In view of the potential biases in the published studies and the lack of prospective randomized trials, half of the panel was hesitant to assign the published evidence much credence and therefore rejected the statement. Notwithstanding the inherent limitations in the available data,

the other half of workshop participants felt that patients detected with esophageal adenocarcinoma enrolled in surveillance endoscopy programs appeared to have fared better than those who were not enrolled and therefore accepted the statement.

Statement 23: Endoscopic Surveillance in Selected Patients With BE Can Be Cost-Effective

Rating the nature of evidence is not applicable for this statement because all evidence is based on economic decision models rather than clinical trials. Although these models were well constructed, they adhered to different standards than those applicable to clinical trials. The panel did not feel that surveillance of all BE patients in general is cost-effective. However, it is important to emphasize 2 caveats that were incorporated into the statement: “selected patients” and “can be.” The cost-effectiveness of surveillance has been analyzed in at least 4 published studies using mathematical modeling and was discussed in detail. In all studies, the same key parameters have been shown to influence cost-effectiveness^{84,94,113,116}: the cost and frequency of surveillance endoscopy, the sensitivity and specificity of endoscopy for detection of neoplasia, the incidence of neoplasia, and the impact of surgical (or alternative) therapy for BE-associated neoplasia on mortality and health-related quality of life. Although these economic analyses reached somewhat different conclusions, they all indicate that highly sensitive surveillance endoscopy followed by efficacious intervention in a selected group of patients characterized by high cancer risk *can be* cost-effective.

Statement 24: Endoscopic Surveillance Detects Curable Neoplasia in Patients With BE

Among BE patients undergoing surveillance who develop adenocarcinoma, the cancer stage appears less advanced than among patients who develop adenocarcinoma in the absence of surveillance.^{83,112,114} These results indicate that surveillance can detect esophageal cancer at an earlier stage but does not prevent its occurrence altogether. There was unanimous agreement among the workshop members on this statement.

Statement 25: Endoscopic Surveillance Should Be Limited to Patients With BE With Dysplasia

Workshop members recognized that only a small fraction of patients with BE without dysplasia progress to cancer. However, the majority rejected this statement in the face of data that many patients who do progress to cancer do so after initial endoscopies that do not reveal

dysplasia. More than 20% of cancers reported in prospective surveillance studies arise in patients in whom dysplasia was not detected at the initial endoscopy.^{49,67,68,117–120} If patients without high-grade dysplasia, who are frequently referred for intervention rather than entered into surveillance, are excluded, as many as 60% of cancers arise in patients without dysplasia at their first endoscopy. Furthermore, the interpretation of dysplasia is highly operator dependent (see statement 2).²⁷

Statement 26: Patients With Short- and Long-Segment BE Should Have the Same Endoscopic Surveillance

Although prospective studies and retrospective case-control studies have shown a trend for increasing cancer risk with longer segments of BE, there does not appear to be a sharp increase in cancer incidence above any particular length (see statement 6).^{48,50,121,122} Thus, the majority of workshop members felt that division of BE into short and long segments was artificial and should not be used to guide decisions about surveillance endoscopy. The timing and frequency of surveillance endoscopy, however, were not discussed by the workshop.

Statement 27: Endoscopy With Multiple Systematic Biopsies Is Needed for the Detection of Dysplasia or Adenocarcinoma for the Surveillance of BE

The workshop accepted the above statement unanimously. The distribution of dysplasia and cancer is usually patchy in BE.^{123–125} A systematic 4-quadrant, 2-cm biopsy protocol using large biopsy forceps is based on expert opinion,⁴ although some prospective studies have suggested that it may detect high-grade dysplasia at the baseline endoscopy in many patients who progress to cancer within 5 years.^{117,126} In patients with high-grade dysplasia, a 4-quadrant, 2-cm biopsy protocol can miss coexisting cancers.^{112,123,127,128} Detection of early cancers in patients with known high-grade dysplasia requires taking a large number of biopsy specimens using a 4-quadrant, 1-cm protocol.¹²⁸

Statement 28: The Use of Flow Cytometry or Biomarkers (Such as p53 and p16 Mutations) Is Promising and Merits Further Clinical Research

Although BE is the only known precursor to esophageal adenocarcinoma, most BE patients do not develop cancer.^{85,99,108,129–131} The identification of a subset of BE at increased risk could greatly improve the efficacy and cost-effectiveness of endoscopic surveillance. The group felt that the available evidence for flow cy-

tometry and molecular assessment of p16 and p53 was promising and merited further clinical research. Flow cytometry (tetraploidy, aneuploidy), p16 (methylation, mutation, and loss of heterozygosity or LOH), and p53 (mutation, LOH) have been evaluated in prospective studies using cancer as an outcome.^{117,132–134} In the largest study, flow cytometry identified low- and high-risk subsets with 0% and 28% 5-year cumulative incidences of cancer, respectively.¹¹⁷ The use of p53 immunohistochemistry as a surrogate for p53 mutations does not appear to be warranted, based on existing evidence that it has a one-third false-negative rate for detecting p53 mutations.^{135,136} A recent case-control study reported that nearly two thirds of cancers arose in patients whose p53 immunostaining was negative.¹³⁷ However, when assessed by molecular methods, p16 and p53 genotype show promise and merit further clinical research.

Statement 29: The Distinction Between Focal and Diffuse High-Grade Dysplasia in BE Has Important Clinical Implications

In a single study, “focal” high-grade dysplasia was defined as the finding of high-grade dysplasia in less than 5 mucosal crypts in a single biopsy specimen.¹³⁸ In follow-up, patients with focal high-grade dysplasia demonstrated longer survival than patients with diffuse high-grade dysplasia, although these findings were not supported by another retrospective study.¹³⁹ Hence, all participants expressed either weak support or weak dissent with this statement. The group, however, emphasized that the entity of focal high-grade dysplasia defined above should be contrasted with high-grade dysplasia in the presence of a visible esophageal nodule. This was recognized to be associated with a significant risk of invasive cancer and should be approached differently.¹⁴⁰

Statement 30: After Antireflux Surgery, Patients With BE Should Have the Same Endoscopic Surveillance as Medically Treated Patients

The workshop members felt that there was good evidence to support the above statement. Following antireflux surgery, a variable proportion of patients (1%–5%) with BE can progress to high-grade dysplasia or carcinoma.^{129,141–145} Because antireflux surgery does not guarantee protection from the future development of esophageal adenocarcinoma in patients with BE, workshop members unanimously agreed that surgically treated patients with BE should have the same surveillance strategy as medically treated patients, regardless of the outcome of surgery.

Statement 31: Intensive Endoscopic Surveillance Is an Appropriate Strategy in a Subgroup of Patients With High-Grade Dysplasia in BE

In case series, the outcome of patients undergoing esophagectomy for early cancer is similar to those with high-grade dysplasia not undergoing resection. However, in each series, at least 1 patient (3%–25% of patients) who entered the trial without incurable cancer developed incurable cancer on protocol.^{119,126,128} The risk of developing incurable cancer with intensive endoscopic surveillance must be weighed against the high surgical mortality rate from esophagectomy in this population, which can be >15% in low-volume centers.^{146–149} The panel supported the statement that intensive surveillance with multiple systematic biopsies may be appropriate in select patients, acknowledging that the natural history of high-grade dysplasia may be variable and that cancers may be missed when this strategy is employed. This suggests the need for careful discussion with both the patient and an esophageal surgeon before pursuing a strategy of surveillance in patients with high-grade dysplasia.

Barrett's Esophagus: Treatment

Reflux esophagitis often is severe in patients with BE, especially those with longer segments. Once- to twice-daily proton pump inhibitor (PPI) therapy is effective in the treatment of reflux-induced symptoms and esophagitis in BE patients, but there is a lack of systematic research of the optimal use of PPI therapy.¹⁵⁰ It is hypothesized that normalization of esophageal acid exposure by intensive PPI will reduce progression to high-grade dysplasia or adenocarcinoma by removal of mucosal irritant. This intuitively appealing hypothesis has gained plausibility from *in vitro* incubation studies done on biopsy specimens taken from esophageal columnar metaplasia.¹⁵¹

There are limited reports of outcomes after conventional antireflux surgery in patients with BE. Some centers have reported excellent control of reflux-related symptoms and esophagitis after laparoscopic surgery,^{152,153} but others have reported high failure rates for laparoscopic¹⁵⁴ and open¹⁴² antireflux surgery within 10 years of follow-up. Some authorities have claimed that antireflux surgery is protective against the development of adenocarcinoma in patients with BE.^{155,156} Although it is biologically plausible that a major reduction of esophageal reflux could prevent the development of adenocarcinoma in BE, there are few clinical outcomes data on the impact of antireflux surgery on adenocarcinoma risk.^{155–157} It is a reasonable proposition that ablation or resection of esophageal intestinal metaplasia that is fol-

lowed by replacement of squamous epithelium may lead to a reduction in risk of esophageal adenocarcinoma. The mortality and morbidity of mucosal ablation have not been adequately defined, and these must be factored into the risk/benefit assessment to determine the appropriateness of these ablative therapies.¹⁵⁸

Chemopreventive drug therapy is a rapidly emerging option to reduce risk for development of esophageal adenocarcinoma in BE. Compared with other management strategies, chemoprevention may be less expensive, more acceptable to patients, and have lower attendant morbidity. Recent review of data¹⁵⁹ indicates that chemoprevention may be the most promising approach for reduction of adenocarcinoma risk.^{159,160}

Statement 32: Acid Suppressive Therapy Has Been Shown to Improve Symptoms and to Heal and Prevent Relapse of Erosive Esophagitis in Patients With BE

There are few studies for which the short-term efficacy of PPI therapy has been evaluated specifically in BE patients.^{161–165} Indirect evidence suggests that the rate of symptom relief and healing of esophagitis in response to acid suppression in patients with BE is similar to patients with Los Angeles grades C and D esophagitis but inferior to patients with grades A and B esophagitis. The panel discussed a few long-term PPI maintenance studies in BE patients.^{150–161} Most available studies are small and have focused on issues other than symptom relief and esophagitis healing (e.g., regression of columnar metaplasia). Nonetheless, all members felt that available data indicate that long-term PPI therapy is effective in patients with BE.^{161–165}

Statement 33: Patients With Long-Segment (≥ 3 cm Circumferentially) BE Have High Levels of Nocturnal Esophageal Acid Exposure

The workshop unanimously accepted the above statement. In several case series, patients with long-segment BE studied with 24-hour pH monitoring have documented increased nocturnal as well as daytime acid exposure.^{166,167} In an initial study, complicated reflux disease patients had high levels of nocturnal reflux, with esophageal pH being <4 for 35.6% of the time compared with only 5.2% in patients with uncomplicated reflux disease.¹⁶⁶ Subsequent studies focusing on nocturnal reflux found similar results.^{44,167,168} A recent prospective nonrandomized treatment trial found that patients with BE with persistently high levels of acid reflux despite twice daily omeprazole therapy were more likely to have nighttime than daytime acid reflux.¹⁶⁸ The role

of H₂ receptor antagonists in nocturnal acid breakthrough was not discussed.

Statement 34: These Patients Should Be Treated With Twice Daily PPI Therapy (See Statement Number 33)

Twice daily PPI therapy may be recommended for patients with BE who do not respond clinically to once daily therapy. There were no data presented, however, that supported a statement that all BE patients should be treated routinely with double-dose therapy.¹⁵⁰ Although it is established that patients with BE on PPI therapy frequently have continued abnormal levels of gastroesophageal reflux in the absence of symptoms,^{168,169} there are no studies that provide evidence that escalation of PPI therapy provides benefit for prevention of esophageal adenocarcinoma (see statement 35).

Statement 35: Normalization of Esophageal Acid Exposure by Acid Suppression Reduces the Risk for Development of Esophageal Adenocarcinoma

The group acknowledged that there are no clinical data that indicate that normalization of esophageal acid exposure by acid suppression reduces the risk of development of esophageal adenocarcinoma in patients with BE. Observations that partial regression of metaplastic mucosa may be induced by suppression of acid (and bile) reflux with either PPIs or antireflux surgery provide some plausibility for the notion that PPIs may be able to reduce cancer risk.^{141,143,163–165} In the shorter term, intermediate markers of biopsy specimens from patients with BE in whom intraesophageal pH had been normalized on PPI therapy showed decreased cell proliferation and improved differentiation.¹⁵¹ In contrast, incomplete acid suppression may allow short episodes of acid reflux that may lead to epithelial changes and could select for poorly differentiated cells with increased proliferative potential.¹⁵¹ Preliminary evidence from *in vitro* tissue cultures demonstrates that attenuation of acid reverses these surrogate markers in the short term. The majority of workshop members nevertheless felt that, in the absence of clinical data, the statement should be rejected.

Statement 36: Epidemiologic Studies Show a Significant Risk Reduction in Esophageal Adenocarcinoma Development in Aspirin/NSAID Users

Workshop members unanimously agreed with this statement. Nonselective COX-2 inhibitors such as aspirin and NSAIDs are associated with a decreased

incidence of esophageal adenocarcinoma.^{159,160} A recent meta-analysis of previous cohort studies was discussed, which showed that even infrequent aspirin use led to a significant risk reduction in the development of esophageal cancer.¹⁵⁹ COX-2 is implicated in epithelial adaptation in injured or inflamed mucosa,¹⁷⁰ and its expression increased serially along the metaplasia-dysplasia-adenocarcinoma sequence.¹⁷¹⁻¹⁷³ Compared with BE mucosa without dysplasia, up-regulation of COX-2 expression is slightly increased in low-grade dysplasia but is increased several fold in high-grade dysplasia.¹⁷¹

Statement 37: The Use of Aspirin/NSAID Therapy as a Chemopreventive Agent for Risk Reduction in Patients With BE Is Promising But of Unproven Value

Chemoprevention using aspirin (ASA) NSAIDs may be an effective strategy for reducing cancer risk in BE patients; however, no randomized controlled trials confirming their efficacy have been performed. Some members noted that chemoprevention may be a viable alternative strategy to surveillance endoscopy in patients with serious comorbid conditions (e.g., ischemic heart disease, diabetes, and others). Given the potential chemopreventive benefits of these widely available agents, workshop members felt that there is an immediate need for randomized controlled trials assessing their benefit in low- and high-risk patients with BE.

Statement 38: Among Patients With BE, the Reported Short- and Long-Term Control of Reflux Symptoms After Antireflux Surgery Varies Widely

Published long-term results of antireflux surgery in patients with gastroesophageal reflux disease are from centers with a special interest and expertise in this disease, but there are^{142,152,154} limited outcomes data available from community hospitals.¹⁷⁴ Among BE patients, reported medium and long-term outcomes of antireflux surgery are conflicting; some centers report inferior results in BE, whereas others¹⁴² found no difference in outcomes between reflux patients with and without BE.^{153,154,175,176} The reasons for these discrepancies are not evident but may be due to patient selection, type of operation performed, or factors such as shortened esophagus or hiatal hernia size. The workshop specifically noted that the rigor of outcomes assessment varies substantially among studies, with some using objective outcome variables and validated instruments and others relying on symptom responses. This makes detailed comparison across studies difficult.

Statement 39: In Patients With BE, Antireflux Surgery Has Not Proven to Have a Major Protective Effect Against the Development of Esophageal Adenocarcinoma

Workshop members unanimously supported the above statement. Case reports, case series, and cohort studies show a variable incidence of cancer in BE patients after antireflux surgery.^{129,141,142} A large, population-based, epidemiologic study did not show a reduction in the incidence of esophageal or cardia adenocarcinoma in GERD patients after antireflux surgery.¹⁷⁷ In other series, few patients with BE have developed high-grade dysplasia and/or invasive adenocarcinoma >5 years after an antireflux operation.^{141,154} Notwithstanding the favorable results reported in some series, progression to dysplasia and cancer does occur in patients with BE who have undergone antireflux surgery (also see statement 30).

Statement 40: Mucosal Ablation in Conjunction With Intensive Acid Suppression or Antireflux Surgery Leads to Partial or Complete Replacement of Metaplastic Columnar Epithelium by Squamous Mucosa

Many uncontrolled studies demonstrate that endoscopic ablative therapy, combined either with acid inhibition or with surgical fundoplication, can result in squamous reepithelialization of the Barrett's mucosa. Re-epithelialization was first shown in studies using argon laser therapy or multipolar coagulation in conjunction with PPI therapy to induce acid suppression.^{178,179} Similar results have been demonstrated using photodynamic therapy, argon plasma coagulation, or Nd:YAG laser therapy.¹⁸⁰⁻¹⁸⁴ Fundoplication also has been used to reduce acid in conjunction with Nd:YAG laser or argon plasma coagulation therapy in prospective series.^{184,185} The results of 1 small, prospective, randomized, blinded European trial utilizing photodynamic therapy demonstrated that squamous reepithelialization requires prior columnar mucosal injury, providing level I evidence in support of this statement.¹⁸⁶

Statement 41: Mucosal Ablation With Intensive Acid Suppression or Antireflux Surgery Prevents Adenocarcinoma in Patients With BE Without Dysplasia

There are no studies in BE patients without dysplasia that have evaluated the end point of cancer prevention. The primary end points of mucosal ablation studies have been regression in length or surface area of BE mucosa.^{187,188} Thus, there is no direct evidence to suggest that there is a reduction in cancer risk in these patients after mucosal ablation therapy. There appears to

be a correlation between the length of BE and cancer risk,^{48,50,69} but the group concluded that there is no evidence that mucosal ablation that results in reduced length and/or surface area of BE results in decreased risk of cancer.

Statement 42: Mucosal Ablative Techniques (Including Mucosal Resection) Are Appropriate Strategies in a Subgroup of Patients With High-Grade Dysplasia in BE

A prospective multicenter trial of 208 patients with BE and high-grade dysplasia who were randomized to photodynamic therapy (PDT) or observation suggests a decrease in the development of high-grade dysplasia and adenocarcinoma after 24 months.¹⁸⁹ Problems with this study, including a short duration of follow-up, the uncertain incidence of complications of PDT therapy (e.g., strictures, perforation), a lack of complete elimination of dysplastic tissue, and the development of cancer in 13% of patients treated with PDT, were discussed. Other nonrandomized trials using PDT for treatment of high-grade dysplasia^{190–193} also have demonstrated reduction or elimination of high-grade dysplasia. The advent of endoscopic mucosal resection (EMR) to resect local areas of high-grade dysplasia within BE and/or provide accurate staging of early cancers was discussed.^{194–197} Compared with other techniques, EMR provides histologic confirmation of treatment success. Recent data from German investigators report high local remission rates.¹⁹⁷ However, other reports suggest that residual columnar mucosa may develop high-grade dysplasia or neoplasia in 30% of patients treated with EMR alone within 2 years of observation.¹⁹⁶ Other mucosal ablation methods that have been reported in small series for high-grade dysplasia in BE include argon plasma coagulation, KTP:YAG, and Nd:YAG laser therapy.^{198–202} The exact criteria for the patient subgroup that would benefit from mucosal ablation therapy were not discussed by the working group.

Summary

The workshop addressed 42 statements that deal with controversial areas pertaining to the management of BE. For each statement, evidence supporting or refuting the statement was reviewed and graded by a group of experts. This working group voted unanimously to accept or reject these statements based on the strength of available evidence. It was not the intention of this working group to develop “consensus guidelines” for management of BE. Rather, the group wished to evaluate the strength of current evidence in these areas of controversy. We must acknowledge limitations of the workshop

methodology that may have introduced bias. Given the limited resources available, only a limited number of gastroenterologists, pathologists, and surgeons were invited to participate in the workshop. Although all participants had an established clinical or research interest in Barrett’s esophagus, it is possible that the perspectives and opinions of these participants are not reflective of the broader academic field. Furthermore, other relevant stakeholders with a different perspective were not invited, including primary care physicians, oncologists, government health officials, and third party payers. The statements were written prior to the conference by the 4 group leaders and were revised in consultation with the chairman and moderator. The selection of particular statements by the workshop organizers, which address areas of controversy, may have subtly influenced the opinions of the remaining conference participants. Furthermore, the use of both positive and negative statement constructs may reflect a subconscious bias on the part of the organizers that also may have influenced participant voting response. The 5-point group voting system is skewed toward statement acceptance. Moreover, a formal systematic review of the literature was not performed prior to the workshop. Although all participants were asked to review the literature referable to their assigned statements prior to the conference, no specific guidelines were given for conducting this search. Participants in the workshop were presumed to be well familiar with the literature pertaining to Barrett’s esophagus and skilled in performing literature reviews. Nevertheless, relevant studies may have been intentionally or unintentionally overlooked by the participants.

The major areas of disagreement related to issues of surveillance in patients with BE, highlighting the lack of high quality and prospective data in this area. Based on this review, the opinion of workshop members on issues pertaining to screening (i.e., detection of Barrett’s) and surveillance of patients with BE may be considered to be at variance with other published clinical guidelines and with the clinical practice of many gastroenterologists. It is not the intention of workshop members to dictate that screening and surveillance for BE should not be performed but rather to acknowledge that the strength of currently available evidence does not yet demonstrate that screening and surveillance of all BE patients are efficacious or cost-effective. It is hoped that clinicians may find the conclusions of this workshop useful as they grapple with difficult management issues. The findings furthermore may provide guidance to physicians on important clinical problems and may also influence clinical researchers in identifying areas in which better data are needed.

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Members of the workshop composed a group of international experts in BE from gastroenterology, surgery, pathology, molecular biology, outcomes, and epidemiology. Conference chairman: Prateek Sharma; conference moderator: Kenneth McQuaid; group leaders: John Dent, M. Brian Fennerty, Richard Sampliner, Stuart Spechler; participants: Alan Cameron, Douglas Corley, Gary Falk, John Goldblum, John Hunter, Janusz Jankowski, Lars Lundell, Brian Reid, Nicholas Shaheen, Amnon Sonnenberg, Kenneth Wang, and Wilfred Weinstein.