Biopsy depth after radiofrequency ablation of dysplastic Barrett's esophagus

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Background: After endoscopic radiofrequency ablation (RFA) of dysplastic Barrett's esophagus (BE), endoscopic biopsy samples are obtained to assess response to therapy. Whether these biopsies are of adequate depth to assess efficacy is unknown.

Objective: To compare the depth of endoscopic biopsy samples after RFA with those of untreated controls and to determine the prevalence of subepithelial structures in endoscopic biopsy fragments.

Design: Secondary analysis of the AIM Dysplasia Trial, a multicenter, randomized, sham-controlled study.

Setting: Nineteen treatment centers.

Patients: Subjects with dysplastic BE, either status post RFA or ablation naïve (sham).

Main Outcome Measurements: The proportion of biopsy samples demonstrating subepithelial structures, stratified by tissue type (columnar vs squamous) in sham- and RFA-treated subjects.

Results: A total of 5648 biopsy fragments were analyzed from 113 subjects (78 RFA, 35 sham; mean 50.0 fragments per subject). Most fragments (4653, 82.4%) contained subepithelium. Squamous biopsy samples from RFA and sham subjects demonstrated subepithelium at similar rates (78.4% vs 79.1%, respectively, P = not significant [NS]). Columnar biopsy samples from RFA and sham subjects also included subepithelium at similar rates (99.0% vs 98.8%, respectively, P = NS). Regardless of treatment assignment, more columnar than squamous biopsy samples demonstrated subepithelium (98.8% vs 78.5%, $P < .001$).

Limitations: Biopsy samples were not individually mounted.

Conclusions: In both squamous and columnar tissue, endoscopic biopsy samples after RFA were as likely to demonstrate subepithelium as untreated controls. Almost 80% of all biopsy samples were adequate to evaluate for subsquamous intestinal metaplasia. The primary determinant of biopsy depth is the type of epithelium that underwent biopsy, with squamous less likely to yield subepithelium than columnar. Biopsy samples after RFA appear to be of adequate depth to assess response to therapy. (Clinical trial registration number NCT00282672.) (Gastrointest Endosc 2010;72:490-6.)

Abbreviations: BE, Barrett's esophagus; IM, intestinal metaplasia; LP, lamina propria; NS, not significant; RFA, radiofrequency ablation; SSIM, subsquamous intestinal metaplasia.

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Barrett's esophagus (BE) is characterized by intestinal metaplasia (IM) of the esophagus, a premalignant change in the esophagus from squamous to specialized columnar epithelium.[1] Because of the risk of progression to esophageal adenocarcinoma, endoscopic techniques have been developed to ablate BE with the goal of decreasing the progression to malignancy. Radiofrequency ablation (RFA) is an endoscopic ablation technique involving the application of a bipolar electrical array to deliver a standardized thermal injury. This injury, followed by aggressive acid suppressive therapy, results in the regeneration of a histologically normal-appearing neosquamous epithelium in most subjects.[2,3] Successful eradication of BE appears to be associated with a decreased risk of cancer.[4,5]

Endoscopic surveillance with biopsies is commonly performed after endoscopic ablation. Endoscopic biopsy samples are obtained from the neosquamous epithelium to confirm treatment response and to assess for subsquamous intestinal metaplasia (SSIM)–residual intestinal metaplasia that is buried beneath the neosquamous epithelium. The ability to accurately assess for a complete response depends on the quality and depth of surveillance biopsies. Biopsy to at least the depth of the lamina propria (LP) is required to assess for SSIM.[6]

It is unclear whether surveillance biopsy samples adequately assess the subsquamous space. If mucosal scarring or other changes inhibit biopsy depth, current endoscopic surveillance practices may not detect SSIM. Previous studies did not establish whether most endoscopic biopsy samples after ablation therapy are from an adequate depth to include subepithelial structures and/or detect SSIM. To address this question, we performed a secondary analysis of the AIM Dysplasia Trial.[4] The objectives of this study were (1) to compare the depth of endoscopic biopsy in subjects who underwent RFA of dysplastic BE with concurrently enrolled, untreated controls and (2) to determine the prevalence of subepithelial structures in biopsy fragments obtained from both arms in the trial, stratified by the type of tissue that underwent biopsy.

Take-home Message

- In both squamous and columnar tissue, endoscopic biopsy samples from patients treated with radiofrequency ablation were as likely to demonstrate subepithelium as untreated controls. The primary determinant of biopsy depth is the type of epithelium that underwent biopsy, with squamous tissue less likely than columnar tissue to yield subepithelial structures. Biopsy samples after RFA appear to be of adequate depth to assess the response to therapy.

METHODS

Parent study design

The AIM Dysplasia Trial (see online Appendix for complete list of investigators; available at www.giejournal.org) is a multicenter, randomized, sham-controlled study in which patients with dysplastic BE (low-grade dysplasia [LGD] or high-grade dysplasia [HGD]) were randomized to receive RFA therapy plus endoscopic surveillance or a sham intervention plus surveillance. A detailed description of the study methods was reported elsewhere, but is briefly described here.[4] Patients were eligible if they were ages 18 to 80 and had 8 cm or less of non-nodular dysplastic BE. Subjects were randomly assigned in a 2:1 ratio to receive either RFA or a sham endoscopic procedure. In the ablation group, the BE segment was ablated with RFA (HALO^{360} and HALO^{90}; BÂRRX Medical, Sunnyvale, Calif). Each subject received esomeprazole 40 mg twice daily throughout the study. All subjects underwent endoscopic surveillance at 3-month (HGD cohort) or 6-month (LGD cohort) intervals. Biopsy samples were obtained at each endoscopy with jumbo or maximum capacity forceps in 4 quadrants every 1 cm from the baseline extent of BE and from areas of mucosal atypia. The primary outcomes at 12 months were complete eradication of dysplasia and metaplasia, reported separately.[4]

The study protocol was approved by each site's institutional review board. The parent study was supported by BÂRRX Medical, maker of the ablation devices, with study medication provided by AstraZeneca.

Histological analysis

Our analysis used biopsy specimens obtained at 1 year after randomization, the primary endpoint. Biopsy specimens of subjects who were found to have esophageal adenocarcinoma in the first year of follow-up and who underwent nonendoscopic treatment were excluded. Tissue was fixed in formalin and stained with hematoxylin and eosin. Fragments from each 1-cm segment were collected in a separate jar. Each individual fragment was interpreted by a single expert GI pathologist (J.R.G.) at a central laboratory (Cleveland Clinic) for its tissue type and depth.

Each fragment was classified as (1) squamous only, (2) glandular only (no IM), (3) glandular (no IM) plus squamous (mixed fragment), and (4) any IM present.

For the purpose of our analysis, columnar biopsy samples included fragments classified as glandular only, glandular plus squamous, or IM.

The maximum histological depth of each fragment was characterized as follows: partial epithelium (Fig. 1A), full epithelium (basement membrane present [Fig. 1B]), LP (Fig. 1C), muscularis mucosae (Fig. 1D), and submucosa (Fig. 1E). A biopsy fragment that included LP papillae was categorized as LP (Fig. 1F). A subepithelial biopsy sample was considered any fragment that included LP, muscularis mucosae, or submucosa. Biopsy samples were considered adequate for evaluation of SSIM if they contained any subepithelial structures.