How should patients with Barrett's esophagus be monitored?

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EVIDENCE-BASED ANSWER

Some patients who have been diagnosed with Barrett's esophagus will develop dysplasia and, in some cases, esophageal carcinoma (strength of recommendation [SOR]: **A**, based on consistent cohort studies). Endoscopic surveillance is recommended for all patients with Barrett's esophagus as it is superior to other methods for detecting esophageal cancer (SOR: **B**, based on systematic review). The degree of dysplasia noted on biopsy specimens correlates with the risk of esophageal carcinoma development and should guide the frequency of subsequent evaluations (SOR: **B**, based on consistent cohort studies). The optimal frequency of endoscopy has yet to be determined in any randomized trial.

Recommendations from the 2002 American College of Gastroenterology (ACG) Practice Guideline provide guidance as to the frequency of endoscopy surveillance but were not based on an explicit systematic review of the literature (SOR: **C**, based on expert opinion; see **TABLE 1**).

CLINICAL COMMENTARY

Reduced monitoring for most patients with Barrett's esophagus appears safe

Family physicians have long been at the mercy of expert opinion when considering how to monitor patients with Barrett's esophagus. This review of the evidence clearly shows that the days of yearly EGD for all Barrett's esophagus patients are over.

Unlike other conditions—such as cervical dysplasia, where monitoring and therapies to remove dysplasia are proven to save lives—Barrett's esophagus progresses slowly and unpredictably. Thus, until technological advances allow identification of higher risk Barrett's esophagus patients, an EGD every 3 years for those without dysplasia seems to be a reasonable monitoring interval. Perhaps most importantly, family physicians can reassure Barrett's esophagus patients in the community that they are likely to live a normal lifespan and die of something other than esophageal cancer.

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Evidence summary

Barrett's esophagus has been defined as "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."[1] Intestinal metaplasia is a premalignant lesion for adenocarcinoma of the esophagus. Surveillance by serial endoscopy with biopsy has been recommended in an effort to find high-grade dysplasia or carcinoma in an early, asymptomatic, and potentially curable stage.[1–4] Approximately 75% of patients involved in a Barrett's esophagus surveillance program will present with resectable tumors, compared with only 25% of those not receiving surveillance.[4]

A recent systematic review assessing screening tools for esophageal carcinoma found standard endoscopy to be superior (90%–100% sensitivity) to other less

TABLE

Grade of dysplasia and recommendations for Barrett's esophagus surveillance as proposed by the ACG

DYSPLASIA	DOCUMENTATION	FOLLOW-UP ENDOSCOPY
None	Two EGDs with biopsy	3 years
Low-grade	Highest grade on repeat	1 year until no dysplasia
High-grade	Repeat EGD with biopsy to rule out cancer/document high-grade dysplasia; expert pathologist confirmation	Focal: every 3 months Multifocal: intervention Mucosal irregularity: EMR

ACG, American College of Gastroenterology; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection. Intervention: ie, esophagectomy. Ablative therapies only in the setting of a clinical trial or for those unable to tolerate surgery.

FAST TRACK

Endoscopic surveillance for esophageal cancer is recommended for all patients with Barrett's esophagus

invasive methods such as questionnaire (60%–70%), and fecal occult blood testing (20%).[4] Additional endoscopy tools such as brush and balloon cytology increased the cost of surveillance without any improvement in diagnostic yield.

The degree of dysplasia on esophageal biopsy in Barrett's esophagus patients is currently the best indicator of risk of progression to esophageal carcinoma. The data reviewed by the ACG for the practice guideline was drawn from several prospective studies and one available registry. In sum, a total of 783 Barrett's esophagus patients were followed for a mean of 2.9 to 7.3 years. Esophageal carcinoma developed in 2% of patients with no dysplasia, 7% of patients with low-grade dysplasia (LGD) and 22% of patients with high-grade dysplasia (HGD).[1] The ACG recommendations regarding frequency of esophagogastroduodenoscopy (EGD) were not based on an explicit critical appraisal of the literature. Recent cohort studies are consistent with recommendations for graded surveillance frequency. A randomized clinical trial to determine optimal endoscopic frequency and benefit has not been reported.

Several concerns have been raised regarding the utility of degree of dysplasia in determining optimal frequency of endoscopic surveillance. First, the progression of esophageal lesions over time is unpredictable. Skacel et al[5] reported a series of 34 patients with LGD at initial pathologic examination. On subsequent surveillance endoscopy with repeat biopsy, 73% no longer demonstrated dysplasia. Such patients can be allowed to return to having surveillance every 3 years.

In addition to the non-linear progression of dysplasia, inter-rater reliability of the interpretation of pathology specimens varies substantially. Adequate reliability has been demonstrated among pathologists assigning results to 2 categories (either no dysplasia and LGD or HGD and carcinoma) (κ=0.7). Assignment to four distinct pathologic grades, however, was not reliable (κ=0.46, where 1.0 is complete agreement).[1] In order to make a diagnosis of HGD or carcinoma, interpretation must be independently confirmed by 2 expert pathologists.[1–3]

Recommendations for frequent endoscopic surveillance are also weakened by the overall low rate of mortality from esophageal carcinoma noted in Barrett's esophagus patients. A recent population based study demonstrated that there was no difference in overall mortality in those with a Barrett's esophagus diagnosis compared with the general population.[6] An increased risk of death from esophageal carcinoma was seen in patients with Barrett's esophagus (4.7% seen in Barrett's esophagus patients compared with 0.8% predicted in the general population; $P<.05$). The overall increased effect on mortality, however, was

relatively small. Esophageal carcinoma accounted for less then 5% of deaths in Barrett's esophagus patients reported during the study's 6-year follow-up period.

Data from prospective studies published after 2002 may better predict prognosis for Barrett's esophagus patients.[6–9] Even lower rates of progression to esophageal carcinoma (<0.5% a year or <1/220 patient-years) have been reported in these studies drawing from the general population rather than referred patients, likely stemming from differences in gender mix, patient age, and risk factors.

In addition to grade of dysplasia, the length of the dysplastic Barrett's esophagus segment is emerging as a potentially predictive risk factor. While the ACG cautions that esophageal cancer has been reported in patients with so-called "short segment" Barrett's esophagus (SSBE) (≤3 cm),[1] recent prospective studies have shown an increased risk of carcinoma development with long segment Barrett's esophagus (LSBE).[7–9] Weston et al[7] reported a 2.4% progression rate to HGD or esophageal carcinoma with SSBE and no dysplasia compared with 6.8% with LSBE (*P*=.002). If patients had LGD, the rate of progression to esophageal carcinoma with SSBE was 5.3% and jumped to 35% in patients with LSBE (*P*<.001). Conio et al[8] reported that 4 of 5 cases of esophageal carcinoma noted through surveillance had LSBE. Hage et al[9] reported a significantly increased risk of progression to HGD or esophageal carcinoma with long segment disease (*P*<.02).

While currently still considered investigational, DNA content flow cytometry may be a future tool used in risk stratification. Reid et al[10] report a 5-year cumulative risk of esophageal carcinoma of 1.7% in Barrett's esophagus patients with negative, low-grade or indefinite grades of dysplasia. Subsequent application of flow cytometry allowed for further stratification of these low-risk patients. Those with neither aneuploidy nor an increased 4N had a 5-year cumulative risk of cancer of 0% while the risk for those with abnormalities on cytometry increased to 28% (relative risk=19; *P*<.001).

Recommendations from Others

The French Society of Digestive Endoscopy has published guidelines on monitoring Barrett's esophagus.[3] Their recommendations differ only slightly from the ACG in advocating a slightly increased frequency of EGD surveillance based on degree of dysplasia, and utilizing the length of the dysplastic segment in decision-making. Neither the American Academy of Family Physicians nor the US Preventive Services Task Force make any specific recommendations about Barrett's esophagus surveillance.

FAST TRACK

The degree of dysplasia on esophageal biopsy is the best indicator of risk of progression to esophageal carcinoma

REFERENCES

1. Sampliner RE. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol* 2002; 97:1888–1895.
2. Management of Barrett's esophagus. The Society for Surgery of the Alimentary Tract (SSAT), American Gastroenterological Association (AGA), American Society for Gastrointestinal Endoscopy (ASGE) Consensus Panel. *J Gastrointest Surg* 2000; 4:115–116.
3. Boyer J, Robaszkiewicz M. Guidelines of the French Society of Digestive Endoscopy: Monitoring of Barrett's esophagus. The Council of the French Society of Digestive Endoscopy. *Endoscopy* 2000; 32:498–499.
4. Gerson LB, Triadafilopoulos G. Screening for esophageal adenocarcinoma: an evidence-based approach. Am J Med 2002; 113:499–505.
5. Skacel M, Petras RE, Gramlich TL, et al. The diagnosis of low grade dysplasia in Barrett's esophagus and its implications for disease progression. *Am J Gastroenterol* 2000; 95:3383–3387.
6. Anderson LA, Murray LJ, Murphy SJ, et al. Mortality in Barrett's oesophagus: results from a population based study. *Gut* 2003; 52:1081–1084.
7. Weston, AP, Sharma P, Mathur S, et al. Risk stratification of barrett's esophagus: updated prospective multivariate analysis. *Am J Gastroenterol* 2004; 99:1657–1666.
8. Conio M, Blanchi S, Laertosa G, et al. Long-term endoscopic surveillance of patients with Barrett's esophagus. Incidence of dysplasia and adenocarcinoma: a prospective study. *Am J Gastroenterol* 2003; 98:1931–1939.
9. Hage M, Siersema PD, van Dekken H, Steyerber EW, Dees J, Kuipers EJ. Oesophageal cancer incidence and mortality in patients with long-segment Barrett's oesophagus after a mean follow-up of 12.7 years. *Scand J Gastroenterol* 2004; 39:1175–1179.
10. Reid, BJ, Levine, DS, Longton, G, Blount P, Rabinovitch PS. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. *Am J Gastroenterol* 2000; 95:1669–1676.