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

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Q6 **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/per 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.

Abbreviations used in this paper: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; HR, hazard ratio; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; ND, no dysplasia; PALGA, nationwide registry of histopathology diagnoses in the Netherlands; RFA, radiofrequency ablation.

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Barrett's esophagus (BE) is a premalignant condition in which squamous epithelium is replaced by intestinal columnar epithelium.[1] It is considered to be a complication of longstanding gastroesophageal reflux disease and is a well-known risk factor for developing esophageal adenocarcinoma (EAC).[2] 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.[3] 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.[3]

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.[4] Despite numerous studies on possible biomarkers to predict malignant progression, dysplasia is the most important factor determining the management of BE.[1,5,6] Patients with LGD have a higher risk for malignant progression compared with patients with ND,[7–9] and intensified surveillance is recommended to identify patients before progression to EAC.[5,10–12] 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.[12–15]

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.[13,16] In addition, the authors also reported that 28% of patients in the control group had ND detected during follow-up.[13] 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.[17] All histopathology reports in the database are registered as written conclusions of pathologists combined with the diagnostic code derived from Systemized Nomenclature of Medicine.[18] 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 χ^2 test, Mann-Whitney *U*