SYSTEMATIC REVIEWS AND META-ANALYSES

Fasiha Kanwal, Section Editor

Efficacy and Durability of Radiofrequency Ablation for Barrett's Esophagus: Systematic Review and Meta-analysis

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BACKGROUND & AIMS: **In patients with Barrett's esophagus (BE), radiofrequency ablation (RFA) safely and effectively eradicates dysplasia and intestinal metaplasia. We aimed to determine the efficacy and durability of RFA for patients with dysplastic and nondysplastic BE.**

METHODS: **We performed a systematic review and meta-analysis of studies identified in PubMed and EMBASE that reported the proportion of patients treated with RFA who had complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM), and the proportion of patients with recurrent IM after successful treatment. Pooled estimates of CE-D, CE-IM, IM recurrence, and adverse events were calculated.**

RESULTS: **We identified 18 studies of 3802 patients reporting efficacy and 6 studies of 540 patients reporting durability. Ten were prospective cohort studies, 9 were retrospective cohort studies, and 1 was a randomized trial. CE-IM was achieved in 78% of patients (95% confidence interval [CI], 70%–86%) and CE-D was achieved in 91% (95% CI, 87%–95%). After eradication, IM recurred in 13% (95% CI, 9%–18%). Progression to cancer occurred in 0.2% of patients during treatment and in 0.7% of those after CE-IM. Esophageal stricture was the most common adverse event and was reported in 5% of patients (95% CI, 3%–7%). Confidence in most summary estimates was limited by a high degree of heterogeneity, which did not appear to be caused by single outlier studies.**

CONCLUSIONS: **Treatment of BE with RFA results in CE-D and CE-IM in a high proportion of patients, with few recurrences of IM after treatment and a low rate of adverse events. Despite the large amount of study heterogeneity, these data provide additional information for patients and providers to make informed treatment decisions.**

Keywords: Esophageal Cancer; Gastroesophageal Reflux; Prevention; Endoscopy.

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Barrett's esophagus (BE) is a precancerous condition characterized by the replacement of the normal stratified squamous epithelium of the distal esophagus by intestinal metaplasia (IM), affecting 1%–2% of the general population.[1–3] Multiple endoscopic ablative techniques have been developed for BE, with the goal of eradicating IM and preventing neoplastic progression to esophageal adenocarcinoma (EAC).[4–7] Of these techniques, radiofrequency ablation (RFA) is used commonly and was shown in a randomized controlled trial (RCT) to have low complication rates, substantial rates of complete eradication of dysplasia (CE-D) and IM (CE-IM), and a decrease in progression to cancer.[8]

Although RFA is safe and effective in eradicating IM, the absolute magnitude of the benefit has not been well described. Different studies have varied considerably in their reports of absolute rates of CE-D and CE-IM and in estimates of durability of the neosquamous epithelium that appears after RFA.[9–11] These studies are often from tertiary care centers, subject to local expertise with limited generalizability; have small sample sizes that limit the precision of effect estimates; and have varied in the inclusion of different histologic grades of BE. The latter issue is important because the risk-benefit ratio of ablation changes with the risk of malignancy, which is tied closely to histologic grade. In addition, pretreatment histology may predict treatment efficacy, although such a relationship has been

Abbreviations used in this paper: AIM, Ablation of Intestinal Metaplasia; BE, Barrett's esophagus; CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; CI, confidence interval; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; IM, intestinal metaplasia; IMC, intramucosal carcinoma; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; RFA, radiofrequency ablation; RCT, randomized controlled trial; RR, risk ratio.

1542-3565/$36.00

http://dx.doi.org/10.1016/j.cgh.2013.03.039

seen inconsistently.[12,13] Inclusion of a limited histology distribution in an individual study may not allow for adequate power to make such comparisons. Estimates of adverse events also may be unreliable because of insufficient power in individual studies.

We therefore performed a systematic review and meta-analysis of studies of RFA for dysplastic and nondysplastic BE (NDBE). We aimed to determine the proportion of patients achieving CE-D and CE-IM after treatment with RFA as well as the proportion with recurrence of IM after successful treatment. We also sought to evaluate the association of pretreatment histology with CE-D and CE-IM and the incidence of adverse events.

Methods

Search Strategy and Eligibility Criteria

We followed the Meta-analysis Of Observational Studies in Epidemiology guidelines for the conduct and reporting of systematic reviews of observational studies.[14] Two authors (E.S.O. and N.L.) independently searched the PubMed and EMBASE databases for relevant articles on August 24, 2012. PubMed was queried with the search terms "((Barrett) OR Barrett's) AND (radiofrequency OR radio-frequency OR ablation)" and EMBASE was queried with "Barrett AND ('radiofrequency'/exp OR radiofrequency OR radio+frequency OR ablation)." Abstracts identified in EMBASE that were published in 2011 and 2012 were included. Two additional manuscripts from the authors' institution accepted for publication and in press at the time of the search but not yet indexed in either database also were included.[15,16]

The identified records then were reviewed independently according to strict eligibility criteria. We excluded letters to the editor; editorials; non-English language studies; nonclinical or nonhuman studies; review articles; case reports; studies that were not observational or RCTs; studies without biopsy-proven BE; studies that did not use focal RFA; studies of patients who had received other ablative therapies (with the exception of endoscopic mucosal resection [EMR] in combination with RFA); studies not reporting either efficacy (CE-IM or CE-D) or durability (histologic recurrence after CE-IM or CE-D); efficacy studies with mean or median follow-up periods less than 12 months from the first RFA session; durability studies with mean or median follow-up periods less than 12 months from the first post-RFA endoscopy showing eradication; studies with fewer than 20 subjects receiving RFA; duplicate reports of study samples; abstracts published before 2011; and studies not reporting a follow-up duration. Abstracts published before 2011 were excluded because those that have not been converted into manuscript form in the 2 years after submission may have significant flaws in methodology or interpretation that have limited their acceptability for publication. After exclusion of ineligible abstracts, a full-text review of remaining studies was performed independently using the same eligibility criteria, with discrepancies resolved by consensus. We attempted to contact study authors for clarification when multiple reports potentially described the same patient population. For multiple reports describing a common patient sample, we included the most recent report unless only the older report described our a priori outcome variables. Duplicate reports were included, however, if 1 reported efficacy outcomes and the second reported durability. After exclusion of full-text records, the reference sections of included articles were searched manually for additional records.

Data Collection

Data were abstracted from each study and organized into formalized evidence tables independently by the authors. We recorded study characteristics including year of publication, country, study design, setting, inclusion and exclusion criteria, RFA and surveillance protocol, sample size, proton pump inhibitor use, use of circumferential RFA and EMR, number of RFA sessions and surveillance endoscopies, and follow-up duration. For the RFA protocols, we recorded the timing and type of RFA (circumferential vs focal). For the surveillance protocols, we recorded intervals of surveillance endoscopy, inclusion of cardia biopsies, and follow-up evaluation start time (ie, the time at which treatment was considered complete, and surveillance was begun). For studies that reported both efficacy and durability, sample size was considered separately for each outcome. Recorded patient characteristics included age, sex, BE length, and pretreatment dysplasia assessment. The quality of each study was assessed using the previously validated Downs and Black[17] instrument, which can assess both randomized and nonrandomized studies. This tool assesses the quality of reporting, external validity, bias, confounding, and power using a checklist of 27 items, and scores reports from 0 to 32, with higher scores representing greater methodologic quality. After abstraction, the authors reviewed the evidence tables and discrepancies again were resolved by consensus.

Outcomes

The primary efficacy outcomes were CE-IM, defined as the absence of IM on endoscopy and histology after RFA; and CE-D, defined as the absence of dysplasia on histology (in subjects with baseline dysplastic BE). Residual IM at the gastroesophageal junction was considered to be failure of CE-IM in the efficacy analysis and recurrence in the durability analysis, but IM in the cardia was not. The presence of IM in these locations was determined according to the descriptions in the manuscripts. Efficacy outcomes were tabulated according to baseline histology where available. Progression to EAC during treatment was recorded as well. The primary durability outcome was recurrence of IM defined histologically after CE-IM. The presence of dysplasia or EAC at the time of recurrence also was recorded. Adverse events (most commonly strictures, pain, and bleeding) were recorded as secondary outcomes. These were ascertained based on the individual study definitions of adverse events.

Statistical Analysis

We calculated the proportion of patients who met the primary efficacy and durability outcomes in each study. The denominator for the IM recurrence durability outcome comprised only those patients who had achieved CE-IM after RFA. The proportion of patients who achieved CE-IM and CE-D was calculated for each pretreatment histologic group, and unadjusted risk ratios (RRs) were calculated to compare the outcomes between these groups, with low-grade dysplasia (LGD) as the comparator. LGD was chosen as the comparison group because it was present in more studies than NDBE and because it is the lowest grade of dysplasia that can be compared for the CE-D end point.

Statistical analysis was performed using Stata version 12.1 (StataCorp LP, College Station, TX) and Open Meta-Analyst (Tufts Medical Center, Boston, MA).[18] To determine the pooled proportion of patients achieving CE-IM and CE-D and