Patients With Barrett's Esophagus and Persistent Low-grade Dysplasia Have an Increased Risk for High-grade Dysplasia and Cancer

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BACKGROUND & AIMS: In some patients with Barrett's esophagus (BE) and a confirmed diagnosis of low-grade dysplasia (LGD), the LGD is not detected during follow-up examinations. We would like to avoid the unnecessary risks and costs of ablative treatment for these patients. Therefore, we investigated whether persistent LGD increases risk for high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) and what proportion of patients are no longer found to have dysplasia after an initial diagnosis of LGD.

METHODS: In a retrospective study, we collected information on 1579 patients with BE and LGD from 2005 through 2010 by using a nationwide registry of histopathology diagnoses in the Netherlands (PALGA). Confirmed LGD was defined as a diagnosis of LGD that was confirmed by any other pathologist. Persistent LGD was defined as LGD detected at the first and follow-up endoscopy. Data were collected on patients until treatment for HGD, detection of EAC, or the last endoscopy at which a biopsy was collected (through July 2014). We evaluated whether persistent LGD was a risk factor for malignant progression by using univariable and multivariable Cox regression analyses.

RESULTS: Of individuals with BE and LGD in the database, the diagnosis of LGD was confirmed for 161 patients (10% of total). In these patients, the incidence of HGD and/or EAC was 5.18/100 person-years (95% confidence interval [CI], 4.32–8.10/100 person-years) compared with 1.85/100 person-years (95% CI, 1.52–2.22/100 person-years) in patients for whom LGD was not confirmed at the first endoscopy. The incidence of EAC alone in patients with confirmed LGD was 2.51/100 person-years (95% CI, 1.46–3.99/100 person-years), compared with 1.01/100 person-years (95% CI, 0.41–2.10/100 person-years) in patients for whom LGD was not confirmed at the first endoscopy. Of patients in whom LGD was confirmed at the first endoscopic examination, 51% were not found to have dysplasia at the first follow-up endoscopy, and 30% had persistent LGD. In patients with persistent LGD, the incidence of HGD and/or EAC was 7.65/100 person-years (95% CI, 4.45–12.34) and of only EAC was 2.04/100 person-years (95% CI, 0.65–4.92); in patients without persistent LGD, the incidence of HGD and/or EAC was 2.32/100 person-years (95% CI, 1.08–4.40/100 person-years) and of only EAC was 1.45 (95% CI, 0.53–3.21/100 person-years). Persistent LGD was found to be an independent risk factor for the development of HGD and/or EAC, with hazard ratio of 3.5 (95% CI, 1.48–8.28).

CONCLUSIONS: In a large population-based cohort study of patients with BE and LGD, the risk of progression to HGD and/or EAC was higher in patients with confirmed LGD and highest in those with confirmed and persistent LGD.

Keywords: Esophageal Cancer; Prognostic Factor; Esophagus; Marker.
See editorial on page 963.

Barrett’s esophagus (BE) is a premalignant condition in which squamous epithelium is replaced by intestinal columnar epithelium. It is considered to be a complication of longstanding gastroesophageal reflux disease and is a well-known risk factor for developing esophageal adenocarcinoma (EAC). During the past decades, the incidence of EAC has been rapidly rising in the Western world, with an average annual increase of 7.5% in men and 5.2% in women. Because EAC is frequently detected at an advanced stage, the prognosis of patients remains poor, with a reported 5-year survival rate of 25% for non-metastatic disease and a 2-year survival rate of 9% for metastatic disease.

Malignant progression in BE develops through consecutive histologic stages as defined by the Vienna classification from no dysplasia (ND) to low-grade dysplasia (LGD) and high-grade dysplasia (HGD), with EAC being the end stage. Despite numerous studies on possible biomarkers to predict malignant progression, dysplasia is the most important factor determining the management of BE. Patients with LGD have a higher risk for malignant progression compared with patients with ND and intensified surveillance is recommended to identify patients before progression to EAC. However, there are some uncertainties related to the natural course of LGD, because some patients progress to HGD, whereas in others the diagnosis of LGD is not reproduced over time.

Therapeutic interventions, ie, radiofrequency ablation (RFA) or endoscopic mucosal resection, are reserved for patients with HGD or early stage EAC. A recently published randomized trial suggested that patients with LGD, confirmed by an expert pathologist, also benefit from ablative therapy. However, ablative treatments are not without complications, eg, stricture formation after RFA has been reported in 7%-12% of cases. In addition, the authors also reported that 28% of patients in the control group had ND detected during follow-up. To avoid unnecessary risks and costs associated with ablative treatment, further risk stratification of patients with confirmed LGD is indicated.

The aims of the current study were to evaluate whether the finding of persistent LGD affects the incidence rates of HGD or EAC (HGD/EAC) and to report the proportion of patients with a diagnosis of ND in BE after an initial diagnosis of LGD in a large cohort of patients with BE.

Methods

Data Collection

The nationwide registry of histopathology diagnoses in the Netherlands (PALGA) database is a nationwide database including all pathology laboratories in the Netherlands. It was established in 1971 and has had nationwide coverage since 1991. The PALGA database was set up to facilitate communication between histopathology and cytopathology laboratories and to provide data to health care researchers. All histopathology reports in the database are registered as written conclusions of pathologists combined with the diagnostic code derived from Systemized Nomenclature of Medicine. It includes sample type, topologic and morphologic code. Patient identification is encrypted, and gender, age, and site of pathologic assessment are available for research purposes only.

In the current study, we used all histopathology reports from January 2005 to December 2010, with follow-up data until July 2014. The database was searched for all patients with a diagnostic code of BE and LGD. For detailed information see Supplementary Table 1. Cases with LGD, HGD, and EAC were detected by manually reviewing the collected summaries of the pathology reports of the first 100 cases. All synonyms and codes used for LGD, HGD, and EAC were documented. Then reports of all other cases were automatically searched for these earlier identified synonyms and codes. Exclusion criteria were HGD/EAC in the same set of biopsies during the index LGD diagnosis, a history of HGD/EAC before the index LGD diagnosis, index LGD diagnosis before 2005, and cases with no follow-up or follow-up of less than 1 year. Because a diagnostic code for indefinite for dysplasia (IND) is lacking and to exclude cases of gastric type metaplasia, which were incorrectly coded as intestinal type metaplasia, all included cases were manually reviewed to exclude these cases. In addition, we also documented whether another pathologist reviewed the diagnosis of LGD. A diagnosis of LGD was based on a revision if this was stated with a diagnostic code (*revision) or if it was clearly stated in the written conclusion of the pathology report. No difference was made between an expert and a general pathologist. Cases of prevalent HGD/EAC, defined as detected within 1 year after the initial LGD diagnosis, were excluded.

The Review Board of the PALGA foundation approved the study.

Definitions Used in This Study

Confirmed LGD was defined as present if a second pathologist confirmed the index LGD diagnosis, whereas it was defined as unconfirmed LGD if a diagnosis of LGD was not reviewed by a second pathologist. Persistent LGD was defined as LGD at 2 consecutive endoscopies (index LGD diagnosis and the first follow-up diagnosis).

Statistical Analysis

Baseline characteristics were analyzed by calculating means or medians for continuous variables and
frequencies and percentages for categorical variables. Comparisons between groups for baseline characteristics were calculated by using the χ² test, Mann-Whitney U test, or Student t test when appropriate. The malignant progression rate was calculated per 100 person-years of follow-up. Kaplan-Meier curves were used to evaluate the progression-free survival until the development of HGD/EAC. The equality of these curves was compared by using the log-rank test. Incidence rates were compared by using a mid-P exact test. To evaluate whether persistent LGD was a risk factor for malignant progression, univariable and multivariable Cox regression analysis was performed. Estimates of relative risk are presented as hazard ratios (HRs) with 95% confidence interval (CI). Statistical analyses were performed by using SPSS version 20.0 (IBM Corp, Armonk, NY). A two-sided P value of less than .05 was considered to be statistically significant.

**Results**

In total, 4109 patients with BE and LGD were identified in the PALGA database between 2005 and 2010. As shown in Figure 1, 1579 cases were included after using the exclusion criteria. Of these, 231 cases had a revision of the initial LGD diagnosis, and in 161 cases (70%) the diagnosis of LGD was confirmed by a second pathologist. The diagnosis was not reviewed by a second pathologist in the other 1348 cases (Figure 1). Table 1 shows baseline characteristics for the total cohort, the cases with confirmed LGD and cases with unconfirmed LGD.

The median time interval between index endoscopy and the first follow-up endoscopy was 11.7 months (interquartile range [IQR], 3.7–19.4). Patients with confirmed LGD had ND BE more frequently and for a longer period before the index LGD diagnosis compared with patients with unconfirmed LGD.

**Incidence of High-grade Dysplasia and Esophageal Adenocarcinoma**

In total, 144 of 1579 cases developed HGD/EAC and 82 of 1579 cases developed EAC during a median follow-up of 4.20 years (IQR, 2.76–5.96; 6918 patient-years), resulting in an incidence rate for HGD/EAC and EAC of 2.10 (95% CI, 1.78–2.46) and 1.19 (95% CI, 0.96–1.48) per 100 person-years, respectively. HGD/EAC was detected after a median follow-up of 2.25 years (IQR, 1.26–4.02), whereas the median follow-up before detecting EAC was 2.93 years (IQR, 1.71–4.37).

**Confirmed Low-grade Dysplasia and Incidence of High-grade Dysplasia/Esophageal Adenocarcinoma and Esophageal Adenocarcinoma**

Thirty-three patients of the 161 cases with confirmed LGD developed HGD/EAC during a median follow-up of 1.77 years (IQR, 1.24–2.99; 637 patient-years), resulting in an incidence rate of 5.18 (95% CI, 3.63–7.19) per 100 person-years. In contrast, 110 of the 1348 patients with unconfirmed LGD developed HGD/EAC during a median

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**Figure 1.** Flow chart of included patients in this study. PA, pathologic.
follow-up of 4.28 years (IQR, 2.83–6.04; 5939 patient-years), resulting in an incidence rate of 1.85 (95% CI, 1.52–2.22) per 100 person-years. Figure 2 shows the statistical difference in progression-free survival between confirmed and unconfirmed LGD ($P < .0001$).

Sixteen of 161 patients with confirmed LGD developed EAC, resulting in an incidence rate of 2.51 (95% CI, 1.49–3.99) per 100 person-years. In the cohort with unconfirmed LGD, 66 of 1348 patients developed EAC, resulting in an incidence rate of 1.01 (95% CI, 0.41–2.10) per 100 person-years.

Persistent Low-grade Dysplasia and Incidence of High-grade Dysplasia and Esophageal Adenocarcinoma

Eighteen patients (51%) with confirmed LGD diagnosis were diagnosed with ND BE in the follow-up endoscopy, whereas 49 (30%) had persistent LGD, as shown in Figure 3. In patients with confirmed and persistent LGD (median follow-up, 3.72 years; IQR, 1.78–5.38), the incidence rate of developing HGD/EAC or EAC alone was 7.65 (95% CI, 4.45–12.34) and 2.04 (95% CI, 0.65–4.92) per 100 person-years, respectively. The incidence rate in patients with ND BE at the first follow-up endoscopy after an initially confirmed LGD diagnosis was significantly lower, 2.32 (95% CI, 1.08–4.40; $P < .0001$) and 1.45 (95% CI, 0.53–3.21; $P = .007$) for HGD/EAC and EAC, respectively. In addition, patients with 2 consecutive endoscopies showing ND BE after a confirmed LGD diagnosis (29%, $n = 46$) developed no HGD/EAC during a follow-up of 117 patient-years.

Similar results were observed in patients with unconfirmed LGD. In the group with unconfirmed persistent LGD ($n = 396$) (median follow-up, 4.41 years; IQR, 2.89–6.38), the incidence rate of developing HGD/EAC and EAC alone was 2.63 (95% CI, 1.73–3.15) and 1.43 (95% CI, 0.95–2.06) per 100 person-years, respectively. In contrast, in patients with ND BE after an unconfirmed LGD diagnosis ($n = 765$) (median follow-up, 4.35 years; IQR, 2.99–5.95), the incidence rate was significantly lower, 0.99 (95% CI, 0.70–1.37; $P < .001$) and 0.38 (95% CI, 0.21–0.63; $P < .0001$) per 100 person-years, respectively.

In addition to persistent LGD, the incidence rate of developing HGD/EAC showed a tendency ($P = .19$) to be higher in patients with confirmed LGD with LGD duration $>1$ year ($n = 24$) compared with those with confirmed LGD with LGD duration $<1$ year ($n = 25$), 9.91 (95% CI, 4.94–17.73) and 4.60 (95% CI, 1.24–11.77), respectively.

Risk Factors for Malignant Progression

Persistent LGD was found to be an independent risk factor for the development of HGD/EAC with HR of 3.5 (95% CI, 1.48–8.28) (Table 2). Gender, age, and history of ND BE did not affect the risk of developing HGD/EAC. Because persistent LGD was the only independent risk factor for progression to HGD/EAC, no multivariate Cox regression analysis was performed.

Discussion

In this large population-based cohort study of patients with BE and LGD, we observed in patients with confirmed and persistent LGD an increased risk of malignant progression during follow-up. In addition, we also found that more than 50% of patients with confirmed LGD had a diagnosis of ND during the first follow-up endoscopy (Figure 3).
A considerable number of studies have reported on the risk of malignant progression in BE with LGD. The incidence rate of 2.10 (95% CI, 1.78–2.46) per 100 person-years for developing HGD/EAC and 1.19 (95% CI, 0.96–1.48) for developing EAC in the whole group of patients with LGD, as observed in this study, is comparable with the results reported in a recent meta-analysis. These authors calculated a pooled annual incidence rate of 1.73 (95% CI, 0.99–2.47) for HGD/EAC and 0.54 (95% CI, 0.32–0.76) for EAC alone in BE with LGD. Nonetheless, substantial heterogeneity was reported to be present between studies.

The malignant progression rate in BE with LGD has been debated for a long time. Reasons for this are the well-known interobserver variability between various pathologists, the population in which progression of BE is studied, and sampling error because only a small proportion of the Barrett’s segment is sampled during surveillance endoscopy.

High interobserver variability is a well-known problem during histologic assessment of BE. LGD diagnosed in general practice is regularly downgraded to ND BE when reviewed by expert pathologists. Moreover, several studies have reported that confirmation of LGD by an expert pathologist is associated with an increased risk of malignant progression, although this has not uniformly been shown.

In this nationwide cohort study, we provide further evidence that a diagnosis of confirmed LGD is indeed associated with an increased risk of progression to EAC as demonstrated by a significantly increased incidence rate of 2.51 (95% CI, 1.49–3.99) per 100 person-years in these cases. Unfortunately, because of the retrospective design of this study, we were not able to discriminate between expert and non-expert pathologists, but it can be anticipated that the incidence rate of HGD/EAC could have been even higher if all confirmed LGD diagnoses were made by expert pathologists. Nonetheless, even after confirmation of LGD by an expert pathologist, we and other studies found that a significant proportion of LGD diagnoses are not reproduced during follow-up, which may be explained by the same factors mentioned earlier, eg, an over-estimation of the original LGD diagnosis or sampling error.

To our knowledge, until now only one study has reported on the persistence of LGD as potential predictor.

**Table 2. Risk Factors for Malignant Progression (Identified by Using Univariable Cox Regression Analysis) for Patients With BE Diagnosed as Confirmed LGD (n = 161)**

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<td>Persistent LGD</td>
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of progression, but no statistically significant difference was found between patients with and without persistent LGD.\textsuperscript{11} In this study, 68 patients with persistent LGD were identified and followed up for a period of 297 patient-years. Increased incidence rates of 3.37\% (95\% CI, 1.8–6.26) and 0.93\% per year (95\% CI, 0.3–2.9) for HGD/EAC and EAC, respectively, were found in patients reported to have persistent LGD in BE.\textsuperscript{11} Although the overall incidence rates of HGD/EAC were comparable with findings in our study, the incidence rates for HGD/EAC and EAC in patients with persistent LGD were considerably higher, ie, 7.65 (95\% CI, 4.45–12.34) and 2.04 (95\% CI, 0.65–4.92) per 100 person-years, respectively. These findings in combination with the relatively large number of LGD patients with ND during follow-up support the conclusion that persistent LGD can serve as a marker for risk stratification in patients with LGD. Although considered to be relatively safe, RFA is associated with complications, eg, 7\%–12\% of patients develop esophageal strictures after treatment.\textsuperscript{3,16} Therefore, before considering endoscopic treatment of LGD, further identification of patients at risk of malignant progression is warranted.

In addition to persistent LGD, we evaluated whether duration of persistent LGD influenced the incidence rate of malignant progression. We observed a tendency to increased incidence rates to developing HGD/EAC in patients with persistent LGD longer than 1 year. Unfortunately, not enough follow-up data were available to evaluate this for longer time frames.

There are some limitations to this study. First, the pathologic data were extracted from the PALGA database and do not include clinical data. As a result, the reported incidence rates of HGD/EAC could not be corrected for endoscopic factors such as length of the BE segment and presence of esophagitis and hiatal hernia. Second, additional immunohistochemistry findings, eg, p53 staining (which serves as a marker for malignant progression\textsuperscript{5,20}), were available in only a subgroup of patients and could therefore not be used for risk stratification. Third, because of the retrospective design of the study, no standardized endoscopy protocol was used. However, in the Netherlands it is general practice to follow international guidelines and take biopsies according to the Seattle protocol.\textsuperscript{21} Fourth, a proportion of the patients were excluded from the study because they did not undergo follow-up endoscopy. The reason for this remains unknown, but older age and comorbidities could be an explanation. This may result in selection bias, making the actual incidence rates lower if symptomatic patients would have undergone endoscopy more frequently.

This study has also some unique features that may overcome some of these drawbacks. Patients in the Netherlands have free access to health care, which largely eliminates diagnostic bias. As a result, the generalization of our results is high because this nationwide cohort involves BE patients of all ages and both sexes with LGD diagnosed in a primary, secondary, and tertiary setting. Furthermore, in this study, we included a large number of LGD cases, and we were therefore able to follow up a relatively large number of patients with ND BE after a diagnosis of LGD.

In conclusion, in this large nationwide cohort of BE patients with LGD, we demonstrate that confirmed and persistent LGD identifies a subgroup of patients with an increased risk of malignant progression. In addition, in half of these patients LGD was no longer detected during follow-up, and one-fourth of them exhibited persistent ND BE. Therefore, we believe that endoscopic treatment of LGD BE is indicated in patients with confirmed and persistent LGD. In patients in whom confirmed LGD does not persist, it may well be that a wait and see policy is justified.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at [http://dx.doi.org/10.1016/j.cgh.2015.12.027](http://dx.doi.org/10.1016/j.cgh.2015.12.027).

**References**


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Conflicts of interest
The authors disclose no conflicts.
Supplementary Table 1. Diagnostic Codes Used in the PALGA Search Strategy

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