Published in final edited form as:

Dig Dis Sci. 2016 January ; 61(1): 158–167. doi:10.1007/s10620-015-3697-6.

Yield of repeat endoscopy in Barrett's esophagus with no dysplasia and low-grade dysplasia: A population-based study

Kavel Visrodia, MD¹, Prasad G. Iyer, MD, MS², Cathy D. Schleck, BS³, Alan R. Zinsmeister, PhD³, and David A. Katzka, MD²

¹Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

²Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

³Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

Abstract

Background—The yield of early repeat endoscopy in patients with Barrett's esophagus (BE) is not well established.

Aims—To determine how often early repeat endoscopy detected missed dysplasia or esophageal adenocarcinoma (EAC) in a population-based cohort of patients with BE. Secondary aims were to identify risk factors for missed dysplasia/EAC, and compare detection of prevalent versus incident HGD/EAC.

Methods—A population-based cohort of BE subjects in Olmsted County, MN was studied. Patients with initial non-dysplastic BE (NDBE) or low-grade dysplasia (LGD) who underwent repeat endoscopy within 24 months were included. Those with a worse histologic diagnosis on repeat endoscopy were considered to have missed dysplasia/EAC. Baseline characteristics among patients with and without missed dysplasia/EAC were compared. The absolute numbers of asymptomatic prevalent or missed, and incident HGD/EAC in the entire cohort were ascertained.

Results—Of 488 BE cases, 210 were included for the primary aim of this study. Repeat endoscopy revealed 4 HGD/EAC (1.9%) and 16 LGD (8.8%) for a combined miss rate of 9.5%. Long-segment BE (LSBE) and lack of PPI use were predictors of missed dysplasia/EAC ($P = 0.008$), but adherence to biopsy protocol was not. Increased prevalent HGD/EAC ($n = 30$) rather than incident HGD/EAC ($n = 22$) was identified during a median 4.8 years of follow-up in this cohort.

Corresponding author: Prasad G. Iyer, MD, Barrett's Esophagus Unit, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Avenue SW, Rochester, Minnesota 55905 (iyer.prasad@mayo.edu); T: (507) 255-6930; F: (507) 255-7612.

Disclosures: The authors have no conflicts of interest.

Author contributions:

Kavel Visrodia: Study conception and design, data collection, manuscript drafting, critical revision, and final approval

Prasad G. Iyer: Study conception and design, manuscript drafting, critical revision, and final approval

Cathy D. Schleck: Statistical analysis, manuscript drafting, critical revision, and final approval

Alan R. Zinsmeister: Statistical analysis, manuscript drafting, critical revision, and final approval

David A. Katzka (Guarantor): Study conception and design, manuscript drafting, critical revision, and final approval

Conclusions—Dysplasia/EAC is commonly missed at initial BE diagnosis, particularly in patients with LSBE and no PPI use. Efforts should be made to enhance the sensitivity of detecting dysplasia/neoplasia around the time of initial BE diagnosis.

Keywords

Barrett's esophagus; Repeat endoscopy; Missed dysplasia; Prevalent dysplasia

Introduction

Barrett's esophagus (BE) is a precursor to esophageal adenocarcinoma (EAC), a lethal disease with a 5-year survival rate of 15–20%. [1] Dysplasia detected at the time of BE diagnosis serves as a surrogate marker for increased risk of progression to EAC and is relied upon to guide preventative management and endoscopic surveillance. For example, detection of high-grade dysplasia (HGD) typically warrants therapeutic intervention, whereas low-grade dysplasia (LGD) entails surveillance in shorter intervals than in patients with non-dysplastic Barrett's esophagus (NDBE). Therefore, an accurate assessment for the presence of EAC or grade of dysplasia at the time of diagnosis is crucial. This unfortunately can be limited by poor adherence to biopsy protocols, [2,3] sampling error, [4,5] and overlying erosive esophagitis. [6] Thus, repeating the endoscopy at a later time may help ensure that pathology requiring more aggressive management or surveillance is not missed. The yield of performing a repeat endoscopy is not, however, well established as there is lack of consensus regarding the need for this practice amongst gastrointestinal societies, particularly in patients with baseline NDBE. [6–8] While the American College of Gastroenterology (ACG) has maintained the recommendation to perform an early repeat endoscopy within 12 months of BE diagnosis, [7,9] the current American Society for Gastrointestinal Endoscopy and American Gastroenterological Association guidelines suggest that subsequent endoscopy occur after 3–5 years per routine surveillance protocol. [6,8]

We aimed to assess the utility of repeat endoscopy within 24 months in detecting dysplasia/EAC not identified on index endoscopy in a large population-based cohort consisting of carefully followed BE patients with baseline NDBE, indeterminate dysplasia, and LGD. Secondary aims were to identify risk factors for missed dysplasia and compare the proportion of prevalent HGD/EAC to incident HGD/EAC.

Methods

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

The Rochester Epidemiology Project

The Rochester Epidemiology Project (REP) is a searchable medical records linkage system for the population of Olmsted County, MN. Olmsted County has a population of approximately 140,000, of which 83% are Caucasian. County residents receive their care almost exclusively from two local institutions: Mayo Clinic and Olmsted Medical Center.

Case definition

The identification of BE cases has been described in detail previously.[10] BE cases were identified from 1976 to 2011 by performing an electronic search of the REP using an International Classification of Disease, Ninth Edition, code for BE, followed by a review of the endoscopic and histologic reports by a single gastroenterologist. Cases were classified as BE cases if the endoscopist noted the presence of at least 1 cm of visible columnar mucosa in the esophagus and histology showed intestinal metaplasia. Patients with 3 cm or more of visible columnar mucosa were classified as long-segment BE (LSBE) and those with less than 3 cm of visible columnar mucosa were classified as short-segment BE (SSBE). Endoscopies were performed by board-certified gastroenterologists. Histology was interpreted by gastrointestinal pathologists and the presence of dysplasia was confirmed by an additional gastrointestinal pathologist per published criteria[11]. Standard surveillance practices at the two institutions for patients with BE were dictated by surveillance guidelines recommended in the relevant time periods, and dictated by the highest grade of dysplasia noted on surveillance biopsies. Of note, none of the patients in this cohort were found to have been treated with antireflux procedures or radiofrequency ablation.

Data collection

Nurse abstractors reviewed the complete medical records of each case and collected information regarding demographics, endoscopic findings, and worst histologic grade on each endoscopy. Data regarding social history (any use of inhaled tobacco or alcohol), and previous and current medication history (NSAID or PPI) were also recorded. The complete medical records of all BE cases in the database were reviewed by a single investigator (K.V.) to update the endoscopic follow-up period through January 1, 2014. Additional data were gathered from endoscopy reports and pathology reports regarding the presence of gross esophagitis and number of biopsies taken, respectively.

Patient selection

Patients were included for the primary aim of this study if they (1) met the above diagnostic criteria for BE, (2) had an initial histologic diagnosis of NDBE, indeterminate dysplasia, or LGD, and (3) underwent repeat surveillance endoscopy within 24 months of initial BE diagnosis. Patients who met the above diagnostic criteria for BE, but were diagnosed with prevalent HGD/EAC, did not undergo repeat endoscopy, or underwent repeat endoscopy after 24 months, were excluded from the primary aim, and included for the secondary aim of comparing the proportion of prevalent HGD/EAC to incident HGD/EAC.

The 24 month cutoff for repeat endoscopy was chosen from a biologic point of view based on the current understanding of progression rates of HGD or LGD to EAC,[12,13] so that dysplasia/EAC detected within this period would still be considered to represent prevalent and not incident.

Groups of Patients with Missed Dysplasia/EAC

Cases meeting the inclusion criteria were divided into three groups based on initial histologic diagnosis: NDBE, indeterminate dysplasia, and LGD. Each group of cases was reviewed to determine if dysplasia/EAC was missed on index endoscopy. This was defined

as the presence of a worse histologic grade on the repeat endoscopy than on index endoscopy. Specifically, this meant cases with initial NDBE or indeterminate dysplasia found to have LGD, HGD, or EAC on repeat endoscopy, or cases with initial LGD found to have HGD or EAC on repeat endoscopy. Cases identified from the three groups constituted the missed dysplasia/EAC group while the remainder constituted the group without missed dysplasia/EAC.

Data regarding the earlier-stated variables were analyzed for the missed dysplasia/EAC group and group without missed dysplasia/EAC. Given the extended study period, proportions of missed dysplasia/EAC among patients diagnosed with BE in the first and second halves of the study period were also compared to evaluate the impact of study timeline on relevant outcomes.

Adherence to biopsy protocol was assumed if at least 4 biopsies were noted *and* the ratio of the number of biopsies to BE length was 2 or greater, suggesting four-quadrant biopsies were taken every 2 cm in accordance with the Seattle biopsy protocol.[6–8] Nonadherence was assumed if fewer than 4 biopsies were taken and/or the ratio was less than 2.

Prevalent HGD/EAC vs. Incident HGD/EAC

To compare the yield of screening and repeat endoscopy vs. surveillance endoscopy, the entire cohort was reviewed to determine the absolute number of prevalent and incident cases of HGD/EAC detected, respectively, among patients not presenting for presumably tumor-related symptoms (i.e. dysphagia, odynophagia or weight loss). Prevalent HGD/EAC was defined as the detection of HGD or EAC on index endoscopy or on repeat endoscopy within 24 months. Incident HGD/EAC was defined as the detection of HGD or EAC at surveillance endoscopy performed more than 24 months from the time of index endoscopy. The follow-up period was defined as the time interval between the index endoscopy revealing BE and the most recent follow-up endoscopy with biopsies, or date of progression to HGD/EAC.

Statistical Analyses

Data are summarized as mean ($\pm$ SD) or median (range) for quantitative variables and proportions (%) for discrete variables. The Wilcoxon Rank Sum test was used to assess the associations of specific quantitative variables with group status. Fisher's Exact test was used to assess the associations of specific discrete variables with group status. All analyses were done using SAS® version 9.3 (SAS Institute, Cary North Carolina). A *P* value of less than .05 was considered statistically significant.

Results

210 of 488 BE cases were included for the primary aim of the study. The remaining 278 cases were excluded from the primary aim of the study, but included for the secondary aim, based on an initial finding of HGD/EAC (n=49), no repeat endoscopy (n= 117; 101 NDBE, 5 indeterminate, 11 LGD), or repeat endoscopy after 24 months (n=112; 105 NDBE, 1 indeterminate, 6 LGD). The majority of all BE cases (99.0%) were identified from 1986–2011, including all patients meeting the inclusion criteria for the primary aim. The flow of cases is shown in Figure 1.

Baseline characteristics for the 210 cases and the remaining 278 cases are provided in Table 1. The median age was 63 (range 24–91) years, with most patients being Caucasian (88.1%) and male (69.5%). NSAID and PPI use was recorded in 11.9% and 49.5% of cases, respectively. The median BE length was 3.0 (range 1–26) cm, with 56.7% of cases having LSBE. Hiatal hernia was present in 83.7% of cases. The median time to repeat endoscopy was 12.1 (range 1.0–24.0) months.

Missed dysplasia

Of the 210 cases included in this study, 162 cases initially had NDBE, 19 had indeterminate dysplasia, and 29 had LGD (Figure 1). Repeat endoscopy in patients with (1) NDBE detected 1 HGD, 1 EAC, and 13 LGD, (2) in those with indeterminate dysplasia detected 3 LGD, and (3) in those with LGD detected 1 HGD and 1 EAC. Among the three groups, the rate of missed HGD/EAC ($n = 4$) was 1.9%. In the groups of NDBE and indeterminate dysplasia, the rates of missed LGD were 8.0% ($n = 13$) and 15.8% ($n = 3$), respectively, and 8.8% ($n = 16$) combined. The overall rate of missed dysplasia and/or EAC was 9.5%.

More patients were diagnosed with BE during the latter half of the study period (1998–2011; 73.8% vs. 26.2%), which had a lower rate of missed dysplasia/EAC (5.2% vs. 21.8%) but notably included 3 of the 4 missed HGD/EAC (Table 2).

Baseline characteristics for the missed dysplasia/EAC group and the group without missed dysplasia/EAC are shown in Table 3. The groups were similar with respect to median age, sex, and race. Tobacco, alcohol, and NSAID use were similar. Lack of PPI use was significantly associated with missed dysplasia/EAC (20% PPI use in the missed dysplasia/EAC group vs. 53% in the remainder, $P = 0.008$). Concurrently, there was a numerically greater proportion of esophagitis in the missed dysplasia/EAC group (55% vs. 40%; $P = 0.24$).

Longer median BE length (6.0 cm in the missed dysplasia/EAC group vs. 3.0 cm in the remainder, $P = 0.006$) and LSBE (85% in the missed dysplasia/EAC group vs. 54% in the remainder, $P = 0.008$) were significantly associated with missed dysplasia/EAC. Seventeen of 115 (14.8%) patients with LSBE had missed dysplasia/EAC, compared to 3/88 (3.4%) patients with SSBE ($P = 0.008$).

Overall adherence to recommended biopsy protocol at the time of index endoscopy was low at 41%, and lower in the missed dysplasia/EAC group (36.8%) than in the group without missed dysplasia/EAC (45.1%), but this was not statistically significant ($P = 0.63$). Among both groups, 7/76 (9.2%) patients with adequate biopsies still had missed dysplasia/EAC.

The median interval between index and repeat endoscopy was similar between groups with and without missed dysplasia/EAC. In each case of missed dysplasia/EAC, the interval is shown (Figure 2). Eight cases (40%) of missed dysplasia/EAC, including both HGD and 1 EAC, were detected within 12 months. The remaining EAC was detected after 13 months. The majority (85%) of missed dysplasia/EAC were detected within 18 months.

Characteristics for the 4 patients with missed HGD/EAC are provided in Table 4. All were white males with an age range of 65–71 years. Three had very long BE segments (range 10–13 cm), 2 of which had an inadequate number of initial biopsies with substantially greater numbers of biopsies on repeat endoscopy (36 and 24 pieces compared to 4 and 12 biopsies on index biopsy, respectively). Both patients with HGD were determined to be unifocal (detected at only one level). The two EAC arose from new lesions visualized on repeat endoscopy and were staged IIA and IIB. Both were treated with esophagogastrectomy and the latter received adjuvant chemotherapy. Both patients are alive after 7 and 10 years of clinical follow-up, respectively.

Prevalent HGD/EAC vs. Incident HGD/EAC

Of the total 488 BE cases in the database, 49 patients presented with HGD/EAC on index endoscopy and 26 of these were deemed to not have presumable tumor-related symptoms at the time of presentation. Indications for endoscopy in these subjects included evaluation for unrelated gastrointestinal bleeding ($n = 11$) or anemia ($n = 6$), reflux ($n = 7$), dyspepsia ($n = 1$), or a radiographic finding ($n = 1$). Accounting for the 4 additional cases of missed HGD/EAC detected on repeat endoscopy, the entire cohort consisted of 30 prevalent HGD/EAC cases.

Patients who did not have prevalent HGD/EAC were followed for a median of 4.8 years (range 1.2 months to 18.1 years). A total of 22 cases of incident HGD/EAC were identified during endoscopic surveillance (Figure 1). Nine of these cases were detected in the group without missed dysplasia/EAC (range 2.0 to 7.4 years after initial endoscopy), 2 of which were on the second follow-up endoscopy. The remaining 13 were detected in the group that was not included for the primary aim of the study because repeat endoscopy was performed more than 24 months from the time of index endoscopy (range 3.5 to 18.1 years after initial endoscopy). Interestingly, 6 of these 13 cases of HGD/EAC were identified on the subsequent endoscopy (range 2.7 to 9.7 years). No progressors were identified in the groups with initial indeterminate dysplasia or missed LGD during a median follow-up of 6.3 years (range 1.2 months to 18.1 years) and 2.2 years (range 3.4 months to 5.5 years), respectively.

Discussion

We present the first population-based study specifically evaluating the yield of repeat endoscopy in patients with initial NDBE, indeterminate dysplasia, and LGD. We report that the miss rates for HGD/EAC (1.9%) and LGD (8.8%) are not insignificant, as about 1 in 10 (9.5%) patients with newly diagnosed BE will concurrently have a higher grade, undetected dysplasia or EAC that would alter clinical management.

The current lack of consensus regarding the need for early repeat endoscopy in patients specifically with NDBE should be addressed due to the potential we demonstrated for delayed recognition and management of prevalent HGD/EAC.[6–8] Both cases of missed HGD and EAC in our patients with NDBE were detected on repeat endoscopy at an early stage (unifocal and stage IIA, respectively) and treated curatively. Repeating endoscopy 3–5 years later would likely have resulted in disease progression with diminished chances for cure and survival.[1,14] Our findings support the concept of performing an early repeat

endoscopy in patients with NDBE to evaluate for prevalent HGD/EAC missed during index endoscopy.

In contrast to patients with NDBE, the guidelines do recommend repeating endoscopy in patients with initial LGD within 6–12 months.[6–8] Repeat endoscopy in our 29 patients with LGD also yielded an early HGD (unifocal) and EAC (stage IIB). This would support continued recommendation of early repeat endoscopy in patients with LGD.

The majority of missed dysplasias in our cohort were LGD in patients with initial NDBE and indeterminate dysplasia (n = 16, 80%), as confirmed by two expert gastrointestinal pathologists. Provided patients with LGD vs. NDBE have a greater propensity for progression[15] and radiofrequency ablation is increasingly being considered, unrecognized LGD can result in misclassification and surveillance at insufficient intervals (i.e. endoscopy every 3–5 years instead of 6–12 months) or missed opportunity for therapeutic intervention. Despite the increased risk, we did not identify any progression to HGD/EAC in this small group during the time period studied. This is consistent with variable progression rates described previously.[16] Moreover, 7/14 cases had no evidence of LGD on subsequent endoscopy, which may be a consequence of true regression, sampling error, or pathologist interobserver disagreement, and perhaps is associated with a lower risk of progression. [13,17]

The extent of metaplasia may be a risk factor for missed dysplasia/EAC as these cases had significantly longer BE length, the majority being LSBE (85%). Abdalla and colleagues reported this association in their cohort of missed dysplasias as well.[18] Other studies have found that adherence to biopsy protocol decreases in patients with longer BE, resulting in a lower detection rate of dysplasia/EAC.[2,3] Although our overall rate of adherence was poor (41%), adherence did not significantly differ between the groups with and without missed dysplasia/EAC, raising the question of sampling error.[19] Moreover, missed dysplasia/EAC was detected on repeat endoscopy in some patients who initially had adequate biopsy sampling. This is consistent with prior studies documenting missed EAC in patients with HGD where the recommended biopsy protocol was followed.[19]

Our findings suggest that not using a PPI or presence of esophagitis may also contribute to missed dysplasia/EAC. Gross esophagitis can mask significant lesions, prevent targeted biopsies, and obscure histological diagnosis.[6] Ideally, BE biopsies should not be performed in the setting of esophagitis, but when done, should be repeated after the patient has been on an appropriate antireflux regimen to evaluate for missed dysplasia. However, we believe our findings likely reflect real-world practice and further underscore the need for a repeat endoscopy.

Given the wide span of our inclusion period, we attempted to account for the evolution of endoscope technology and BE diagnosis by temporally examining our findings. There was a dramatic decrease in the rate of esophagitis over time (supplementary table), perhaps due to the use of more rigid criteria (LA Classification) in defining esophagitis and/or increase in PPI use. Patients diagnosed during the latter half of the study (1998–2011) also had a lower rate of missed dysplasia/EAC. However, 3 of the 4 most advanced lesions were missed

during this time period and notably were detected more recently (EAC: 2004, 2008; HGD: 2005), supporting the need for early repeat endoscopy in the modern era of endoscopy.

In the entire cohort, we found a greater absolute number of prevalent HGD/EAC (including the 4 missed HGD/EAC detected within 24 months) than incident HGD/EAC detected during a median endoscopic surveillance period of 4.8 years. This disparity held even after excluding those that had presumed tumor-related symptoms on presentation (i.e. dysphagia, odynophagia, or weight loss), and may still be an underestimate considering several patients did not undergo a repeat endoscopy within 24 months, but were found to have HGD/EAC on the repeat endoscopy thereafter. This distribution highlights the greater potential for the screening and early repeat endoscopy to identify more HGD/EAC than surveillance endoscopy over many years, and has been noted most impressively in previous large population-based studies as well as a meta-analysis.[20–22] Given that the cost-effectiveness of surveillance endoscopy in patients with BE is debatable,[23–26] perhaps more resources should be invested in detecting prevalent dysplasia and cancer around the time of BE diagnosis. This may include more careful inspection of the BE segment for visible abnormalities,[27] a more aggressive biopsy protocol such as four-quadrant biopsies every 1 cm instead of 2 cm for patients with NDBE, more frequent early endoscopies in an effort to miss fewer prevalent HGD/EAC, and greater use of advanced imaging techniques. Further research in the form of prospective studies evaluating these potential strategies would be the next step in determining a more fruitful and cost-effective method of detecting HGD/EAC, particularly at an earlier stage with improved survival.

Despite applying a 24 month cutoff for repeat endoscopy, most dysplasia/EAC was detected much sooner within 18 months, including all cases of HGD/EAC in less than 13 months. However, it remains possible that some cases of incident rather than prevalent dysplasia/EAC were still identified, particularly with respect to cases of NDBE and LGD in which LGD and HGD, respectively, were subsequently detected. To reduce the chances of this further and evaluate the ACG's current recommendation for repeat endoscopy, the more conventional cutoff for prevalence of 1 year could be considered, especially in more robust population-based cohorts with greater statistical power.

Our study has several inherent limitations. Although this is a relatively large population-based BE study, it is retrospective in nature with relatively few cases of dysplasia and EAC. The number of biopsies performed during index endoscopy was not available in 19.9% (97/488) of patients. A small fraction of endoscopies was performed prior to the implementation of systematic biopsies, potentially contributing to the low adherence rate and perhaps inflating the rate of missed dysplasia. Also, the adequacy of biopsies was judged using a formula that did not account for separate targeted biopsies and assumed a circumferential distribution of BE. Furthermore, the early detection of LGD in patients with initial indeterminate dysplasia was considered missed dysplasia, but given that the management strategy for indeterminate dysplasia and LGD is currently the same, an alternative interpretation of this data is that there were 17 instead of 20 cases of missed dysplasia/EAC resulting in slightly reduced miss rates for LGD (7.2%) and overall dysplasia/EAC (8.1%).

In conclusion, our study demonstrates a sizeable percentage of patients will have missed dysplasia/EAC at the time of BE diagnosis, and thus underscores the need for repeat endoscopy or improved detection methods during initial endoscopy to avoid delay in the recognition and management of prevalent dysplasia/EAC. Furthermore, factors such as the presence of LSBE, lack of PPI use, or presence of erosive esophagitis may place patients at greater risk for missed dysplasia/EAC, mandating the need for improved screening for prevalent dysplasia in these groups. Finally, as a greater number of HGD/EAC is detected during index and repeat endoscopy than long-term surveillance, perhaps more resources should be invested earlier in patients with BE to detect prevalent dysplasia/EAC and provide in the long run a more cost-effective means of monitoring patients with BE when compared to long-term surveillance strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant support: Supported by the National Institutes of Health (Grant RC4DK 090413), the Mayo Center for Clinical and Translational Sciences (Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health), and the Rochester Epidemiology project (supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676). The contents are solely the responsibility of the authors and do not necessarily represent the official view of National Institutes of Health.

References

1. Sharma P, McQuaid K, Dent J, Fennerty MB, Sampliner R, Spechler S, Cameron A, Corley D, Falk G, Goldblum J, Hunter J, Jankowski J, Lundell L, Reid B, Shaheen NJ, Sonnenberg A, Wang K, Weinstein W. A critical review of the diagnosis and management of barrett's esophagus: The aga chicago workshop. *Gastroenterology*. 2004; 127:310–330. [PubMed: 15236196]
2. Abrams JA, Kapel RC, Lindberg GM, Saboorian MH, Genta RM, Neugut AI, Lightdale CJ. Adherence to biopsy guidelines for barrett's esophagus surveillance in the community setting in the united states. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2009; 7:736–742. quiz 710. [PubMed: 19268726]
3. Curvers WL, Peters FP, Elzer B, Schaap AJ, Baak LC, van Oijen A, Mallant-Hent RM, Ten Kate F, Krishnadath KK, Bergman JJ. Quality of barrett's surveillance in the netherlands: A standardized review of endoscopy and pathology reports. *European journal of gastroenterology & hepatology*. 2008; 20:601–607. [PubMed: 18679060]
4. Chatelain D, Flejou JF. High-grade dysplasia and superficial adenocarcinoma in barrett's esophagus: Histological mapping and expression of p53, p21 and bcl-2 oncoproteins. *Virchows Archiv : an international journal of pathology*. 2003; 442:18–24. [PubMed: 12536310]
5. McArdle JE, Lewin KJ, Randall G, Weinstein W. Distribution of dysplasias and early invasive carcinoma in barrett's esophagus. *Hum Pathol*. 1992; 23:479–482. [PubMed: 1568744]
6. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American gastroenterological association technical review on the management of barrett's esophagus. *Gastroenterology*. 2011; 140:e18–e52. quiz e13. [PubMed: 21376939]
7. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of barrett's esophagus. *Am J Gastroenterol*. 2008; 103:788–797. [PubMed: 18341497]
8. Evans JA, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi KV, Decker GA, Fanelli RD, Fisher DA, Foley KQ, Hwang JH, Jain R, Jue TL, Khan KM, Lightdale J, Malpas PM, Maple JT, Pasha SF, Saltzman JR, Sharaf RN, Shergill A, Dominitz JA, Cash BD. The role of

endoscopy in barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointestinal endoscopy*. 2012; 76:1087–1094. [PubMed: 23164510]

9. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of barrett's esophagus. The practice parameters committee of the american college of gastroenterology. *Am J Gastroenterol*. 1998; 93:1028–1032. [PubMed: 9672324]
10. Jung KW, Talley NJ, Romero Y, Katzka DA, Schleck CD, Zinsmeister AR, Dunagan KT, Lutzke LS, Wu TT, Wang KK, Frederickson M, Geno DM, Locke GR, Prasad GA. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and barrett's esophagus: A population-based study. *Am J Gastroenterol*. 2011; 106:1447–1455. quiz 1456. [PubMed: 21483461]
11. Montgomery E, Bronner MP, Goldblum JR, Greenson JK, Haber MM, Hart J, Lamps LW, Lauwers GY, Lazenby AJ, Lewin DN, Robert ME, Toledano AY, Shyr Y, Washington K. Reproducibility of the diagnosis of dysplasia in barrett esophagus: A reaffirmation. *Hum Pathol*. 2001; 32:368–378. [PubMed: 11331953]
12. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with barrett's esophagus and high-grade dysplasia: A meta-analysis. *Gastrointestinal endoscopy*. 2008; 67:394–398. [PubMed: 18045592]
13. Wani S, Falk GW, Post J, Yerian L, Hall M, Wang A, Gupta N, Gaddam S, Singh M, Singh V, Chuang KY, Boolchand V, Gavini H, Kuczynski J, Sud P, Bansal A, Rastogi A, Mathur SC, Young P, Cash B, Goldblum J, Lieberman DA, Sampliner RE, Sharma P. Risk factors for progression of low-grade dysplasia in patients with barrett's esophagus. *Gastroenterology*. 2011; 141:1179–1186. 1186 e1171. [PubMed: 21723218]
14. Verbeek RE, Leenders M, Ten Kate FJ, van Hillegeersberg R, Vleggaar FP, van Baal JW, van Oijen MG, Siersema PD. Surveillance of barrett's esophagus and mortality from esophageal adenocarcinoma: A population-based cohort study. *Am J Gastroenterol*. 2014; 109:1215–1222. [PubMed: 24980881]
15. Singh S, Manickam P, Amin AV, Samala N, Schouten LJ, Iyer PG, Desai TK. Incidence of esophageal adenocarcinoma in barrett's esophagus with low-grade dysplasia: A systematic review and meta-analysis. *Gastrointestinal endoscopy*. 2014; 79:897–909. e894. [PubMed: 24556051]
16. Sharma P, Falk GW, Weston AP, Reker D, Johnston M, Sampliner RE. Dysplasia and cancer in a large multicenter cohort of patients with barrett's esophagus. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2006; 4:566–572. [PubMed: 16630761]
17. Curvers WL, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, Bohmer C, Mallant-Hent RC, van Oijen A, Naber AH, Scholten P, Busch OR, Blaauwgeers HG, Meijer GA, Bergman JJ. Low-grade dysplasia in barrett's esophagus: Overdiagnosed and underestimated. *Am J Gastroenterol*. 2010; 105:1523–1530. [PubMed: 20461069]
18. Abdalla M, Dhanekula R, Greenspan M, Mobarhan S, Patil A, Jakate S, Giusto D, Silva R, Li H, Melson J. Dysplasia detection rate of confirmatory egd in nondysplastic barrett's esophagus. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE*. 2012
19. Kariv R, Plesac TP, Goldblum JR, Bronner M, Oldenburgh M, Rice TW, Falk GW. The seattle protocol does not more reliably predict the detection of cancer at the time of esophagectomy than a less intensive surveillance protocol. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2009; 7:653–658. quiz 606. [PubMed: 19264576]
20. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with barrett's esophagus. *The New England journal of medicine*. 2011; 365:1375–1383. [PubMed: 21995385]
21. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, Murray LJ. Risk of malignant progression in barrett's esophagus patients: Results from a large population-based study. *Journal of the National Cancer Institute*. 2011; 103:1049–1057. [PubMed: 21680910]
22. Thomas T, Abrams KR, De Caestecker JS, Robinson RJ. Meta analysis: Cancer risk in barrett's oesophagus. *Alimentary pharmacology & therapeutics*. 2007; 26:1465–1477. [PubMed: 17900269]

23. Corley DA, Mehtani K, Quesenberry C, Zhao W, de Boer J, Weiss NS. Impact of endoscopic surveillance on mortality from barrett's esophagus-associated esophageal adenocarcinomas. *Gastroenterology*. 2013; 145:312–319. e311. [PubMed: 23673354]
24. Armstrong D. Should patients with barrett's oesophagus be kept under surveillance? The case for. *Best practice & research Clinical gastroenterology*. 2008; 22:721–739. [PubMed: 18656826]
25. Barritt, AStSN. Should patients with barrett's oesophagus be kept under surveillance? The case against. *Best Pract Res Clin Gastroenterol*. 2008; 22:741–750. [PubMed: 18656827]
26. Moayyedi P, Burch N, Akhtar-Danesh N, Enaganti SK, Harrison R, Talley NJ, Jankowski J. Mortality rates in patients with barrett's oesophagus. *Alimentary pharmacology & therapeutics*. 2008; 27:316–320. [PubMed: 18062791]
27. Gupta N, Gaddam S, Wani SB, Bansal A, Rastogi A, Sharma P. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in barrett's esophagus. *Gastrointestinal endoscopy*. 2012; 76:531–538. [PubMed: 22732877]

Figure 1. Flow diagram of BE cases and their outcomes. A total of 210 BE subjects with initial NDBE, indeterminate dysplasia, or LGD underwent repeat endoscopy within 24 months. Missed dysplasia/EAC appears in red. The overall rate of missed HGD/EAC was 1.9% (4/210). The rates of missed LGD in patients with NDBE and indeterminate dysplasia were 8.0% (13/162) and 15.8% (3/19), respectively. The combined rate of missed dysplasia/EAC was 9.5% (20/210). In the entire cohort, there were 30 asymptomatic prevalent (including 4 missed) HGD/EAC vs. 22 incident HGD/EAC detected during surveillance.

^a 26 deemed asymptomatic at the time of index EGD

^b Includes 7 patients with indeterminate dysplasia and 13 patients with no BE on repeat endoscopy

^c Includes 11 patients with NDBE or no BE on repeat endoscopy

^d Includes 14 patients with NDBE or no BE on repeat endoscopy

^e Median endoscopic follow-up period of 4.8 years.

Figure 2.

Interval to repeat endoscopy in patients with missed dysplasia/EAC. Symbols represent missed dysplasia/EAC detected on repeat endoscopy. Eight of 20 (40%) cases were detected within 12 months of index endoscopy, including 2 HGD and one EAC. Seventeen (85%) cases were detected within 18 months.

Table 1

Baseline characteristics of patients with BE undergoing repeat endoscopy within 24 months and the remainder of the BE cohort.

Variable	Patients undergoing repeat EGD within 24 months (n = 210)	Patients not undergoing repeat EGD within 24 months (n = 278)	P value
Median age (range), years	61 (24–87)	64 (28–91)	0.007
Male, n (%)	146 (69.5)	200 (71.9)	0.61
Caucasian, n (%)	185 (88)	226 (81.3)	0.04
Tobacco use, n (%)	127 (61.7) ^a	176 (63.3) ^a	0.57
Alcohol use, n (%)	97 (48.3)	132 (47.5) ^b	0.64
Aspirin use, n (%)	52 (24.8)	82 (29.5)	0.26
NSAID use, n (%)	25 (11.9)	22 (7.9)	0.16
PPI use, n (%)	104 (49.5)	95 (34.2)	<0.001
Esophagitis, n (%)	87 (41.4)	43 (18.4)	<0.001
Median BMI, kg/m ² (range)	29.7 (17.8–56.8)	29.0 (15.5–60.0)	0.79
Histologic diagnosis on index endoscopy, n (%)			<0.001
NDBE	162 (77.1)	206 (74.1)	
Indeterminate	19 (9.0)	6 (2.2)	
LGD	29 (13.8)	17 (6.1)	
HGD	0	14 (5.0)	
EAC	0	35 (12.6)	
Median BE length, cm (range)	3.0 (1–26) ^a	4.0 (1–16) ^b	0.01
SSBE, n (%)	88 (43.3)	78 (31.0)	0.008
LSBE, n (%)	115 (56.7)	174 (69.0)	
Hiatal hernia present, n (%)	175 (83.7) ^a	91 (81.3) ^c	0.64
Median time to repeat endoscopy, months (range)	12.1 (1.0–24.0)	38.8 (24.1–140.1)	
Date of initial endoscopy, range in years	1986–2011	1976–2011	

Proportions are among subjects with available data.

^a < 5% data not available

^b 5–10% data not available

^c 40% data not available

Table 2

Temporal comparison of missed dysplasia/EAC.

Interval of BE diagnosis, years	Patients undergoing repeat EGD within 24 months (n= 210)	Patients with missed dysplasia/EAC (n= 20)	Number and type of missed dysplasia/EAC (year of BE diagnosis)
1986–1998	55	12 (21.8%)	1 HGD (1994) 11 LGD (range 1991–1995)
1998–2011	155	8 (5.2%)	2 EAC (2004, 2008) 1 HGD (2005) 1 LGD (range 2000–2009)

Table 3

Association between characteristics of patients at the time of index endoscopy and presence or absence of dysplasia/EAC on repeat endoscopy.

Variable	Patients with missed dysplasia/EAC (n = 20)	Patients without missed dysplasia/EAC (n = 190)	P value
Median age (range), years	61 (35–77)	61 (64–87)	0.76
Male, n (%)	16 (80.0)	130 (68.4)	0.44
Caucasian, n (%)	18 (90.0)	167 (87.9)	1.00
Tobacco use, n (%)	11 (61.1) ^a	116 (61.7) ^a	1.00
Alcohol use, n (%)	9 (50.0) ^a	88 (48.1) ^a	1.00
Aspirin use, n (%)	3 (15)	49 (25.8)	0.42
NSAID use, n (%)	2 (10.0)	23 (12.1)	1.00
PPI use, n (%)	4 (20.0)	100 (52.6)	0.008
Esophagitis, n (%)	11 (55)	76 (40.0)	0.24
Median BMI, kg/m ² (range)	27.6 (17.7–35.5)	29.9 (19.5–56.8)	0.04
Median BE length, cm (range)	6.0 (1–13)	3.0 (1–26) ^a	0.006
SSBE, n (%)	3 (15.0)	85 (46.4)	0.008
LSBE, n (%)	17 (85.0)	98 (53.6)	
Hiatal hernia present, n (%)	16 (80.0)	159 (84.1) ^a	0.75
Histologic diagnosis on index endoscopy, n (%)			0.59
NDBE	15 (75)	147 (77.4)	
Indeterminate	3 (15)	16 (8.4)	
LGD	2 (10)	27 (14.2)	
Median time to repeat endoscopy, months (range)	12.4 (1.2–23.9)	12.0 (1.0–24.0)	0.79
Adequate biopsies, n (%)	7 (36.8) ^a	69 (45.1) ^b	0.63
Date of initial endoscopy, range in years	1991–2009	1986–2011	

Proportions are among subjects with available data.

^a 10% data not available

^b 20% data not available

Table 4

Characteristics of the 4 patients with missed HGD/EAC.

Case	Age (y)	Gender	Race	Procedure Date (y)	Index EGD				Interval between index and repeat EGD (months)	Repeat EGD				Outcome
					Segment length (cm)	Esophagitis	Number of biopsies	Grade of dysplasia		Esophagitis	New visible lesion	Number of biopsies	Grade of dysplasia (stage)	
A	71	M	W	2005	11	No	4	NDBE	1.2	No	No	36	HGD (unifocal)	Patient opted for surveillance, which did not reveal further evidence of HGD; alive (follow-up of 9 years)
B	66	M	W	1994	13	No	N/A	LGD	3.5	No	No	6	HGD (unifocal)	Progression to EAC after 3 years requiring esophagogastrectomy; unrelated death 14 years later
C	73	M	W	2008	1	No	4	LGD	7.9	No	Induration	N/A	EAC (IIB)	Esophagogastrectomy with adjuvant chemotherapy; alive (follow-up of 7 years)
D	65	M	W	2004	10	No	12	NDBE	13.1	No	Nodule	24	EAC (IIIA)	Esophagogastrectomy; alive (follow-up of 10 years)

Abbreviations: EMR, endoscopic mucosal resection; N/A, not available.