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Focal endoscopic mucosal resection before radiofrequency ablation is equally effective and safe compared with radiofrequency ablation alone for the eradication of Barrett's esophagus with advanced neoplasia

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Abstract

Background—Endoscopic mucosal resection (EMR) is commonly performed before radiofrequency ablation (RFA) for nodular dysplastic Barrett's esophagus (BE).

Objective—To determine the efficacy and safety of EMR before RFA for nodular BE with advanced neoplasia (high-grade dysplasia (HGD) or intramucosal carcinoma (IMC)).

Design—Retrospective study.

Setting—University of North Carolina Hospitals, from 2006 to 2011.

Patients—169 patients with BE with advanced neoplasia – 65 patients treated with EMR and RFA for nodular disease and 104 patients treated with RFA alone for non-nodular disease.

Interventions—Endoscopic mucosal resection, radiofrequency ablation.

Main Outcome Measurements—Efficacy (complete eradication of dysplasia, complete eradication of intestinal metaplasia, total treatment sessions, RFA treatment sessions), safety (stricture formation, bleeding, and hospitalization).

Results—EMR followed by RFA achieved complete eradication of dysplasia and complete eradication of intestinal metaplasia in 94.0% and 88.0%, respectively, compared with 82.7% and 77.6%, respectively in the RFA only group (p=0.06 and p=0.13, respectively). The complication rates between the two groups were similar (7.7% vs. 9.6%, p=0.79). Strictures occurred in 4.6% of patients in the EMR before RFA group compared with 7.7% of patients in the RFA only group (p=0.53).

Limitations—Retrospective study at a tertiary-care referral center.

Conclusion—In patients treated with EMR before RFA for nodular BE with HGD or IMC, no differences in efficacy and safety outcomes were observed compared with RFA alone for non-

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nodular BE with HGD or IMC. EMR followed by RFA is safe and effective for patients with nodular BE and advanced neoplasia.

Keywords

Endoscopic mucosal resection; radiofrequency ablation; Barrett's esophagus; efficacy; safety

Introduction

Barrett's esophagus (BE) is a precancerous condition associated with adenocarcinoma of the esophagus,[1, 2] a condition with a marked increase in incidence over the past four decades.[3, 4] BE with high-grade dysplasia (HGD) may progress to adenocarcinoma in as many as 20% of patients per year.[5] Similarly, BE with intramucosal carcinoma (IMC) is a high risk lesion in the absence of disease-altering therapy. Radiofrequency ablation (RFA) is a safe and effective therapy for the eradication of non-nodular dysplastic BE.[5-7] However, many patients with HGD or IMC have nodularity in their Barrett's segment. Endoscopic mucosal resection (EMR) is commonly performed to remove these nodular areas before treatment with RFA.[8, 9] Despite being frequently performed, the safety and efficacy of RFA after EMR is poorly understood.

The aims of this study were to compare the safety and efficacy of combined EMR/RFA treatment for nodular Barrett's to treatment with RFA alone for non-nodular Barrett's. We assessed whether preceding EMR leads to either a higher complication rate or decreased efficacy compared to subjects requiring RFA alone.

Methods

Patient eligibility and data collection

We performed a retrospective study of adult patients treated with RFA for BE with HGD or IMC at University of North Carolina (UNC) Hospitals between 2006 and 2011. Subjects were identified by review of our electronic endoscopic database (Provation MD, Wolters Kluwer, Minneapolis, MN) from January 1, 2006 through November 1, 2011 using the following terms: Barrett, esophageal adenocarcinoma, cancer, carcinoma in situ, dysplasia, ablation, radiofrequency. We also performed a search using a procedure code for esophagoscopy with ablation (CPT 43228).

Each subject was then reviewed by one of two investigators (HK, WB) using the electronic medical record (WebCIS, University of North Carolina Health Care System) to determine eligibility for inclusion. Patients were excluded if they never received treatment with RFA, were treated with RFA for a non-BE related disease, did not have a pre-ablation histology of HGD or IMC, or underwent EMR *after* RFA initiation. All eligible patients were included in the safety analysis, whereas the efficacy analysis excluded individuals receiving ongoing RFA therapy as of November 1, 2011.

Pertinent data were extracted from clinical, endoscopy, and pathology reports for each subject and included demographic information (age, gender, race, body mass index (BMI)), pertinent medical history (erosive esophagitis, peptic stricture), substance use (alcohol, tobacco), medication use (anti-secretory therapy, non-steroidal anti-inflammatory drugs (NSAID)), EGD findings (length of BE, Prague C and M classification, hiatus hernia, erosions, ulcers, nodules), pre-ablation histology, treatment provided, ablation outcomes, and complications. At all treatment sessions, patients provided interim history regarding any complications of therapy or visits to other institutions for treatment-related issues. To standardize methodology, the first ten subjects were reviewed by both investigators jointly

with discrepancies in data collection resolved by consensus. For additional quality control, every 20th study subject was reviewed independently by both investigators to assess inter-rater agreement of abstracted data.

Pre-treatment evaluation and procedural protocol

All patients had an initial consultation visit to discuss BE and dysplasia, its risk of progression to cancer, and the risks and benefits of different treatment options including continued endoscopic surveillance, ablative therapy, and esophagectomy. Worst histologic grade of BE was determined by review of original pathology records. All cases were reviewed by an expert gastrointestinal pathologist as part of routine care, and if findings between the initial pathology report and the secondary review were discordant, an additional expert gastrointestinal pathologist reviewed the case with histologic classification by consensus.

Patients who opted for RFA had pre-treatment staging by EGD and EUS to exclude invasive or metastatic disease that would preclude curative endoscopic treatment. If the BE segment had no visible mucosal abnormalities, RFA was performed as outlined below. If the BE segment contained any mucosal abnormality with the exclusion of deep ulceration, EMR was performed before the beginning of RFA therapy. Nodules were defined endoscopically as any contoured irregularity and elevation of the mucosa without breaks, including Paris classification 0-I and 0-IIa lesions.[10] All visible lesions were resected endoscopically using either the Olympus 18 mm oblique cap kit (Olympus America, Center Valley, PA) or the Duette device (Cook Medical, Winston-Salem, NC). EMR performed with the Olympus device was preceded by submucosal injection of saline solution, whereas EMR with the Duette device was performed without prior injection. RFA therapy was initiated two months after all visible lesions were removed and if pathology specimens did not reveal submucosal infiltration of adenocarcinoma. Twice daily proton pump inhibitor therapy was prescribed to all patients before and throughout RFA treatment.

Patients with circumferential disease were treated with circumferential RFA using the HALO^{360} device, whereas focal lesions were treated with focal RFA using the HALO^{90} device (BARRX Medical, Sunnyvale, CA). Standard procedural technique was used as previously described.[6] Patients returned every two months for repeat EGD to assess treatment response, and residual BE was treated with focal ablation until no visible BE was observed on white-light and narrow band imaging endoscopy. At this point, four-quadrant biopsies were taken from just distal to the gastroesophageal junction and at 1 cm intervals along the length of the original BE segment. Treatment was considered complete and successful if the subject displayed no endoscopic or histological evidence of residual intestinal metaplasia in the tubular esophagus.

Outcomes and statistical analysis

Safety outcomes included death, esophageal perforation, stricture formation, bleeding, and hospitalization. A stricture was defined as any narrowing of the esophageal lumen that was treated with dilation, regardless of symptoms of dysphagia. Bleeding was considered clinically significant if it required a blood transfusion or hospitalization. Safety outcomes were described for patients who received EMR before RFA and for subjects who received RFA only, and were reported per patient and per procedure, relative to the total number of treatment sessions.

Upon completion of endoscopic therapy, all biopsy specimens were reviewed by an expert gastrointestinal pathologist to determine the presence of residual BE and degree of dysplasia. Any specimen demonstrating dysplasia was confirmed with a second histological

analysis by a second GI pathologist. Assessment of RFA efficacy included complete eradication of dysplasia (CED), complete eradication of intestinal metaplasia (CEIM), total treatment sessions, and RFA treatment sessions. CED was defined as the absence of dysplasia from all esophageal biopsies, and CEIM was defined as complete endoscopic resolution and the absence of IM from all esophageal biopsies. Total treatment sessions include any ablation or endosopic mucosal resection treatment, whereas RFA sessions include only circumferential and focal RFA treatments.

The proportion of subjects achieving CED or CEIM, total treatment sessions, and RFA sessions are described on an intention-to-treat (ITT) and per protocol (PP) basis. Any patient who was lost to follow-up, died during the RFA treatment period from an unrelated cause, or had treatment halted due to an unrelated life-limiting comorbidity was considered a treatment failure in the ITT analysis. The PP analysis included all subjects in whom treatment was considered complete. Efficacy outcomes were described for patients who received EMR before RFA and for subjects who received RFA only.

Statistical analysis was performed using Stata software (version 12.0; StataCorp LP, College Station, TX). Safety and efficacy outcomes were reported for subjects who had EMR before RFA and for those who had RFA only, and comparative analyses were performed using the Student's t-test or the Wilcoxon rank sum test for continuous variables and the Pearson's chi-square test or the Fisher exact test for categorical variables. P-values less than 0.05 were considered significant. This study was approved by the UNC IRB.

Results

Patient Eligibility

A total of 286 patients received EGD with ablative therapy at UNC hospitals between 2006 and 2011. Of these patients, 117 were excluded: 19 never received RFA and were treated with a different ablative modality (15 cryoablation, 2 argon plasma coagulation, 2 photodynamic therapy); 5 were treated for a non-BE related disease (3 squamous cell carcinoma, 1 gastric antral vascular ectasia, 1 gastric cardia dysplasia); 71 had pre-ablation histology other than HGD or IMC (11 non-dysplastic BE, 53 low-grade dysplasia, 7 invasive adenocarcinoma); and 22 underwent EMR after the initiation of RFA therapy.

Safety Outcomes

The remaining 169 patients were included in the safety analysis – 65 patients underwent EMR before RFA and 104 patients received RFA only. The baseline characteristics of these patients are summarized in Table 1. Patients who had EMR before RFA were older (mean age 68.8 vs. 64.2, p=0.008) and were more likely to have IMC (43.1% vs. 2.9%, p<0.001) compared with those who had RFA only.

All patients who underwent EMR before RFA therapy had nodular disease (Paris 0-I and 0-IIa lesions). These 65 patients underwent a total of 66 EMR sessions with a single patient having 2 EMR sessions. Fifty-five percent of patients underwent EMR with the Olympus 18mm oblique cap kit and 45% of patients underwent EMR with the Duette device. Sixty-one percent of patients had one resection performed during the EMR session, whereas 39% had multiple resections performed. Of those who had multiple resections, subjects underwent a mean of 2.5 resections during a given EMR session.

Patients in the EMR before RFA group underwent 212 total treatment sessions (3.3 per patient), and patients receiving RFA only underwent 293 total treatment sessions (2.8 per patient) (p=0.09). Of patients who received EMR before RFA, 37% received combination therapy with circumferential and focal ablation and 57% received focal ablation only. Of

patients who received RFA only, 56% received combination therapy with circumferential and focal ablation and 36% received focal ablation only.

Complications occurred in 5 of 65 patients (7.7% of patients, 2.4% of procedures) who had EMR before RFA, compared with 10 of 104 patients (9.6% of patients, 3.4% of procedures) who had RFA only. There were no deaths or esophageal perforations in either group; all complications were related to either stricture or bleeding. A stricture occurred in three patients who had EMR before RFA (4.6% of patients, 1.4% of procedures) compared with eight patients who had RFA only (7.7% of patients, 2.7% of procedures). All strictures developed after an RFA treatment session, were <1 cm in length, and resolved after a median of 1 endoscopic dilation. Of those in the EMR before RFA group, strictures occurred in 2 patients treated with the Olympus cap, whereas stricture occurred in 1 patient treated with the Duette device (6% vs. 4%, p=1.00). There were no stricture recurrences in the EMR before RFA group on subsequent endoscopies. Three patients in the RFA only group had stricture recurrence, and 2 of these patients required additional intervention with endoscopic dilation. Post-procedural hemorrhage occurred in 2 patients who had EMR before RFA and in 2 patients who had RFA only. In those who had EMR before RFA, both patients had post-procedural hemorrhages after an EMR session. One patient was treated with the Olympus cap, whereas the other was treated with the Duette device (3% vs. 4%, p=1.00). All 4 patients with post-procedural hemorrhage were subsequently hospitalized – 3 patients were hospitalized for 1 day each and the fourth patient for 2 days. Complication rates of those with EMR before RFA versus RFA alone were not statistically different (p>0.05 for all comparisons, see Table 2).

Efficacy Outcomes

Twenty-one of the 169 patients included in the safety analysis were receiving ongoing RFA therapy and were excluded from the efficacy analysis. The remaining 148 patients (50 EMR before RFA, 98 RFA only) were included in the ITT analysis, including 16 patients who did not complete treatment and were considered treatment failures: 11 were lost to follow-up; 4 were diagnosed with a life-threatening comorbidity unrelated to their esophageal condition, which precluded further therapy; and 1 died of an unrelated event during the treatment period. There were no cancer-related deaths in the cohort. Two of the 16 patients who did not complete treatment belonged to the EMR/RFA group, whereas 14 of them belonged to the RFA only group (4% EMR/RFA ITT efficacy cohort vs. 14% RFA only ITT efficacy cohort; p=0.09). The PP analysis included 132 patients (48 EMR before RFA, 84 RFA only) after excluding the 16 patients who did not complete treatment. The baseline characteristics for all patients included in the efficacy analysis were similar to the overall cohort, with patients who had EMR before RFA again older (mean age 68.1 vs. 63.9, p=0.02) and more likely to have IMC (42.0% vs. 3.1%, p<0.001) compared with those who had RFA only.

CEIM was achieved in 88% ITT (92% PP) who had EMR before RFA compared with 78% (91% PP) who had RFA only (p>0.05 for both ITT and PP comparisons). CED was achieved in 94% (98% PP) who had EMR before RFA compared with 83% (96% PP) who had RFA only (p>0.05 for both ITT and PP comparisons). Disease progression occurred despite therapy in two patients who had RFA only and in no patients who had EMR before RFA. There was no clinical or statistical difference in the ability of EMR/RFA to achieve CED and CEIM compared with RFA alone (Table 3). Compared with RFA alone, EMR/RFA required more total treatment sessions (mean 3.5 vs. 2.8, p=0.02) to achieve completion, but no difference in the number of RFA sessions was observed (mean 2.5 vs. 2.8, p=0.28). Prior EMR was also associated with a decreased number of circumferential ablation sessions (mean 0.40 vs. 0.67, p=0.003). Mean follow-up to eradication was 9.0 months.

Discussion

In this retrospective study, we report the largest series of patients treated with EMR before RFA, as well as the largest series examining endoscopic treatment of HGD and IMC with RFA. We compared the safety and efficacy of EMR before RFA for nodular BE with RFA only for non-nodular BE in adult patients with BE and advanced neoplasia. Both treatment modalities were found to be effective, and similar rates of CED and CEIM were achieved in both groups. The two treatment groups also experienced similar rates of complication, consisting mostly of benign strictures that were successfully treated with endoscopic dilation. Previous work demonstrated that prior EMR may diminish efficacy of RFA, and that more extensive EMR results in a 25-37% stricture rate.[11-13] However, our work demonstrates that focal EMR for nodular disease, which is commonly performed in the U.S., is not associated with either a decreased likelihood of successful eradication of intestinal metaplasia or an increased risk of esophageal stricture.

Endoscopic therapy consisting of EMR combined with mucosal ablation has been found to be an effective treatment modality for BE with advanced neoplasia and visible lesions.[14, 15] Although RFA is safe and effective, our understanding of combined therapy consisting of EMR before RFA for nodular BE is limited. Several case series have been reported by a European medical center (Amsterdam Medical Center, Netherlands), limited in each instance by small study populations and the absence of a control group for comparison.[16-20] In the largest series published by this center, Pouw et al. performed a study of 44 patients who had RFA with or without prior EMR, in which 98% of patients achieved CED and CEIM. Of the 44 patients, 31 of them had prior EMR. Five patients experienced an adverse event from EMR (4 mild hemorrhages, 1 esophageal perforation), and 4 patients developed dysphagia after RFA, with all cases occurring in patients who had prior EMR. The lack of two distinct groups in this publication – those with and those without prior EMR – prevented examination of the effects of EMR on the safety and efficacy of RFA.[18] A second study by Pouw et al. consisted of 24 patients, of which 23 (96%) had EMR before RFA. CED and CEIM were achieved in 95% and 88%, respectively, and 8% of patients experienced a complication, including 1 stricture formation.[19]

A recent study from the Mayo Clinic (Rochester, MN) directly compared patients who received RFA after EMR (n=44) versus RFA alone (n=46).[13] In contrast to our study, eradication of intestinal metaplasia was markedly diminished in patients treated with EMR then RFA, with only 43% of those undergoing EMR/RFA achieving complete eradication of intestinal metaplasia compared with 74% of those undergoing RFA alone. If, as suggested in the previous study, only a minority of subjects achieve complete eradication of intestinal metaplasia with EMR then RFA, then physicians might be more inclined to consider surgical options for these patients with nodular BE. However, we found no difference in the efficacy of RFA with or without prior EMR, suggesting that EMR then RFA is a suitable primary therapeutic option for these patients. Additionally, in the previous Mayo study, stricture formation was more frequent in the RFA after EMR group (13.6%) compared with the RFA only group (8.7%), whereas in our study, no significant difference in stricture rate was observed. The reasons for these differences are not entirely clear. However, unlike our study, which featured only subjects with advanced neoplasia (HGD and IMC), most patients in the previous study who had RFA only had non-dysplastic BE or low-grade dysplasia, whereas almost all those undergoing EMR had more severe disease (89% either HGD or IMC). Because degree of baseline dysplasia may be associated with decreased rates of eradication or higher complication rates, these data may be confounded. The unbalanced representation of advanced neoplasia may also contribute to the higher stricture rate observed in the RFA after EMR group. Although multivariate analysis was performed in an effort to account for these differences, the results are limited in their interpretability given

the high degree of collinearity between the treatment used and the patients' pre-treatment histology, as well as the relatively small numbers of patients in the study.

In our study, patients who had EMR before RFA achieved CED in 94.0% and CEIM in 88.0% by intention to treat analysis. The rates of CED and CEIM in nodular disease treated with RFA after EMR were similar to those achieved in patients undergoing RFA only for non-nodular dysplasia. This suggests that treatment with EMR before RFA does not diminish the efficacy of RFA. The differences in eradication rates between the two groups were more significant in the ITT vs. PP analysis. For example, the ITT CED rates between the two groups approached statistical significance (94.0% EMR/RFA vs. 82.7% RFA only; p=0.06); however, this is largely attributable to the differential loss to follow-up between the two groups (2 in EMR/RFA vs. 14 in RFA alone; p=0.09).

We also found that prior EMR was associated with a decreased number of circumferential ablation sessions. Although it is unclear why the number of circumferential treatments was less in subjects who underwent EMR before RFA therapy, one reasonable explanation is that the initial EMR induced reversion of a substantial portion of the original BE segment to neosquamous epithelium. Therefore, in subsequent treatment sessions, the endoscopist may have opted to treat with the focal device due to the more limited nature of the residual disease. This, however, is a hypothesis and cannot be confirmed without measurement of the surface involvement of Barrett's, which was not done in this retrospective study.

No difference in complication rate was observed between the two groups, suggesting that undergoing EMR before RFA does not increase the risk of complication associated with RFA. Stricture formation was not more common in those with EMR before RFA (4.6% of patients) compared with patients treated with RFA alone (7.7% of patients). However, the low number of complications in this cohort limits the conclusions that can be drawn regarding differences in complication rates between the groups.

A significant number of subjects had resection with the Olympus cap and the Duette device. However, due to the low number of complications in each of the EMR groups, our study was unable to assert the superiority of one method over the other. It is the practice at our institution to use the Olympus cap and snare when a single large resection is to be performed, and the Duette band ligation device for either smaller resections or piecemeal resections. Previous work demonstrates that the mucosal area resected with the cap and snare device is somewhat larger than that of the banding device.[21]

There are several strengths to our study. This study represents the largest published cohort of patients with BE and advanced neoplasia treated with EMR before RFA for nodular BE. By limiting our study to only those subjects undergoing endoscopic therapy for either HGD or IMC, we are able to more reasonably compare treatment groups with less concern of confounding by baseline degree of dysplasia. Although a higher proportion of subjects who underwent EMR then RFA had IMC than those that underwent RFA alone, confounding by degree of dysplasia would only be expected to further strengthen our findings because more severe disease was present at baseline in the EMR group. Another strength is that biopsy samples were analyzed by expert gastrointestinal pathologists, with all dysplasia confirmed by 2 readings.

Our study also had several limitations. This study was conducted at a tertiary-care referral center. Endoscopies and interventions were performed by the same experienced gastroenterologists. Therefore, whether or not these results can be generalized to community practice settings is unknown. Also, almost all patients in this study had only 1 EMR treatment session. Patients, however, may need treatment with more than 1 EMR session to achieve non-nodular BE.[13] Therefore, we cannot comment on the effects of more than one

EMR session before RFA with respect to efficacy and safety of treatment. Additionally, there were only 3 patients with IMC treated with RFA alone in our study, making it difficult to draw conclusions about this subset of patients. Finally, despite our rigorous attempts at complete collection of data, the retrospective nature of this study makes underestimation of complications or misclassification errors possible.

In summary, RFA after EMR is a safe and effective treatment option for patients with nodular BE and advanced neoplasia. In our cohort, the performance of EMR before RFA was not associated with a diminished likelihood of success of therapy, or an increased rate of stricture compared with those with advanced neoplasia undergoing RFA alone. Further studies are necessary to determine the effects of EMR before RFA on the durability of RFA treatment, and to determine the effects of multiple EMR sessions on RFA outcomes.

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Table 1

Safety Cohort Baseline Characteristics

	EMR before RFA (n=65)	RFA only (n=104)	p-value
Age – mean (SD)	68.8 (10.0)	64.2 (11.2)	0.008
Gender – no. males (%)	52 (80.0)	79 (76.0)	0.54
Race – no. Caucasian (%)	63 (96.9)	99 (95.2)	0.57
BMI – mean (SD)	30.2 (6.6)	29.1 (5.7)	0.22
Substance use			
Tobacco – no. (%)	12 (18.5)	27 (26.0)	0.28
Alcohol – no. (%)	33 (50.8)	40 (38.5)	0.10
NSAID use – no. (%)	33 (50.8)	51 (49.0)	0.83
EGD findings			
Length of BE – mean (SD)	4.4 (3.1)	4.8 (3.4)	0.41
Erosive esophagitis – no. (%)	5 (7.7)	2 (1.9)	0.07
Hiatus hernia – no. (%)	58 (89.2)	93 (89.4)	0.81
Pre-ablation histology			
HGD – no. (%)	37 (56.9)	101 (97.1)	<0.001
IMC – no. (%)	28 (43.1)	3 (2.9)	

Table 2

Safety Outcomes

	EMR before RFA	RFA only	p-value
Complications per Patient – no. (%)			
N	65	104	
Any complication	5 (7.7)	10 (9.6)	0.79
Stricture	3 (4.6)	8 (7.7)	0.53
Bleeding	2 (3.1)	2 (1.9)	0.64
Hospitalization*	2 (3.1)	2 (1.9)	0.64
Complications per Procedure – no. (%)			
N	212	293	
Any complication	5 (2.4)	10 (3.4)	0.60
Stricture	3 (1.4)	8 (2.7)	0.37
Bleeding	2 (0.9)	2 (0.7)	1.00
Hospitalization*	2 (0.9)	2 (0.7)	1.00

* Hospitalizations were secondary to post-procedural hemorrhage

Table 3

Efficacy Outcomes

	EMR before RFA	RFA only	p-value
Intention-to-treat			
N	50	98	
CED	47 (94.0)	81 (82.7)	0.06
CEIM	44 (88.0)	76 (77.6)	0.13
Total treatment sessions, mean (SD)	3.5 (1.6)	2.8 (1.7)	0.02
RFA treatment sessions, mean (SD)	2.5 (1.5)	2.8 (1.6)	0.28
Per protocol			
N	48	84	
CED	47 (97.9)	81 (96.4)	0.63
CEIM	44 (91.7)	76 (90.5)	0.82
Total treatment sessions, mean (SD)	3.5 (1.6)	2.8 (1.5)	0.008
RFA treatment sessions, mean (SD)	2.5 (1.5)	2.7 (1.4)	0.44