Published in final edited form as:

Am J Gastroenterol. 2008 August ; 103(8): 1892–1897. doi:10.1111/j.1572-0241.2008.01892.x.

Barrett's Esophagus on Repeat Endoscopy: Should We Look More Than Once?

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Abstract

BACKGROUND—Barrett's esophagus (BE) is the precursor lesion for esophageal adenocarcinoma. The major risk factor for BE is chronic gastroesophageal reflux disease (GERD). Screening patients with longstanding GERD for BE with upper esophagogastrroduodenoscopy (EGD) has become the standard practice, and guidelines from national gastrointestinal (GI) societies recommend only a single screening EGD because of limited evidence, suggesting that BE develops early in the course of GERD. We hypothesized that BE may be present in patients in whom initial endoscopy was negative, either due to a missed diagnosis or due to the later development of BE.

AIM—The purpose of the study was to determine how often BE is identified on repeat endoscopy performed after an initial negative examination.

METHODS—The Clinical Outcomes Research Initiative (CORI) National Endoscopic Database was searched for all patients who had more than one EGD during the 5-yr period between January 1, 2000, and December 31, 2004. Patients who had either procedure for an indication of surveillance of BE were excluded. The primary outcome was a finding of newly suspected BE on repeat examination after an initial negative examination.

RESULTS—In total, 24,406 patients underwent more than one endoscopy during the study period. Five hundred sixty-one (2.3%) were found to have suspected BE on repeat EGD following an initial negative examination. More men than women had BE on repeat examination (3.1% vs 1.2%, $P < 0.0001$). BE on repeat examination was more common in patients with reflux as an indication for endoscopy than in patients with any other indication (5% vs 1.6%, $P = 0.0001$). In reflux patients with esophagitis on initial examination, 9.9% were found to have suspected BE on repeat examination versus 1.8% of reflux patients with no esophagitis on initial examination ($P < 0.0001$).

CONCLUSIONS—BE is rarely found on second endoscopy performed less than 5 yr after an initial negative examination except in patients with esophagitis on the first endoscopy. Repeat EGD for Barrett's screening should not be performed out of concern for a missed diagnosis except when BE may have been obscured by overlying esophageal inflammation.

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Specific author contributions: Sarah Rodriguez wrote the manuscript. David Lieberman, Brian Fennerty, and Glenn Eisen edited the manuscript for content and clarity. Nora Mattek performed all statistical analyses and edited the manuscript.

CONFLICT OF INTEREST

Guarantor of the article: Sarah Rodriguez, M.D.

Potential competing interests: None.

INTRODUCTION

Barrett's esophagus (BE), defined as specialized intestinal metaplasia of the tubular esophagus, is a precursor lesion for esophageal adenocarcinoma (1). Patients with chronic gastroesophageal reflux disease (GERD) are at risk for the development of BE and esophageal adenocarcinoma (2, 3), and although screening these patients for BE with upper endoscopy has not been definitively shown to improve outcomes, it has become the standard practice (4). It is not known exactly when BE develops, but demographic factors such as age greater than 50 yr, white race, and male gender are associated with a higher prevalence of the lesion (5–7). It is thought that BE occurs early in the course of acid reflux disease, developing to its full length with little subsequent change (5). Because of these factors, national societies have endorsed screening patients with chronic GERD, especially older men, for BE with upper endoscopy (4, 8). Some authorities have recommended that if patients do not have BE on the initial examination, subsequent endoscopy for screening is not warranted (4), which is very dissimilar to the other types of screening such as colonoscopy for colon polyps or mammography in which patients undergo periodic repeat screening.

Screening for BE is problematic for several reasons, including a high prevalence of the lesion in the GERD population, but a relatively low incidence of esophageal adenocarcinoma, a lack of evidence that screening actually saves lives, and cost issues. Additionally, the time course of development of BE is not exactly known, and it may be that a single esophagogastroduodenoscopy (EGD) does not exclude BE for the remainder of a patient's life. Finally, the performance characteristics of endoscopy as a screening test are not exactly known. One study showed that the sensitivity of endoscopic visualization might be only 82% (9), possibly leaving nearly 20% of patients who are screened with a missed diagnosis. Therefore, another potential problem with screening for BE is that endoscopy is an imperfect screening tool. The incidence of BE found on a second endoscopy after an initial negative examination is not known. We hypothesized that BE may be present in patients in whom initial endoscopy was negative, either due to a missed diagnosis or due to the later development of BE. The purpose of the study was to determine how often BE is identified on repeat endoscopy performed after an initial negative examination.

Methods

The Clinical Outcomes Research Initiative (CORI) national endoscopic database was used for this study. CORI was established in 1995 to study utilization and outcomes of endoscopy in diverse practice settings. All participating sites agree to use a standardized computerized report generator to create all endoscopic reports and comply with quality control requirements. The sites' data files are transmitted electronically to a central data repository. Only those practice sites that had contributed data continuously for the entire study period were used. Thirty-six stable practices from 22 states contributed to the study. The majority of procedure reports were from community practices (68%), while 20% were from Veterans Affairs/military sites and 12% from university hospitals. The study population consisted of adult patients of 20 yr of age or older who had undergone more than one upper endoscopy (EGD) during the 5-yr period from January 1, 2000, through December 31, 2004. Patients who had either procedure for the indication of BE surveillance were excluded. The primary outcome of interest was an endoscopic finding of newly suspected BE on repeat examination. Data collected included patient demographic factors, indication for the procedure, findings on both examinations, and histologic data when available.

Statistical Analysis

Results were analyzed using SAS software version 9.1 (SAS Institute, Inc., Cary, NC). The frequency of suspected BE on second examination was compared across various patient and procedure characteristics using Pearson's χ^2 test for categorical variables. Multivariate logistic regression was used to estimate the adjusted risk of BE on repeat examination according to selected predictor variables. Odds ratios and 95% confidence intervals are presented. An a priori determined P value of 0.05 was considered statistically significant.

RESULTS

Of the 180,148 unique patients who underwent upper endoscopy during the study period, 29,097 (16.2%) had more than one examination. In total, 4,691 patients who had either procedure for the indication for surveillance of BE were excluded, leaving a study population of 24,406 patients. Out of this, 10,357 (42.4%) were female patients and 13,049 (57.5%) were male patients. In total, 5,993 (24.6%) patients were between ages 20 and 49 yr, and 18,413 (75.4%) were over the age of 50 yr. The prevalence of suspected BE found on second examination according to the age at time of initial endoscopy, gender, and race/ethnicity is presented in Table 1.

Five hundred sixty-one of 24,406 (2.3%) patients with a repeat EGD during the study period had a finding of suspected BE on the second examination, but not the first. Men with a repeat examination were more likely than women to have suspected BE identified (3.1% vs 1.2%, $P < 0.0001$). When stratified by age, patients in the 50- to 59-yr-old demographic had the highest prevalence of suspected BE on repeat examination.

In patients who had reflux as an indication for the first examination, 254 out of 5,081 (5%) had suspected BE on the second examination compared to 307 out of 19,325 (1.6%) patients with any other indication ($P < 0.0001$) (Fig. 1).

Among the 5,081 patients with reflux symptoms as the indication for endoscopy, 2,011 (39.5%) had an evidence of esophageal inflammation and 3,070 (60.4%) did not. We found that if active esophageal inflammation was present at the first examination, there was a higher likelihood of finding BE on the second examination compared to patients with no inflammation on the initial examination (9.9% vs 1.8%, $P < 0.0001$; Fig. 2). LA (Los Angeles) grade of esophagitis was documented in 675 (33%) of the 2,011 patients with esophagitis on initial examination. When documented, there was a significant trend toward finding BE on repeat examination with worsening grade of esophagitis such that in patients with LA grade 0 (no mucosal breaks or healed breaks) on the initial examination, 2.4% of patients had BE on second examination, vs 18.9% of patients with LA grade D (severe esophagitis) on initial examination. These data are presented in Figure 3.

Multivariate logistic regression was used to estimate the adjusted risk of BE on repeat examination according to selected predictor variables (patient age, timing between examinations, and presence of esophagitis on first examination) (Table 2). Using age <40 yr as the reference, the adjusted risk for finding BE on second examination after normal initial examination was highest among the 50- to 59-yr-olds. For the 40- to 49-yr-olds, the relative risk (RR) of BE on second examination was 1.4. For ages 50–59, 60–69, 70–79, and 80+ yr, the RR was 1.7, 1.3, 1.0, and 0.5, respectively ($P < 0.0001$). As compared to patients with no esophagitis, the adjusted risk of finding BE on second examination in patients with esophagitis on initial examination was 5.8 ($P < 0.0001$). Patients with repeat examination at <1 yr after the initial examination were 1.5 times more likely to have BE suspected on repeat examination, after adjusting for age and presence of esophagitis.

The timing between repeat endoscopies among the 561 with suspected BE on repeat examination is presented in Table 3. The majority of these repeat examinations (73%) were performed within less than 1 yr of the initial examination. There was little difference in the frequency of finding BE on repeat examination according to the time interval between examinations. For patients with the second examination at less than 1 yr after the first examination (N = 15,342), the frequency of finding BE was 2.7%; for patients with examinations at 1–2 yr and ≥ 2 yr, the frequencies were 1.4% and 1.9%, respectively.

The length of BE was available for 509 examinations; 234 (45.9%) were <2 cm and 275 (54%) were greater than 2 cm. Further, among our repeat examination cohort, if hiatal hernia (HH) was reported on first examination only versus no HH on either examination, the patient was more likely to have BE identified on second examination only (2.9% vs 1.4%, $P < 0.0001$). Additionally, if BE was reported only on first examination versus on neither examination, the patient was more likely to have HH identified on second examination only (23.3% vs 14.8%, $P < 0.0001$).

Histologic confirmation was available for 133 out of 561 (23.7%) patients with suspected BE. In total, 60 out of 133 (45.1%) had intestinal metaplasia confirmed histologically.

DISCUSSION

Guidelines for the management of BE were published by the American College of Gastroenterology in 1998 and were updated in 2002 (4). These guidelines, which are based on consensus opinion, state that patients with chronic reflux disease should undergo screening endoscopy to look for BE. The guidelines do not give a specific age at which to consider screening and do not mention repeat endoscopy if BE is not found on the initial examination. The American Gastroenterological Association (AGA) also recently published guidelines on the management of esophageal cancer (10). This guideline states that screening patients with reflux who are older than age 50 “may be of value,” but that this has not been studied prospectively. Although no comment is made regarding repeat endoscopy, the authors note that screening and surveillance for esophageal cancer is still controversial. The American Society of Gastrointestinal Endoscopy (ASGE) also published guidelines for the surveillance of premalignant lesion of the GI tract, which recommends that screening EGD should be considered in patients with chronic reflux symptoms, but that after a negative examination, further screening endoscopy is not warranted (8). The main finding of the present study corroborates this recommendation. Our data show that BE is rarely discovered on a second endoscopy after an initial negative study, with only 2.3% of the total study population having suspected BE at the second examination.

A limited amount of published data suggest that BE is an early occurrence in patients with GERD and later development is rare (5). Therefore, a single screening endoscopy after years of reflux symptoms should identify the majority of patients with BE. This raises two important questions. First, what are the performance characteristics of endoscopy as a test for diagnosing BE? In other words, how sensitive of a test is endoscopy for picking up BE and how often is BE actually present on biopsy when it is suspected endoscopically? If endoscopy is an imperfect screening tool, BE might be missed on a single examination. Second, does BE develop later in the course of GERD in some individuals?

In one study, the correlation between the endoscopic appearance and histologic confirmation of BE was poor. BE was suspected by the endoscopist in 146 patients, but only 55% of these were found to have intestinal metaplasia on biopsy (11). Histologic confirmation of BE with a length of <3 cm, or short-segment BE (SSBE), was even worse, with intestinal metaplasia found in only 25% of patients with suspected BE. The positive predictive value of an

endoscopic assessment for BE was only 34%. Importantly, however, the negative predictive value was 97%. Therefore, if the endoscopist did not suspect BE, this would be correct 97% of the time. This study suggests that endoscopy is a good test for ruling out BE, and if BE is not suspected on initial EGD, a repeat EGD would not be necessary to rule out a missed diagnosis. However, the positive and negative predictive values vary depending on the prevalence of disease in the population studied. In a higher risk group, the negative predictive value would likely be lower. Our study, which includes patients presenting for a variety of indications, shows that only 2.3% of patients had suspected BE on the second examination after an initial negative examination. This suggests that the sensitivity of endoscopic visualization is high, as there do not appear to be many missed diagnoses. Although missing a diagnosis of BE in any patient is an undesirable outcome for a screening strategy, this extremely low number suggests that repeat endoscopy to rule out missed BE cannot be justified. It is possible, however, that BE, especially SSBE, was missed on the second examination as well as the first. As all patients in our study were not biopsied, we cannot give the performance characteristics of EGD from these data.

Interestingly, the presence of an HH may make the diagnosis of BE more difficult. The gastric mucosa present in an HH may be confused for BE by the endoscopist, and conversely, BE might be missed if the endoscopist mistakes it for an HH. In our study, among patients with BE on second examination, but not the first, HH was more commonly reported on the initial examination versus no HH at all (2.9% vs 1.4%, $P < 0.0001$). This suggests that the first endoscopist thought that the BE was an HH. Similarly, among patients who had BE on the first examination only, HH was reported on the second examination only in 23.3%, compared to 14.8% who had no hernia at all, suggesting that the second endoscopist thought that the BE was actually an HH. Difficulty in identifying landmarks such as the most proximal portion of the gastric folds may explain some of the variability seen in the endoscopic diagnosis of BE.

One situation in which BE may be missed more often is when erosive esophagitis (EE) is present on initial examination, which may mask the presence of coexistent BE. A recent study of 172 patients with reflux symptoms and EE but no BE at initial endoscopy found BE in 12% on repeat endoscopy performed after acid suppression and esophageal healing (12). The repeat endoscopy was performed at a mean duration of 11 wk. We agree with the authors' conclusions that if EE is found on the initial examination, repeat endoscopy after acid suppression may be considered to exclude the presence of BE, which had been obscured by the overlying inflammatory changes. In our study, we had similar findings. Nearly 10% of patients who had EE on the initial examination were later found to have suspected BE on the second examination, and the risk of missing BE increased with worsening esophagitis as determined by the LA grade classification.

A second issue raised by the recommendation for a single screening endoscopy is the matter of when BE actually develops. If a patient has ever had an EGD in his or her life that was negative for BE, does this exclude the possibility of later development, especially if GERD has only been a recent occurrence? The timing of development of BE is unknown. It is extremely rare in the pediatric population. In one study of 6,371 patients less than 20 yr old, BE was found in $<0.25\%$, so it does not appear to be a congenital lesion (13). The prevalence of BE is known to increase with advancing age, reaching a peak in the seventh to ninth decade of life (5, 14). A recent study using the Surveillance, Epidemiology, and End Results (SEER) database found that the incidence of esophageal cancer is rising in younger groups, a so-called "birth-cohort" phenomenon (15). However, the increase in cancer overall is primarily among older men and it remains relatively uncommon in those less than 50 yr of age.

Because the timing of onset of BE is not exactly known, the question of timing for a single screening EGD has not been definitively answered. If it is performed too early, BE might not have developed yet, and obviously performing it too late may miss some patients who have already gone on to develop advanced neoplasia. In our study, BE was found on second examination most often in the 50- to 59-yr-old age range, but was also found in all age groups studied. Of note, the latest version of BE practice guidelines published by the ACG does not give an age recommendation at which to screen reflux patients but instead advise screening all patients with chronic reflux (4).

Some authors have questioned whether patients should even be offered a single screening examination. Citing data regarding the very high prevalence of GERD and BE in the population, the low incidence of adenocarcinoma, and the lack of randomized trial data demonstrating decreased cancer incidence or mortality as a result of screening, these authors call into question the utility of offering routine screening for BE (16). Furthermore, an AGA-sponsored workshop consisting of 18 experts in BE concluded that “screening for BE and dysplasia has not been demonstrated to improve mortality from esophageal adenocarcinoma” (17). This is clearly a controversial area. Based on our study, we agree with the guidelines of the ACG that if a screening examination is normal, patients do not need to be rescreened out of concern for a missed diagnosis.

Study Limitations

The strengths of this study are the large number of patients undergoing endoscopy for a variety of indications, as well as the diverse practice sites. These factors make the results generalizable. Additionally, this is a mostly community-based study and the patient sample size is the largest studied to date.

The major limitation of the study is that pathology was not available for most cases of suspected BE. Histologic confirmation of intestinal metaplasia in the esophagus is essential to make the diagnosis of BE. Pathology was available in 133 (23.7%) of our 561 patients with suspected BE. Of these 133 patients, only 60, or 45.1%, had intestinal metaplasia demonstrated on biopsy. Accuracy for the diagnosis of BE using only endoscopic visualization has been previously demonstrated to be slightly less than 60% overall (9). In this study, we found an accuracy for endoscopic diagnosis of only 45%. If we broaden this to the entire study population and assume that only 45% of our cases of “suspected BE” actually had Barrett's mucosa, we find that BE would be found in only 1.03% of the total number of patients, 2.2% of patients with reflux, and 4.4% of reflux patients with EE on the initial examination. Endoscopists are more accurate in diagnosing BE when it is >3 cm in length (9). If we use length of BE >2 cm as a surrogate marker for histologic confirmation, the results are similar to limiting the diagnosis to those with biopsy-proven BE: 275 out of 24,406 or 1.1% of all patients undergoing second endoscopy would have a finding of BE, 2.6% of reflux patients, and 5% of those with esophageal inflammation on initial EGD.

Another limitation is that only 82 of the 561 patients with suspected BE found on a second look had their second examination more than 2 yr after the first one. The study period was limited to 5 yr, so we are, therefore, only able to confidently address the question of whether endoscopists are missing BE on the initial examination. Although there was little difference in the frequency of finding BE on repeat examination based on lengthening the time interval between examinations, we cannot answer the question of whether BE is developing later in life after an initial negative examination because the majority of our patients had their second look at less than 1 yr. Given the high interobserver variability for diagnosing BE, especially SSBE, the few patients who had BE on the second examination likely also had it on the first, but it was missed by the first endoscopist.

A final limitation is that some patients may have endoscopy at centers that do not use CORI as their database. Some patients with an initial negative examination may have a subsequent endoscopy elsewhere. This could potentially falsely lower our rate of finding BE on repeat examination.

SUMMARY AND CONCLUSIONS

In summary, the chief finding of this study is that BE is rarely diagnosed on repeat endoscopy performed at less than 5 yr after an initial normal examination. We conclude that BE is not often missed unless EE is present. BE may be present in up to 9–10% of patients with EE on initial examination, and in those patients only, repeat EGD for Barrett's screening after acid suppression may be warranted. In patients with no BE on initial examination, repeat EGD only to screen for BE is not indicated, at least in the 5 yr following a negative examination. Fear of a missed diagnosis of BE should not prompt patients nor endoscopists to seek a second examination for screening.

Acknowledgments

Financial support: This project was supported with funding from NIDDK UO1 DK57132. David Lieberman is the executive director of the Clinical Outcomes Research Initiative (CORI), a nonprofit organization that receives funding from federal and industry sources. The CORI database is used in this study. This relationship has been reviewed and managed by the OHSU Conflict of Interest in Research Committee and the VA Conflict of Interest in Research committee.

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Figure 1.
Percentage with suspected BE on second examination by indication.

Figure 2.
Percentage with BE on second examination by finding on the initial examination.

Figure 3.
Percentage with BE on second examination according to the LA grade of esophagitis.

Table 1

Prevalence of newly suspected BE on second exam N=24,406 patients with a repeat EGD

	Repeat Exams	New Suspected BE N (%)	p-value
TOTAL	24,406	561 (2.3%)	
Gender			
Female	10,357	123 (1.2%)	<0.0001
Male	14,049	438 (3.1%)	
Age (yrs)			
20-29	638	5 (0.8%)	<0.0001
30-39	1608	40 (2.5%)	
40-49	3747	101 (2.7%)	
50-59	5411	178 (3.3%)	
60-69	5162	124 (2.4%)	
70-79	5399	94 (1.7%)	
>=80	2441	19 (0.8%)	
Race/Ethnicity			
White Non-Hispanic	19336	476 (2.5%)	0.001
Other	5070	85 (1.7%)	
Indication on First Exam			
Reflux Symptoms	5081	254 (5.0%)	<0.0001
No Reflux Symptoms	19325	307 (1.6%)	
Findings on First Reflux Exam			
Esophagitis	2011	198 (9.9%)	<0.0001
No Esophagitis	3070	56 (1.8%)	

Table 2

Adjusted Relative Risk of Barrett's Esophagus on 2nd Exam

	Odds Ratio	95% CI	p-value
Time Interval between exams			
≥1 year	1.0 (referent)		<0.0001
<1 year	1.5	1.3-1.8	
Esophagitis on first exam			
No	1.0 (referent)		<0.0001
Yes	5.8	4.9-6.9	
Age Group (years)			
<40	1.0 (referent)		<0.0001
40-49	1.4	1.0-2.1	
50-59	1.7	1.2-2.4	
60-69	1.3	0.9-1.9	
70-79	1.0	0.7-1.5	
80+	0.5	0.3-0.8	

Table 3

Descriptors of BE second exam N=561

	N (%)
Length of BE	
<2cm	234 (41.7%)
>=2cm	275 (49.0%)
Blank	52 (9.3%)
Time from first exam	
Same day	2 (0.4%)
<1 year	409 (72.9%)
1-<2 years	68 (12.1%)
>=2 years	82 (14.6%)
Major Indications *	
Reflux symptoms	176 (31.4%)
Dysphagia	86 (15.3%)
Screening for BE	54 (9.6%)
Suspected BE	62 (11.1%)
Abdominal Pain	32 (5.7%)
Gastric Ulcer Evaluation	31 (5.5%)
Screening/Surv of Varices	18 (3.2%)
Other	102 (18.2%)

* multiple indications may be chosen