

PRACTICE GUIDELINES

Updated Guidelines for the Diagnosis, Surveillance, and Therapy of Barrett's Esophagus

Richard E. Sampliner, M.D., and

The Practice Parameters Committee of the American College of Gastroenterology

Southern Arizona VA Health Care System, Tucson, Arizona

PREAMBLE

Guidelines for the diagnosis and treatment of Barrett's esophagus were published by the American College of Gastroenterology in 1998 (1). These and other guidelines undergo periodic review. Significant advances have been made in the area of Barrett's esophagus over the past several years, leading us to review and revise our previous guidelines statements. These advances have included more information on the natural history of high-grade dysplasia and the chronic use of proton pump inhibitors. These and the original guidelines are intended to apply to all physicians who address Barrett's and are intended to indicate the preferable, but not only acceptable, approach. Physicians must always choose the course best suited to the individual patient and the variables that exist at the moment of the decision. These guidelines are intended to apply to adult patients with the diagnosis of Barrett's esophagus defined in the guidelines.

Both these and the original guidelines were developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. The world literature was reviewed extensively for the original guidelines and was once again reviewed using the National Library of Medicine database. All appropriate studies were reviewed, and any additional studies found in the reference list of these papers were obtained and reviewed. Evidence was evaluated along a hierarchy, with randomized controlled trials given the greatest weight. Abstracts presented at national and international meetings were only used when unique data from ongoing trials were presented. When scientific data were lacking, recommendations were based on expert consensus. During preparation, the guidelines were reviewed by the American Gastroenterological Association and the American Society for GI Endoscopy. Recommendations and comments obtained from these reviews were incorporated into the final document whenever possible.

DEFINITION OF BARRETT'S ESOPHAGUS

(No change) *Barrett's esophagus is a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by*

biopsy of the tubular esophagus and excludes intestinal metaplasia of the cardia.

The current definition of Barrett's identifies individuals in whom the abnormal epithelium can be identified at endoscopy and in whom surveillance endoscopy and biopsy are appropriate. The definition of Barrett's esophagus has evolved over the last 2 decades from the columnar-lined esophagus (2), to 3 cm of columnar lining or intestinal metaplasia in the esophagus (3), to the requirement for intestinal metaplasia in the esophagus without specification of length.

Adenocarcinoma of the esophagus continues to be the most rapidly rising incidence cancer in the United States (4, 5). Intestinal metaplasia of the esophagus is the premalignant lesion for adenocarcinoma of the esophagus and the esophagogastric junction. The vast majority of adenocarcinomas of the esophagus are accompanied by intestinal metaplasia (6–10), and many adenocarcinomas of the esophagogastric junction are associated with esophageal intestinal metaplasia (11–13).

There has been a recent focus on "short-segment" Barrett's esophagus—intestinal metaplasia in the distal esophagus <3 cm in length (14–16).

There is increasing evidence that the physiological abnormalities—esophageal pH exposure and lower esophageal sphincter pressure—in short-segment Barrett's are less severe than in long-segment Barrett's but are qualitatively similar (17, 18). Short-segment Barrett's was arbitrarily excluded in older definitions of Barrett's esophagus that did not include histological criteria. Short-segment Barrett's esophagus needs to be distinguished from intestinal metaplasia of the gastric cardia, a lesion of the stomach that cannot be seen on routine endoscopy, with less well-defined epidemiology and significance (19–21). Importantly, dysplasia is more common in short-segment Barrett's than intestinal metaplasia of the gastric cardia (22).

SCREENING FOR BARRETT'S ESOPHAGUS IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE (GERD)

(Old) *Patients with long-standing GERD symptoms, particularly those >50 yr of age, should have upper endoscopy to detect Barrett's.*

(New) Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy.

The major reason to evaluate patients with chronic symptoms of GERD is to recognize Barrett's esophagus (see American College of Gastroenterology guidelines for GERD) (23). Unfortunately, the epidemiology of Barrett's is incompletely described. However, we know from series of surgical resections of adenocarcinoma of the esophagus associated with Barrett's esophagus that white men overwhelmingly predominate (6–10). Additionally, there are data suggesting that the longer the duration of reflux symptoms, the higher the prevalence of Barrett's esophagus at the time of upper endoscopy (24, 25). In one population-based study, the severity of reflux symptoms was correlated with the risk of esophageal adenocarcinoma (26). Some experts recommend a one-time endoscopy to exclude Barrett's during the lifetime of a patient with GERD (1, 27). The specific timing of this endoscopy by patient age and duration of symptoms is not yet defined. The age threshold for initial endoscopy is being reevaluated (28).

The factors of gender, race, and age can be used to determine the threshold for endoscopy in patients with GERD to screen for the presence of Barrett's. The highest yield of Barrett's esophagus would be expected in white men with chronic symptoms of GERD. However, the specific criteria to select patients to screen for Barrett's are not yet defined.

The recognition of asymptomatic individuals with Barrett's esophagus remains a problem. Such people may account for the higher number of patients presenting with cancer and Barrett's (prevalence cases) than patients with Barrett's developing adenocarcinoma (incidence cases) in published series (29). Asymptomatic Barrett's highlights the need to assess the distal esophagus carefully in all patients undergoing upper endoscopy for any indication.

THE DIAGNOSIS OF BARRETT'S ESOPHAGUS

(No change) The diagnosis of Barrett's esophagus requires systematic biopsy of the abnormal-appearing esophageal mucosa to document intestinal metaplasia and to detect dysplasia.

At the time of endoscopy, when "gastric-appearing mucosa" or apparent "columnar-lined esophagus" is evident, multiple biopsies are indicated to detect intestinal metaplasia. For the recognition of Barrett's esophagus, it is essential to specifically identify the squamocolumnar junction and the esophagogastric junction. When the squamocolumnar junction is displaced proximal to the esophagogastric junction, then Barrett's esophagus may be present. Erosive esophagitis or erythema of the esophagus may be confused visually with Barrett's esophagus. This is one reason that biopsy is so essential in making a diagnosis of Barrett's esophagus. Erosive esophagitis may impair the recognition of Barrett's esophagus, necessitating re-endoscopy to rule out Barrett's

(30, 31) after treating with acid suppression therapy. This scenario provides the rationale for evaluating a patient after reflux symptoms are controlled with therapy.

As a group, patients with Barrett's esophagus have a very low lower esophageal sphincter pressure (17, 32). This may make recognition of the end of the esophagus difficult. The proximal margin of the gastric folds within a hiatal hernia when the distal esophagus is deflated serves as a marker for the end of the esophagus and the location of the esophagogastric junction (1, 33).

A variety of endoscopic staining techniques have been used to enhance the recognition of Barrett's esophagus. Vital stains used include Lugol's iodine (34), toluene blue (35), indigo carmine (36), and methylene blue (37, 38). Methylene blue may be the most promising technique with evidence that Barrett's can be diagnosed with fewer biopsies with targeting of the stained mucosa and in increased yield of short-segment Barrett's (39). Staining can be tedious, can prolong the procedure time, and may not be reproducible by all endoscopists.

Magnification endoscopy may improve the recognition of Barrett's (40, 41) by enhancing the recognition of mucosal detail and identifying high-yield sites for biopsy.

The number of biopsies necessary to detect intestinal metaplasia has not been defined. The more biopsies taken, the greater the likelihood of recognizing intestinal metaplasia. The greater the length of abnormal-appearing esophagus, the higher the yield of intestinal metaplasia by biopsy (39, 42). The recognition of intestinal metaplasia on biopsy, *i.e.*, specifically goblet cells, is increased by the use of alcian blue stain at pH 2.5 (43). This will decrease the chance of missing the presence of goblet cells or of misinterpreting cells with cystic structures in the cytoplasm as goblet cells. If the endoscopist suspects Barrett's esophagus, biopsy of the lesion at the time of endoscopy is essential for the recognition of dysplasia. Dysplasia is a change in the cytology and architecture of the metaplastic glands that is the first step in the neoplastic process.

SURVEILLANCE OF BARRETT'S ESOPHAGUS

(Old) Patients with Barrett's esophagus should undergo surveillance endoscopy and biopsy at an interval determined by the presence and grade of dysplasia.

(New) The grade of dysplasia determines the endoscopy interval, and an abnormal epithelial surface such as a nodule or ulcer requires special sampling attention. Surveillance endoscopy intervals are lengthening in the absence of dysplasia on two consecutive endoscopies with biopsy—a 3-yr interval is appropriate.

The rationale for surveillance in Barrett's esophagus is based on the increased risk of developing adenocarcinoma and the fatal nature of this cancer. Preliminary data suggest that esophageal adenocarcinoma detected by surveillance is at an earlier stage with a more favorable survival than carcinoma detected at the time of the diagnosis of Barrett's,

typically when patients present with dysphagia (44–46). In contrast, the low incidence of adenocarcinoma is used to support an approach of not surveying patients with Barrett's esophagus. A cohort study of patients with Barrett's esophagus not undergoing surveillance demonstrated that esophageal cancer was an uncommon cause of death—2.5% of the deaths of 155 patients followed a mean of 9 yr (47). The follow-up of a smaller cohort of Barrett's patients comes to a similar conclusion, although 9% of the patients died from esophageal cancer (48).

Patients with short-segment Barrett's esophagus can develop dysplasia (49, 50) and cancer (51–53), the incidence of the development of cancer in these patients is not fully defined. In a series that may not have been adequately powered to detect a difference, patients with short-segment Barrett's esophagus had the same incidence of cancer as patients with long-segment Barrett's esophagus (53). This provides a rationale for surveillance of patients with short-segment Barrett's esophagus.

The goal of surveillance in patients with Barrett's esophagus is the detection of dysplasia and early cancer. Dysplasia occurs on the background of metaplasia—a fundamental and distinctive change in the epithelium of the esophagus from one differentiated cell type to another. Dysplasia represents the final step of neoplasia and is characterized by cytological and architectural changes. Dysplasia is the best current indicator of the risk of cancer. The grading of dysplasia in Barrett's esophagus is based on the system developed for ulcerative colitis (54).

Observer variation in the grading of dysplasia is a problem. Interobserver agreement is in the range of 85% when separating high-grade dysplasia and intramucosal carcinoma from low-grade dysplasia, indefinite for dysplasia and negative (55). The reproducibility of the diagnosis of dysplasia has been recently researched using kappa (κ) statistics (56). Interobserver agreement for no dysplasia, indefinite, and low-grade dysplasia *versus* high-grade dysplasia and carcinoma was substantial ($\kappa = 0.7$ —a κ of 1 means complete agreement) and for four grades—no dysplasia, indefinite, and low-grade dysplasia, high-grade dysplasia, and carcinoma, moderate ($\kappa = 0.46$). It is important to realize that dysplasia is a first step in the neoplastic process and that any grade of dysplasia may overlie or may be adjacent to a frank carcinoma. Therefore, the reading of dysplasia of any grade on a biopsy warrants a repeat endoscopy and intensive biopsy of the area with dysplasia to rule out coexisting carcinoma, with attention given to maximum acid suppression before rebiopsy.

Patients with Barrett's esophagus are candidates for surveillance if there is a potential to prolong life expectancy with a therapeutic intervention for early cancer. Therefore, age and comorbid conditions are important factors to weigh. Documentation of efficacy of promising endoscopic eradication technologies may make more patients eligible for surveillance (57–61) because endoscopic therapy may be applicable to patients whose functional status and/or major

Table 1. Grade of Dysplasia and Development of Esophageal Adenocarcinoma

Dysplasia (%)	n	Cancer (%)
None	382	9 (2)
Low grade	72	5 (7)
High grade	170	37 (22)

A total of 783 patients followed a mean of 2.9–7.3 yr (61–65).

cardiopulmonary disease might preclude resectional surgery.

The appropriate surveillance intervals for patients with Barrett's esophagus are a function of the grade of dysplasia (Table 1). However, the published database of the natural history of dysplasia is limited to five centers that have performed prospective studies (62–66) and one registry (67). A total of 783 patients have been followed for 2.7–7.3 yr. Nine of 382 (2%) patients have been followed from no dysplasia to cancer. Five of 72 (7%) patients have been followed from low-grade dysplasia to cancer. Recently, it has been demonstrated that low-grade dysplasia is commonly a “transient” finding. In a series of 34 patients who had low-grade dysplasia, 73% had no evidence of dysplasia on at least one subsequent surveillance endoscopy (68). If two experienced GI pathologists agreed on the diagnosis of low-grade dysplasia, there was a significant association with progression to high-grade dysplasia or cancer (69). In contrast, 37 of 170 (22%) patients with high-grade dysplasia have progressed to cancer.

Unfortunately, it is not always possible to determine the length of follow-up of patients with different grades of dysplasia. Not knowing the percent progressing to cancer over a specific time interval limits the usefulness of the information. Furthermore, uniform criteria and exclusion of prevalence cancers have not been applied. For example, eliminating the cancers that developed in the first year, a common criterion for prevalence (*versus* incidence) cancers would exclude an estimated 15 of 33 cancers from one series (64). In this same series, the cumulative 5-yr incidence of cancer drops from 59% to 31% by analyzing only the incident high-grade dysplasia patients. The latter analysis presumably reduces the referral bias. By adjusting the data in this manner, the apparently broad range of cancer incidence is dramatically narrowed from 16% to 59% to 16% to 24%! This estimate is substantiated by a recently published retrospective series of patients with high-grade dysplasia (69). After eliminating the first 6-month prevalence cancers, 16% of 86 patients developed cancer over an approximate 3-yr interval.

Another variable commonly not defined in series of high-grade dysplasia is mucosal nodularity. This feature increases the risk of cancer 2.5 times ($p = 0.01$) (69). After adjusting for nodularity, patients with diffuse high-grade dysplasia had a 3.7-times increased risk of cancer compared with patients with focal high-grade dysplasia—five crypts or less involved in one biopsy specimen from the entire set of biopsies ($p = 0.02$).

Table 2. Graded Dysplasia and Proposed Surveillance

Dysplasia	Documentation	Follow-Up Endoscopy
None	Two EGDs with biopsy	3 yr
Low grade	Highest grade on repeat	1 yr until no dysplasia
High grade	Repeat EGD with biopsy to rule out cancer/document high-grade dysplasia, expert pathologist confirmation	Focal—every 3 mo Multifocal—intervention Mucosal irregularity—EMR

EGD = esophagogastroduodenoscopy; EMR = endoscopic mucosal resection.

Mucosal nodularity offers the opportunity for endoscopic mucosal resection (70, 71). This results in the capability of assessing more tissue than obtained with endoscopic biopsy and to more accurately identify and stage early cancer.

Surveillance endoscopy and biopsy intervals are lengthening as the database on the outcomes of dysplasia increases. Surveillance of Barrett's esophagus patients lacking dysplasia with a systematic biopsy protocol at two endoscopies may be extended to a 3-yr interval (Table 2).

THE MANAGEMENT OF DYSPLASIA

In patients with low-grade dysplasia as the highest grade after a follow-up endoscopy with concentrated biopsies in the area of dysplasia, annual endoscopy is recommended until there is no dysplasia. The finding of high-grade dysplasia requires a repeat endoscopy with special attention to any mucosal irregularity potentially including endoscopic mucosal resection. An intensive biopsy protocol ideally with a therapeutic endoscopic and large capacity biopsy forceps should be performed. An expert pathologist should confirm the interpretation of high-grade dysplasia. Focal high-grade dysplasia (less than five crypts) may be followed with 3-month surveillance. Intervention may be considered in a patient with confirmed multifocal high-grade dysplasia.

The treatment of high-grade dysplasia is controversial, especially with the recognition of the lower risk of progressing to cancer, particularly if the high-grade dysplasia is focal. High-grade dysplasia may be present only intermittently or may regress to low grade even over a long-term follow-up (64). Although esophagectomy is commonly recommended for patients with high-grade dysplasia (72, 73), given the morbidity of this procedure, the mortality at low-volume institutions (74), and the variability of the natural history of high-grade dysplasia, caution is justified. Esophagectomy at a high-volume institution remains a reasonable strategy in the surgically fit patient with recurrent diffuse high-grade dysplasia confirmed by an expert GI pathologist.

An intensive biopsy protocol may be successful at endoscopically differentiating high-grade dysplasia from cancer (75). The surgical literature contrasts with this experience. Of 126 cases with high-grade dysplasia alone by endoscopic biopsy, 41% had cancer at the time of esophagectomy (76, 77). These studies did not follow a uniform endoscopic

biopsy protocol, yet the majority of cancers were early stage, with a more favorable patient survival.

The goal of surveillance is to decrease the mortality from adenocarcinoma so that intervention before frank cancer, which has the risk of metastasis, is reasonable. The precise threshold for intervention needs to be individualized and agreed upon after a formal discussion of the concerned clinician with the concerned patient. These discussions may include the therapeutic endoscopist and the surgeon. The recent excellent outcomes of expert surgeons resecting early adenocarcinoma in Barrett's esophagus need to be taken into account. In the 16–26% of cancers that are early, the 5-yr survival exceeds 80% and ranges up to 90% (78–82).

The details of surveillance endoscopy are important. Before surveillance biopsies, patients with GERD should be treated so that mucosal healing is achieved. Active inflammation can result in cellular atypia that can be misinterpreted as dysplasia. The technique of four-quadrant biopsies taken every 2 cm of the Barrett's segment has been described (83). Multiple biopsies are necessary because of the often focal nature of dysplasia and cancer in these patients. Systematic biopsies need to be taken of the normal-appearing Barrett's epithelium. Additionally, specific biopsies need to be taken of any mucosal abnormality including erosion, ulcer, nodule, and stricture.

Recently, this four-quadrant biopsy protocol has been applied every 1 cm in the setting of high-grade dysplasia (84). This results in multiple biopsies (average 35), which require an additional person for handling and a prolonged procedure time that may last up to 90 min. The personnel and duration may not be feasible in the clinical setting. A 2-cm protocol missed 50% of the cancers detected by a 1-cm protocol in Barrett's segments 2 cm or longer without visible lesions. Sixty-nine percent of the cancers were detected in a single endoscopic biopsy specimen. In these cases, an average of 17.6 biopsies per 1-cm interval were taken, and surgical pathology detected cancer in only 39% of the esophagectomy specimens (84). This is a level of research endoscopy that is not practical in the clinical setting.

Biological and genetic markers have been intensively studied in Barrett's esophagus in an effort to better understand carcinogenesis. Enzymes (85), proliferation indices (86, 87), DNA content abnormalities (88–90), genetic mutations (91–93), and growth factors (94, 95) have been

investigated. Most recently, cyclooxygenase-2 expression has been documented to be elevated in Barrett's esophagus and Barrett's adenocarcinoma (96–98).

Single-center studies have documented the predictive value of flow cytometric abnormalities and 17p loss of heterozygosity (LOH) (99). Flow cytometry detects abnormal DNA content of cells, and LOH is a mechanism that inactivates the p53 cell cycle control. In 322 patients with Barrett's esophagus, the relative risk of cancer in patients with increased 4 N (7.5×) or aneuploidy (5×) was significantly greater than in patients without these abnormalities (100). Combining histology and cytometric results of 247 patients with negative, indefinite, or low-grade dysplasia, the cumulative cancer incidence at 5 yr was 0 (95% CI = 0–4.7) (100). Confirming the predictive value of this combination of results would enable the extension of surveillance intervals in these patients. Similar results were found in a smaller study—none of the 17 patients who remained diploid progressed to dysplasia or cancer (101).

Similarly, in 269 patients with Barrett's esophagus, 17p (p53) LOH identified patients at increased risk of progression to adenocarcinoma—3-yr cumulative incidence of cancer 38% versus 3.3% for patients with two 17p alleles (99). The validity of these markers needs to be documented in multicenter long-term follow-up studies of cohorts with Barrett's esophagus.

THE THERAPY OF PATIENTS WITH BARRETT'S ESOPHAGUS

(Old) *The goals of therapy of Barrett's esophagus are the same as for GERD (see American College of Gastroenterology guidelines): the control of symptoms of GERD and the maintenance of healed mucosa. The diagnosis of Barrett's does not lead to specific therapy.*

(New) *The goals of therapy of Barrett's esophagus are the same as for GERD (see American College of Gastroenterology guidelines): the control of symptoms of GERD and the maintenance of healed mucosa.*

The goal of therapy of Barrett's esophagus should be the control of symptoms of GERD. A subgroup of patients may still have regurgitation despite control of esophageal acid exposure (102). These patients, as well as those with extraesophageal manifestations, may warrant antireflux surgery. As a group, patients with Barrett's have greater esophageal acid exposure than other GERD patients (103, 104), and control of symptoms may require higher than usual doses of proton pump inhibitors (105, 106). If once-a-day dosing of a proton pump inhibitor fails to control symptoms, then increasing the dose to *b.i.d.* is rational given the pharmacology of the effect on the parietal cell.

Patients who are appropriate surgical candidates may elect antireflux surgery. Fundoplication effectively controls reflux symptoms in most patients (107, 108) but uncom-

monly leads to elimination of the premalignant epithelium (109).

Patients with Barrett's esophagus may be found incidentally and may deny symptoms of reflux. There is suggestive evidence that many more patients have Barrett's esophagus than are detected by symptoms (110). This undetected group of patients is a result of factors including patient threshold for seeking medical attention and the presumed elevated threshold to the perception of acid exposure of Barrett's patients (111, 112). Because GERD can be such an insidious long-standing process, even a patient with Barrett's esophagus lacking symptoms may benefit from a trial of proton pump inhibitor therapy. The patient may well have accommodated to long-standing symptoms so that only with a therapeutic intervention will there be a retrospective recognition of symptoms.

Whether the endpoint for the therapy of Barrett's esophagus is symptom control or "normalization" of esophageal acid exposure is controversial. However, evidence suggests that even high-dose proton pump inhibitor therapy nearly eliminating esophageal acid exposure will not usually result in reversal of Barrett's esophagus (102, 113, 114).

Because standard medical and surgical therapy fail to commonly eliminate intestinal metaplasia, many endoscopic injury techniques have been used in an effort to achieve this goal. In combination with proton pump inhibitor therapy (57–59, 61) or antireflux surgery, these technologies have resulted in the squamous re-epithelialization of the esophagus. The problems of the completeness of this reversal and the durability of this new epithelium remain. The impact of medical, surgical, and endoscopic ablative therapy on neoplastic progression in Barrett's esophagus has not been defined.

In case-control studies, aspirin and other nonsteroidal anti-inflammatory drugs reduced the risk of esophageal cancer (115) and specifically adenocarcinoma (116). This suggests the exciting possibility of using these agents in chemoprevention trials.

Future research should be based on better defining ongoing controversies:

- The specific criteria for endoscopy in patients with GERD.
- Documentation of the surveillance intervals for patients with Barrett's esophagus.
- Biomarkers to identify patients at increased risk of adenocarcinoma.
- The appropriate intervention for high-grade dysplasia.
- The ideal level of acid suppression.
- The role of endoscopic therapy for ablation of dysplasia and early cancer.

Reprint requests and correspondence: Richard E. Sampliner, M.D., Southern Arizona VA Health Care System, Chief, Gastroenterology (111G-1), 3601 South 6th Avenue, Tucson, AZ 85723.

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