Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis

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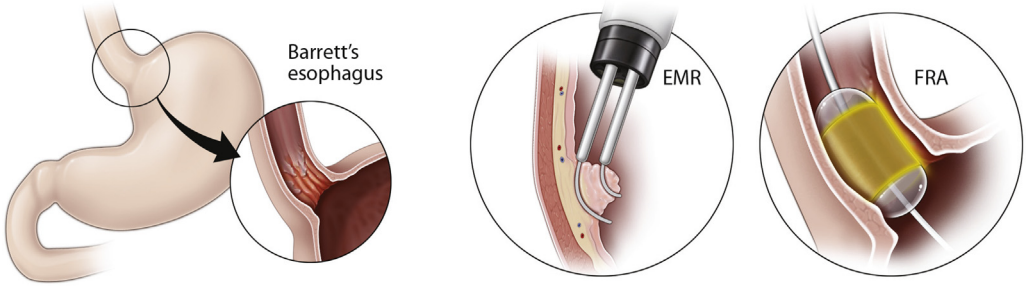
GRAPHICAL ABSTRACT



Background and Aims: Focal EMR followed by radiofrequency ablation (f-EMR + RFA) and stepwise or complete EMR (s-EMR) are established strategies for eradication of Barrett's esophagus (BE)-related high-grade dysplasia (HGD) and/or esophageal adenocarcinoma (EAC)/intramucosal carcinoma (IMC). The objective of this study was to derive pooled rates of efficacy and safety of individual methods in a large cohort of patients with BE and to indirectly compare the 2 methods.

Methods: PubMed, Embase, Web of Science, Cochrane, and major conference proceedings were searched. A systematic review and pooled analysis were carried out to determine the following outcomes in patients with BE undergoing either f-EMR + RFA or s-EMR: (1) complete eradication rates of neoplasia (CE-N) and intestinal metaplasia (CE-IM); (2) recurrence rates of cancer (EAC), dysplasia, and IM; (3) incidence rates of adverse events. Mixed logistic regression was performed as an exploratory analysis to examine differences in outcomes between the 2 methods.

Results: Nine studies (774 patients) of f-EMR + RFA and 11 studies (751 patients) of s-EMR were included. Patients undergoing f-EMR + RFA had high BE eradication rates (CE-N, 93.4%; CE-IM, 73.1%), whereas strictures occurred in 10.2%, bleeding in 1.1%, and perforations in 0.2% of patients. Recurrence of EAC, dysplasia, and IM was 1.4%, 2.6%, and 16.1%, respectively, in this group. Patients undergoing s-EMR also showed high BE eradication rates (CE-N, 94.9%; CE-IM, 79.6%) but a higher rate of adverse events (strictures in 33.5%, bleeding in 7.5%, and perforation in 1.3%). Recurrence of EAC, dysplasia, and IM was 0.7%, 3.3%, and 12.1%, respectively, in the s-EMR group. Mixed logistic regression showed that patients undergoing s-EMR might be more likely to develop esophageal strictures (odds ratio [OR], 4.73; 95% confidence interval [CI], 1.61-13.85; $P = .005$), perforation (OR, 7.00; 95% CI, 1.56-31.33; $P = .01$), and bleeding (OR, 6.88; 95% CI, 2.19-21.62; $P = 0.001$) compared with f-EMR + RFA.

Conclusions: In patients with HGD/EAC, f-EMR followed by RFA seems to be equally effective as and safer than s-EMR. (Gastrointest Endosc 2017;85:482-95.)

(footnotes appear on last page of article)

INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition that is defined by the replacement of normal stratified squamous epithelium in the distal esophagus by metaplastic columnar epithelium.[1] The annual risk of esophageal adenocarcinoma (EAC) is approximately 0.25% for patients without dysplasia and 6% for patients with high-grade dysplasia (HGD).[2] Endoscopic eradication has already replaced esophagectomy for the treatment of HGD and early EAC.[1] EMR is the cornerstone of endoscopic eradication therapy in BE because it is useful for diagnosing, staging, and treating BE-associated dysplasia.[1,3-6] If EAC has spread into the submucosa, then esophagectomy is the recommended treatment approach. Because metachronous lesions are common from the residual areas of BE, complete eradication of all residual BE is recommended after diagnostic EMR.[7-9]

Stepwise or complete EMR (s-EMR) is a radical endoscopic modality to treat BE-related neoplasia with intent of cure. However, a multimodal endoscopic intervention strategy with focal EMR followed by serial radiofrequency ablation (f-EMR + RFA) has been increasingly used and is considered better than EMR alone.[1,10] f-EMR + RFA has been shown to be a potent, safe, and durable endoscopic strategy for BE eradication,[10-12] but the long-term efficacy and safety data of each modality is not known aside from individual studies.

Composite analysis of the clinical usefulness of each strategy is not available for a large cohort of patients with BE. s-EMR and f-EMR + RFA strategies have been examined previously in a randomized controlled trial,[10] but the sample size was small, making it difficult to extrapolate outcomes on a larger scale. The lack of direct comparison between 2 main strategies for BE eradication drives the uncertainty in clinical decision making, governed by cost issues and technical expertise.

Therefore, we conducted a systematic review and pooled analysis of previous literature to determine the efficacy of f-EMR + RFA and s-EMR for complete eradication of BE-related neoplasia (HGD/EAC) (CE-N) and intestinal metaplasia (CE-IM) with indirect comparison between the 2 methods. We also evaluated the recurrence rates of neoplasia and IM as well as adverse events for each method after successful treatment with f-EMR + RFA and s-EMR.

METHODS

Search strategy

Two independent investigator teams at different sites (M.D., Kansas City, and C.H., Milan) conducted an individualized search up to June 2016. Methods of analysis and inclusion criteria were based on PRISMA recommendations.[13]

Relevant studies were identified by an in-depth search of PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials with no restriction on language. Abstracts from Digestive Disease Week and United European Gastroenterology Week were searched manually. Similar articles (in major databases) and the bibliography of selected studies were used as secondary sources. A search for relevant studies was performed using the following text words and corresponding Medical Subject Heading or Emtree terms: "Barrett or Barrett's," "oesophagus or esophagus," AND "resection" or "endoscopic resection" or "endoscopic mucosal resection," "ablation," OR "radiofrequency ablation." The study flowchart and selection process are shown in Figure 1.

Eligibility criteria

The following inclusion criteria were used for the f-EMR + RFA and s-EMR groups: human studies, patient aged 18 years or more, prospective and retrospective studies, HGD, superficial EAC/intramucosal carcinoma (IMC) limited to mucosa, sample size of 10 patients or greater, and follow-up of more than 12 months (to assess the effect of therapy and recurrence rates). We excluded studies on the basis of 1 or more of the following criteria: case reports/series, review articles, letters to editors, conference or symposium abstracts with limited information, studies without biopsy-proven BE or histology other than HGD/EAC, studies not reporting either efficacy or recurrence, other endoscopic modalities used in a majority of patients, unavailability of variables of interest, methodological differences in technique or intent, and duplicate reports of study samples.

We considered all clinical studies in which patients with BE-related neoplasia (HGD/EAC) underwent either f-EMR + RFA or stepwise (or complete) EMR with intent of complete eradication of BE-related neoplasia. If there was any suspicion of cohort overlap between studies, only the most recent study was included. This included considering the last available or published results from the same group of authors (or where a similar database was used). Inclusion studies were limited to studies with f-EMR performed in more than 70% of patients for the f-EMR + RFA group analysis. This cut-off was considered for estimation of the effect of f-EMR with additional RFA treatments toward pooled analysis of the f-EMR + RFA group. Therefore, studies with patients undergoing f-EMR in fewer than 70% of the total participants were excluded.

Data collection

Both reviewer groups screened all the titles and abstracts of articles retrieved in the pre-specified search. After the initial screening of articles, study data were evaluated for inclusion in the analysis. After secondary exclusion, the final chosen studies were carefully re-examined. Data were extracted from the eligible articles by 1 reviewer and verified by a second reviewer. All variables of interest were organized into formalized tables independently by the authors.

From each article, the reviewers independently abstracted the following information: study name, year of