Treatment of Barrett's esophagus with radiofrequency ablation

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Abstract

Introduction: Barrett's esophagus (BE) represents the distal esophageal epithelium changes that carry a high risk of developing esophageal adenocarcinoma. One of the most challenging aspects of diagnosing BE by endoscopy is precisely discerning between normal epithelium and BE changes, which is essential for therapy success. The objectives of this study were to compare the success of radio-frequency ablation (RFA) therapy to conservative treatment with proton pump inhibitor (PPI) drugs between the clinical presentation and endoscopy findings of BE at 2, 6, 12, and 24 months after administered therapy.
Material and methods: Seventy-five subjects were divided into two groups (RFA and PPI) based on the BE treatment regimen in this case-control study to compare the quality of treatments applied over a 24-month follow-up. Subjects who received RFA therapy were further divided into groups: those who received focal HALO 90 and those who received circumferential HALO 360, based primarily on EGDS findings or endoscopist experience.
Results: The results show that using the RFA therapeutic modality in the treatment of BE is more effective (by 94.2% in the second month of follow-up, i.e., by 99% at the final visit after 24 months) than using PPI therapy alone. Re-RFA therapy was given to 15% of the subjects, mostly applied in the same therapeutic modality (HALO 90).
Conclusions: Our findings show that RFA and re-RFA therapy have a high efficacy and safety profile, with no registered worsening of histology findings, the occurrence of esophageal adenocarcinoma, or adverse effects of the therapy.

Key words: Barrett's esophagus, radio-frequency ablation, proton pump inhibitors.

Introduction

Barrett's esophagus (BE) is an acquired condition in which the distal esophageal epithelium changes into a specialized intestinal (columnar) epithelium containing goblet cells [1]. The prolonged time of transient lower esophageal sphincter relaxations (TLOSR) contributes to acid, bile,

pepsin, and pancreatic enzyme reflux, causing esophageal mucosa damage and the development of BE [2, 3]. The esophagus has several defense mechanisms, including an anti-reflux barrier maintained by tonic contractions of the lower esophageal sphincter (LOS). External compression of the right hemidiaphragm and intra-abdominal placement of the LOS also contribute to maintaining high pressure on the lower esophagus, preventing reflux. Even in healthy people, LOS relaxes regularly. Several dietary factors, including the consumption of chocolate, fatty foods, and alcohol, as well as the harmful influence of smoking habits, can cause a decrease in LOS contractility. All of these factors increase the duration of TLOSR, which contributes to acid, bile, pepsin, and pancreatic enzyme reflux, causing damage to the esophageal mucosa [4, 5].

Furthermore, BE refers to a group of esophageal conditions characterized by a high risk of developing esophageal adenocarcinoma (EAC) [6, 7]. The prevalence of BE in the general population has yet to be determined, owing to differences in the study protocols, population heterogeneity, and BE criteria. According to the literature, Caucasian men aged 55–65 account for roughly 80% of all BE cases [8–10]. BE is diagnosed in 10–20% of all patients undergoing endoscopy for reflux disease symptoms [11, 12]. Another reason for the low prevalence of BE in the general population is that the condition is frequently asymptomatic [13]. More specifically, 46% of patients do not have reflux disease symptoms [12, 14].

According to clinical guidelines, the presence of salmon-pink columnar epithelium ≥ 1 cm in length proximal to the gastroesophageal junction indicates BE, with biopsy analysis revealing intestinal metaplasia and the presence of mucin-containing goblet cells [15–19]. However, one of the most challenging aspects of diagnosing BE by endoscopy was defining a normal gastroesophageal junction in the presence of a cylindrical epithelium. According to the Prague classification, high-resolution endoscopy is the gold standard diagnostic procedure for detecting and histologically differentiating BE, with biopsies performed following the Seattle protocol [2, 20].

Proton pump inhibitors (PPI) are used to treat associated gastroesophageal reflux disease (GERD) in BE patients [21–23]. Although PPIs help reduce GERD symptoms in patients with BE, they are frequently ineffective when patients with BE resist anti-reflux therapy. BE treatment aims to eradicate the affected squamous epithelium and completely replace it with normal esophageal squamous epithelium [19, 21]. The most commonly used ablation technique for BE is radiofrequency ablation (RFA) [19, 24]. RFA can be circumferential or focal, depending on the energy applied and the length and type of BE [16, 25].

Furthermore, depending on the tissue response and the length of the BE, RFA can be repeated every 2 to 3 months [25, 26]. BE recurred after 2.4 years in one out of every 50 patients with completely removed intestinal metaplasia [27]. Factors such as the presence of a longer segment of dysplasia and the duration of BE (i.e. late admission of the patient), poor control of GERD, genetic changes (primarily at the p16 and p53 loci), and RFA non-responders may influence the incomplete or insufficiently effective removal of dysplasia by the RFA technique [28–31]. Even though RFA is an effective treatment option for BE with few side effects, some facts about the origin, pathogenesis, diagnosis and prevention of BE are still unclear [3, 13].

The objectives of this study were to compare RFA therapy with conservative treatment with PPIs, to analyze the correlations between endoscopic and histological diagnosis of BE, and between clinical and endoscopy findings of BE, over 2 years.

Material and methods

Study participants

The case-control study included 75 subjects divided into two groups (RFA and PPI) based on the BE treatment regimen to compare treatment quality over a 24-month follow-up at the University Clinical Hospital Zemun (UCHZ). The UCHZ Ethics Committee approved the study (approval number 507/1), and it was carried out in accordance with the World Medical Association's code of ethics (Declaration of Helsinki), which was published in the British Medical Journal. (July 18, 1964).

The subjects (n = 75) were referred to the Endoscopy Unit after being examined by a gastroenterologist at the Gastroenterology Outpatient Clinic. The suspected patients were referred for an endoscopy examination – esophagogastroduodenoscopy (EGDS) – based on the patients' complaints and clinical examination, in addition to the findings of the abdominal ultrasound examination performed by a single experienced ultrasonographer. An interview was conducted with the respondents immediately before the EGDS examination, during which, in addition to demographic data (general, gender, age), the questions with structured answers (yes or no) about the subjective complaints (the presence of stomach pain, heartburn/acidity, and vomiting) were obtained. Following the structured interview, the patients received EGDS.

The presence of BE at the EGDS examination was the inclusion criterion for the study's continuation. The characteristics of present complaints,

EGDS, histology findings, the availability of equipment and staff, as well as the subject's consent, determined the administration of BE's appropriate treatment modality, endoscopy, or conservative (only pharmacological). The first EGDS check-up and the performance of the same structured interview covering subjective complaints and information about the applied therapy (drug dosage and compliance) were after 2 months, followed by 6, 12, and 24 months. The subject signed each time to be informed about the EGDS examination with/without RFA therapy and any potential complications. In addition to the usual EGDS report, BE was precisely analyzed during each control EGDS, according to a standardized procedure.

Endoscopy examination

Following pharyngeal anaesthesia, all subjects underwent EGDS with an Olympus endoscope, with findings documented on video. The EGDS procedure was performed in a standard manner, with the upper digestive system examined in anatomical order (esophagus, esophagogastric junction, stomach and duodenal bulb). The duodenum, antrum and body of the stomach, esophagocardial junction, and BE were then biopsied according to the Seattle protocol. In terms of BE, the endoscopist precisely measured the maximum distance of the intestinal metaplasia in cm from the esophagogastric junction and its circumference, defining the endoscopic presentation of intestinal metaplasia according to the Prague classification [21]. If the most distant segment of BE is longer than 3 cm, it is classified as long-segment BE; if the segment of intestinal metaplasia is shorter than 3 cm, it is classified as short-segment BE. Following the description of BE, mucosal biopsies were collected. At least two biopsies were taken from each region, with biopsies taken from four quadrants every 1–2 cm in the BE region. After being placed in adequately labelled vials with a fixative and accompanied by documentation, the samples were sent to the UCHZ Department of Pathology for analysis.

Histology analysis

Following preparation, the same pathologist examined all biopsies under a microscope. Histology findings are classified into three types: no dysplasia, low-grade dysplasia (LGD), and high-grade dysplasia (HGD). All follow-up visits included histology analysis of BE biopsies (2, 6, 12 and 24 months).

Radiofrequency ablation

The EGDS findings determined the types of RFA modality used. Focal radiofrequency ablation (HALO 90) is performed in two steps using a special electrode attached to the tip of the endoscope, with previously treated esophageal mucosa peeled off during the pause between the two steps. Circumferential radiofrequency ablation therapy (HALO 360) is also performed in two steps, with a special balloon of the appropriate size carrying an RF current and being introduced into the esophagus via a wire guide.

Statistical analysis

Statistical methods included descriptive and analytical statistics. Among the methods of descriptive statistics, relative numbers, central tendency measures and variability were used. Among the methods of analytical statistics, tests were used to assess the correlation (Spearman's rank correlation test) and significant difference. To assess the significance of the difference, the χ^2 test was used in the case of categorical data, while the Mann-Whitney test was used for interval data, which do not follow a normal distribution. The predictability of demographic, clinical and endoscopy variables for the response to the applied therapy after 2, 6, 12 and 24 months of follow-up was determined by uni- and multivariate logistic regression analysis.

The level of statistical significance is 0.05. The obtained data were analyzed using the statistical package SPSS for Windows 18.0.

Results

The 75 subjects studied were divided into groups: those with longer BE segments treated with RFA (n = 41) and those with shorter BE segments treated with PPI (n = 34). Subjects receiving RFA therapy were further divided into groups: those receiving focal HALO 90 (n = 31) and those receiving circumferential HALO 360 (n = 9), based primarily on EGDS findings or endoscopist experience. Both RFA modalities were applied in one subject. Out of 6 (15%) subjects who received re-RFA, 4 and 2 of them were performed 6 and 24 months after the initial RFA, respectively. In 83% of cases, re-RFA was performed using the same modality as the initial one (HALO 90). There were no registered complications after the performance of RFA and re-RFA.

The distribution analysis results show that the examined groups do not differ by gender (χ^2 = 0.199; df = 1; p = 0.656) or age (t = 1.713; df = 73; p = 0.091).

In order to standardize the endoscopic findings of BE, we used the Prague classification to assess the circumferential length (C) and the maximal length (M) of the extension of the endoscopically visualized segment [32]. The studied groups do not differ by Prague classification C (Z = 0.396; p = 0.692), but they do differ by Prague classification M (Z = 3.755; p < 0.001). Table I depicts

the distribution of patients based on the type of clinical presentation. The research shows that the groups do not differ regarding the prevalence of stomach pain, heartburn, or vomiting at admission or two months later. However, the results show that after 6, 12, and 24 months, the number of patients with symptoms of stomach pain and heartburn in the RFA therapy group was significantly lower than in the PPI group.

Table II shows the distribution of subjects in the examined groups based on the degree of dysplasia. The examined groups did not differ based on the degree of dysplasia at the time of admission. Furthermore, the results show that the group of subjects treated with RFA has a significantly higher number of subjects who no longer have BE after 2, 6, 12, and 24 months than the group of PPI patients.

Table I. Distribution of patients according to clinical presentation

Stage	Clinical presentation	PPI	RFA	*P*-value
On admission	Stomach pain	10 (31.3%)	11 (26.8%)	$\chi^2 = 0.171$; d$f = 1$; $p = 0.679$
	Heartburn	25 (78.1%)	32 (78.0%)	$\chi^2 = 0.795$; d$f = 1$; $p = 0.994$
	Vomiting	1 (3.1%)	6 (14.6%)	$\chi^2 = 2.746$; d$f = 1$; $p = 0.097$
After 2 months	Stomach pain	11 (32.4%)	10 (24.4%)	$\chi^2 = 0.585$; d$f = 1$; $p = 0.445$
	Heartburn	22 (64.7%)	20 (48.8%)	$\chi^2 = 1.913$; d$f = 1$; $p = 0.167$
	Vomiting	1 (2.9%)	3 (7.3%)	$\chi^2 = 0.705$; d$f = 1$; $p = 0.401$
After 6 months	Stomach pain	11 (32.4%)	2 (4.9%)	$\chi^2 = 9.792$; d$f = 1$; $p = 0.002$
	Heartburn	22 (64.7%)	8 (19.5%)	$\chi^2 = 15.818$; d$f = 1$; $p < 0.001$
	Vomiting	0 (0%)	1 (2.4%)	$\chi^2 = 0.840$; d$f = 1$; $p = 0.359$
After 12 months	Stomach pain	9 (26.5%)	1 (2.4%)	$\chi^2 = 9.289$; d$f = 1$; $p = 0.002$
	Heartburn	22 (64.7%)	3 (7.3%)	$\chi^2 = 27.547$; d$f = 1$; $p < 0.001$
	Vomiting	0 (0%)	0 (0%)	–
After 24 months	Stomach pain	5 (14.7%)	2 (4.9%)	$\chi^2 = 2.121$; d$f = 1$; $p = 0.145$
	Heartburn	18 (52.9%)	4 (9.8%)	$\chi^2 = 16.722$; d$f = 1$; $p < 0.001$
	Vomiting	1 (2.9%)	0 (0%)	–

PPI – proton pump inhibitor, RFA – radiofrequency ablation, p – significance.

Table II. Distribution of subjects according to degree of dysplasia

Stage	Dysplasia	PPI	RFA	Significance
On admission	No dysplasia	22 (64.7%)	24 (58.5%)	$\chi^2 = 0.303$; d$f = 2$; $p = 0.859$
	LGD	10 (29.4%)	14 (34.1%)	
	HGD	2 (5.9%)	3 (7.3%)	
After 2 months	No BE	1 (2.9%)	14 (34.1%)	$\chi^2 = 11.312$; d$f = 1$; $p < 0.001$
	No dysplasia	22 (64.7%)	15 (36.6%)	
	LGD	9 (26.5%)	11 (26.8%)	
	HGD	2 (5.9%)	1 (2.4%)	
After 6 months	No BE	1 (2.9%)	29 (74.4%)	$\chi^2 = 38.273$; d$f = 1$; $p < 0.001$
	No dysplasia	22 (64.7%)	3 (7.7%)	
	LGD	10 (29.4%)	7 (17.9%)	
	HGD	1 (2.9%)	0 (0%)	
After 12 months	No BE	1 (2.9%)	34 (82.9%)	$\chi^2 = 47.777$; d$f = 1$; $p < 0.001$
	No dysplasia	22 (64.7%)	1 (2.4%)	
	LGD	11 (32.4%)	6 (14.6%)	
	HGD	0 (0%)	0 (0%)	
After 24 months	No BE	1 (2.9%)	35 (85.4%)	$\chi^2 = 51.039$; d$f = 1$; $p < 0.001$
	No dysplasia	20 (58.8%)	3 (7.3%)	
	LGD	11 (32.4%)	3 (7.3%)	
	HGD	2 (5.9%)	0 (0%)	

BE – Barrett's esophagus, LGD – low-grade dysplasia, HGD – high-grade dysplasia.

Table III shows the relationship between the clinical presentation of the disease and the endoscopy finding of BE according to the Prague classification C and M. There was a link discovered between the Prague classification M and vomiting: the subjects with a higher M value in the Prague classification vomited more frequently.

Table IV shows the results of univariate and multivariate logistic regression analysis of treatment response predictors at various follow-up stages in subjects with BE who underwent different treatment modalities (RFA and PPI). Only the RFA therapeutic option was found to be a significant predictor of therapy response after 2 months of follow-up, reducing the likelihood of BE after 2 months by 94.2% when compared to the PPI therapeutic option. After 6 months of follow-up, a higher Prague C classification value is a risk factor for the presence of BE. Furthermore, compared to the PPI therapeutic option, the RFA therapeutic option reduces the likelihood of BE by 99% after 6 months of follow-up. The Prague M classification and RFA therapeutic option were identified as significant predictors of response to therapy in univariate logistic regression at 12 and 24 months of follow-up. Compared to the PPI treatment option, the RFA treatment option reduces the likelihood of having BE by 99% after 12 and 24 months of follow-up.

Table III. Correlation between clinical manifestations of the disease and endoscopic finding of BE

Clinical manifestations of the disease		Prague classification C	Prague classification M
Stomach pain	rho	0.105	0.058
	P-value	0.375	0.624
Heartburn	rho	0.004	0.049
	P-value	0.972	0.681
Vomiting	rho	0.042	0.242
	P-value	0.724	0.039

Table IV. Predictors of response to therapy in patients with BE treated with RFA and PPI

Stage	Parameters	Univariate logistic regression			Multivariate logistic regression		
		P-value	RR	95% CI for RR	*P*-value	RR	95% CI for RR
After 2 months	Prague classification C	0.213	1.534	0.782–3.008	/	/	/
	Prague classification M	0.657	0.969	0.842–1.114	/	/	/
	Stomach pain	0.405	1.800	0.452–7.169	/	/	/
	Heartburn	0.619	1.394	0.377–5.161	/	/	/
	Vomiting	0.669	1.615	0.179–14.546	/	/	/
	PPI vs. RFA	0.008	0.058	0.007–0.473	/	/	/
After 6 months	Prague classification C	0.059	1.701	0.980–2.953	0.012	7.161	1.55–33.06
	Prague classification M	0.338	0.939	0.825–1.068	/	/	/
	Stomach pain	0.195	2.074	0.688–6.251	/	/	/
	Heartburn	0.842	0.889	0.278–2.837	/	/	/
	Vomiting	0.689	0.711	0.133–3.792	/	/	/
	PPI vs. RFA	< 0.001	0.010	0.001–0.087	< 0.001	0.001	0.00–0.04
After 12 months	Prague classification C	0.803	1.046	0.734–1.491	/	/	/
	Prague classification M	0.049	0.849	0.721–0.999	0.607	1.045	0.88–1.24
	Stomach pain	0.287	1.755	0.623–4.941	/	/	/
	Heartburn	0.852	1.111	0.366–3.369	/	/	/
	Vomiting	0.610	0.664	0.138–3.203	/	/	/
	PPI vs. RFA	< 0.001	0.006	0.001–0.054	< 0.001	0.004	0.00–0.04
After 24 months	Prague classification C	0.640	1.090	0.761–1.560	/	/	/
	Prague classification M	0.039	0.839	0.710–0.991	0.572	1.050	0.89–1.24
	Stomach pain	0.226	1.896	0.673–5.341	/	/	/
	Heartburn	0.951	1.036	0.342–3.140	/	/	/
	Vomiting	0.664	0.706	0.146–3.403	/	/	/
	PPI vs. RFA	< 0.001	0.005	0.001–0.045	< 0.001	0.004	0.00–0.04

Discussion

The findings of this study indicate that the RFA therapeutic modality is more effective than PPI therapy alone (by 94.2% in the second month of follow-up, i.e., by 99% at the final visit after 24 months). Furthermore, the findings revealed that vomiting indicates the immediate application of invasive BE treatment modalities such as RFA. Re-RFA therapy was given to 15% of the subjects, most of the time in the same therapeutic modality (HALO 90).

In the last decade, the frequency of BE per 1000 endoscopies has ranged from 2.9% to 18.9% of newly registered cases [33, 34], posing a severe public health concern given the high risk of EAC [12]. There are several risk factors for the development of BE, with GERD being the most important [35, 36]. As a result, the first approach in treating BE patients is to treat GERD to prevent esophageal erosion [26]. PPIs are now a class of drugs that are the first line of treatment for various gastrointestinal disorders, including GERD [37] and BE [38]. However, independent PPI treatment without a prior or subsequent application of other, primarily invasive BE treatment modalities produces unsatisfactory results.

RFA is a widely accepted endoscopic technique for treating BE and destroying residual altered tissue after EAC resection [24, 39]. The goal of using RFA to treat BE is to remove dysplasia and intestinal metaplasia while completely restoring the esophageal squamous epithelium [26, 40]. RFA is a safe procedure with few complications, including bleeding, post-procedural chest pain and perforation [41, 42]. Based on two meta-analyses, among patients with BE-LGD, the risk of progression to HGD or EAC was reduced after RFA treatment compared with patients undergoing endoscopic surveillance [43, 44]. Following RFA, further treatment with PPIs is advised, with a recommendation to repeat EGDS in 3 months [25]. Our unpublished data show that the distribution of subjects by PPI dose revealed that a dose of 40 mg was more common in patients receiving conservative therapy, whereas a post-RFA dose of 80 mg was more common in patients receiving RFA therapy. Roorda *et al.* found that subjects on PPI therapy tolerated RFA therapy with no additional complications [45].

A larger circumference and BE segment length are important reasons to choose invasive RFA therapy over conservative PPI therapy because histology findings of biopsies sampled from endoscopic regions with such characteristics usually indicate a more severe degree of dysplasia and an increased risk of threatening malignant alteration [26, 46]. In our study, subjects who received RFA had longer BE segment lengths than those who received PPI. Furthermore, our study revealed a positive correlation between the endoscopic findings defined by the Prague classification (C and M) and the severity of the histology findings of BE, as expected. The presence of vomiting in our study subjects was positively correlated with the severity of the endoscopic finding in terms of the prominence of the segment length, according to the Prague M classification. Retrograde peristaltic waves, which accompany vomiting, contribute to its occurrence while also worsening existing acid biliary reflux and favoring an adverse effect on the esophageal mucosa [35, 47]. Given the association of the length of the BE segment with the severity of dysplasia, the presence of vomiting should influence the clinician's decision to implement the RFA therapeutic option over individual PPI therapy. The PPI therapeutic option is undeniably important in the continuation of BE treatment (maintenance therapy), whether performed after or, more often, concurrently with other treatment modalities, such as RFA therapy. The findings of this study, which were related to the predictability of the response to the application of RFA and PPI therapeutic options in various stages of subject follow-up, show that only the RFA therapeutic option reduces the probability of BE (by 94.2% in the second month of follow-up, i.e. by 99% at the final visits after 24 months). Finally, the rate at which the examinee's quality of life improves (reduction in the number of clinical manifestations and BE presentation types, as well as PPI dose reduction), as well as the regression of histology findings towards lower degrees of dysplasia to normal findings (without BE), support the primacy of RFA therapy over individual conservative therapy for BE eradication. The majority of RFA subjects are treated with focal-HALO 90 modalities. The study's limitation was the small subpopulation of subjects treated with HALO 360 modality RFA therapy, primarily based on EGDS findings or the endoscopist's experience. Aside from re-RFA in six subjects at the end of the 24-month follow-up period, no complications or EAC occurrences were observed, according to medical records. The findings of our study agree with those of other authors. Pouw *et al.* found that RFA in BE patients with established LGD reduces the risk of malignant transformation significantly, with sustained clearance of BE in 91% and LGD in 96% of patients after a 73-month follow-up [48].

Furthermore, eradicating intestinal metaplasia and BE dysplasia has been shown to significantly reduce the incidence of EAC [21]. Two protocols are currently in use for the application of RFA in the treatment of BE: standard (2 × 12–15 J/cm^2 – cleaning – 2 × 12–15 J/cm^2) and simplified (3 × 12 J/cm^2, no cleaning) [49–51]. Both protocols have similar effects, but the simplified protocol is used more for focal RFA in treating BE and takes

less time to apply [25, 52]. Intestinal metaplasia present under the new squamous cell epithelium may pass undetected during the endoscopy examination, significantly increasing the risk of malignancy [53]. Smith *et al.* demonstrated that RFA energy of 12 J/cm^2 can be used to ablate HGD completely [54]. Fleischer *et al.* achieved a complete response to RFA therapy in 98.4% of patients after a 2.5-year follow-up of patients with varying degrees of BE intestinal metaplasia [55]. In a multicenter American study, 16 researchers examined the efficacy and safety of RFA (circumferential and focal) combined with endoscopic mucosal resection of larger lesions, achieving an efficacy of 90% with a complete response after one year of patient follow-up [56].

RFA, the most commonly used ablation technique for the treatment of BE, is now regarded as a reliable endoscopic technique not only for the removal of BE, but also for the removal of BE residual after endoscopic resection of EAC detected in the early stages of the disease [26, 57]. Despite the existence of reliable treatment methods for BE, additional research is required to improve existing or discover new methods of treating this disease. The use of advanced technology will significantly improve RFA outcomes. Better visualization and prevention of serious complications could be expected by combining other invasive diagnostic procedures (for example, mediastinoscopy). It is in the patient's best interests to establish a national or regional BE center with skilled and educated personnel required for complex diagnostic and therapeutic procedures.

In conclusion, the results from this study show that the use of the RFA therapeutic modality is a more effective approach in the treatment of BE than the use of independent PPI therapy, as evidenced by the impact on clinical manifestations of the disease and the faster establishment of improvement in endoscopy and histology findings. The following relationship was demonstrated between the components of the initial Prague endoscopic classification of BE and the severity of the biopsy histology: the greater the circumference and length of the tongue of most significant clinical interest (the longest tongue), the more common the presence of a more severe degree of dysplasia. In addition, our results indicate that RFA and re-RFA therapy have a high efficiency and safety rate without worsening histology findings, EAC occurrence, or treatment complications in any subjects.

It is unclear whether future advances in BE treatment methods will result in complete clinical-endoscopic resolution of BE or will introduce new and unexpected complications in treating this pathology.

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Conflict of interest

The authors declare no conflict of interest.

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