American Gastroenterological Association Technical Review on the Role of the Gastroenterologist in the Management of Esophageal Carcinoma

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The goal of this evidence-based review was to examine the clinical practice of the gastroenterologist in the management of patients with esophageal carcinoma. The methods for this review were to search and review the literature available on MEDLINE and PREMEDLINE on the topics of esophageal neoplasm, esophageal cancer, and Barrett’s esophagus from 1968 to 2004. Bibliographies of significant reports were also reviewed to ensure that the pertinent literature was reviewed. Recommendations are graded as to the level of evidence available on a scale of I–V. Level I evidence is the presence of at least one prospective, randomized, controlled trial, level II evidence is based on well-designed cohort or case-controlled studies, level III evidence is based on case series or flawed clinical trials, level IV evidence is based on opinions of respected authorities or expert committees, and level V evidence is insufficient evidence to form any opinions.

Significance of Esophageal Cancer

Esophageal cancer is associated with one of the highest cancer mortality rates in the United States. In 2000, the last year of complete data available from the national cancer Surveillance, Epidemiology, and End Results database, the 5-year relative survival rates from esophageal cancer were the fifth lowest at 15.4%. In addition, the incidence of esophageal cancer is still significantly trending upward in white men with a 0.4% annual percentage increase from 1992 to 2000. This can be compared with colon cancer, which has actually had a significant decrease of 0.9% annual percentage change over the same period. Esophageal cancer is a predominantly male condition with a male/female incidence of 3.6:1. Esophageal cancers affect older patients, with the peak incidence in those 65–74 years old. It is estimated that, in 2003, there were 13,900 new cases of esophageal cancer and 13,000 deaths due to esophageal cancer. The mortality rate of esophageal cancer is significantly higher in minority populations than in white people.

There are 2 major types of esophageal cancer: adenocarcinoma and squamous cell cancer. The primary known risk factors for adenocarcinoma of the esophagus are smoking, chronic gastroesophageal reflux disease, and Barrett’s esophagus. Known risk factors for squamous cell cancer of the esophagus include smoking, alcohol use, exposure to nitrosamines, ingestion of lye, Fanconi’s anemia, achalasia, Plummer–Vincent webs, and tylosis.

Screening and Surveillance for Esophageal Cancer

Screening for esophageal cancer depends on the determination of the patient’s risk for cancer, the cost and efficacy of the screening procedure, the stage at which the cancer can be diagnosed, and the treatment options available. At the current time, there is no direct evidence that has validated the use of screening for esophageal cancer in the United States. Screening for esophageal adenocarcinoma has been primarily focused on the detection of Barrett’s esophagus with subsequent surveillance. Although screening for Barrett’s esophagus has not been proven to decrease the risk of cancer, it has become accepted that surveillance for Barrett’s esophagus can detect disease at earlier stages.1–3 Barrett’s esophagus has traditionally been found to be associated with chronic gastroesophageal reflux disease, and case series have found increasing incidences of Barrett’s esophagus depending on the number of years of reflux symptoms.4 However, a single-center study of 110 subjects found that 7% of asymptomatic individuals had long-segment...
(>3 cm) Barrett’s esophagus. A multicenter study of 536 subjects found that long-segment Barrett’s esophagus was only present in 0.36% of subjects, although short-segment Barrett’s esophagus was found in 5.6%. This study did find that patients with heartburn had a significantly higher prevalence of long-segment Barrett’s esophagus than those who did not. This is significant because past studies have shown that the degree of neoplasia found in Barrett’s esophagus appears to be correlated with the length of Barrett’s esophagus. Other groups that may be at risk would include those with familial occurrence of adenocarcinoma, but this has only been described in a limited number of families. The cost-efficacy of screening family members because of a history of Barrett’s esophagus has not been demonstrated.

Screening methods for detection of Barrett’s esophagus have included standard endoscopy, unsedated endoscopy with ultrathin endoscopes, catheter-based cytology, and balloon cytology. Although preliminary studies indicate some promise with these technologies in terms of screening for adenocarcinoma, there have not been any definitive trials to allow recommendation of these techniques.

Squamous cell cancer. Screening for squamous cell cancer in the general population of the United States cannot be justified because of the low incidence of this form of cancer. However, specific subgroups may be identified that warrant screening endoscopy for squamous cell cancer. The most likely to benefit from screening would be those who have tylosis, which is a genetic defect in the 17q25 region that is found in patients with thickened palms and soles. This group is likely to develop cancer by the age of 65 years and should undergo screening for squamous cell cancer. Patients with lye-induced or caustic strictures develop cancers approximately 46 years after ingestion and have been described to have an 8% incidence of cancer. The development of cancer in patients with long-standing achalasia is infrequent, especially in women, and it is unclear if surveillance is warranted in these patients. Most patients with achalasia are found to have prevalent cancers because they are usually diagnosed when obstruction and esophageal dilation are found. Fanconi’s anemia has also been associated with the development of esophageal cancer and may become more common as patients survive longer after bone marrow transplantation. Patients with existing aerodigestive tumors, especially those of the oral cavity, who have had long-term extensive exposure to alcohol and tobacco might benefit from screening for cancers of the esophagus, although the rationale for this is based on case series. Screening for esophageal cancer should be performed at the time of diagnosis of the head-and-neck cancer. Extensive alcohol consumption alone has been found to be an important criterion for screening in Asian patient populations. Partial gastrectomies have been associated with an increased incidence of squamous cell cancers of the esophagus; these reports stem from areas of the world where squamous cell cancer is commonly found, and there is no convincing evidence to support the screening of patients in the United States. The occurrence of squamous cell cancer is not decreasing in minority populations in the United States and remains the most frequent form of esophageal cancer in black and Hispanic populations. Other conditions such as Plummer-Vinson webs have also been identified as being associated with an increased risk for squamous cell cancers, but the decreasing frequency of these webs makes this almost a historical footnote in Western countries.

Screening methods such as cytologic balloons or sponges for screening for squamous cell cancers have been extensively tested in Asia. Balloons appear to be better than sponges, with an increased sensitivity of 44% compared with 18% for sponges. This technology has been used as the primary screening tool in high-risk areas of China.

Summary of Evidence—There is level III evidence that endoscopic screening of male white patients older than 50 years of age with symptoms of gastroesophageal reflux may be cost-effective. Patients with tylosis, lye-induced strictures, or Fanconi’s anemia would benefit from screening endoscopy for squamous cell cancers (level III evidence). In addition, patients with long-term tobacco and alcohol use, achalasia, or prior head-and-neck cancers could be considered for screening, depending on their other risk factors (level III evidence). The interval for surveillance of these patients has not been established, but yearly investigations would seem to be reasonable (level IV evidence).

Surveillance for Esophageal Cancer

Significance of surveillance. The importance of Barrett’s esophagus derives from its association with esophageal adenocarcinoma. Approximately 5%–10% of patients diagnosed with Barrett’s esophagus may develop esophageal adenocarcinoma based on older studies. The incidence of cancer will most likely decrease with the increasing detection of Barrett’s esophagus through screening programs. Surveillance of Barrett’s esophagus can detect dysplasia in Barrett’s esophagus, which can predict the risk of future diagnosis of esophageal cancer in these patients.
The incidence of cancer in patients with Barrett’s esophagus is low in general, which makes surveillance cost-ineffective unless at-risk populations can be identified.\textsuperscript{38,39} At the current time, dysplasia is used as the primary means to discriminate at-risk patients. A systematic endoscopic biopsy protocol, generally accepted to be 4 quadrant biopsy specimens taken every 2 cm of Barrett’s mucosa, can provide tissue for histologic diagnosis of dysplasia. The grading system used to classify dysplasia in Barrett’s esophagus is based on the system developed for ulcerative colitis.\textsuperscript{40–42} Although molecular markers have shown promise, dysplasia is currently the best indicator for the risk of cancer. Increasing grade and extent of dysplasia are associated with increasing risk of cancer.\textsuperscript{37,43–48} Information from several prospective studies and a Barrett’s esophagus registry provide a total of 783 patients with a follow-up of 2.7–7.3 years.\textsuperscript{37,41,45,47,49,50} These combined series indicate that 2% of patients without dysplasia progressed to cancer. Progression from low-grade dysplasia to cancer was noted in 7% of patients and from high-grade dysplasia to cancer in 22% of patients. Unfortunately, it is difficult to obtain true cancer incidence per year of observation based on the data provided in these series. It is also apparent that low-grade dysplasia had a wide range of rates of progression between the series. This may be because of the variability in interpretation of low-grade dysplasia.\textsuperscript{46}

Other findings on endoscopy that have been shown to predict the development of esophageal cancer include the presence of any mucosal abnormalities noted on endoscopy and the extent of high-grade dysplasia noted on histology.\textsuperscript{48} The presence of mucosal nodularity has been associated with a 2.5-fold increased risk of cancer development in patients with high-grade dysplasia ($P = .01$). Focal high-grade dysplasia, defined as involvement of $\leq 5$ crypts in one biopsy specimen from the entire set of biopsy specimens, has been found to be associated with significantly less risk of cancer development than those with greater amounts of high-grade dysplasia ($P = .02$).\textsuperscript{48}

Unfortunately, the classification of dysplasia is subjective and does have significant observer variation. Interobserver pathologic agreement can improve to 85%–87% when the degree of dysplasia is placed in a 2-tier system. This is done by combining high-grade dysplasia and intramucosal carcinoma in one category and low-grade dysplasia, indefinite for dysplasia, and no dysplasia in another.\textsuperscript{51} This was substantiated by a recent study using a group of expert pathologists.\textsuperscript{52} In this study, when analysis was performed using 2 broad diagnostic categories (Barrett’s esophagus without dysplasia, indefinite and low-grade dysplasia vs high-grade dysplasia and carcinoma), intraobserver agreement was near perfect (mean $\kappa = 0.82$ and 0.80) and interobserver agreement was substantial ($\kappa = 0.66–0.70$). When the analysis was performed using the 4 separate classifiers (Barrett’s without dysplasia, indefinite for dysplasia and low-grade dysplasia, high-grade dysplasia, and carcinoma), the mean intraobserver $\kappa$ was once again substantial (0.64–0.68) but the mean interobserver $\kappa$ was only 0.43–0.46 (moderate agreement). Because of this difficulty in determining the presence of dysplasia, using recent recommendations to screen and perform surveillance only if dysplasia is found may be ineffective if histologic interpretation is not accurate.\textsuperscript{53}

Despite the difficulties with surveillance, the detection of high-grade dysplasia or early cancer has been shown to have the potential to improve survival in patients with Barrett’s esophagus.\textsuperscript{34,55} Cancers confined to the esophagus are associated with a 5-year survival rate of 70% compared with a survival rate of 20% for patients with more invasive cancers.\textsuperscript{56} Nodal involvement, which helps determine prognosis, is far less likely to occur in patients who are found to have cancer on surveillance endoscopies compared with those patients who are not undergoing surveillance.\textsuperscript{1,3,56,57} This leads to significantly improved survival in surveyed patients compared with those patients who underwent surgery for symptomatic disease. Retrospective studies of patients in surveillance programs suggest that the patients with incidental cancers detected during surveillance are likely to have earlier staged disease than those who present because of symptoms.\textsuperscript{38,39} Although these case series seem convincing, there are several concerns. Many of the retrospective studies compared patients in surveillance groups with historical controls. Patients of advanced age or with significant comorbidity are less likely to be enrolled in a surveillance program. On the other hand, subjects enrolled in surveillance programs might have healthier lifestyles, might have health-seeking behaviors, or were selected because of overall better health status. Survival differences between these 2 groups may well be due to selection bias. In addition, earlier detection of cancer can lead to a false increase in survival time because of lead-time bias, which results from an early diagnosis of preclinical cancer rather than any true effect of detection on subsequent mortality.

In at least 2 small surveillance cohorts, esophageal cancer has been reported to be an uncommon cause of death in patients with Barrett’s esophagus.\textsuperscript{60,61} Therefore, the morbidity and mortality from surveillance and subsequent treatment might overshadow any advantage that surveillance provides by early detection of cancer. However, a retrospective population-based cohort study
of endoscopic surveillance in 23 patients with Barrett’s esophagus among 589 patients with adenocarcinoma found an improved survival benefit.\(^{62}\) Eleven of 15 patients who were diagnosed with cancer while in surveillance programs were alive compared with none of 8 patients not under surveillance. None of the deaths in the surveillance group were from cancer compared with 4 deaths in the nonsurveillance group that were directly related to cancer. Three patients in the surveillance group and one patient in the nonsurveillance group died as a result of complications of surgery.

Allocation of resources based on risk stratification has the potential to make surveillance more cost-effective. A recent decision analysis model examined the cost-utility ratio for different surveillance strategies.\(^{38}\) A cohort of 50-year-old patients with Barrett’s esophagus without dysplasia was evaluated for surveillance strategies every 1–5 years and no surveillance, with esophagectomy performed if high-grade dysplasia was diagnosed. This study suggested that, with an annual cancer risk of 0.4%, surveillance every 5 years was the only cost-effective strategy. More frequent surveillance was associated with more cost and yielded a lower life expectancy. The incremental cost-utility ratio for surveillance every 5 years was $98,000 per quality-adjusted life year (QALY) gained, comparable to the incremental cost-effectiveness ratios of accepted practices.

Another detailed cost-utility analysis assessed the strategy of surveillance of Barrett’s esophagus detected during screening.\(^{53}\) The strategy of surveillance of only patients with dysplasia appears to be cost-effective relative to other currently accepted medical practices. The strategy yielded an incremental cost-effectiveness ratio of $10,440 per QALY saved compared with no screening. A strategy of no screening would incur direct medical costs of caring for those developing cancer of $16 million. Screening and surveillance of patients with dysplasia would prevent 2580 deaths caused by esophageal adenocarcinoma at a cost of $262 million. Fifty-nine patients would need to be screened and surveyed to prevent one death from cancer. Although this model was thorough, it is limited by several assumptions, such as that surveillance for patients with high-grade dysplasia can cease after 2 years and that there are no adverse effects on the quality of life of patients undergoing surveillance, which other studies have shown to be decreased.\(^{63}\)

**Biopsy method.** Patients who are undergoing surveillance should follow a systematic endoscopic biopsy protocol after they are free from esophagitis.\(^{54}\) The evidence for this is based on expert opinion, limited data, and the outcome of cohorts of patients managed empirically. Biopsy specimens are first taken from any mucosal abnormality, followed by rigorous sampling from each of the 4 quadrants of the esophagus every 1–2 cm starting at the gastroesophageal junction and stopping at the squamocolumnar junction using standard or jumbo biopsy forceps. The goal is to determine if the patient has high-grade dysplasia or early cancer so that appropriate management can be initiated. The effectiveness of taking 4-quadrant biopsy specimens every 1 cm along the length of the Barrett’s segment with jumbo biopsy forceps instead of the traditional standard biopsy forceps has been assessed.\(^{42}\) In a retrospective analysis of the Seattle protocol, it was shown that taking 4-quadrant biopsy specimens every 2 cm would have missed 50% of the cancers that were found by taking 4-quadrant biopsy specimens every 1 cm.\(^{65}\) Jumbo biopsy forceps acquire more tissue in a single biopsy than regular biopsy forceps and have not been associated with increased complications.\(^{66}\) The use of jumbo biopsy forceps has not been shown to decrease the number of samples necessary for surveillance, and they require the use of a therapeutic endoscope. The need for use of jumbo biopsy forceps has been questioned, and one study found no statistical difference in the rate of unsuspected cancers found at esophagectomy when patients with Barrett’s esophagus with high-grade dysplasia underwent preoperative endoscopy using jumbo biopsy forceps versus standard biopsy forceps.\(^{67}\)

It is generally accepted that patients with mucosal abnormalities in Barrett’s esophagus should undergo endoscopic mucosal resection to increase detection of neoplasia. In one small series, endoscopic mucosal resection of suspicious lesions diagnosed superficial adenocarcinoma in 13 patients (52%) and high-grade dysplasia in 4 (16%) of 25 patients with Barrett’s esophagus.\(^{68}\)

**Methods of surveillance.** Several methods have been studied to perform surveillance. These include brush cytology, chromoendoscopy, magnification endoscopy, and optical imaging techniques. All of these techniques have certain potential advantages over routine biopsy.

**Brush cytology.** Brush cytology has been advocated in the surveillance of patients with Barrett’s esophagus because it is faster to perform and it can sample more than the 1% of the total Barrett’s mucosal area typically achieved with standard biopsy. The diagnostic value of cytology in patients with Barrett’s esophagus was assessed using 66 pairs of endoscopic biopsy specimens and cytology specimens.\(^{69}\) Cytologic analysis was used to correctly identify 7 of 8 esophageal cancers, with one false-negative sample described on analysis as highly suspicious for cancer. In other studies, cytologic brushing was found to be a complementary technique in detecting
serious Barrett’s lesions when combined with the histologic examination of esophageal biopsy specimens. However, there was only 72% (47/65) concordance between the 2 diagnostic techniques. In the 18 cases that were discordant, cytologic analysis diagnosed 13 at a higher level of abnormality than the biopsy diagnosis and underdiagnosed 5. There is potential to further improve the efficacy of cytology by using objective assessment tools such as digital image analysis, which involves a computerized analysis of the digitized microscopic image. This has been demonstrated in China, where quantitative DNA fluorescence has been found to enhance detection of squamous cell cancers when applied to cytology taken in a high-risk population. As mentioned previously, balloon cytology for the surveillance of squamous cell cancers has become an accepted part of practice in high incidence areas, although such devices have not been shown to be beneficial in Western populations.

Chromoendoscopy. Chromoendoscopy involves the topical application of dyes during endoscopy in an effort to enhance the detection of mucosal patterns or lesions on the basis of their staining characteristics. Stains are classified as vital (absorptive), contrast, or reactive, according to their mode of action. Vital stains (e.g., Lugol’s solution and methylene blue) enter specific cell types by preferential absorption or diffusion across the cell membrane. Contrast stains (e.g., indigo carmine and acetic acid) seep into mucosal interstices to highlight mucosal topography. Reactive stains chemically react with cellular constituents.

The body of the literature regarding chromoendoscopy in the esophagus consists primarily of staining with Lugol’s solution for detection of squamous dysplasia and superficial carcinoma and staining with methylene blue for assessment of Barrett’s esophagus. Lugol’s solution is an iodine-based vital dye that has an affinity for glycogen contained in nonkeratinized squamous epithelium. Chromoendoscopy with Lugol’s solution has been used primarily to screen individuals at high risk for squamous cell cancer. The application of Lugol’s solution during endoscopy is not standardized, with nonuniform concentrations (1%–3%) and volumes (10–50 mL) as well as variable definitions of “unstained” areas that merit biopsy. Despite these differences, these studies in aggregate show unstained lesions to have a high sensitivity (91%–100%) and moderate specificity (40%–95%) for squamous dysplasia and carcinoma. Lesions are found to be more clearly defined and can be significantly larger after staining, providing critical information, particularly if local therapy, such as endoscopic mucosal resection, is contemplated. Studies of chromoendoscopy with Lugol’s solution in Western populations are sparse. A prospective analysis of a French cohort of 158 alcoholic and/or smoking patients showed no significant advantage of staining with Lugol’s solution relative to the visual diagnostic accuracy achieved by videodendoscopy alone. Lugol’s-assisted endoscopy may be useful in populations living in highly endemic regions for esophageal squamous cell cancer.

Methylene blue stains absorptive cells (intestinal-type epithelium), including specialized intestinal metaplasia, but does not stain normal squamous or gastric epithelium. Methylene blue may be particularly useful in the diagnosis of short segments of columnar-lined esophagus. Other uses include identifying dysplastic foci within Barrett’s epithelium and identifying residual foci of Barrett’s esophagus following mucosal ablative therapy. Chromoendoscopy with methylene blue requires pretreatment of the mucosa with a mucolytic agent, a dwell time for the dye to take effect, and a rinse phase to remove excess dye. In general, methylene blue staining adds 5–10 minutes to the procedure time, but the accessories required are inexpensive. Specialized intestinal metaplasia typically stains blue, while a “lighter” intensity and increased heterogeneity in the staining pattern predict high-grade dysplasia and/or cancer. Focal unstained areas may represent dysplastic foci within a background of heterogeneous methylene blue staining. These findings, however, are not consistently replicated in other studies, and the reproducibility of staining patterns among Barrett’s tissue types remains debatable. This technique has been used to allow the gastroenterologist to perform fewer biopsies to find significantly more dysplasia or cancer in a biopsy specimen (12% vs 6%) compared with the random biopsy technique. However, 2 prospective trials comparing the methylene blue–guided biopsy technique with the random biopsy technique found no significant differences in the detection of dysplasia or early cancer between the 2 techniques. Methylene blue has also recently been shown to induce oxidative damage of DNA because of photoactivation of the dye by the white light of the endoscope, which certainly increases the risk of its use in premalignant tissue.

Magnification endoscopy. Most new electronic videendoscopes are equipped with charge-coupled device chips of high pixel density (400K), enabling high-image resolution (ability to discriminate 2 closely approximated points). Megapixel density (850K) endoscopes have recently been introduced, which may further enhance detection. Magnification endoscopy enlarges the image, which enhances mucosal detailing and is generally used in combination with chromoscopy. Magnifica-
tion chromoendoscopy has been used primarily to characterize Barrett’s esophagus.90–93 Ridged or villous mucosal patterns observed under magnification endoscopy using a variety of stains have been correlated with intestinal metaplasia or dysplasia in case series.91–93 Whether magnification endoscopy will decrease the need for endoscopic biopsy or significantly enhance the diagnostic yield over conventional techniques remains to be determined in large controlled trials.

Optical biopsy. Optical biopsy is a term that encompasses a variety of techniques that use light to enhance detection of dysplastic lesions. Included in this category are spectroscopic techniques and low coherence interferometry (optical coherence tomography [OCT]). Spectroscopy is a light-based diagnostic technique that exploits properties of light-tissue interactions, such as fluorescence, elastic scattering, and Raman scattering, for tissue characterization. Collected in the form of spectra, these optical (light) signals are sensitive to microstructural and/or molecular changes accompanying various stages of tissue pathology, and spectral differences can then be correlated to specific histopathologic diagnoses.

Assessment of optical spectroscopic techniques in the esophagus has been limited to small-scale, proof-of-principle studies.91–102 Most studies deal with fluorescence spectroscopy, which shows moderate to high sensitivity (75%–100%) and specificity (65%–95%) in differentiating high-risk (high-grade dysplasia/adenocarcinoma) from low-risk (nondysplastic to low-grade dysplasia) samples of Barrett’s esophagus.94–98 False positives occur in the presence of inflammatory or reactive changes.94 The range of diagnostic accuracies primarily relates to methodological differences, because the technique has yet to be optimized for Barrett’s esophagus. It is also unclear whether fluorescence spectroscopy, aided by an exogenously administered fluorescent agent with affinity for neoplastic tissues (e.g., porfimer sodium or 5-aminolevulinic acid), improves discrimination of Barrett’s epithelia over naturally occurring tissue fluorescence (autofluorescence).99–101,103 Future comparative studies are required to address this issue. Other emerging spectroscopic techniques, including elastic scattering spectroscopy,102 Raman spectroscopy,103 and multimodal optical spectroscopy,104 have shown initial promise in differentiating Barrett’s epithelia in feasibility studies.

Fluorescence endoscopy is an extension of its spectroscopic counterpart into an imaging technique, which consists of sensitive cameras capturing the emitted fluorescence emanating from a mucosal field of view approaching that of a conventional endoscope. The obvious advantage over point spectroscopy is the ability to perform widespread assessment of the mucosa for areas likely to harbor dysplastic or early cancerous changes. Recent studies of fluorescence endoscopy, however, have showed limited diagnostic utility in Barrett’s esophagus.88,105 In a small prospective study of 35 patients, the sensitivity and specificity of autofluorescence imaging for the diagnosis of dysplasia or cancer versus Barrett’s mucosa without dysplasia were 21% and 91%, respectively.88 A prospective, randomized, crossover study of 50 patients with Barrett’s esophagus, published in abstract form, showed no significant benefit of fluorescence-guided biopsies over a standard surveillance biopsy protocol for the detection of high-grade dysplasia and early adenocarcinoma.105 Fluorescence endoscopy is an evolving technology. Optical biopsy and imaging techniques are not yet optimized for clinical use.

OCT is analogous to ultrasonography but uses light instead of sound waves to produce high-resolution, cross-sectional imaging of tissue. The spatial resolution of 10–25 μm achieved by endoscopic OCT systems is 10-fold better than that of high-frequency ultrasonography but at the expense of a limited sampling depth (∼2 mm).106–109 Current endoscopic OCT devices are catheter based (2–2.7 mm in diameter), allowing scanning of the esophagus in a linear,107 transverse,106 or radial108 fashion. Using predetermined OCT criteria for specialized intestinal metaplasia, the linear scanning OCT system was found to be 97% sensitive and 92% specific for identifying specialized intestinal metaplasia.110 A quantitative analysis of the OCT signal seemed to identify high-grade dysplasia with high sensitivity (100%) and specificity (85%) in a small retrospective study, which will require prospective validation on a larger sample size.110 Similar to spectroscopy, OCT is a technique in evolution, and further refinements are anticipated that may improve its diagnostic accuracy for the detection of preneoplastic lesions.

Frequency of surveillance. The frequency of endoscopic surveillance in patients with Barrett’s esophagus has been debated without the benefit of well-constructed studies. Surveillance intervals recommended in this section are supported by limited evidence, which is based on our understanding of the natural history of development of esophageal adenocarcinoma depending on the grade and extent of dysplasia in Barrett’s esophagus. The goal of surveillance is to identify patients at risk and assess them in a timely fashion to prevent or detect cancer at an earlier treatable stage. Summaries of the studies that have investigated the incidence of cancer in Barrett’s esophagus appear in Tables 1–4. Patients with nondysplastic Barrett’s esophagus should undergo repeat endoscopy 1 year after the initial endoscopy. Patients with persistent nondysplastic Barrett’s esophagus
<table>
<thead>
<tr>
<th>Institute or geographic area</th>
<th>Study type</th>
<th>Study duration</th>
<th>No. of patients</th>
<th>Mean or median age (y)</th>
<th>Duration of follow-up</th>
<th>Total cancers (%)</th>
<th>Incidental cancers (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Chile, Santiago, Chile</td>
<td>Prospective</td>
<td>1978–1991</td>
<td>152</td>
<td>52</td>
<td>100 mo (mean)</td>
<td>4 (2.6)</td>
<td>4 (2.6)</td>
<td>LGD developed in 15 patients on follow-up</td>
<td>Csendes et al, 1998</td>
</tr>
<tr>
<td>University of Otago Medical School, Dunedin, New Zealand</td>
<td>Prospective</td>
<td>1980–1986</td>
<td>52</td>
<td>63</td>
<td>16.4 mo (mean)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Cooper et al, 1987</td>
</tr>
<tr>
<td>Deutsche Klinik fur Diagnostik, Wiesbaden, Germany</td>
<td>Prospective</td>
<td>1980–1999</td>
<td>60</td>
<td>61</td>
<td>10 y (mean)</td>
<td>2 (3.3)</td>
<td>2 (3.3)</td>
<td>5 patients developed LGD</td>
<td>Eckardt et al, 2001</td>
</tr>
<tr>
<td>University Hospital, El Palmar, Murcia, Spain</td>
<td>Prospective</td>
<td>1982–1993</td>
<td>59</td>
<td>37</td>
<td>287 patient-years</td>
<td>2 (3.3)</td>
<td>2 (3.3)</td>
<td>One patient developed HGD, 3 had persistent LGD, 18 had transient LGD, and 56 remained nondysplastic. Patients with prevalent cancer diagnosed at entry or within the first 6 months were excluded</td>
<td>Ortiz et al, 1996</td>
</tr>
<tr>
<td>VA Medical Center and University of Kansas Medical Center</td>
<td>Prospective</td>
<td>—</td>
<td>80</td>
<td>61</td>
<td>40 mo (mean) or 362 patient-years</td>
<td>2 (2.5)</td>
<td>2 (2.5)</td>
<td>5-year cumulative incidence of cancer was reported to be 1.7% and 8-year cumulative incidence was reported to be 8.4%</td>
<td>Weston et al, 1999</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center, University of Washington</td>
<td>Prospective cohort</td>
<td>1983–1998</td>
<td>129</td>
<td>62</td>
<td>2.4 y (median) or 3.9 y (mean) for those who did not develop cancer</td>
<td>5 (3.9)</td>
<td>5 (3.9)</td>
<td>Reqd et al, 2000</td>
<td></td>
</tr>
</tbody>
</table>

LGD, low-grade dysplasia; HGD, high-grade dysplasia.
Table 2. Diagnosis of Prevalent or Incidental Cancer on Follow-up of Patients in Which the Degree of Dysplasia Was Not Defined or There Were <10 Patients in a Single Dysplasia Category

<table>
<thead>
<tr>
<th>Institute or geographic area</th>
<th>Study type</th>
<th>Study duration</th>
<th>No. of patients</th>
<th>Mean or median age (y)</th>
<th>Duration of follow-up</th>
<th>Total cancers (%)</th>
<th>Incidental cancers (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic, Rochester, MN</td>
<td>Retrospective</td>
<td>1960–1983</td>
<td>122</td>
<td>58</td>
<td>8.5 y (mean)</td>
<td>20 (16)</td>
<td>2 (1.9)</td>
<td></td>
<td>Cameron et al, 1985</td>
</tr>
<tr>
<td>Boston VA Medical Center, Boston University School of Medicine, and Tufts University School of Medicine</td>
<td>Retrospective</td>
<td>1962–1983</td>
<td>115</td>
<td>58</td>
<td>3.3 y (mean)</td>
<td>11 (9.5)</td>
<td>2 (1.9)</td>
<td>4 patients had LGD at baseline; one of them progressed to HGD and finally to cancer. HGD developed in 7 patients</td>
<td>Spechler et al, 1984</td>
</tr>
<tr>
<td>VA Outcomes Group, Dartmouth-Hitchcock Medical Center</td>
<td>Retrospective</td>
<td>1970–1994</td>
<td>102</td>
<td>63</td>
<td>4.8 y (median)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>8% of nondysplastic patients developed dysplasia. In 2 patients, HGD developed before cancer</td>
<td>Katz et al, 1998</td>
</tr>
<tr>
<td>Castle Hill Hospital, Cottingham, United Kingdom</td>
<td>Retrospective</td>
<td>1971–1991</td>
<td>26</td>
<td>62</td>
<td>11.5 y (mean)</td>
<td>4 (15.4)</td>
<td>4 (15.4)</td>
<td></td>
<td>Moghissi et al, 1993</td>
</tr>
<tr>
<td>Lahey Clinic, Burlington, MA</td>
<td>Retrospective</td>
<td>1973–1989</td>
<td>176</td>
<td>56</td>
<td>3 y (median)</td>
<td>5 (2.8)</td>
<td>5 (2.8)</td>
<td>11% of patients developed dysplasia on follow-up</td>
<td>Williamson et al, 1991</td>
</tr>
<tr>
<td>University of Rotterdam, Dutch cohort</td>
<td>Retrospective</td>
<td>1973–1994</td>
<td>155</td>
<td>42</td>
<td>9.3 y (mean) or 1440 patient-years</td>
<td>8 (5.3)</td>
<td>8 (5.3)</td>
<td></td>
<td>Van der burgh et al, 1996</td>
</tr>
<tr>
<td>Helsinki University, Central Hospital, Finland</td>
<td>Retrospective</td>
<td>1975–1985</td>
<td>32</td>
<td>59</td>
<td>166 patient-years</td>
<td>3 (9.3)</td>
<td>3 (9.3)</td>
<td>Patients in this study underwent fundoplication; one patient developed HGD</td>
<td>Ovaska et al, 1989</td>
</tr>
<tr>
<td>Mayo Clinic, Rochester, MN</td>
<td>Retrospective</td>
<td>1975–1994</td>
<td>113</td>
<td>68</td>
<td>6.5 y (median)</td>
<td>3 (2.6)</td>
<td>3 (2.6)</td>
<td></td>
<td>McDonald et al, 1996</td>
</tr>
<tr>
<td>University Hospital, Nottingham, England</td>
<td>Prospective</td>
<td>1976–1990</td>
<td>102</td>
<td>63</td>
<td>54 mo (mean)</td>
<td>4 (3.9)</td>
<td>4 (3.9)</td>
<td>2 patients had dysplasia at baseline and a total of 12 had dysplasia on follow-up</td>
<td>Iftikhar et al, 1992</td>
</tr>
<tr>
<td>Ninewells Hospital and Medical School, Dundee</td>
<td>Retrospective</td>
<td>1976–1986</td>
<td>44</td>
<td>58</td>
<td>9.5 y (mean)</td>
<td>2 (4.5)</td>
<td>2 (4.5)</td>
<td>Patients were not in formal surveillance program</td>
<td>Rana et al, 2000</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Registry</td>
<td>1979–1995</td>
<td>136</td>
<td>58</td>
<td>4.2 y (mean)</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>One patient without dysplasia and one with LGD developed cancer. Five patients developed HGD, and 24 developed LGD.</td>
<td>O’Connor et al, 1999</td>
</tr>
</tbody>
</table>
Table 2 (continued). Diagnosis of Prevalent or Incidental Cancer on Follow-up of Patients in Which the Degree of Dysplasia Was Not Defined or There Were <10 Patients in a Single Dysplasia Category

<table>
<thead>
<tr>
<th>Institute or geographic area</th>
<th>Study type</th>
<th>Study duration</th>
<th>No. of patients</th>
<th>Mean or median age (y)</th>
<th>Duration of follow-up</th>
<th>Total cancers (%)</th>
<th>Incidental cancers (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic Medical Center, University of Amsterdam</td>
<td>Prospective</td>
<td>—</td>
<td>50</td>
<td>59</td>
<td>5.2 y (mean)</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>6 patients had LGD and one had HGD at baseline. At the end of the study, 10 had LGD and 3 had HGD</td>
<td>Hameeteman et al, 349 1989</td>
</tr>
<tr>
<td>University of Minnesota, Duluth Clinic</td>
<td>Retrospective</td>
<td>1980–1995</td>
<td>149</td>
<td>—</td>
<td>510 patient-years</td>
<td>20 (13.4)</td>
<td>7 (5)</td>
<td>13 prevalent cancers were detected at esophagectomy</td>
<td>Streitz et al, 350 1998</td>
</tr>
<tr>
<td>Princess Alexandra Hospital, Brisbane, Australia</td>
<td>Prospective</td>
<td>1981–1988</td>
<td>81</td>
<td>63</td>
<td>3.6 y (mean)</td>
<td>3 (3.7)</td>
<td>3 (3.7)</td>
<td>2 patients had HGD at baseline, and both progressed to adenocarcinoma. Ten patients had LGD, and one progressed to adenocarcinoma.</td>
<td>Miros et al, 37 1991</td>
</tr>
<tr>
<td>VA Medical Center, Arizona Health Sciences Center</td>
<td>Prospective cohort</td>
<td>1982–1995</td>
<td>177</td>
<td>62</td>
<td>4.8 y (mean) or 834 patient-years</td>
<td>11 (6.2)</td>
<td>4 (2.3)</td>
<td>All patients who progressed to cancer developed dysplasia before the development of cancer</td>
<td>Drewitz et al, 351 1997</td>
</tr>
<tr>
<td>University of Leeds, Leeds, England</td>
<td>Retrospective</td>
<td>1984–1995</td>
<td>307</td>
<td>58</td>
<td>72 mo (mean)</td>
<td>12 (3.9)</td>
<td>12 (3.9)</td>
<td>Patients were excluded if the cancer was present at baseline or within the first 6 months</td>
<td>Bani-Hani et al, 59 2000</td>
</tr>
<tr>
<td>VA Cooperative Study Group</td>
<td>Retrospective</td>
<td>1986–1999</td>
<td>108</td>
<td>58</td>
<td>1037 patient-years</td>
<td>4 (3.7)</td>
<td>4 (3.7)</td>
<td>Patients were not in formal surveillance program</td>
<td>Spechler et al, 125 2001</td>
</tr>
<tr>
<td>GOSPE, Torino, Italy</td>
<td>Prospective cohort</td>
<td>1987–1995</td>
<td>187</td>
<td>—</td>
<td>36 mo (mean)</td>
<td>3 (1.6)</td>
<td>3 (1.6)</td>
<td>3 patients had LGD at baseline. 5 patients developed LGD, and 2 developed HGD</td>
<td>Ferraris et al, 352 1997</td>
</tr>
</tbody>
</table>

LGD, low-grade dysplasia; HGD, high-grade dysplasia.
Table 3. Diagnosis of Prevalent or Incidental Cancer on Follow-up of Patients With Low-Grade Dysplasia

<table>
<thead>
<tr>
<th>Institute or geographic area</th>
<th>Study type</th>
<th>Study duration</th>
<th>No. of patients</th>
<th>Mean or median age (y)</th>
<th>Duration of follow-up</th>
<th>Total cancers (%)</th>
<th>Incidental cancers (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Outcomes Group, Dartmouth-Hitchcock Medical Center</td>
<td>Retrospective</td>
<td>1970–1994</td>
<td>24</td>
<td>63</td>
<td>4.8 y (median) or 3.9 y (mean) for those who did not develop cancer</td>
<td>*</td>
<td>*</td>
<td>3 patients had HGD or cancer. Cancer and HGD were pooled together</td>
<td>Katz et al,343 1998</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center, University of Washington</td>
<td>Prospective cohort</td>
<td>1983–1998</td>
<td>43</td>
<td>62</td>
<td>2.4 y (median) or 3.9 y (mean) for those who did not develop cancer</td>
<td>3 (7)</td>
<td>3 (7)</td>
<td>5- and 8-year cumulative incidence of cancer was reported to be 12%</td>
<td>Reid et al,43 2000</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Retrospective</td>
<td>1986–1997</td>
<td>25</td>
<td>67</td>
<td>11 mo (median)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>An additional 5 patients developed HGD. When pathologists agreed on the diagnosis of LGD, 7 of 17 progressed to HGD or cancer</td>
<td>Skacel et al,46 2000</td>
</tr>
<tr>
<td>VA Medical Center and University of Kansas Medical Center</td>
<td>Prospective</td>
<td>—</td>
<td>48</td>
<td>62</td>
<td>41 mo (mean)</td>
<td>4 (8); one patient had definite and 3 had suspected intramucosal cancer</td>
<td>4 (8); one patient had definite and 3 had suspected intramucosal cancer</td>
<td>Patients with prevalent cancer diagnosed at entry were excluded</td>
<td>Weston et al,351 2001</td>
</tr>
</tbody>
</table>

*Not defined in manuscript, 24 patients developed LGD anytime during follow up, the high grade dysplasia or cancers were pooled; HGD, high-grade dysplasia; LGD, low-grade dysplasia.
<table>
<thead>
<tr>
<th>Institute or geographic area</th>
<th>Study type</th>
<th>Study duration</th>
<th>No. of patients</th>
<th>Mean or median age (y)</th>
<th>Duration of follow-up</th>
<th>Total cancers (%)</th>
<th>Incidental cancers (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Hospital, Hines, IL</td>
<td>Prospective cohort</td>
<td>1979–1996</td>
<td>75</td>
<td>62</td>
<td>7.3 y (mean)</td>
<td>12 (16)</td>
<td>12 (16)</td>
<td>4 patients in whom cancer was detected in the first year of surveillance were excluded and considered to have prevalent cancers</td>
<td>Schnell et al, 2001</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center, University of Washington</td>
<td>Prospective cohort</td>
<td>1983–1998</td>
<td>76</td>
<td>62</td>
<td>2.4 y (median) or 3.9 y (mean) for those who did not develop cancer</td>
<td>33 (43.4)</td>
<td>33 (43.4)</td>
<td>5-year cumulative incidence of cancer was reported to be 59%</td>
<td>Reid et al, 2000</td>
</tr>
<tr>
<td>VA Medical Center and University of Kansas Medical Center</td>
<td>Prospective</td>
<td>—</td>
<td>15</td>
<td>61</td>
<td>37 mo (mean)</td>
<td>7 (470; 4 patients had definitive cancer and 3 had possible intramucosal cancer)</td>
<td>7 (470; 4 patients had definitive cancer and 3 had possible intramucosal cancer)</td>
<td>Patients had unifocal HGD. In 4 patients, the extent of dysplasia increased. 5 patients became nondysplastic, and 2 had LGD. Patients with prevalent cancer diagnosed at entry were excluded</td>
<td>Weston et al, 2000</td>
</tr>
<tr>
<td>Mayo Clinic, Rochester, MN</td>
<td>Retrospective cohort</td>
<td>1991–1999</td>
<td>100</td>
<td>67.5</td>
<td>30 mo (mean) for focal HGD and 15 mo (mean) for diffuse HGD</td>
<td>32 (32%)</td>
<td>13 (16) after excluding cancers that were detected in the first 6 months</td>
<td>Patients with cancer at entry were excluded. 4 patients with focal and 28 patients with diffuse HGD were diagnosed with cancer</td>
<td>Buttar et al, 2001</td>
</tr>
</tbody>
</table>

HGD, high-grade dysplasia; LGD, low-grade dysplasia.
should have periodic surveillance at 5-year intervals, depending on the patient's health. The rationale of repeating surveillance twice in the first year is to diagnose any prevalent dysplasia that may have been missed during initial endoscopy. Most initial procedures that diagnose Barrett's esophagus do not involve complete surveillance biopsies because the diagnosis has not been established. The reason to increase the surveillance interval to 5 years is based on decision analysis models showing that surveillance in this group of patients is not cost-effective. The caveat is that this recommendation is based on set assumptions made in the cost-utility model, and any major change in these assumptions in the future will require modification of the surveillance interval in patients with nondysplastic Barrett's esophagus.\(^{38}\) This is different from prior gastrointestinal societal guidelines, which suggested that surveillance should be performed at more frequent intervals, but there has not been sufficient evidence to support prior recommendations.\(^{64}\) Therefore, we recommend ending surveillance when the anticipated life expectancy is limited (<1 year) or the patient is unable to tolerate any therapeutic measures. Even younger patients may not warrant surveillance if therapy for cancer cannot be performed.

Patients with low-grade dysplasia should undergo repeat endoscopy twice in the first year, and those patients who have persistent low-grade dysplasia in Barrett’s esophagus should have periodic surveillance at 1- to 2-year intervals until the age of 80 years, depending on health status. The risk of cancer development in patients with low-grade dysplasia is intermediate.\(^{46}\) Patients with low-grade dysplasia whose diagnosis is agreed on by 2 pathologists carry a relatively higher risk of cancer diagnosis; therefore, we recommend a surveillance interval of 1 year for this group of patients. Patients whose diagnosis of low-grade dysplasia is not agreed on by 2 pathologists but who do not have any evidence of high-grade dysplasia can be surveyed at 2-year intervals.

Patients with high-grade dysplasia in Barrett’s esophagus that has been confirmed by 2 experienced pathologists should be recommended to proceed with definitive surgical or endoscopic management, especially if the high-grade dysplasia is diffuse or mucosal abnormalities are found on endoscopy. If the patient does not wish to proceed with definitive treatment until the diagnosis of cancer is made, surveillance should be considered. Surveillance endoscopy should be repeated every 3 months in the first 2 years, followed by 6-month intervals indefinitely. The rationale for recommending immediate surgical or endoscopic therapy is that many patients may already have coexisting esophageal cancer that was not detected due to the limitations of surveillance.\(^{111}\) The rationale for repeating surveillance every 3 months for the first 2 years is to capture any prevalent cancers that were not detected initially. This surveillance interval should be used even if ablative procedures are performed for high-grade dysplasia or cancer because of the risk of recurrence of the disease.\(^{112,113}\) The reason to increase the surveillance interval to 6 months after the first 2 years is that the majority of cancers detected in patients with high-grade dysplasia are within the first year and the risk of incidental cancer after the first 2 years of surveillance is low.\(^{47,48}\) After ablative therapy, surveillance should be continued as per the preablative recommendation because the long-term consequences of ablation are as yet undetermined and because of reports of recurrent neoplasia after ablation.

**Summary of Evidence**—The use of surveillance in patients with Barrett’s esophagus is supported by level II evidence, although it seems that the most cost-effective approach is to target patients at higher risk for development of cancer. Surveillance should be performed using 4-quadrant biopsy specimens taken every 1–2 cm of Barrett’s mucosa, depending on the degree of dysplasia (based on level III evidence). The use of jumbo biopsy forceps in routine surveillance is not recommended based on existing evidence. The use of jumbo biopsy forceps in patients with high-grade dysplasia has not been proven to provide increased benefit. There are as yet insufficient data to recommend chromoendoscopy with Lugol’s solution over conventional videobescopy in Western cohorts at risk for esophageal squamous cell cancer (based on level III evidence). Methylene blue–assisted chromoendoscopy is not clearly beneficial and should not be used in the routine assessment of Barrett’s esophagus (based on level II evidence). Magnification, optical spectroscopy, and imaging techniques are still being developed and should be considered research tools at the current time (based on level III evidence). Surveillance of nondysplastic Barrett’s mucosa established by 2 endoscopies should be at 5-year intervals (based on level III evidence). Surveillance of patients with low-grade dysplasia established by 2 endoscopies should be at 1- to 2-year intervals, depending on whether or not the diagnosis is confirmed by 2 pathologists. If both pathologists concur that low-grade dysplasia is present, 1-year surveillance intervals should be used; if agreement cannot be reached (dysplasia is not believed to be present by at least one pathologist), 2-year intervals should be sufficient (based on level IV evidence). High-grade dysplasia should be confirmed in a second endoscopy and reviewed by expert pathologists. If this is confirmed, the patient can be offered surveillance at 3-month intervals for 2 years and then every 6 months (based on level III evi-
Any mucosal abnormality should be carefully investigated and removed for diagnosis. Surgical resection should be recommended and mucosal ablation with photodynamic therapy (PDT) can be offered for patients with confirmed high-grade dysplasia (based on level III evidence).

Chemoprevention for Esophageal Cancer

Acid Inhibition

Because esophageal cancer is uncommon and interventions are usually only warranted in high-risk groups, strategies for chemoprevention of this condition are being advocated. These include the use of acid suppression, nonsteroidal anti-inflammatory drugs (NSAIDs), and lifestyle modifications. Antireflux surgery or prolonged acid suppression using high doses of proton pump inhibitors result in the appearance of squamous islands in Barrett’s esophageal segment but have not consistently been shown to regress metaplastic epithelium or prevent esophageal adenocarcinoma. Although the rationale for intensive antireflux therapy seems reasonable, there is not good clinical evidence to support this approach. The primary rationale for these proposals is that proton pump inhibitors incompletely suppress gastric acid and fail to completely reduce duodenal-esophageal bile reflux. Acid and bile salts can activate several key cellular pathways in Barrett’s esophagus that are normally associated with progression of neoplasia in Barrett’s esophagus, and inhibition of these pathways may prevent the development of adenocarcinoma of the esophagus in an animal model of Barrett’s esophagus. In patients with Barrett’s esophagus who were asymptomatic on acid suppressive therapy and also had normalization of intraesophageal acid exposure on pH monitoring, there was significantly more differentiation and less proliferation compared with patients who continued to have abnormal intraesophageal acid exposure. However, even on high dosages of proton pump inhibitors, acid inhibition may be difficult to achieve, with 4 of 25 patients having pathologic acid reflux on 80 mg/day of omeprazole. Fundoplication is not successful in controlling acid reflux on a long-term basis and did not prevent development of cancer, as demonstrated by a follow-up to a randomized prospective trial comparing medical with surgical therapy.

Ablation Therapy

Ablation therapy in conjunction with acid control has been promoted for the treatment of Barrett’s esophagus to decrease the risk for esophageal cancer. This is based on the observation that elimination of the metaplastic epithelium can result in squamous mucosa regeneration. Multiple ablation therapies have been proposed and involve the use of multipolar coagulation, argon plasma coagulation, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser coagulation, and PDT. Multipolar coagulation has been performed in a prospective multicenter study with 58 patients that eliminated histologic evidence of Barrett’s mucosa in 78% of treated patients. Argon plasma coagulation has been used in one randomized, nonblinded, prospective trial in 40 patients after fundoplication for acid control. Barrett’s mucosa was initially found underneath squamous mucosa in this study in more than 35% of patients 1 month after treatment but decreased to 5% at 1 year. Patients who did not achieve complete ablation had 95% regression in the amount of Barrett’s mucosa. Multiple case series of argon plasma coagulation have been reported with significant reduction in Barrett’s mucosa and decrease in dysplasia. Many ablation trials emphasize that reduction in the length or area of Barrett’s mucosa should correspond with a decreased risk for cancer, although this has not been shown in a prospective study. PDT has been approved by the Food and Drug Administration (FDA) for use in patients with high-grade dysplasia to decrease the risk of cancer formation. Case series of patients with high-grade dysplasia treated with PDT using sodium porfimer have found that dysplasia can be eliminated in 78% of patients with elimination of 75%–80% of the Barrett’s mucosa, but esophageal strictures occurred in 34% of patients. Unfortunately, the residual Barrett’s mucosa after ablation therapy has been found to contain genetic mutations similar to those found before ablation, suggesting that histologic improvement may not correlate with elimination of cancer risk. A prospective randomized trial studied PDT using 2 different dosages of 5-aminolevulinic acid (a less potent agent than sodium porfimer) followed by argon plasma coagulation compared with argon plasma coagulation alone in 40 patients. These investigators found that argon plasma coagulation alone or in combination with PDT was only effective in eliminating about 70% of the Barrett’s mucosa.

NSAIDs

The rationale for the use of NSAIDs to prevent cancer in Barrett’s esophagus is based on experimental
and epidemiologic evidence. No randomized controlled trials have found aspirin to be effective for prevention of cancer. It has been shown that bile salts in a pH-dependent manner can activate the arachidonic acid pathway and may promote neoplasia in Barrett’s esophagus.\textsuperscript{121,122} The activation of the arachidonic acid pathway leads to increased production of prostaglandin E\textsubscript{2}, which increases cellular proliferation.\textsuperscript{142,143} Inhibition of prostaglandin E\textsubscript{2} normalizes proliferation in Barrett’s epithelial cells and decreases it to a level that is seen in normal squamous epithelium.\textsuperscript{143} Inhibition of the cyclooxygenase enzyme with selective and nonselective cyclooxygenase inhibitors has been shown to reduce the risk of adenocarcinoma of the esophagus in an animal model of Barrett’s esophagus.\textsuperscript{123} Finally, cyclooxygenase-2 expression has also been shown to parallel the progression of neoplasia in human Barrett’s esophagus.\textsuperscript{144}

Epidemiologic studies have found that NSAIDs protect against the risk of esophageal cancer.\textsuperscript{145–149} Case-controlled studies have shown a 36%–90% relative risk reduction for esophageal cancer in patients using aspirin or other NSAIDs occasionally or on a long-term basis.\textsuperscript{145–147,149} A decision analysis model has been used to evaluate the feasibility and cost-effectiveness of NSAIDs to prevent esophageal adenocarcinoma. It suggested that the high incidence of esophageal adenocarcinoma in Barrett’s esophagus with high-grade dysplasia renders chemoprevention a cost-effective option.\textsuperscript{150} NSAIDs were not a cost-effective measure in the general population of all patients with Barrett’s esophagus, but this was sensitive to variations in the cost of chemoprevention, the incidence of cancer, and the efficacy of the NSAID in prevention of cancer. In patients with gastroesophageal reflux, a chemopreventive approach will only be cost-effective if the agents are very safe and effective to prevent the development of adenocarcinoma of the esophagus.

**Lifestyle**

Lifestyle factors for the development of esophageal cancer have been identified through epidemiologic studies. Obesity seems to be one of the most important risk factors associated with esophageal cancer.\textsuperscript{151,152} In a recently completed study of patients with esophageal and gastric cancer, smoking and dietary habits were found to be important risk factors.\textsuperscript{152} Smoking was found to have a population attributable risk (PAR) of 39.7% (95% confidence interval [CI], 25.6%–55.8%). The frequency of gastroesophageal reflux disease symptoms also showed a positive trend in the PAR, with symptoms at least once per day accounting for almost one half of the PAR associated with the presence of any gastroesophageal reflux disease symptoms (29.7%; 95% CI, 19.5%–42.3%). Consumption of fruits and vegetables less than twice a day on average had a modest PAR of 15.3% (95% CI, 5.8%–34.6%). In this population, 78.7% (95% CI, 66.5%–87.3%) of esophageal adenocarcinoma cases could be attributed to one or more of these well-established risk factors, with smoking and body mass index contributing the most.

**Summary of Evidence**—Based on level II evidence, fundoplication should not be recommended solely to prevent esophageal cancer in patients with gastroesophageal reflux disease. The use of high-dose proton pump inhibitors to prevent esophageal cancers in patients with gastroesophageal reflux disease has also not been established and cannot be recommended in clinical practice (based on level III evidence). Level II evidence suggests that ablation therapy may decrease dysplasia in Barrett’s esophagus and could potentially decrease cancer risk. NSAIDs should not be recommended at the current time solely for the prevention of esophageal adenocarcinoma but have promise as a chemopreventative agent, which might be beneficial if required for other medical indications (based on level II evidence). Patients at risk for esophageal cancer should be counseled to adapt healthier lifestyles, in particular attaining normal weight and eliminating tobacco use (based on level II evidence).

**Diagnosis and Staging of Esophageal Cancer**

**Diagnosis**

Most patients with esophageal cancer present at a late stage when the diagnosis of cancer is made, with dysphagia as the cardinal symptom.\textsuperscript{153} In particular, persistent dysphagia that progresses from solids to liquids should heighten suspicion for esophageal cancer and prompt an endoscopic evaluation. Up to 75% of patients have experienced anorexia and weight loss when seeking medical attention. Patients may also present with odynophagia, chest pain, or gastrointestinal bleeding. Cough aggravated by swallowing raises the possibility of an esophagopulmonary fistula, a devastating complication associated with a high 30-day mortality rate.\textsuperscript{154}

The diagnosis of esophageal cancer is established by flexible endoscopy with biopsy. The features, location, and size of the tumor can be more accurately assessed by endoscopy than by radiographic studies.\textsuperscript{153} Barium swallow as an initial diagnostic test is of limited value.\textsuperscript{156,157} However, it may be useful to confirm the presence of esophagopulmonary fistulas or document complete luminal obstruction when clinically suspected. In patients...
with advanced cancers, esophageal dilation may be required to allow for a standard (OD, 9.8 mm) endoscope to traverse the obstructed lumen. Alternatively, an ultrathin (OD, 5.3–6 mm) endoscope may pass through the stenosis and allow completion of the examination in 75% of cases.\textsuperscript{158}

Biopsy specimens are required for histologic confirmation. The diagnostic yield reaches 100% when 6 or more samples are obtained using a standard endoscopic biopsy forceps.\textsuperscript{159,160} Biopsy specimens of necrotic or fibrotic areas should be avoided. The adequacy of biopsy specimens obtained via ultrathin endoscopes has not been formally assessed. As an adjunct, brush cytology can be helpful in sampling tight malignant strictures, which may not be easily accessible by conventional biopsy techniques.\textsuperscript{161} Brushings should be collected before biopsy to maximize the diagnostic yield.\textsuperscript{162} Endoscopic ultrasonography (EUS) should be considered when standard biopsy and/or brush cytology fail to confirm the diagnosis in the setting of high clinical suspicion (e.g., submucosal tumors).\textsuperscript{163} Fine-needle aspiration or Tru-cut biopsy can be performed at the time of EUS.

**Staging**

The staging of esophageal cancer is critical to guide further therapy for the patient. Patients with cancer confined to the mucosa or superficial submucosa can be treated using surgical resection or potentially endoscopic therapy.\textsuperscript{137,164} However, patients who have more advanced disease will require surgical resection or chemoradiation.\textsuperscript{165,166} None of the currently available staging technologies have been shown to be able to stage all aspects of the tumor. The selection of the best staging tests depends on the probability of detecting metastatic cancer. Although endoscopy is not a staging tool, it can be helpful to guide the gastroenterologist toward which additional staging studies are needed. In one series of 209 patients, endoscopy was 89% accurate in determining tumor staging compared with surgical or EUS staging.\textsuperscript{167} Patients with large bulky circumferential tumors who present with dysphagia are likely to have advanced disease and will require tests to confirm this. Patients who have cancers that are <2 cm in diameter and are asymptomatic are more likely to have early disease. Algorithms for evaluation of advanced and early esophageal cancers are found in Figures 1 and 2.

The most commonly used staging procedure in esophageal cancer is computed tomography (CT). The particular strength of this test is the ability to detect distant metastatic disease.\textsuperscript{168} The primary reason this is used as the first staging study is because of its availability and the change in the treatment course that would occur should metastasis or invasion of other organs be detected. On initial presentation, most patients with metastatic disease had involvement of abdominal lymph nodes (45%), liver (35%), lung (20%), and cervical lymph nodes (18%) based on findings at esophagectomy.\textsuperscript{169} CT of the chest and abdomen correctly identified metastatic disease in only 69% of the cases. In this series, patients without metastasis on CT did not have involvement of the bones or brain. CT has limited accuracy in staging the extent of tumor invasion, with correct staging found in 50%–90%.\textsuperscript{170–172} CT has been shown to produce false negatives in 30%–60% of patients.\textsuperscript{173} Even with improvements in technology such as the helical CT scanner, comparisons with EUS and fine-needle aspiration indicate that it is still not as sensitive for detecting celiac lymph node disease or T4 carcinoma.\textsuperscript{174}

EUS consists of 3 fundamentally different devices that may not be available to all gastroenterologists. There are probes that can be placed within the endoscope or used as stand-alone instruments, radial scanning echoendoscopes, and linear array echoendoscopes that permit fine-
needle aspiration. EUS can be directed primarily at the mucosa with the use of probes that usually involve high-frequency scanning at 20–30 MHz or can be directed to more distant structures by scanning at 7.5–12 MHz with the radial echoendoscopes. The diagnostic utility of EUS is in determining the depth of tumor invasion and the presence of local-regional adenopathy. This technology is limited in terms of detecting distant metastasis because visualization of other organ systems, particularly the lung, is not possible because air disrupts ultrasound conduction. Identification of abnormal-appearing lymph nodes has been found to be specific (85%–97%) for nodal metastasis but not very sensitive (72%–77%) in case series. If abnormalities are found, biopsies can be performed on the lesions using a small aspiration needle positioned in a linear array instrument. The sensitivity of this technique in tumor staging has been reported in clinical series between 59% and 90%. Some of this variation can be attributed to the difficulty in passing the ultrasound instrument through a malignant stricture. Histologic confirmation of nodal disease altered planned therapy in only 13% of patients with esophageal cancer in one retrospective case series. This may be because the majority of esophageal cancers are found at an advanced stage. Minipробes that have higher resolution are the best at defining early-stage cancer. Decision analysis models have been used to determine the value of EUS in assessment of esophageal cancer. These models have found that EUS is a more cost-effective initial staging strategy if the probability that EUS can find advanced disease is >30% or if the cost of EUS is less than 3.5 times that of CT. Additional analysis based on the use of EUS in a national database found that preoperative use of this technique could prevent 26% of patients from unnecessary combined-modality therapy.

Positron emission tomography (PET) is a technology that uses $^{18}$F-fluorodeoxyglucose for the detection of nodal or distant metastasis in esophageal cancer. This is used to detect neoplastic tissues because they normally metabolize glucose at a faster rate than normal tissues. However, inflammatory tissues are also fast glucose metabolizers and metastases often have to be differentiated from inflamed tissue, leading to false positives. A number of case series have found that PET is not as sensitive as EUS or CT for locoregional disease. This technology cannot define the tumor stage because it cannot resolve the layers of the esophagus. In addition, patients with hyperglycemia are not good candidates for PET. Because of these factors, PET cannot be envisioned as an initial staging tool in esophageal cancer. New advances in PET technology include fusion PET, which actually combines the CT image with the PET image to allow better tumor localization. This may increase the specificity of the test.

Other staging procedures that have been investigated include minimally invasive surgery or laparoscopic staging before esophagectomy. Case series have found that performance of laparoscopic- or thoracoscopic-guided biopsies of lymph nodes increases the detection of metastatic disease and can change management in 17% of patients. Thoracoscopy has a significant advantage in detecting thoracic lymph nodes and when combined with laparoscopy appears to be superior to EUS, PET, and CT staging. These series generally do not have uniform staging procedures performed before the laparoscopy, which makes it difficult to assess the role of these procedures in relation to the standard staging modalities. Bronchoscopy has been suggested as a staging procedure for patients with tumors that are found above the tracheal bifurcation. In one prospective study, almost 10% of patients were found to have tracheal involvement on the basis of bronchoscopy alone, although EUS was not used in this study. Magnetic resonance endoscopy has also been used in staging esophageal cancer but as yet has not been shown to be superior to existing tests. Recent cost analyses of these various staging modalities alone and in combination have suggested that CT combined with EUS with fine-needle aspiration if appropriate offered the least expensive and reasonable efficacy in terms of QALYs. PET and EUS plus fine-needle aspiration offered more QALYs but was also more expensive at $60,544 per QALY.

Summary of Evidence—Given the state of the current information, we recommend the following strategy. CT of the chest and upper abdomen should be the first staging procedure, followed by EUS and fine-needle aspiration if no evidence of distant metastasis is found on CT and the procedure is available. If surgical resection is still considered, PET can be considered if available due to its increased sensitivity for distant metastasis. This is based on level III evidence. In patients with potentially early-stage disease (tumors <2 cm and nonobstructing), EUS with endoscopic mucosal resection may be considered as an alternative staging procedure if available for histologic staging of the cancer and potential therapy.

**Treatment of Esophageal Cancer**

**Treatment of Early Cancers**

Early esophageal cancers, those confined in the mucosa or upper submucosa of the esophagus, are termed T1, N0, M0 by the American Joint Commission on Cancer terminology (see Table 5). There have not been
any randomized treatment trials for these cancers because they are rare, accounting for $<5\%$ of esophageal cancers diagnosed in most series. In Japan, there has been a further division in T1 lesions. An early cancer is termed T1m if confined to the mucosa and T1sm if submucosal invasion is found. There has even been further division of T1 lesions into penetration into the upper third (sm1), the middle third (sm2), or the lower third (sm3) of the submucosa.\(^{202}\) In the Japanese experience with squamous cell cancers, penetration of the superficial submucosa is associated with a 6\% risk of metastasis. However, if deeper penetration of the submucosa is found, the risk of metastasis increased to 47\%. There is a problem in the interpretation of some of the literature from Japan.\(^{203}\) Overall, Japanese pathologists will diagnose intramucosal carcinoma based primarily on patterns of the cell nucleus rather than on the demonstration of invasion as required by Western pathologists. Some of the data concerning the lack of metastatic potential for early cancers may be biased by the inclusion of cases of what would be classified by Western pathologists as high-grade or even low-grade dysplasia.

The traditional approach for these squamous cell cancers has been surgical resection because cure can be achieved in $>90\%$ of T1m cancers.\(^{204,205}\) A survey of major medical centers in Europe found that 253 patients with early cancers treated with esophagectomy had a mortality rate of 9.1\%.\(^{205}\) Patients with intraepithelial cancers had a 5-year survival rate of 93\%, while those with intramucosal cancers had a decreased survival rate of 73\%. If cancer progressed into the submucosa, the survival rate further decreased to 44\%. Twenty of 21 patients with recurrent disease had submucosal involvement with cancer. These results are similar to those found in Japan.

There is less information available regarding surgical resection of early adenocarcinoma. Early cancers have primarily been reported as part of larger surgical series. Overall, limited reports have results with a 100\% rate of total excision without any operative mortality.\(^{206–211}\) However, this is likely to be influenced by reporting bias. The reported mortality rate for esophagectomy performed on patients with high-grade dysplasia is between 2\% and 6\%.\(^{212,213}\) The major concern with surgical therapy for high-grade dysplasia is the 40\% incidence of morbidity associated with the procedure. Possible procedure-related complications include anastomotic stenosis, leaks, chronic aspiration, infection, and chylethorax.

Endoscopic mucosal resection has been performed on a number of patients with early cancers, particularly in Asia, where the technique has been established for early gastric cancers. Studies have shown that squamous cell cancers confined to the mucosa or upper submucosa could be treated successfully with endoscopic therapy.\(^{214}\) Five-year cure rates for patients with intramucosal cancers were 100\%, while those who had cancers that penetrated into the deep submucosa had 5-year survival rates of 59\%–54\% in a series of 152 cases. Reports from other institutions for superficial cancers in Japan reported a 95\%–100\% 5-year survival rate with recurrences estimated at 3\%–7\%. Even these recurrences were believed to be treatable with additional endoscopic therapy.\(^{215}\) In a survey of 143 Japanese medical institutions, endoscopic mucosal resection was regarded as the treatment of choice for intramucosal cancers.\(^{216}\) Complications in 2418 patients were primarily stenosis, hemorrhage, or perforation, which were found in 7\% of patients. The most important predictors of stenosis were resection of more than three fourths of the circumference of the esophageal lumen or if the lesion was $>3$ cm in length.\(^{217}\)

Early mucosal resections were performed using a transparent overtube through which an endoscope could be positioned.\(^{218}\) The lesion was first identified visually, and
then a fluid cushion was created under the lesion by injecting saline and epinephrine submucosally beneath the lesion. If the lesion could not be elevated from the remainder of the esophageal wall, the resection could not be performed. Later developments involved the use of band ligation and eventually the cap-fitted endoscope. New variations of this technique have been described and termed endoscopic submucosal dissection, including the use of an insulated tipped electrocautery knife, needle knife, or triangular tipped knife that can completely resect the lesion with the use of a special snare designed to resect the lesion without any need for suction. These techniques were all designed for the relatively flat lesions associated with early squamous cell cancers. Endoscopic mucosal resection performed in the United States involves the use of variceal band ligation, which allows the formation of a pseudopolyp that can be resected by a regular snare. A second common technique involves the use of a specialized cap that can be fitted onto an endoscope. This requires the use of a crescent snare that is designed to form a loop around the lip of the distal end of the cap. The targeted tissue can then be suctioned into the cap and the snare closed to perform the resection. A prospective comparison study of these 2 techniques in 100 resections performed in 72 patients with early cancers did not find any differences in terms of size of the specimen or complication rates. Early esophageal adenocarcinomas have been endoscopically treated in the setting of Barrett’s esophagus. These have been described in large case series using mucosal resection alone or in combination with PDT. Lesions most amenable to mucosal resection are those that are polypoid, elevated, <2 cm in size, and having a low-grade cancer. Mucosal resection was used in 115 patients (83% with early cancers) and resulted in a 3-year overall survival rate of 88%. Complications occurred in 9% of patients, including decreases in hemoglobin and stricture formation. However, because Barrett’s esophagus without high-grade dysplasia or cancer was left untreated, 30% of the patients developed additional neoplastic lesions. For this reason, it is generally advised that the remainder of the Barrett’s esophagus be treated after resection of a cancer. PDT has been used for this purpose, with 94% initial success rates at 1 year. Although not widely performed, mucosal resection has been performed to completely eliminate the Barrett’s segment in 2 reports. Circumferential mucosal resection does tend to generate strictures; this has been reported in 3 of the 13 reported cases. Endoscopic therapy using PDT, laser therapy, and argon plasma coagulation has also been reported. These treatments have had limited success in completely eliminating Barrett’s esophagus and cancer, with response rates of 25%–94%. These small case reports have had a wide variation in the depth of invasion of these cancers (T0–T2) and the type of therapy delivered. Laser therapy with Nd:YAG, which operates at a wavelength of 1063 nm, penetrates quite deeply and has been favored for tumor ablation. Lasers that operate in the 540-nm wavelength, such as the argon or KTP-YAG lasers, have a much more limited depth of penetration. Thermal therapies, such as argon plasma coagulation applied at high-power settings, have also been used to treat early cancers. PDT is influenced by the type of photosensitizer used for therapy. Aminolevulinic acid is not approved in the United States at this time, but it has found favor in Europe because it is not associated with the prolonged cutaneous photosensitivity that is found with the sodium porphyrin that is used in the United States. Due to its very limited depth of penetration, aminolevulinic acid has only been found to be useful for cancer therapy if the thickness of the cancer is <2 mm. Other treatments that have been reported in case series for the treatment of patients with superficial cancers include radiation therapy and brachytherapy. Radiation therapy has been used in Japan as a single-modality therapy for superficial squamous cell cancers. Five-year survival rates after treatment in 2 series with a total of 183 patients ranged from 39% to 45%. These studies have also shown a trend toward nodal recurrence of cancer in patients who have had submucosal penetration. Patients with cancer strictly confined to the mucosa did not have nodal recurrence. Brachytherapy alone and in combination with external beam radiation has also been reported, although the 3-year survival rate in these patients is only 14%. Treatment of Advanced Cancers The gastroenterologist is often asked to determine whether there is a role for oncologists before surgical resection. There has been substantial controversy over the use of neoadjuvant therapy before esophagectomy for the treatment of patients with locally advanced esophageal carcinoma, primarily patients with stage IIb or III disease (Table 5). Primary surgical therapy for cancers limited to the esophagus, stage I or IIa disease, has had good results without the need for or morbidity of chemother-apy. Surgical therapy for more advanced cancer has been performed as either a limited resection or en-bloc removal of lymph nodes, which can be performed via a transhiatal or transthoracic (Ivor–Lewis) approach. Extensive resection of lymph nodes has been more commonly practiced in Asia and involves removing nodes in the neck, chest, and abdomen in a
Table 6. Summary of Randomized Controlled Trials Comparing Neoadjuvant Chemotherapy and Radiation in Addition to Surgical Resection With Surgical Resection Alone

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Survival period (y)</th>
<th>Surgery alone (%)</th>
<th>Chemoradiation and surgery (%)</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nygaard et al</td>
<td>186</td>
<td>3</td>
<td>9</td>
<td>17</td>
<td>.30</td>
<td>2.81</td>
<td>0.61–12.95</td>
</tr>
<tr>
<td>Le Prise et al</td>
<td>86</td>
<td>3</td>
<td>13.8</td>
<td>19.2</td>
<td>.56</td>
<td>1.57</td>
<td>0.50–5.00</td>
</tr>
<tr>
<td>Apinop et al</td>
<td>69</td>
<td>5</td>
<td>10</td>
<td>24</td>
<td>.40</td>
<td>3.1</td>
<td>0.74–12.8</td>
</tr>
<tr>
<td>Walsh et al</td>
<td>113</td>
<td>3</td>
<td>6</td>
<td>32</td>
<td>.01</td>
<td>8.44</td>
<td>2.33–30.57</td>
</tr>
<tr>
<td>Bosset et al</td>
<td>282</td>
<td>5</td>
<td>32</td>
<td>33</td>
<td>.78</td>
<td>1.06</td>
<td>0.64–1.74</td>
</tr>
<tr>
<td>Kelsen et al</td>
<td>440</td>
<td>2</td>
<td>35</td>
<td>37</td>
<td>.53</td>
<td>1.1</td>
<td>0.74–1.63</td>
</tr>
<tr>
<td>Urba et al</td>
<td>100</td>
<td>3</td>
<td>16</td>
<td>30</td>
<td>.15</td>
<td>2.25</td>
<td>0.85–5.93</td>
</tr>
</tbody>
</table>

3-field lymph node dissection. This procedure is rarely practiced in the United States because of the prolonged operating times and the morbidity associated with the procedure. An en-bloc lymph node dissection of the stomach and chest is practiced in the United States in an attempt to achieve complete surgical removal of tumor and appears in small series to eliminate recurrence of tumor in the resected area. In general, esophagectomy for squamous cell cancer seems to have been more successful in Asia than in Western countries in terms of survival and operative mortality. Minimally invasive esophagectomy has recently been promoted for resection of esophageal cancer with the use of laparoscopy for gastric mobilization and resection. The gas- tro-esophageal anastomosis is accomplished with a thoracoscope or manually. Although the procedure has not been shown to improve patient outcomes in terms of morbidity or mortality, it has been attractive to patients with superficial cancer or high-grade dysplasia who desire an improved cosmetic result.

It has been well recognized that survival is related to disease stage. Thus, it is not surprising that the concept of neoadjuvant (preoperative) chemotherapy and radiation had significant appeal to oncologists and surgeons. By reducing the number of involved lymph nodes and decreasing cancer stage, neoadjuvant therapy could enhance the ability of surgical resection to cure patients. A number of prospective, randomized, controlled trials have investigated the use of neoadjuvant therapy followed by surgery versus surgery alone, and these are summarized in Table 6. Only one of these studies, that by Walsh et al., actually showed an advantage to chemotherapy and radiation with an odds ratio of 8.44 and a 95% CI that does not cross 1. This study has been criticized for its high surgical mortality rate that biases against the surgical therapy alone group. A recent meta-analysis combined all of these studies and concluded that neoadjuvant therapy increased patient survival at 3 years with an odds ratio of 2.5 (P = .04) and had a decreased risk of locoregional recurrence with an odds ratio of 0.83 (P < .01). This study found that there was a nonsignificant trend toward an increase in treatment mortality. The concurrent administration of chemotherapy and radiation therapy was believed to be significantly better than sequential therapy. A significant percentage (21%) of the patients in these series had a complete pathologic response at the time of resection.

With these high pathologic response rates with radiation and chemotherapy alone, it has been questioned whether surgical therapy is needed in the treatment of patients with more advanced cancers. Initial studies comparing neoadjuvant regimens found that the small groups of patients who refused surgery after chemotherapy and radiation had a 5-year survival rate of 18% if they had squamous cancers but no 5-year survival if they had adenocarcinomas. The Intergroup 0123 trial studied a nonsurgical approach to esophageal cancer using high-dose radiation (64.8 Gy) versus standard-dose radiotherapy (50.4 Gy) in combination with 5-fluorouracil and cis-platinum in 216 evaluable patients. The trial was terminated after interim analysis because the results indicated that 50.5-Gy radiation was as effective as the higher dose, with 2-year survival rates of 40%.

The need for combined chemotheraphy and radiation therapy has been best established in a randomized prospective trial from the Radiation Therapy Oncology Group 85-01 study, which examined 134 patients randomized to radiation alone versus radiation in combination with chemotherapy with 5-fluorouracil and cis-platinum. This trial clearly established that combined therapy with a 5-year survival rate of 26% was superior to radiation therapy alone with a 0% 5-year survival rate. The odds ratio of this study was 0.02 (95% CI, 0.00–0.38). One caveat from this study was that only 68% of the patients who planned to undergo chemotherapy were able to complete the treatment course.

Summary of Evidence—Patients with early esophageal cancers confined to the mucosa should be treated with surgical resection, with consideration of endoscopic mucosal resection with adjuvant mucosal treatment for any...
remainig preneoplastic tissue (ie, Barrett’s esophagus) (based on level III evidence). Patients with early esophageal cancers that penetrate into the upper third of the submucosa can be treated with endoscopic mucosal resection if surgical mortality is anticipated to be >6% (based on level III evidence). Patients with stage IIb and III disease may benefit from concomitant chemoradiotherapy and radiation therapy before surgical therapy (based on level II evidence). Patients with stage I and IIa disease who are good candidates for surgical therapy do not require neoadjuvant therapy before esophagectomy (based on level II evidence). Patients with more advanced-stage cancer may be treated with chemotherapy and radiation therapy or be considered for palliative therapy.

Palliation of Esophageal Cancer

Esophageal cancer is usually diagnosed at an advanced and incurable stage. Patients with locally unresectable cancer or patients who are surgically unfit may undergo palliation by a variety of nonoperative means. The goals of palliation in this setting are to alleviate dysphagia, aid in nutrition, and improve quality of life. Palliation can be achieved by external beam radiotherapy or intraluminal brachytherapy, with or without chemotherapy. However, patients may not tolerate these therapies or improvement in dysphagia may be slow.259

Endoscopic therapy plays an important role in the palliation of malignant dysphagia. Several endoscopic techniques have been applied, but limited information exists as to the optimal approach. The choice is primarily dictated by tumor characteristics, patient preference, and available expertise. Treatment must be individualized, and different methods of palliation may be appropriate at various stages of the patient’s illness.

Malignant esophageal stenoses can be dilated using through-the-scope balloons or wire-guided polyn vinyl dilators (e.g., Savary dilators), with or without the aid of fluoroscopy. Dilation can be complicated by perforation in up to 10% of cases.260–262 Blind passage of Maloney dilators is not recommended in complex malignant strictures due to a higher risk of perforation.263 Most patients can be dilated to a luminal diameter that allows passage of a liquid to soft diet (~9–12 mm), but improvement is brief and typically measured in days. Dilation is used mostly as an adjunct to other modalities, such as in facilitating placement of an esophageal stent or in patients awaiting improvement in swallowing following chemoradiation therapy.264

Among endoscopic modalities, esophageal stenting has assumed a primary role as a palliative technique because of its effectiveness in rapidly relieving dysphagia in one procedure. In the United States and abroad, self-expanding metal stents (SEMS) have largely supplanted conventional plastic semirigid prosthesis.265,266

In contrast to plastic semirigid stents, SEMS require minimal to no preplacement dilation and are easier to insert.267–269 SEMS also expand the obstructed lumen to a greater degree (18–23 mm) than that provided by plastic semirigid stents bounded by fixed internal diameters (10–12 mm). Both SEMS and plastic semirigid stents have a highly successful rate of insertion (90%–100%). They are also similarly effective at alleviating dysphagia in ≥90% of patients; most are able to tolerate at least liquids following stent placement.270–272 However, the collective experience gathered from prospective randomized trials has shown SEMS to be associated with fewer procedure-related complications (10%–43% vs 0%–16%), shorter hospital stays, and trends toward better quality of life and survival.269–274 Although SEMS are more expensive than plastic semirigid stents, this cost difference was not found to be significant in the overall management of dysphagia.274

A self-expanding plastic stent (Polyflex; Boston Scientific Inc, Natick, MA) has been approved by the FDA for palliation of malignant dysphagia and, more recently, for benign disease. The potential advantage is its removability, but it is priced similar to available SEMS. Initial studies have shown the Polyflex stent to be efficacious in relieving malignant dysphagia.275–278 Prospective randomized trials, however, are needed to assess the cost-effectiveness of self-expanding plastic stents versus SEMS.

Three FDA-approved SEMS are currently available in the United States. These SEMS differ in design and delivery systems, with additional refinements for particular indications (Table 7). The Esophagcoil stent (Medtronic InStent Inc, Eden Prairie, MN) is no longer commercially available. Endoscopic placement of SEMS can be performed with or without the assistance of fluoroscopy.279,280 The majority of SEMS currently in use are partially covered with a thin silicone or polyurethane membrane to prevent tumor ingrowth. In a prospective randomized study of 62 patients, membrane-covered stents offered significantly better palliation than uncovered stents due to decreased rates of tumor ingrowth (3% vs 30%) and decreased need for endoscopic reinterventions (0% vs 27%) for recurrent dysphagia.281 Covered stents, however, tend to migrate more frequently than uncovered ones (26% vs 0%), particularly when placed in the distal esophagus.282 Modifications in design, such as the conical-shaped Flamingo Wallstent and Ultraflex stent with proximal flaring, have improved anchoring of stents to tissue and have made covered SEMS more
migration resistant. These 2 stents have been used successfully for palliation of distal esophageal cancers with an overall migration rate of 6%. There are limited prospective randomized studies comparing various SEMS for palliation of malignant dysphagia. In a study of 100 patients, success rates in alleviating dysphagia were similar among patients who received the Z-stents, Flamingo Wallstents, or Ultraflex stents. Although complication rates were higher in the Z-stents group (36%) than in the Ultraflex or Flamingo Wallstent groups (24% and 18%, respectively), these differences did not reach statistical significance. In a study of 53 patients, Flamingo Wallstents and Ultraflex stents were equally effective at palliating dysphagia with similar complication rates. There are as yet insufficient data that convincingly show the superiority of one SEMS over another. Currently, the choice for a particular SEMS primarily depends on device availability, familiarity, and personal preference.

Types and rates of SEMS-related complications vary widely among studies. Results of a national survey and review of complications from compiled case series showed immediate technical complication rates of 5%–17%, including misplacement (0.3%–5%), failed expansion (4%–7%), failed deployment (1%–3%), and migration (0.3%–2%). Immediate patient complications occurred in 7%–15% of cases, including chest pain (6%–12%), bleeding (0.2%–0.6%), perforation (0.6%–1%), and death (0.5%–1.4%). Delayed technical complications occurred in 9%–18% of cases, including tumor ingrowth/overgrowth (6%–11%) and stent migration (3%–7%). Delayed patient complications occurred in up to 27% of patients, including reflux symptoms (4%–5%), recurrent dysphagia (8%–9%), tracheoesophageal fistulas (1%–3%), bleeding (0.5%–4%), perforation (0.5%–0.8%), and death as a result of underlying malignancy occurring within 30 days (7%).

Tumor ingrowth or overgrowth causing recurrent dysphagia can be managed by placement of another stent or tumor ablation using a variety of endoscopic modalities, including laser therapy, argon plasma coagulation therapy, and PDT. Care must be taken to avoid damaging the indwelling stent when thermal modalities are used.

There are conflicting reports on whether stent-related morbidity is increased in patients who have been treated previously with radiation and/or chemotherapy. Some studies have shown an increased rate of stent-related life-threatening complications in patients who have had prior chemoradiation therapy, whereas others have not. Data are limited regarding the use of palliative chemoradiation therapy after insertion of stents. In a small study of 29 patients, the group of patients undergoing chemoradiation therapy following stent placement survived longer (median, 331 days vs 157 days; P = 0.05) than the stent-only group. On the other hand, a high risk of major complications was noted in patients undergoing radiotherapy after stent placement. The major complications found were creation of a tracheal-esophageal fistula and massive hematemesis from stent erosion into the aorta. Placement of SEMS before radiation therapy should be performed with caution. Comparisons between available studies are difficult because of differences in types of stents used and study designs.

Stents are ideal for obstructing midesophageal cancers. Following stent placement, patients are advised to modify their diet and avoid solid boluses (e.g., meat and bread) that could potentially become impacted within the stent. Stents that straddle the esophagogastric junction may lead to severe reflux symptoms. Therefore, strict antireflux lifestyle precautions and administration of antisecretory medications (i.e., proton pump inhibitors) are required. Clinical experience with the recently intro-

<table>
<thead>
<tr>
<th>FDA-Approved SEMS</th>
<th>Ultraflex</th>
<th>Wallstent II</th>
<th>Z-Stent</th>
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<tr>
<td>Material</td>
<td>Nickel titanium (nitinol)</td>
<td>Elgiloy</td>
<td>Stainless steel</td>
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<td>Design</td>
<td>Mesh</td>
<td>Mesh</td>
<td>Zigzag</td>
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<tr>
<td>Covered</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Radial force</td>
<td>+</td>
<td>+ + +</td>
<td>+ +</td>
</tr>
<tr>
<td>Delivery system (F)</td>
<td>16</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>10, 12, 15</td>
<td>10, 15</td>
<td>8, 10, 12, 14</td>
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<td>Flare-end diameter (mm)</td>
<td>23, 28</td>
<td>28</td>
<td>25</td>
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<tr>
<td>Shaft diameter (mm)</td>
<td>18, 23</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Degree of shortening (%)</td>
<td>30–40</td>
<td>30</td>
<td>0–10</td>
</tr>
<tr>
<td>Fistula closure</td>
<td>Yes</td>
<td>Yes</td>
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</table>

Adapted and reprinted with permission from Baron. aMicrovasive/Boston Scientific Inc (Natick, MA). bWilson-Cook Medical (Winston-Salem, NC).
duced Dua stent (Z-stent with a windsock-like antireflux valve) is limited, but the device seems beneficial in palliating dysphagia and controlling reflux in patients with distal esophageal cancers.\textsuperscript{298,299} Stenting of esophageal cancers in proximity of the upper esophageal sphincter can be problematic, although tumors involving the cervical esophagus occur in <5% of all patients.\textsuperscript{300} Small case series have reported successful placement of SEMS to palliate cancers within 2 cm of the upper esophageal sphincter, although this can be technically challenging.\textsuperscript{292,301} Complications may include foreign body sensation, oropharyngeal aspiration, and tracheal compression with airway compromise.\textsuperscript{285} Stent placement in this setting should only be attempted by an experienced operator, or alternative modalities should be considered.

Stents can be effective for palliating dysphagia secondary to malignant extrinsic compression. Covered stents can also be used to treat malignant tracheoesophageal fistulas and constitute a unique advantage over other endoscopic modalities in this setting. Covered SEMS are considered a primary form of therapy for this ominous condition. Successful closure of malignant tracheoesophageal fistulas using covered SEMS is seen in 90%–100% of patients.\textsuperscript{295,299,301,302} Patients with persistent tracheoesophageal fistulas despite esophageal stenting may benefit from airway stenting (double stenting) to close the fistula\textsuperscript{303} or esophageal bypass in surgically fit patients.\textsuperscript{304} Malignant esophageal obstruction associated with perforation during endoscopic procedures may be palliated successfully with covered SEMS.\textsuperscript{305}

Intratumoral injection of absolute alcohol results in tissue necrosis and sloughing. The technique is cheap, widely available, and relatively simple to perform. The sclerosant is typically injected in 0.5- to 1-mL aliquots using a standard sclerotherapy needle, targeting exophytic parts of the tumor. Experience accrued from case series shows an initial success rate of 80%–100% in improving dysphagia. However, the palliative effect is short-term (<1 month), and repeated sessions are usually required in most patients.\textsuperscript{306–310} Chest pain is common after therapy. Serious complications, including mediastinitis and tracheoesophageal fistulas, occur in up to 5% of cases.\textsuperscript{308} Standardized dosimetry and local control of therapy are problematic due to leaking at the injection site or tracking of the sclerosant along tissue planes. Alcohol injection is probably best reserved for short, protuberant, and nonfibrotic tumors that are not amendable to other endoscopic palliative therapies. Preliminary reports of intratumoral injection of cisplatin/epinephrine gel have shown limited and short-lived efficacy of the locally administered chemotherapeutic agent in relieving dysphagia.\textsuperscript{311,312} This form of injection therapy remains experimental at this time.

Similar to injection therapy, short exophytic tumors are more conducive to thermal modalities, which include bipolar electrocoagulation, argon plasma coagulation, and laser therapy. The use of bipolar electrocautery (BICAP probe) for esophageal tumor ablation has been described but made unpopular by more user-friendly and equally effective thermal modalities such as the Nd:YAG laser.\textsuperscript{313–315}

Argon plasma coagulation therapy is a form of noncontact monopolar electrocautery delivered to tissue via ionized, electrically conductive argon gas. Palliation of dysphagia can initially be achieved in most patients with inoperable cancer, but the median range between reinterventions is approximately 1 month, with an average of 5 treatment sessions per patient.\textsuperscript{316} Despite the limited depth of injury achieved by argon plasma coagulation (~2 mm), perforations have been reported to occur in 1%–2% of treatments. In one study, one third of the patients eventually required esophageal stenting as an alternative mode of palliative therapy.\textsuperscript{316} There is limited benefit in treating advanced bulky tumors with argon plasma coagulation. On the other hand, argon plasma coagulation may be helpful in controlling tumor bleeding and in staving off tumor ingrowth or overgrowth associated with metal stents.

The Nd:YAG laser causes deeper injury than argon plasma coagulation because it vaporizes tissue to recanalize the obstructed lumen. Short-segment exophytic lesions are ideal for laser therapy. The procedure is usually repeated 48 hours later for further treatment and debridement. Laser application is preferably performed in a retrograde fashion, which usually requires prelaser dilatation for passage of the endoscope through the obstructed lumen.\textsuperscript{317} Tumors that are close to the upper esophageal sphincter may be more amenable to laser therapy than stenting. However, laser therapy is less successful than stenting for tumors involving the esophagogastric junction and cardia.\textsuperscript{318} Laser therapy is 70%–95% effective at relieving dysphagia.\textsuperscript{317,319,320} The duration of response ranges from 1 to 2 months, but multiple sessions are usually required due to tumor regrowth.\textsuperscript{321} Response can be enhanced by external beam radiation or brachytherapy.\textsuperscript{322–324} Minor complications of laser therapy include chest pain, transient worsening of dysphagia from treatment-related edema, and leukocytosis. Major complications include bleeding, perforation (0%–5%), and tracheoesophageal fistula (0%–6%). Laser equipment is expensive and may not be widely available. Unlike stenting, laser therapy is contraindicated in the presence of fistulas; is generally not suitable for long, tortuous, cir-
cumferentially narrowed tumors; and is not applicable for dysphagia caused by malignant extrinsic compression.

PDT has also been applied as a palliative technique for the management of malignant dysphagia.\textsuperscript{325,326} PDT is not limited to bulky tumors; infiltrative or flat tumoral areas as well as long-segment tumors may be amenable to PDT. In addition, PDT using sodium porfimer may be easier to apply in cervical esophageal cancers than laser therapy or stenting. The response rate in dysphagia improvement ranges from 60% to 90%. Acute complications (5%–20%) include chest pain, odynophagia, nausea, fever, leukocytosis, and pleural effusion.\textsuperscript{359} A major obstacle to the use of sodium porfimer/PDT in advanced esophageal cancers is the duration of skin photosensitivity (4–6 weeks) associated with the therapy. This is a significant problem in a palliative setting. Costs related to initial purchasing of equipment and photosensitizers are additional drawbacks. PDT using aminolevulinic acid is attractive because of its limited duration of photosensitivity (48 hours), but this therapy has more limited depth of tissue necrosis. PDT with hematoporphyrin derivative (which is a compound similar to sodium porfimer) was significantly more effective than aminolevulinic acid in a nonrandomized study of 49 patients.\textsuperscript{327} Sodium porfimer is the only currently approved photosensitizer for gastrointestinal use in the United States.

Studies comparing various endoscopic modalities for palliation of malignant dysphagia are few and conflicting. Retrospective studies comparing laser therapy with stenting have shown similar outcomes with regard to relief of dysphagia but higher complication rates in the stent group.\textsuperscript{328,329} These studies are limited by their retrospective design and heterogeneous patient populations. On the other hand, a prospective, randomized, controlled trial of laser therapy versus SEMS in 60 patients with previously untreated esophageal cancer demonstrated a significant improvement in the degree of dysphagia and a reduction in the reintervention rate (35.7% vs 100%) in favor of SEMS.\textsuperscript{282} A smaller prospective randomized study of 39 patients evaluating SEMS versus laser therapy combined with radiotherapy showed the former to be more cost-effective.\textsuperscript{330} A study of 65 patients, however, showed longer survival rates in patients undergoing thermal ablative therapy (laser predominantly) compared with those who received stenting.\textsuperscript{331} Stenting cost less but was associated with a greater deterioration of health-related quality of life. In 2 small prospective randomized trials comparing laser therapy with injection therapy, no significant differences were noted with regard to improvement in dysphagia score or complication rates.\textsuperscript{332,333}

In a prospective randomized study involving 236 patients, PDT and laser therapy were similarly efficacious in terms of dysphagia relief, although there was a trend toward a better response with PDT for tumors located in the upper and middle third of the esophagus and for long tumors.\textsuperscript{325} PDT was associated with fewer perforations than with laser therapy (1% vs 7%). However, PDT was limited by photosensitivity in 19% of cases. Termination of sessions due to adverse events occurred in 3% with PDT versus 19% with laser therapy.

Nutritional support is often required in support of patients with esophageal carcinoma. There is evidence that enteral nutrition is beneficial in patients with dysphagia and in those receiving radiation therapy.\textsuperscript{334} Enteral nutrition is generally preferred to the parenteral approach. A randomized prospective study was performed using these 2 approaches in patients who underwent surgery for gastrointestinal tumors.\textsuperscript{335} Although only 10% of the 257 patients had esophageal cancer, the results showed that enteral nutrition was less expensive and improved gut perfusion. Enteral nutrition can be accomplished by feeding tubes that can be placed with nasogastric or nasojejunal approaches, although these types of tubes are associated with increased bodily concerns by patients and could limit their social interactions.\textsuperscript{336} Percutaneous gastrostomy or jejunostomy tubes are preferred because there is less social stigma and the tubes are better tolerated. A retrospective study of percutaneous gastrostomy tubes in 229 patients with esophageal cancer found that they could be placed in 97% of patients, although dilation was required in 45% of patients, with 2 having fatal adverse events from perforations.\textsuperscript{337} Although only anecdotal, radiologists have advocated radiologic placement of feeding tubes in patients with oropharyngeal cancers to decrease the possibility of stomal metastasis.\textsuperscript{338}

Finally, palliative care of patients with esophageal cancer requires the involvement of physicians who are attentive to both physical and emotional needs. Dysphagia is a symptom that has significant impact on a patient’s perception of health, as demonstrated in a recent study of health state utilities in 50 patients with esophageal cancer.\textsuperscript{339} Many patients feel abandoned by physicians after medical therapy has been unsuccessful and further interventions are no longer indicated. These patients require support from hospice personnel and deserve physician attention and compassion. Until esophageal cancer can be effectively treated, compassion may be one of the most important “therapies” we can offer for palliation of this disease.

Summary of Evidence—Endoscopic therapy is effective at alleviating dysphagia. However, the selection of a
particular endoscopic technique should be based on tumor characteristics, patient preference, and available expertise. Esophageal dilation results in short-lived palliation and is best used as an adjunct to other palliative modalities (based on level III evidence). Esophageal stenting is the preferred endoscopic modality in patients with long malignant strictures more than 2 cm from the upper esophageal sphincter and/or with fistulas (also based on level III evidence). There is level I evidence that SEMS are superior to conventional semirigid plastic stents in the management of malignant dysphagia. Other palliative methods such as alcohol injection, laser therapy, and PDT are similarly efficacious as tumor ablative therapies (based on level II evidence).

**Future Directions**

It is clear that further research is needed in the detection, prevention, and treatment of esophageal carcinoma. The cause of the continued increase in incidence of adenocarcinoma of the esophagus still remains undefined. The need to stratify patients for esophageal cancer risk is essential to implement treatment and prevention strategies. Although histologic evidence of dysplasia has been the gold standard to define cancer risk, this is very hard to reproduce and is difficult to detect without laborious biopsy protocols. Biomarkers for cancer risk would be very attractive but will require large prospective studies to validate. Chemoprevention would be a viable strategy for patients at lower risk for development of cancer, and NSAIDs might a fruitful candidate. However, due to the low risks for cancer, very large patient trials will be required to demonstrate benefit. In patients at high risk for cancer, ablative therapies have been applied with some initial promising results. The clinical significance of reduction of the amount of Barrett’s mucosa, elimination of dysplasia, and development of submucosal areas of Barrett’s mucosa needs to be defined. The detection and staging of esophageal cancers could be improved with the advent of higher-resolution imaging modalities such as OCT and fluorescence spectroscopy. Both of these entities require further development before they can be clinically applied. Endoscopic therapy of early cancers seems to be achievable, but large prospective studies are needed to define the best methods and to determine the long-term outcome. Surgical therapy is evolving toward less invasive approaches, but improvements in chemotherapy and radiation might decrease the need for resection in advanced cancers. Palliation is required for the majority of patients with esophageal cancer, and the development of newer stents that prevent reflux and conform better to the esophagus would be beneficial to patients.

**Summary**

Esophageal cancer is increasing in incidence and is associated with a high mortality rate. The ability of gastroenterologists to increase survival in this disease will depend on earlier detection through screening and surveillance strategies. Early cancers can be staged with EUS and endoscopic mucosal resection. More advanced cancers will require the addition of CT and possible PET. Treatment of early cancers is increasingly shifting toward endoscopic treatment. More advanced but localized cancers can be treated by surgical resection. Cancers with regional lymphadenopathy may require neoadjuvant chemotherapy and radiation therapy. Patients with more advanced cancers may respond to primary therapy with radiation and chemotherapy. Palliation of esophageal cancers is based on stent therapy, but physicians should be attentive to the emotional needs of the dying patient. The future of therapy for esophageal cancer may rest with the development of chemoprevention methods, although there is not substantial evidence to support its use at this time.

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