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Risk Stratification of Patients With Barrett's Esophagus and Low-grade Dysplasia or Indefinite for Dysplasia

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BACKGROUND & AIMS: **In patients with Barrett's esophagus (BE), low-grade dysplasia (LGD) is a risk factor for esophageal adenocarcinoma (EAC), progressing at variable rates. Patients at higher risk for progression could benefit from intervention. We assessed rates of progression of LGD and indefinite for dysplasia (IND) and risk factors for progression to high-grade dysplasia (HGD) and EAC.**

METHODS: **We analyzed data from Cleveland Clinic Barrett's Registry on patients with BE and LGD or IND at least 1 year of follow-up from January 1, 2002 through December 31, 2012. Prevalent cases were those diagnosed at or within 1 year of the first endoscopy, and the rest were incident cases.**

RESULTS: **Among 299 patients with BE and LGD or IND, there were 32 cases of HGD and 10 cases of EAC during a follow-up period of 1577.4 patient-years. The annual incidence rates were 2.4% (95% confidence interval [CI], 1.7%–3.3%) for HGD, 0.6% (95% CI, 0.3%–1.2%) for EAC, and 2.7% (95% CI, 1.9%–3.6%) for HGD or EAC. The rates were higher in men than in women with BE and LGD or IND. Prevalent cases were 3-fold more likely to progress than incident cases. Multifocality and nodules were associated with higher risk of progression to HGD or EAC. None of the patients with IND at index biopsy developed EAC. For every 5-year increase in age, chance of regression increased by 7% ($P = .04$). Also, for every 1-cm increase in BE length, probability of regression decreased by 6% ($P = .016$). LGD at index biopsy was associated with 56% lower chance of regression compared with IND ($P < .001$).**

CONCLUSIONS: **On the basis of a database analysis of patients with BE, prevalent LGD, male sex, multifocality, and nodules were associated with higher risk for progression to EAC. Older age at LGD diagnosis, IND at index biopsy, and shorter BE length were associated with regression. These findings help in risk stratification of patients with BE and LGD or IND.**

Keywords: Esophageal Cancer; Carcinogenesis; Tumor; Patient Management.

The lifetime risk of developing cancer in the general population in the United States is about 40%.[1] Scientific advances and public health measures have brought about reduction in the incidence of most cancers, with esophageal cancer being one of the notable exceptions. There are estimated to be 17,990 new cases and 15,210 deaths attributable to esophageal cancer in 2013 in the United States.[1] Barrett's esophagus (BE) is the only known precursor lesion for esophageal adenocarcinoma (EAC), the most common histologic type of esophageal cancer. Although far from infallible, the degree of dysplasia remains the most widely used marker for assessing the risk of EAC in BE. The annual incidence rates of EAC vary between 0.12% and 0.5% for nondysplastic BE (NDBE),[2–6] 0.44%–14.6% for low-grade dysplasia (LGD),[4,7–13] and 6.6%–19% for high-grade dysplasia (HGD).[14,15]

Endoscopic ablation methods have significantly changed the paradigm of management of patients with BE. The guidelines recommend surveillance for NDBE and endoscopic therapy for HGD.[16] However, management of LGD/indefinite for dysplasia (IND) remains an

Abbreviations used in this paper: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus.

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area of controversy. This is due to the fact that (1) LGD/IND is a transient diagnosis because more than 60% of patients "regress" to NDBE on follow-up, (2) diagnosis of LGD/IND itself is fraught with contention because there is poor interobserver agreement for this diagnosis, and (3) recent studies have reported progression rates to HGD/EAC that are similar to those in NDBE.[7] As such, expert opinion remains divided regarding continued surveillance versus endoscopic ablation in BE-LGD/IND.

The reported rates of progression to HGD or EAC in patients with LGD/IND are highly variable, with annual incidence rates varying from 0.44% to 14.6%.[4,7–13] Factors that have been reported in the past to identify LGD at higher risk for progression include extent of dysplasia,[12] incident versus prevalent dysplasia, consensus diagnosis by expert gastrointestinal pathologists,[12,13,17–19] and p53 expression,[20,21] but these findings have not been replicated in later studies.[7]

A great need exists to identify the small subset of BE patients with LGD/IND who are at higher risk of progression to risk stratify and optimally manage them. Therefore, our aims were to determine (1) progression rates of LGD/IND to HGD/EAC, (2) factors associated with neoplastic progression, and (3) factors associated with regression.

Methods

Patient Population

The Cleveland Clinic Barrett's Registry is a prospectively collected database of BE patients seen in the Department of Gastroenterology since 1979. It includes age, gender, race, date of endoscopy, length of BE, size of hiatal hernia, visible lesions (esophagitis, nodules, ulcers), and histologic findings. All patients with BE-LGD/IND and at least 1-year follow-up seen between January 1, 2002 and December 31, 2012 were included in this study. Patients with HGD/EAC diagnosed within 1 year of entry into the registry or diagnosis of LGD/IND and patients who underwent ablation procedures for LGD were excluded. Prevalent cases were those with LGD/IND at the time of first endoscopy or within 1 year of initial diagnosis of BE. LGD/IND diagnosed at least 1 year after diagnosis of NDBE were incident cases. Follow-up was calculated from time of first endoscopy to last surveillance endoscopy or until diagnosis of HGD/EAC.

These were the outcomes: (1) progression to cancer, any surveillance endoscopy showing EAC; (2) progression to HGD, any surveillance endoscopy showing HGD without further progression to EAC; (3) persistent cases, LGD/IND on 2 or more consecutive endoscopies including last endoscopy; (4) persistent LGD/IND with resolution, LGD/IND on 2 or more endoscopies, followed by regression; and (5) regression, no dysplasia found on any surveillance endoscopy.

Endoscopic Protocol and Histologic Evaluation

BE was defined as endoscopic appearance of columnar mucosa of any length with intestinal metaplasia (goblet cells) on biopsy. The biopsy results were categorized as NDBE, IND, LGD, HGD, or EAC. Length of BE was calculated as the distance from the proximal end of the gastric folds to the squamocolumnar junction. Prague C & M classification was not available for all patients. The length of BE and hiatal hernia size included in the study were from the index endoscopy only (first endoscopy on entry into BE registry).

As per published guidelines for LGD/IND, surveillance biopsy protocol consisted of 4 quadrant biopsies every 1–2 cm of BE with a standard or jumbo biopsy forceps every 6–12 months.[16] In addition, ulcers and nodules were biopsied separately. Since 2004, biopsies were read by expert gastrointestinal pathologists (either had 1-year fellowship training in gastrointestinal tract or specialized in gastrointestinal pathology for at least 5 years). In most cases, diagnosis was confirmed by a second gastrointestinal pathologist or reviewed at consensus conference. The extent of dysplasia (unifocal versus multifocal) was recorded.

Statistical Analysis

Data were presented as mean $\pm$ standard deviation or median (25th, 75th percentiles) for continuous variables and N (%) for categorical factors. Analysis of variance or the nonparametric Kruskal–Wallis test was used for continuous variables, and Fisher exact test or Pearson χ^2 test was used for categorical factors. Ad hoc pairwise comparisons were done at significance level of .005. Incidence rates per person-year were estimated along with corresponding Poisson 95% confidence intervals (CIs). Competing risk analysis was performed following approach described by Kalbfleisch and Prentice.[22] Gender, age, BE length, hiatal hernia size, and prevalent vs incident dysplasia were included in the multivariable models. In case of progression and persistence with resolution, automated stepwise variable selection method performed on 1000 bootstrap samples was used to choose the final models. The number of variables in the model was determined by the 10 events per variable rule. A P value $<.05$ was considered statistically significant. SAS version 9.2 (SAS Institute Inc, Cary, NC) and R version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used to perform all analyses.

Results

Patient Cohort

Cleveland Clinic BE registry contained information on 2370 patients; a total of 2071 patients were excluded as shown in Figure 1. Two hundred ninety-nine fulfilled the