Incidence of Progression of Persistent Nondysplastic Barrett's Esophagus to Malignancy

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BACKGROUND & AIMS: **The risk of esophageal adenocarcinoma (EAC) in patients with non-dysplastic Barrett's esophagus (NDBE) is low, so there is debate over the role of ongoing surveillance for patients with NDBE. It is important to identify patients at low risk for progression. We assessed cancer risk based on the subsequent number of endoscopies showing persistence of NDBE in a nationwide study in the Netherlands.**

METHODS: **In a population-based study, patients with a first diagnosis of NDBE were selected from the Dutch nationwide registry of histopathology. We calculated incidence rates and incidence rate ratios (IRR) for high-grade dysplasia (HGD) and EAC to determine whether the number of endoscopies negative for dysplasia and the persistence of NDBE over time associate with progression to malignancy.**

RESULTS: **We identified 12,728 patients with NDBE during 2003 and 2013. HGD or EAC developed in 436 patients (3.4%) during 64,537 person-years of follow up (median, 4.9 years). The rate of progression to HGD or EAC was 0.68 (95% CI, 0.61–0.74) per 100 person-years. In patients with 2 consecutive endoscopies showing NDBE, the rate of progression to HGD or EAC decreased to 0.55 (95% CI, 0.46–0.64) per 100 person-years (IRR 0.72; 95% CI, 0.60–0.87). Overall, the incidence of HGD or EAC decreased by 14% for each year of progression-free follow-up (IRR, 0.86; 95% CI, 0.81–0.92).**

CONCLUSION: **In a population-based study in the Netherlands, we found patients with stable NDBE to have a low risk of progression to HGD or EAC. These findings indicate that surveillance intervals might be lengthened or even discontinued in subgroups patients with persistent NDBE.**

Keywords: PALGA; Prognostic Factor; Biomarker; Risk Factor; Epidemiology.

Barrett's esophagus (BE) is a premalignant condition, in which the normal squamous epithelium of the distal esophagus is replaced by columnar or intestinal epithelium containing goblet cells.[1] BE is considered to be the predominant precursor lesion of esophageal adenocarcinoma (EAC). The progression from BE to EAC occurs through consecutive histological stages of increasing grades of epithelial dysplasia, from intestinal metaplasia without dysplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and finally EAC.[2]

In the Western world, the incidence of BE and EAC is increasing.[3] Because EAC is frequently detected in an advanced stage, patients with EAC have a poor prognosis, with a 5-year survival following a diagnosis of EAC of <20%.[4] To detect HGD and EAC at an early stage and hence prevent further progression to invasive EAC, endoscopic surveillance with biopsy sampling every 3–5 years is recommended in patients with nondysplastic BE (NDBE).[5,6]

However, as the efficacy of surveillance on reducing mortality of patients with BE compared with the general population is unclear, the value of ongoing surveillance

Abbreviations used in this paper: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IR, incidence rate; IRR, incidence rate ratio; IQR, interquartile range; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; ROC, receiver-operating characteristic.

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.08.033

for patients with NDBE is debated.[7,8] In addition, as the absolute risk of malignant progression in patients with NDBE is low (<0.5%/year), the majority of patients with NDBE will never progress beyond NDBE or LGD and will only experience the disadvantages of the surveillance program.[9,10] Therefore, it would be helpful to identify patients at low risk of malignant progression, as in these patients surveillance intervals might be lengthened or even discontinued. There is conflicting evidence whether persistence of NDBE over time is associated with a decreased risk of malignant progression.[11–13]

The aim of this study was to assess the risk of malignant progression associated with the number of consecutive endoscopies showing NDBE and the persistence of NDBE over time in a nationwide cohort of patients with NDBE.

What You Need to Know

Background

Surveillance of patients with nondysplastic Barrett's esophagus (NDBE) has multiple limitations—we might increase the effectiveness of surveillance by identifying patients at low risk for progression.

Findings

In a large cohort of patients with NDBE, the risk of progression to malignancy was 0.68 per 100 person-years. This risk decreased significantly in patients with at least 2 consecutive endoscopies showing NDBE.

Implications for patient care

Stable persistence of NDBE can be used as an indicator of lower risk of progression. Patients with multiple negative findings from endoscopy might not benefit from routine surveillance, so surveillance could be discontinued at an earlier endpoint than currently recommended.

Methods

For this cohort study, we searched PALGA, the nationwide registry of histopathology and cytopathology, with approval of their Review Board to identify all patients with BE in the Netherlands. Since 1991, PALGA has complete national coverage, including all pathology laboratories from all academic and nonacademic hospitals in the Netherlands.[14] All reports in the database are registered as written summaries of conclusions of the original pathology report combined with diagnostic codes in line with the SNOMED (Systematised Nomenclature of Medicine) classification of the College of American Pathologists.[15] For each report, gender, age, date of pathology examination, summary text, and diagnostic codes are available.

Data Collection

Pathology reports between January 2003 and December 2012 were reviewed to identify all adult patients in the Netherlands who underwent endoscopic biopsy and got a new diagnosis of BE. BE was defined as the presence of metaplastic epithelium with goblet cells in esophageal biopsies. The search was performed with the following diagnostic codes, a combination of *esophagus* and *intestinal metaplasia* or *Barrett's metaplasia*. For detailed information, see Supplementary Table 1. The following exclusion criteria were used: a previous or synchronous diagnosis of atypia, dysplasia or EAC at initial diagnosis, histological follow-up <1 year, or development of an adenocarcinoma distal to the gastric cardia or other gastric malignancies. Furthermore, to avoid underestimating of the malignant progression rate, all summary texts of the pathology reports, coded as "Barrett's metaplasia," were manually reviewed to exclude cases without intestinal metaplasia.[16] Pathology reports coded as esophageal malignancy were reviewed to exclude patients who developed other histological subtypes of esophageal cancer. To avoid an effect of the (nondetected) co-presence of dysplasia in the set of biopsies during initial NDBE diagnosis, patients with a diagnosis of dysplasia or EAC within the first year after initial diagnosis were excluded from the primary analysis.

For each patient admitted to the cohort, all pathology reports from 1991 to the end of the study period (May 2016) related to the esophagus were collected. Diagnostic codes and synonyms for indefinite for dysplasia, LGD, HGD, and EAC were identified by manually examining a random sample of 200 reports in the database, after which all other reports were automatically searched for these identified terms. Complete pathology reports (including clinical data and macroscopic and microscopic findings) were retrieved for all patients with dysplasia or EAC during follow-up to document whether another pathologist confirmed the diagnosis. Where present, the pathology reports of surgical and endoscopic resection specimens were evaluated to verify the location of the tumor. For each surveillance endoscopy, the final diagnosis was defined as the highest grade of dysplasia in the same set of biopsies. Since a repeat endoscopy is frequently performed within 3 months in patients with esophagitis, and review by 2 pathologists is warranted for patients with dysplasia of any grade, a pathology report within 3 months was not considered to be a surveillance endoscopy. Therefore, for each pathology report the diagnosis was defined as the highest grade of dysplasia during the 3-month period after that report in case of an endoscopy performed within 3 months, and as agreement after revision when the pathology slides have been reviewed by a second pathologist.

Verification Cohort

In the total study cohort, diagnosing BE required only the histological presence of intestinal metaplasia. However, to diagnose BE, columnar epithelium has to be located at least 1 cm proximal to the gastric folds.[5,6] To verify the diagnosis of BE, we compiled a verification cohort. This cohort consisted of the part of the total cohort that had at least 1 biopsy evaluated at the Radboud University Medical Center in Nijmegen. Subsequently, we collected corresponding endoscopic data and length of the BE segment to assess the rate of misdiagnoses of NDBE (ie, length of the BE segment <1 cm).

Data Analysis

Endpoints were development of EAC, or the combined endpoint of HGD and EAC, occurring at least 12 months after an initial biopsy showing presence of NDBE. Dysplasia occurring in squamous epithelium was not included as an outcome.

For each patient, incidence rates (IRs) with 95% confidence interval (CIs) for progression to EAC, or HGD EAC, were calculated as the number of events divided by person-years of follow-up and were expressed as events per 100 person-years (%/year) of follow-up. Follow-up time was considered as time elapsed from initial NDBE diagnosis to last follow-up endoscopy, defined as EAC diagnosis, HGD diagnosis if EAC did not occur subsequently, or last histopathology report in the database (through May 2016), whichever came first.

We assessed the effects of the number of endoscopies showing NDBE, the persistence of NDBE over time, and the calendar year of BE initial diagnosis (2003–2012) on the malignant progression rates. Poisson regression was used to compare IRs and calculate IR ratios (IRRs).[17] To account for varying periods of follow-up, log-transformed person-time was included in the model as an offset. We adjusted for sex and age at endoscopy date. Descriptive data are presented as mean $\pm$ SD or median (interquartile range [IQR]) (when data are not normally distributed) for continuous variables and frequency and percentage for categorical variables. Comparisons between groups and included and excluded patients were calculated by using Fisher exact test, Mann-Whitney U test, or unpaired t test when appropriate. A 2-sided P value of $<.05$ was considered to be statistically significant. All analyses were conducted using SPSS version 22.0 (IBM Corp, Armonk, NY).

For the analysis of malignant progression rates by the number of consecutive endoscopies showing NDBE, we categorized patients into 5 individual overlapping cohorts according to the number of consecutive endoscopies that showed NDBE. Persistent NDBE was defined as at least 2 consecutive endoscopies showing NDBE (initial NDBE diagnosis and the first follow-up diagnosis). Patients who had 1, 2, 3, 4, and $\geq$5 consecutive endoscopies, beginning with the initial endoscopy, and at least 1 ensuing surveillance endoscopy were included in group 1, 2, 3, 4, and 5, respectively. For each group, the duration of follow-up was calculated from the date of the last persistent NDBE endoscopy until last histopathology report in the database. Hence, this will indicate the malignant progression risk in the period after the last persistent NDBE endoscopy.

To address the time-dependent component and to include mainly endoscopies performed as part of a surveillance program, additional analyses were performed by redefining the patient subgroups. We considered that an endoscopy performed within 1 year of the preceding endoscopy was not performed as a surveillance endoscopy, but possibly due to for example gastrointestinal symptoms or abnormalities at the preceding endoscopy without pathologic confirmation of neoplasia. In this analysis, we considered the first endoscopy showing NDBE as initial BE diagnosis and follow-up endoscopies as those performed at least 1 year apart. For the second, third, fourth, and fifth endoscopy to count, at least 1 year was required as the minimum time interval between endoscopies showing NDBE. Patients with repeat endoscopies <1 year of the preceding endoscopy, thus probably not performed in the context of a surveillance program, were analyzed separately.

To assess the impact of discontinuing surveillance after 1, 2, 3, 4, and 5 endoscopies showing NDBE and, hence, the risk of missing HGD or EAC, we performed an analysis to calculate the sensitivity and specificity for detecting HGD or EAC. Numbers needed to screen, when surveillance after up to 5 endoscopies was not stopped, were calculated using the reciprocal of the absolute risk reduction.

To assess the effect of persistent NDBE over time, we calculated the progression-free time for each patient. The progression-free time is defined as the time from initial NDBE diagnosis until last endoscopy showing NDBE in patients with progression to dysplasia or EAC, or until the penultimate endoscopy showing NDBE in patients without progression. The area under the receiver-operating characteristic (ROC) curve was applied to evaluate the prognostic impact of length of progression-free time in predicting malignant progression. Therefore, we transformed the time-dependent endpoint (HGD or EAC) into a binary endpoint that is clinically relevant (ie, development of HGD or EAC within 10 years). Hence, only patients who had a minimum of 10 years of follow-up or who progressed to HGD or EAC within 10 years could be included in this analysis. The cutoff value for the risk of malignant progression was determined from the ROC curve at the cutoff point with the most optimal sensitivity and specificity.

Sensitivity Analysis

Persistent LGD is an indication for endoscopic treatment according to current guidelines. As sensitivity analysis, we used treated LGD and HGD or EAC development as an outcome for malignant progression to

correct for prevented HGD or EAC by endoscopic treatment. Treated LGD was defined as squamous epithelium without intestinal metaplasia or a neo-Z line on endoscopies following at least 2 LGD diagnoses. The date of the last LGD diagnosis before treatment was taken as the date of malignant progression (the outcome).

In a second sensitivity analysis, we assessed the effect of misclassification of BE on the progression rates toward HGD or EAC given the very low risk of malignant progression in patients with BE <1 cm (Supplementary Methods).

Results

Patients

In total, 35,161 patients with a first histological diagnosis of NDBE between 2003 and 2013 were identified (Figure 1). After using the exclusion criteria, 12,728 patients were included in the main analysis, who were followed up for a maximum of 13 years. The demographic features of the study population are shown in Supplementary Table 2.

Surveillance Patterns

A total of 38,998 surveillance endoscopies were performed within the study cohort, with a median of 3 endoscopies per patient (range, 2–16). Patients were followed for a total of 64,537 years (median time per patient 4.4 [IQR, 3.0–6.8] years). Median time interval between initial endoscopy and first follow-up endoscopy was 2.3 (IQR, 1.8–3.2) years. Mean age at the last performed endoscopy was 63 ± 11 years.

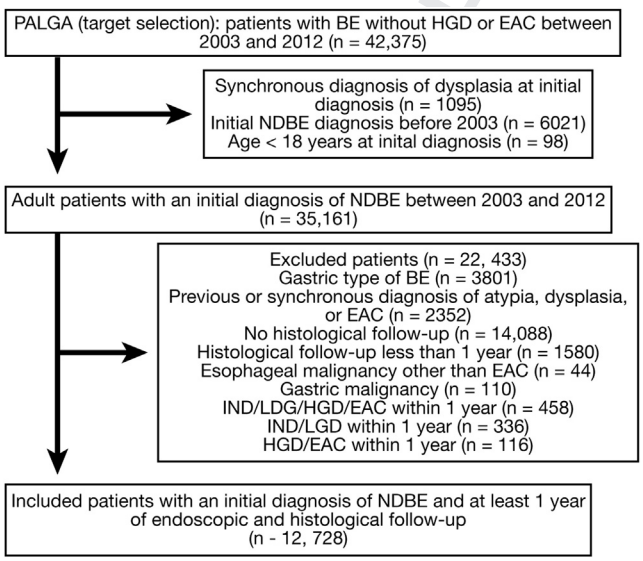


Figure 1. Flowchart of included patients. BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus.

Verification Cohort

Our verification cohort consisted of 218 patients with NDBE who had undergone an upper endoscopy at the Radboud university medical center. Of these, 197 (90.4%) patients had a BE segment ≥1 cm, with a median length of 3.0 (IQR, 1.0–4.3) cm. Twenty-one (9.6%) patients only had an irregular Z line (endoscopic extent of esophageal columnar mucosa <1 cm). Of those, none progressed to dysplasia or EAC during follow-up (median 2.91 years). Patients with BE <1 cm underwent significantly fewer endoscopies than patients with a BE segment ≥1 cm (median 2 [IQR, 2–3] vs 3 [IQR, 2–4]; $P = .01$).

Incidence of Dysplasia and EAC

Progression beyond NDBE was observed in 1654 (13%) patients. Supplementary Tables 3 and 4 show that a substantial number of dysplasia diagnoses (65%) was confirmed by a second pathologist and that the vast majority of detected adenocarcinomas (96%) was clearly originating from a Barrett's segment. During the follow-up period (2003–2016) malignant progression was seen in a total of 436 patients (304 EAC) (3.4%), after a median follow-up of 4.9 (IQR, 3.1–7.3) years. This results in an IR of EAC and the combined endpoint of HGD of EAC of 0.47 (95% CI, 0.42–0.53) and 0.68 (95% CI, 0.61–0.74) per 100 person-years, respectively.

Persistent NDBE and Incidence of HGD and EAC

At the first follow-up endoscopy, 219 (1.7%) patients with an initial diagnosis of NDBE were diagnosed with HGD or EAC after a median of 3.4 (IQR 2.2–6.0) years. Figure 3 demonstrates that only 61 (1.0%) patients and 22 (0.8%) progressed to HGD/EAC after 2 and 3 negative endoscopies, respectively.

Supplementary Table 5 summarizes the characteristics and progression risks across the 5 groups based on the number of endoscopies showing NDBE. On multivariate Poisson regression, there was a significantly decreased risk of malignant progression after at least 2 or 3 endoscopies showing NDBE compared with patients with only 1 NDBE endoscopy (adjusted IRR for 2 negative endoscopies, 0.72; 95% CI, 0.60–0.87; and adjusted IRR for 3 negative endoscopies, 0.65; 95% CI, 0.49–0.86). The IR did not decrease further in patients with at least 4 or 5 endoscopies showing NDBE (Figure 3).

In the subgroup of patients undergoing endoscopies at least 1 year apart, the risk of malignant progression is decreasing in patients with persistence of NDBE over consecutive surveillance endoscopies (HGD or EAC IR: 0.69, 0.50, 0.45, 0.45, and 0.22 per 100 person-years for 1–5 negative endoscopies, respectively) (Table 1 and Figure 3). On the contrary, the HGD or EAC IRs are

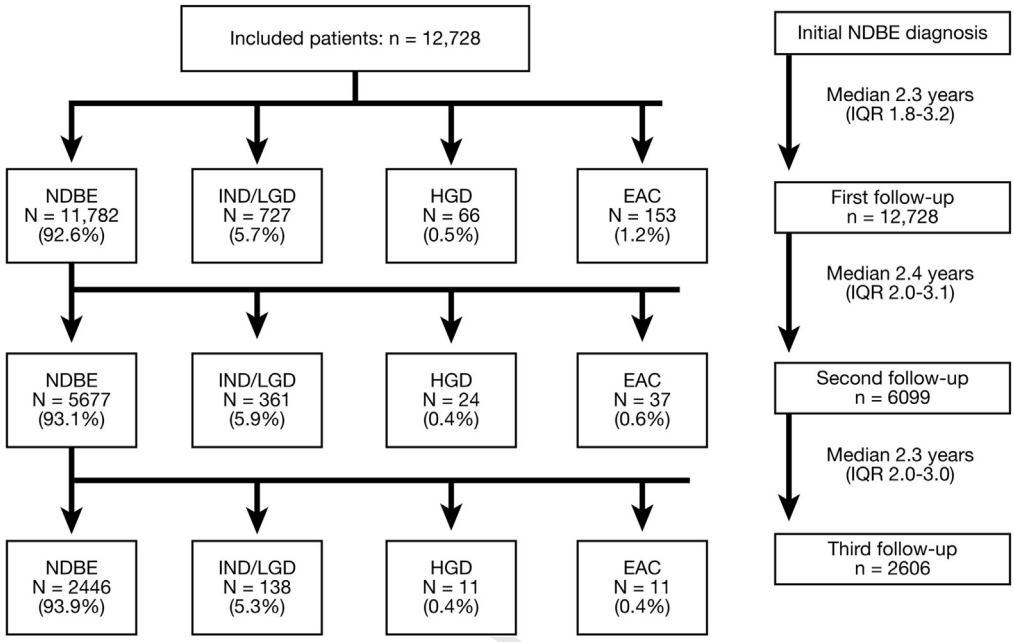


Figure 2. Flowchart of patients with nondysplastic Barrett's esophagus (BE) and their follow-up diagnoses. EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus.

increasing in patients with repeat endoscopies <1 year (HGD or EAC IR: 0.51, 0.69, 0.71, 0.92, and 1.09 per 1000 patient-years for persistence of NDBE on 1–5 endoscopies, respectively).

The sensitivity and specificity for detecting HGD or EAC after discontinuing surveillance after 1, 2, 3, 4, and 5 negative endoscopies are shown in Figure 4. In our cohort, 32 HGD or EAC cases will be missed, but 1800 patients will not undergo unnecessary surveillance endoscopies when surveillance is discontinued after 3 negative endoscopies.

Persistence of NDBE Over Time

Subsequently, we assessed HGD or EAC risk according to the duration of progression-free follow-up regardless of the number of endoscopies. The IR of HGD or EAC decreased with approximately 14% for each year of follow-up without progression (adjusted IRR, 0.86; 95% CI, 0.81–0.92). For the subgroup of patients with at least 10 years of follow-up or development of HGD or EAC within 10 years (n = 1219), the association between the number of patients developing HGD or EAC and progression-free time as a risk stratification tool is shown in Figure 5*A*. Based on these results a ROC curve was constructed, which showed an area under the ROC curve of 0.86 (95% CI, 0.85–0.88; $P < .001$) (Figure 5*B*). Therefore progression-free time can be considered a good predictor for risk of malignant progression. A cutoff value of 4 years of progression-free time was associated with a sensitivity and specificity of 90.4% (95% CI, 87.1%–93.1%) and 72.4% (95% CI, 69.2%–75.5%) for detecting HGD or EAC, respectively.

Lastly, we examined malignant progression rates according to calendar year of BE diagnosis. We did not observe an increasing trend in malignant progression rates across the calendar years in the total cohort (Supplementary Figure 1).

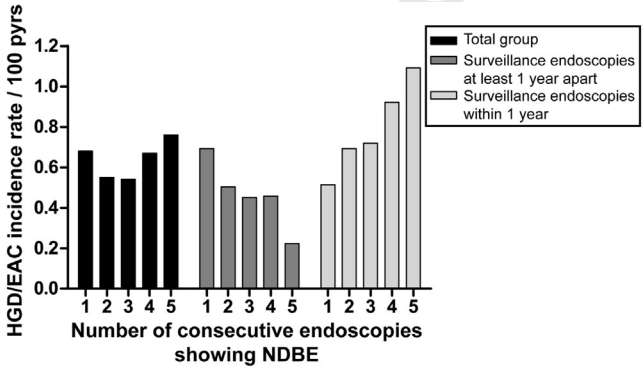


Figure 3. Incidence rates of high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) among consecutive endoscopies showing nondysplastic Barrett's esophagus (NDBE) in the total cohort (left), the group of patients undergoing surveillance endoscopies at least 1 year apart (middle), and the group of patients undergoing surveillance endoscopies within 1 year (right).

Sensitivity Analyses

A comparison between patients who were and who were not included in the main study cohort is shown in Supplementary Table 2. Patients with malignant progression within 1 year of follow-up and patients without follow-up were significantly older than patients in the study cohort (67 ± 12 and 64 ± 14 vs 58 ± 11.5; $P < .001$).

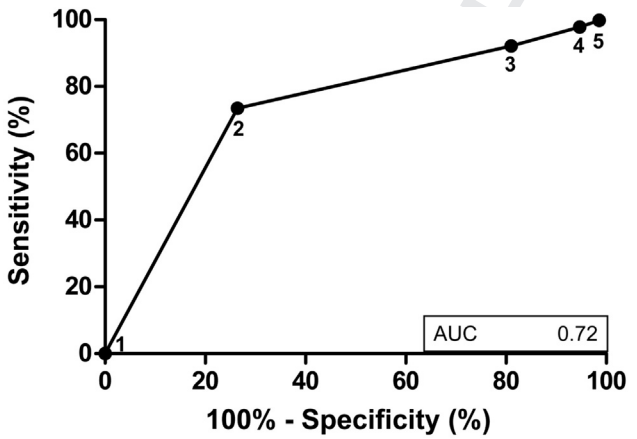
In the sensitivity analysis including treated LGD combined with HGD or EAC as an outcome, the number of outcomes increased by 23 to a total of 459. This resulted in an IR of 0.71 per 100 person-years (95% CI, 0.65–0.78; $P = .43$).

Table 1. Group Characteristics and Risk of Progression to EAC and HGD or EAC Based on the Number of Consecutive Endoscopies Showing NDBE in Patients Undergoing Surveillance Endoscopies at Least 1 Year Apart

Variable	Upper Endoscopies Showing NDBE				
	1 n = 11,684	2 n = 4888	3 n = 1832	4 n = 579	5 n = 161
Male	7928 (67.9)	3399 (69.5)	1275 (69.6)	421 (72.7)	119 (73.9)
Age, y	57.9 ± 11.5	58.8 ± 10.7	59.7 ± 10.3	61.1 ± 10.2	61.2 ± 9.9
Time to nth FU endoscopy, y	0.0 (0.0–0.0)	2.4 (1.8–3.0)	4.3 (3.8–5.2)	6.3 (5.7–7.1)	8.1 (7.3–8.7)
FU after n endoscopies, y	4.4 (3.0–6.7)	3.7 (2.8–5.9)	3.2 (2.5–5.1)	3.1 (2.4–4.1)	2.4 (2.1–3.3)
EAC					
Development of EAC	280 (2.4)	65 (1.3)	18 (1.0)	5 (0.9)	1 (0.6)
EAC incidence rate/100 PY (95% CI)	0.48 (0.42–0.53)	0.30 (0.24–0.38)	0.25 (0.16–0.39)	0.25 (0.09–0.56)	0.22 (0.11–1.10)
Unadjusted incidence rate ratio (95% CI)[a]	1.00 (reference)	0.64 (0.48–0.83)	0.53 (0.32–0.84)	0.53 (0.22–1.29)	0.47 (0.07–1.88)
Adjusted incidence rate ratio (95% CI)[a,b]	1.00 (reference)	0.56 (0.43–0.73)	0.42 (0.26–0.68)	0.36 (0.15–0.87)	0.28 (0.04–1.98)
HGD/EAC					
Development of HGD/EAC	407 (3.5)	108 (2.2)	32 (1.7)	9 (1.6)	1 (0.6)
HGD/EAC incidence rate/100 PY (95% CI)	0.69 (0.63–0.76)	0.50 (0.41–0.61)	0.45 (0.31–0.63)	0.45 (0.22–0.84)	0.22 (0.11–1.10)
Unadjusted incidence rate ratio (95% CI)[a]	1.00 (reference)	0.73 (0.59–0.90)	0.65 (0.45–0.93)	0.66 (0.34–1.28)	0.32 (0.05–2.29)
Adjusted incidence rate ratio (95% CI)[a,b]	1.00 (reference)	0.65 (0.52–0.80)	0.52 (0.36–0.74)	0.46 (0.24–0.88)	0.20 (0.03–1.39)

Values are n (%), mean ± SD, or median (interquartile range), unless otherwise indicated.
CI, confidence interval; EAC, esophageal adenocarcinoma; FU, follow-up; HGD, high-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; PY, patient-years.
[a]Poisson regression used to calculate incidence rate ratio using the first upper endoscopy as the reference group.
[b]Poisson model adjusted for gender and age at nth FU endoscopy.

In a second sensitivity analysis accounting for the possible inclusion of patients without endoscopic presence of BE, we observed that only a misclassification rate of more than 25% will significantly influence the HGD or EAC IR (IR, 0.78; 95% CI, 0.72–0.87; $P = .02$). The possible inclusion of patients with BE <1 cm did not significantly change progression rates in patients with 2 consecutive endoscopies showing NDBE ($P = .67$) (Supplementary Figure 2).



Surveillance after *n* endoscopies	1	2	3	4	5
Number needed to screen	29	45	57	64	161

Figure 4. Impact of discontinuing surveillance and risk of missing high-grade dysplasia or esophageal adenocarcinoma after 1, 2, 3, 4, and 5 endoscopies showing nondysplastic Barrett's esophagus expressed in sensitivity and specificity and corresponding numbers needed to screen to detect 1 case of high-grade dysplasia or esophageal adenocarcinoma, when not ceasing surveillance after 1, 2, 3, 4 and 5 negative endoscopies. AUC, area under the receiver-operating curve.

Discussion

In this large, population-based cohort study of 12,728 patients with NDBE, we observed that the risk of malignant progression decreased by 28% in patients with consecutive endoscopies showing persistence of NDBE. This risk decreases even further among more negative endoscopies in patients with surveillance endoscopies performed at least 1 year apart. For every year of follow-up without progression, the risk of HGD or EAC decreased with 14%.

Previous studies on malignant progression risk in patients with persistent NDBE have shown variable results. The results of our study are largely consistent with those reported in a multicenter prospective study.[11] In this study, 1401 patients were divided into 5 groups depending on the number of endoscopies showing NDBE. The annual risk of EAC declined progressively according to the number of negative endoscopies (1–5), from 0.32% to 0.27%, 0.16%, 0.20%, and 0.11%, respectively. Another study evaluated 480 patients with persistent NDBE.[13] The authors found a non–statistically significant decrease in the risk of progression in subjects with multiple endoscopies showing NDBE (hazard ratio, 0.51; 95% CI, 0.11–1.81). However, in the study population, only 16 subjects progressed to HGD or EAC, resulting in a too-low statistical power. In contrast to our results, a cohort study of 28,561 male BE patients showed that the annual risk of EAC increased with each successive

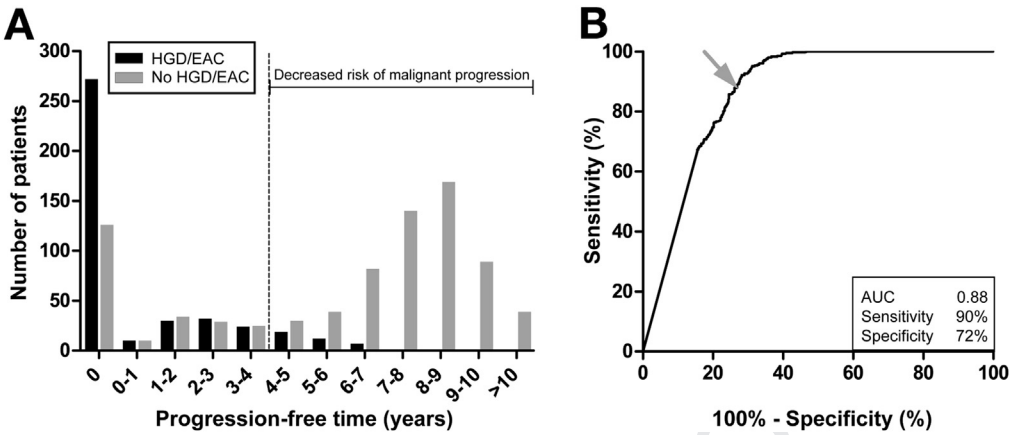


Figure 5. Comparison of length of progression-free time after an initial diagnosis of nondysplastic Barrett's esophagus between patients with and without development of (*A*) high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) and (*B*) the corresponding receiver-operating curve curves for the 1219 patients with at least 10 years of follow-up or development of HGD or EAC within 10 years. The vertical line and the arrow correspond to a cutoff value of 4 years. AUC, area under the receiver-operating curve.

non-neoplastic endoscopy (rate ratio per additional endoscopy, 1.43; 95% CI, 1.25–1.64).[12] However, this study assessed cancer risk in so-called non-neoplastic BE, as the dysplasia status was unknown in the vast majority of patients, while we assessed the risk in persistent NDBE. Therefore, it is possible that this increased risk of EAC was related to intense dysplasia surveillance, and due to repeated endoscopies in patients with dysplasia.

Potential sources of bias for the observed decreasing EAC IRs in patients with persistent NDBE could be the increasing incidence of EAC over years or the improved imaging techniques such as chromoendoscopy or virtual endoscopy in more recent years.[18] Therefore, we additionally assessed HGD or EAC risk according to calendar year. No increase in the risk of HGD or EAC in more recent years was observed, which supports that the decreasing risk is not due to improved diagnostic yield or changes in clinical practice.

In patients with at least 4 or 5 consecutive negative endoscopies, the decreasing risk of malignant progression was not observed in the total cohort. Added to a smaller sample size, we assume that the groups of patients with at least 4 or 5 negative endoscopies in the total cohort may have undergone a selection bias by inclusion of a subgroup of so-called high-risk patients. Patients with for example gastrointestinal symptoms or (slight) endoscopic or pathologic abnormalities, thus at highest risk for malignant progression, are likely to have undergone endoscopies (not in the context of a surveillance program) more frequently. This is supported by the shorter time interval between endoscopies in patients with 4 or 5 endoscopies showing NDBE. Additionally, in patients who are more likely to follow a surveillance program (ie, endoscopies performed at least 1 year apart) the risk of malignant progression is decreasing (0.69, 0.50, 0.45, 0.45, 0.22), which supports our hypothesis.

Dysplasia is commonly missed at initial endoscopy, due to poor adherence to biopsy protocols, sampling error, and overlying erosive esophagitis. This supported by the high rate of progression within 1 year after initial diagnosis in our cohort (n = 458). The decreasing incidence of HGD or EAC among patients with persistent NDBE could be due to the miss rate of prevalent dysplasia or EAC at the time of BE diagnosis.[19] With consecutive nonprogressive endoscopies the risk of false negative results decreases, which improves the negative predictive value of the endoscopy. The results of this study implicate that the risk of prevalent dysplasia or cancer may be increased for more than 1 year after a BE diagnosis.

Recently, an analysis of NDBE patients has suggested that the extent of clonal diversity at baseline is a strong predictor of progression and that this diversity will not change over time.[20] Patients with progression may already have a high level of clonal diversity, whereas patients with persistent NDBE have a low level of diversity, and hence a lower risk of progression.

Despite the growing evidence showing a low risk of EAC in patients with NDBE, guidelines recommend lifelong surveillance every 3–5 years.[5] In the current study, the vast majority (87.0%) of patients with NDBE did not show progression during the study period. Hence, this group would not benefit from a surveillance program and would only experience the associated burden and costs. As currently practiced, endoscopic surveillance has multiple limitations and improving the effectiveness by risk stratification is therefore of interest. Endoscopic treatment should be considered in patients at highest risk for malignant progression, and less strict surveillance for patients at lowest risk. Discontinuing surveillance after a certain age would resemble current colorectal surveillance strategies, where surveillance should not be routinely continued after 75 years of age, with individualized surveillance based on comorbidities and findings in prior colonoscopies for patients 75–85 years of age.[21] When surveillance is continued after 3 negative endoscopies, 57 patients would undergo

unnecessary surveillance endoscopies to detect 1 patient with HGD or EAC. Hence, results from our study imply that in patients with multiple negative endoscopies harms and costs may outweigh the potential benefits of a surveillance program. Surveillance may be discontinued at an earlier endpoint than currently recommended, in particular in patients with life-limiting comorbidity.

This study has several strengths. The study consists of a large cohort of BE patients who had multiple follow-up endoscopies. Due to the population-based design, patients with NDBE of all ages, both sexes, and diagnoses in primary, secondary, and tertiary centers were included. In the Netherlands, health care is basically accessible to all inhabitants, which eliminates diagnostic bias. This study reflects standard clinical practice, and its findings may be widely applicable within standard health care. Furthermore, endoscopic ablation of NDBE was not routinely performed in the Netherlands during the study period, which minimizes the risk of a change of the natural history of BE due to treatment. Additionally, adding treated LGD as an outcome did not significantly change the results.

Some limitations warrant consideration as well. First, no clinical and endoscopic data were available, and details regarding the indication and the number of biopsies are not uniformly registered. Therefore, progression risks could not be adjusted for known risk factors, such as length of the BE segment, presence of esophagitis, and use of medication.[22] Endoscopic confirmation is essential for a diagnosis of BE. Intestinal metaplasia on biopsy without being present on endoscopy could underestimate the malignant progression rate.[23] Our verification cohort suggests that only 10% of patients had a BE segment <1 cm. Furthermore, the sensitivity analysis showed that the possible inclusion of patients without endoscopic evidence of BE has only a minimal effect on the overall conclusions. Hence, the 10% rate we detected in the validation substudy (if extrapolated to the total population) is probably not important, as only a rate above 25% will impact the results. Second, in this study 14,088 NDBE patients did not undergo histologic follow-up. Older age, comorbidities, and misdiagnosis of BE (as patients with BE <1 cm are currently excluded from endoscopic surveillance) could possibly be an explanation.[5] As this group was relatively large, the actual progression risk might be even lower if symptomatic patients had undergone endoscopy more frequently. Third, there was a lack of central pathology review. However, contrary to dysplasia, both the reproducibility of intestinal metaplasia and the accuracy of diagnostic codes for BE are high.[24] Furthermore, additional immunohistochemistry, such as p53 staining and Alcian blue stain, was not performed on a routine basis.[22] Finally, all patients had varying periods of follow-up. We therefore presented the results of this study as events per 100 person-years of follow-up. The study was not designed to definitively answer questions concerning how long or how frequently patients with persistent NDBE should remain in surveillance. Further risk stratification is needed to conclusively identify patients in which surveillance can safely be discontinued.

In conclusion, this population-based analysis demonstrates a very low incidence of HGD or EAC among patients with NDBE. The risk decreases further after consecutive negative endoscopies performed at least 1 year apart. Persistent NDBE may be a useful risk stratification tool for future surveillance programs. Our findings suggest that lengthening of the surveillance intervals could be considered in a subgroup of patients with 3 or more surveillance endoscopies showing NDBE, and contribute to the growing evidence that there may be an endpoint for routine surveillance in patients with persistent NDBE. However, discontinuing surveillance should be considered with caution in patients with symptoms or with previous endoscopic findings that are suspicious for neoplasia development.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.08.033.

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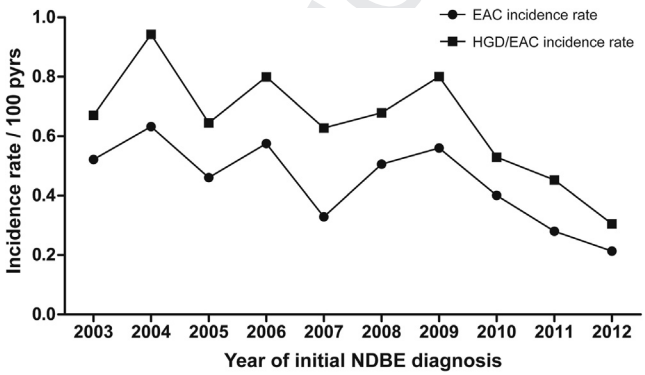
Acknowledgments
The authors would like to thank the PALGA foundation (especially Dr Q.J.M. Voorham and Dr L.I.H. Overbeek) for the help with the PALGA search strategy and PALGA data collection. Q6

Conflicts of interest
The authors disclose no conflicts.

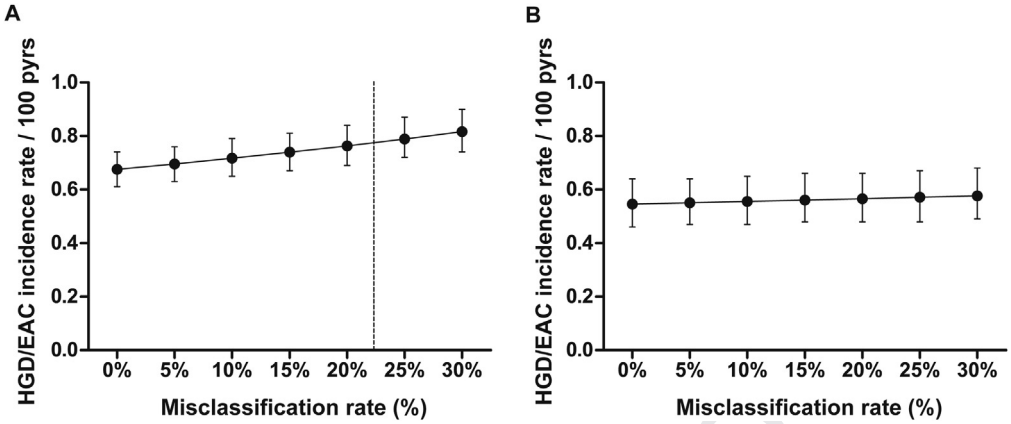
Supplementary Methods

Endoscopic confirmation is essential for a diagnosis of Barrett's esophagus (BE), intestinal metaplasia on biopsy without being endoscopically presented, could underestimate the malignant progression rate. In a sensitivity analysis, we assessed the effect of misclassification of BE on the progression rates toward high-grade dysplasia or esophageal adenocarcinoma. Patients with BE <1 cm likely have a negligible risk of malignant progression. Hence, the possible inclusion of patients with BE <1 cm will increase the total follow-up time, thereby decreasing the malignant progression rate. Based on our verification cohort, the total follow-up time will decrease with 2.91 years (ie, median follow-up) multiplied by the number of misclassified patients. Subsequently, we estimated incidence rates of high-grade dysplasia or esophageal adenocarcinoma for different rates of misclassification of BE.

We performed a similar analysis in patients with persistent nondysplastic Barrett's esophagus at 2 consecutive endoscopies.



Supplementary Figure 1. Incidence rates of esophageal adenocarcinoma (EAC) and the combined endpoint of high-grade dysplasia (HGD) and EAC based on calendar year of initial nondysplastic Barrett's esophagus (NDBE) diagnosis.



Supplementary Figure 2. (*A*) Estimate of the change in incidence rates of high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) based on the percentage of patients misclassified as Barrett's esophagus (BE). Only a misclassification rate of more than 25% will significantly influence the HGD or EAC incidence rate ($P = .02$). (*B*) Estimate of the change in incidence rates of HGD and EAC in patients with persistent nondysplastic BE at 2 consecutive endoscopies based on the percentage patients misclassified as BE at initial endoscopy. The inclusion of patients without BE at initial endoscopy did not significantly change the HGD or EAC incidence rates ($P = .67$).

Supplementary Table 1. Search Strategy, PALGA Diagnostic Codes, and Words Used in Analysis

Variable	PALGA Codes	Words in Pathology Conclusion
Esophagus	T62000, T62010	Slokdarm, oesofagus, esophagus
Barrett's esophagus	T62… + M73320	/
	T62310M73330	Intestinal metaplasia, distinctive type, specialized type
Indefinite for dysplasia	No diagnostic codes	Indefinite, undetermined, correction for misspellings.
Low-grade dysplasia	M74000, M74006, M74007	Laaggradige dysplasie, low grade dysplasia, geringe dysplasie, lichte dysplasie, matige dysplasie
High-grade dysplasia	M74008, M81402	Hooggradige dysplasie, high grade dysplasia, ernstige dysplasie, sterke dysplasie, adenocarcinoom in situ
Esophageal adenocarcinoma	M80003, M80011, M80101, M80103, M80105, M81403, M81453, M84803, M81443	Adenocarcinoom, Intramucosaal carcinoom, Gedifferentieerd carcinoom

PALGA terminology: http://www.palga.nl/palga/thesaurus.nsf.

Supplementary Table 2. Baseline Characteristics and Risk of Progression to EAC and HGD or EAC Combined of Patients Included and Excluded From This Study

	Included Patients	Excluded Patients							
	Total Cohort (n = 12,728)	Progression to HGD/EAC Within 1 Year of Follow-Up (n = 116)	*P* Value	Atypia during initial NDBE diagnosis (n = 555)	*P* Value	FU Endoscopies Without Esophageal Biopsy Sampling (n = 750)	*P* Value	Patients Without Follow-Up (n = 13,338)	*P* Value
Sex			.002		.456		<.001		<.001
- Male	8673 (68.1)	95 (81.9)		370 (66.7)		408 (54.4)		8363 (62.7)	
- Female	4055 (31.9)	21 (18.1)		185 (33.3)		342 (45.6)		4975 (37.3)	
Age, y	57.9 ± 11.5	67.0 ± 12.4	<.001	59.08 ± 11.53	.017	61.29 ± 12.60	<.001	64.6 ± 14.1	<.001
Follow-up, y	4.4 (3.0–6.7)	0.2 (0.1–0.5)	<.001	4.6 (3.0–7.3)	.19	0			<.001
EAC									
Progression to EAC	304 (2.4)	91 (78)	<.001	26 (4.7)	.002	NA		NA	
EAC incidence rate/100 PY (95% CI)	0.47 (0.42–0.53)	NA		0.88 (0.59–1.27)	.006	NA		NA	
Time to EAC diagnosis, y	5.1 (3.3–7.3)	0.17 (0.06–0.50)	<.001	3.99 (2.51–5.31)	.068	NA		NA	
HGD/EAC									
Progression to HGD/EAC	436 (3.5)	116 (100)	<.001	33 (5.9)	.002	NA		NA	
HGD/EAC incidence rate/100 PY (95% CI)	0.68 (0.61–0.74)	NA		1.13 (0.78–1.56)	.016	NA		NA	
Time to HGD/EAC diagnosis, y	4.9 (3.2–7.3)	0.19 (0.07–0.41)	<.001	4.15 (2.91–5.24)	.077	NA		NA	

NOTE. Values are n (%), mean ± SD, or median (interquartile range), unless otherwise indicated.

CI, confidence interval; EAC, esophageal adenocarcinoma; FU, follow-up; HGD, high-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; PY, patient-years.

Supplementary Table 3. Dysplasia Cases Confirmed by a Second Pathologist

Variable	IND n = 510	LGD n = 977	HGD n = 170
External revision[a]	101 (19.8)	191 (19.5)	95 (55.9)
Internal revision[b]	230 (45.1)	409 (41.9)	56 (32.9)
No revision, persistent dysplasia, or progression to LGD/HGD/EAC	34 (6.7)	81 (8.3)	12 (7.1)
No revision	145 (28.4)	268 (27.4)	7 (4.1)

NOTE. Values are n (%).
EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia.
[a]External revision was defined as present if a second expert pathologist in an expert center confirmed the diagnosis.
[b]Internal revision was defined as present if a second pathologist confirmed the diagnosis.

Supplementary Table 4. Location and Presence of Surgical or Endoscopic Resection Specimens of the 304 Detected Adenocarcinomas

Location	Final Diagnosis Made by		
	Biopsy	EMR	Surgical Resection
Esophagus (n = 292)	101 (34.6)	120 (41.1)	71 (24.3)
GE junction or cardia (n = 6)	4 (66.7)	0 (0.0)	2 (33.3)
Unknown (n = 6)	6 (100)	0 (0.0)	0 (0.0)

NOTE. Values are n (%).
EMR, endoscopic mucosal resection; GE, gastroesophageal.

Supplementary Table 5. Group Characteristics and Risk of Progression to EAC and HGD or EAC Based on the Number of Consecutive Endoscopies Showing NDBE

Variable	Consecutive Upper Endoscopies Showing NDBE				
	1 n = 12,728	2 n = 6278	3 n = 2677	4 n = 1051	5 n = 378
Male	8673 (68.1)	4359 (69.4)	1861 (69.5)	751 (72.7)	277 (73.3)
Age, y	57.9 ± 11.5	58.8 ± 11.0	59.7 ± 10.7	60.7 ± 10.7	60.7 ± 10.3
Time to nth FU endoscopy, y	0.0 (0.0–0.0)	2.0 (1.2–2.8)	4.0 (3.0–5.0)	5.8 (4.3–6.6)	6.9 (5.1–8.1)
FU after n endoscopies, y	4.4 (3.0–6.7)	3.7 (2.7–6.0)	3.3 (2.4–5.2)	3.1 (2.3–4.4)	2.4 (2.1–3.9)
EAC					
Development of EAC	304 (2.4)	101 (1.6)	38 (1.4)	18 (1.7)	5 (1.3)
EAC incidence rate/100 PY (95% CI)	0.47 (0.42–0.53)	0.37 (0.30–0.44)	0.36 (0.26–0.49)	0.49 (0.30–0.75)	0.42 (0.16–0.94)
Adjusted incidence rate ratio (95% CI)[a,b]	1.00 (reference)	0.69 (0.55–0.87)	0.62 (0.44–0.86)	0.74 (0.46–1.20)	0.60 (0.25–1.45)
HGD/EAC					
Development of HGD/EAC	436 (3.5)	150 (2.4)	57 (2.1)	25 (2.4)	9 (2.4)
HGD/EAC incidence rate/100 PY (95% CI)	0.68 (0.61–0.74)	0.55 (0.46–0.64)	0.54 (0.41–0.69)	0.67 (0.45–0.98)	0.76 (0.37–1.40)
Adjusted incidence rate ratio (95% CI)[a,b]	1.00 (reference)	0.72 (0.60–0.87)	0.65 (0.49–0.86)	0.73 (0.49–1.09)	0.76 (0.39–1.47)

NOTE. Values are n (%), mean ± SD, or median (interquartile range), unless otherwise indicated.
EAC, esophageal adenocarcinoma; FU, follow-up; HGD, high-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; PY, patient-years.
[a]Poisson regression used to calculate incidence rate ratio using the first upper endoscopy as the reference group.
[b]Poisson model adjusted for gender and age at nth FU endoscopy.