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CLINICAL—ALIMENTARY TRACT

Radiofrequency Ablation Is Associated With Decreased Neoplastic Progression in Patients With Barrett's Esophagus and Confirmed Low-Grade Dysplasia

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this exercise, successful learners will be able to (a) discuss management of low-grade dysplasia in Barrett's esophagus, (b) identify strategies to reduce the risk of low-grade dysplasia advancing to high-grade dysplasia, and (c) discuss the role of specialized GI pathologists in pathologic review of biopsies diagnosed as low-grade dysplasia by general pathologists.

BACKGROUND & AIMS: Barrett's esophagus (BE) with low-grade dysplasia (LGD) can progress to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC). Radiofrequency ablation (RFA) has been shown to be an effective treatment for LGD in clinical trials, but its effectiveness in clinical practice is unclear. We compared the rate of progression of LGD after RFA with endoscopic surveillance alone in routine clinical practice. **METHODS:** We performed a retrospective study of patients who either underwent RFA (n = 45) or surveillance endoscopy (n = 125) for LGD, confirmed by at least 1 expert pathologist, from October 1992 through December 2013 at 3 medical centers in the United States. Cox regression analysis was used to assess the association between progression and RFA. **RESULTS:** Data were collected over median follow-up periods of 889 days (interquartile range, 264−1623 days) after RFA and 848 days (interquartile range, 322−2355 days) after surveillance endoscopy ($P = .32$). The annual rates of progression to HGD or EAC were 6.6% in the surveillance group and 0.77% in the RFA group. The risk of progression to HGD or EAC was significantly lower among patients who underwent RFA than those who underwent surveillance (adjusted hazard ratio = 0.06; 95% confidence interval: 0.008−0.48). **CONCLUSIONS:** Among patients with BE and confirmed LGD, rates of progression to a combined end point of HGD and EAC were lower among those treated with RFA than among untreated patients. Although selection bias cannot be excluded, these findings provide additional evidence for the use of endoscopic ablation therapy for LGD.

Keywords: Eradication; Clinical Setting; Prevention; Esophageal Cancer.

The incidence of esophageal adenocarcinoma (EAC) continues to rise at a rate greater than any other cancer in the Western world and is associated with poor survival.[1] Barrett's esophagus (BE) is a well-established precursor of EAC.[2,3] Despite its limitations, dysplasia is still the most predictive biomarker for progression of BE to EAC, with dysplasia severity correlating with risk of cancer.[4–6] Endoscopic eradication of Barrett's mucosa has become an acceptable strategy to reduce risk of high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) progressing to invasive EAC. However, the optimal approach to management of low-grade dysplasia (LGD) remains uncertain due, in part, to inconsistent reports of the natural history of LGD.[3,4,6,7] Prior studies that have reported high progression rates for untreated LGD have typically included expert pathology review suggesting that misclassification of LGD may contribute to lower progression rates in some studies.[6–12]

Current guidelines suggest performance of endoscopic surveillance every 6 to 12 months after the initial detection of LGD.[3,5] However, data from a recent European clinical trial suggest that radiofrequency ablation (RFA) is superior to continued endoscopic surveillance among patients with LGD confirmed by a panel of expert gastrointestinal (GI) pathologists.[13] As a result, the optimal approach for patients with LGD remains uncertain.[14] If rates of progression are low, continued surveillance might be preferred. If rates of progression are high and RFA is effective in clinical practice, as suggested by clinical trial data, RFA might be preferred. To address this uncertainty, we conducted a

Abbreviations used in this paper: **BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; GI, gastrointestinal; HGD, high-grade dysplasia; HR, hazard ratio; IM, intestinal metaplasia; IMC, intramucosal carcinoma; IQR, interquartile range; LGD, low-grade dysplasia; RFA, radiofrequency ablation.**

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multicenter retrospective cohort study examining patients with LGD confirmed by expert pathologists who received RFA or continued surveillance endoscopy. We sought to define the risk of HGD/EAC after initial detection of LGD in BE patients, and compare the rates of progression to HGD/EAC between patients undergoing RFA and those undergoing endoscopic surveillance. A secondary aim was to identify independent risk factors associated with progression of LGD to HGD/EAC.

Methods

Patients and Settings

The source cohort came from 3 referral centers within the Barrett's Esophagus Translational Research Network (BETRNet) consortium funded by the National Cancer Institute: the University of Pennsylvania, Columbia University, and the Mayo Clinic. Within this cohort, BE patients who had a diagnosis of LGD as verified by histopathology from October 1992 (the date of earliest registration of LGD patients available) to December 2013 were identified for study inclusion. The inclusion criteria for this study were as follows: age older than 18 years, histology of intestinal metaplasia (IM) in biopsies obtained above the gastroesophageal junction, LGD as determined by at least one GI pathologist at a BETRNet site, and undergoing routine endoscopic surveillance or had endoscopic ablation after diagnosis of LGD.

Patients with any of the following characteristics were excluded: prior esophageal surgery or endoscopic therapy for BE, prior diagnosis of HGD or adenocarcinoma, and/or histology indefinite for dysplasia. Patients were assigned to 1 of 2 groups based on exposure to RFA: the surveillance cohort was composed of LGD patients who had at least one endoscopy after detection of confirmed LGD; the ablation cohort was composed of all BE patients who had undergone RFA after a diagnosis of LGD.

Histopathology

Histopathologic assessment of biopsy specimens was reported using established criteria for dysplasia (LGD, HGD) and esophageal adenocarcinoma according to the Vienna classification.[15,16] Only cases with a diagnosis of LGD made at 1 of the 3 participating academic medical centers were included in this study. The worst histologic grade identified within the specimens was the overall histologic grade for that endoscopy. Each site had a group of local GI pathologists with extensive experience in Barrett's histology and neoplasia during the study period. The histopathology interpretations of dysplasia and neoplasia were read by at least one GI pathologist as part of routine practice at each site and performed at the time when endoscopic biopsies were obtained. In cases of uncertainty, a consensus diagnosis was reached between 2 GI pathologists in a dedicated meeting at each center. In cases of discordance between the 2 pathologists, a third GI pathologist was asked to interpret for consensus review as per protocol at each center. For cases when a patient was referred to the participating center with a diagnosis of LGD made at a community institution, outside slides were retrieved and reinterpreted by the participating center pathologists. Central reading of all pathology specimens was not conducted in this study.

Surveillance Endoscopy and Radiofrequency Ablation

Surveillance intervals and biopsy protocols were not standardized across all centers in this study. However, cases from each center had endoscopies performed by experienced endoscopists with expertise in BE who followed American Gastroenterological Association guideline recommendations.[3] After a diagnosis of LGD, surveillance endoscopy was performed within 1 year unless the patient received RFA. In the ablation group, patients received initial RFA within 1 year of diagnosis of LGD. Additional description of surveillance and RFA are included in the Supplementary Methods.

Data Collection and Management

Data were collected from medical records at each center and transferred to the University of Pennsylvania for analysis. Data extracted from medical records included: age at initial diagnosis of LGD, sex, race/ethnicity, endoscopy results (date of procedure, length of BE), presence of nodularity, and histologic diagnosis at each endoscopic procedure. Extent of dysplasia (spatial distribution within Barrett's segment) was recorded and assigned as multifocal if there was evidence of dysplasia on at least 2 specimens taken from different locations in the Barrett's segment on the same endoscopy. See the Supplementary Methods for more detailed description of covariates, data extraction and management, and follow-up intervals.

Study End Points

The primary outcome of interest was the detection of HGD or EAC during follow-up. For the secondary aim of identifying risk factors for progression of LGD, we assessed the impact of previously defined variables (see Supplementary Methods) on the rate of progression.

Statistical Analysis

Descriptive data were expressed as median (interquartile range [IQR]) or mean (SD) as appropriate for continuous data. Chi-square, Fisher's exact, and Mann-Whitney U test were used to assess differences between the 2 study groups.

The start of follow-up for each patient was the initial intervention (either the first endoscopy with RFA in the ablation group or the first endoscopy after the diagnosis of LGD in the surveillance group as to avoid immortal time bias in progression rate estimates). Follow-up ended with the last recorded endoscopy with biopsy or the first diagnosis of HGD or EAC. Data were censored if the patient was lost to follow-up. Cumulative incidence curves were used to assess yearly progression rates and were compared using the log-rank test.

Cox proportional hazard analysis was used to assess effect of RFA on progression controlling for potential confounders. Potential predictors ($P < .20$ from the univariate analyses) were included in a backward, stepwise elimination multivariate Cox hazard model. Factors that no longer had a $P < .05$ in the model were excluded to develop a final parsimonious model. All variables were evaluated for confounding or effect modification. Confounders (as determined by a $\geq$15% difference between the crude and hazard ratio [HR] adjusted for the variable of interest) were also included in the final model. Patients with missing data were excluded from multivariable analysis.