Factors that predict a poor response to radiofrequency ablation for Barrett's oesophagus with dysplasia.

Abstract

Radiofrequency ablation (RFA) can eradicate dysplasia and intestinal metaplasia in patients with dysplastic Barrett's oesophagus (BO)(1, 2).**Objective:** To determine factors that affect response to radiofrequency ablation for BO with dysplasia in a tertiary metropolitan referral centre.

Method: All patients with dysplastic BO treated with regular proton pump inhibitor twice a day and RFA from November 2008 to July 2019 were identified. These patients were sorted into Good Responders (GR) (defined as eradication of dysplasia and intestinal metaplasia within three or less treatment sessions) and Poor Responders (PR) (defined as patients requiring four or more treatment sessions). The following features were compared between the groups: age, gender, presence of hiatus hernia, hiatus hernia size, circumferential and maximal length of BO, grade of dysplasia on histology at referral, and presence of endoscopically visible reflux oesophagitis.

Results: 152 patients received RFA for dysplastic BO, 125 (82%) patients were classified as Good Responders and 27 (18%) patients were classified as Poor Responders.

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PR had a longer circumferential length of BO compared to GR (mean length of 8.3cm vs 3.3cm, respectively; $p<0.0001$). PR also had a longer maximal length of BO compared to GR (mean length of 8.7cm vs 4.8cm, respectively; $p<0.0001$). More patients had reflux oesophagitis identified on gastroscopy in the PR group compared to GR group 12 (44%) vs 20 (16%), $p=0.001$.

Conclusion: Factors such as circumferential and maximal length of BO and presence of reflux oesophagitis on gastroscopy are associated with poorer response to RFA.

Introduction

Barrett's oesophagus occurs when the distal oesophageal squamous mucosa is replaced with columnar epithelium containing intestinal metaplasia(3). This is considered to be induced by chronic gastro-oesophageal reflux(4).

It is believed that the neoplastic progression from non-dysplastic Barrett's oesophagus (NDBO) to low grade dysplasia (LGD) to high grade dysplasia (HGD) and finally oesophageal adenocarcinoma (OAC) is a multistep process(5, 6). The biggest risk factor for malignant progression of Barrett's oesophagus to OAC is the degree of dysplasia(7). Therefore, it is important that dysplasia is identified and treated.

There are various methods to treating Barrett's oesophagus with dysplasia. The two main methods are through endoscopic mucosal resection (EMR) and radiofrequency ablation

(RFA). EMR allows the removal of dysplasia while concurrently obtaining sample for accurate staging(8). It carries a low but significant risk of complications, namely stricture formation(9). RFA can achieve eradication of dysplasia, intestinal metaplasia and consequently reduce progression of Barrett's oesophagus to OAC(1, 2). RFA is safe and effective(10-12), however, approximately 13% of patients show a slow or incomplete response of eradication of Barrett's oesophagus to RFA treatment(13). These patients often require more RFA treatment sessions.

Aims

In this prospective observational study, we aim to determine the factors that predict a poor response to RFA for dysplastic Barrett's oesophagus.

Methods and Patients

St Vincent's Barrett's Unit and database

Our Barrett's Unit is a major referral centre for Barrett's oesophagus in Victoria, Australia. We studied all patients with dysplastic Barrett's oesophagus treated with RFA from November 2008 to July 2019. All data on patients referred to our Barrett's Unit was entered prospectively into a database.

The Barrett's database was established in 2008 using Microsoft Access. Each patient record includes data on demographics, referring specialist and their endoscopy and histology details. Subsequent assessment, treatment and follow up endoscopies performed were prospectively entered.

Assessment and treatment protocol

The initial assessment endoscopy performed at our centre comprised detailed inspection of the Barrett's segment using high definition white light and Narrow Band Imaging (NBI) performed with Olympus HQ180 and HQ190 gastroscope by an expert endoscopist (AT or GC) with extensive experience in assessment of dysplastic Barrett's oesophagus. EMR via the Duetto system (multiband cap and snare technique) was performed for any visible mucosal abnormalities with features suspicious for dysplasia or neoplasia. Quadrantic biopsies were then performed as per the Seattle protocol. The pathological assessment process was performed in conjunction with an expert gastrointestinal pathologist (RW) at a multidisciplinary meeting prior to RFA treatment (typically at 3 months post assessment scope +/- EMR) RFA was performed using either the Halo³⁶⁰ (Medtronic/Barryx Medical, Sunnyvale, California, USA) for circumferential ablation or Halo⁹⁰ for focal ablation depending on the length of Barrett's oesophagus. Each treatment session with HALO⁹⁰ comprised two ablations of 12J/cm², 40 Watt/cm²; with cleaning of ablation zone and catheter followed by two further ablations. Up until March

2017, HALO³⁶⁰ treatment comprised one ablation of 12J/cm²; with cleaning of ablation zone after the first pass, then one further ablation. From April 2017 HALO³⁶⁰ was performed using the 360 Express RFA self-adjusting ablation balloon catheter which delivers 10J/cm², with cleaning of ablation zone after the first pass, then one further ablation. Repeat treatment sessions were performed every three months until complete eradication of dysplasia and intestinal metaplasia was achieved.

Complete eradication is defined as the absence of dysplasia and intestinal metaplasia reported by an expert GI pathologist on biopsies taken from the original length of Barrett's oesophagus as per the Seattle protocol after the completion of RFA treatment.

Anti-reflux therapy protocol

All patients with dysplasia were treated with 40mg of proton pump inhibitor (PPI) therapy twice a day prior to commencement and during RFA treatment. Ranitidine 300mg nocte was added to the treatment regime if there is evidence of reflux oesophagitis at the first RFA treatment session. Sucralfate 1g Four times daily is added to the treatment regime if there was still endoscopic evidence of reflux oesophagitis at the 2nd RFA treatment session or if patients were still experiencing reflux symptoms. Anti-reflux surgery was considered if there was still endoscopic evidence of reflux oesophagitis despite maximal medical therapy.

Surveillance protocol post CEIM and protocol to wean PPI

After complete eradication of intestinal metaplasia (CEIM), surveillance was performed as per clinical guidelines(14). Patients with HGD or IMC have endoscopic surveillance every 3 months for the first year following CEIM, every 6 months in the second year and annually thereafter. In patients with LGD, endoscopic surveillance occurred every 6 months for the first year following CEIM, and annually thereafter. Acid suppression therapy is continued for at least 6 months post resolution of endoscopic evidence of reflux oesophagitis, then weaned to 40mg PPI daily and continued lifelong.

Good Responders and Poor Responders

Patients undergoing RFA treatment for dysplastic Barrett's oesophagus were divided into two groups according to their response to RFA. Good Responders (GR) group were defined as patients with complete eradication of histological dysplasia and intestinal metaplasia after three or less RFA treatment sessions. The Poor Responders (PR) group were defined as patients with incomplete eradication of histological dysplasia and intestinal metaplasia after three RFA treatment sessions.

Patients who have just commenced their RFA treatment sessions were excluded.

Multiple variables were compared between the two groups: age, gender, presence of hiatus hernia, hiatus hernia size, circumferential and maximal length of Barrett's

oesophagus (based on Prague classification), the most advanced grade of dysplasia on histology at the time of referral (after review by expert gastrointestinal pathologist) and presence of endoscopic evidence of erosive reflux oesophagitis, defined as LA grade A (15) or above on assessment or any follow up endoscopies despite twice a day PPI therapy.

Statistical Analysis and Ethics

Statistical analysis was performed using Stata V.13.1 for Mac OS (StataCorp, Texas, USA). Univariate analysis was performed using Chi-squared test, Fishers exact test and Mann-Whitney U test. Baseline variables associated with a poor RFA response from the univariate analysis with a $p < 0.10$ were subsequently entered into a logistic regression model for multivariate analysis. Mean $\pm$ standard deviation was used to describe data with a parametric distribution, while median (interquartile range, IQR) was used for non-parametric distribution.

Ethics permission for data collection was granted by the St Vincent's Hospital Ethics Committee and informed consent was obtained from patients.

Results

Patients

There were 152 patients with dysplastic Barrett's oesophagus undergoing a total of 384 RFA treatment sessions from November 2008 to July 2019. There were 125 (82%) patients in the GR group and 27 (18%) patients in the PR group. The median number of RFA sessions required to achieve complete eradication of intestinal metaplasia (CEIM) in GR group is 2 IQR [1-2] compared to 4 IQR [4-5] in the PR group, $p < 0.0001$.

At the end of the study, 140 (92%) patients had complete eradication of dysplasia and intestinal metaplasia. There were 12 (8%) patients who achieved complete eradication of dysplasia only without eradication of intestinal metaplasia. Majority of these 12 patients were male (92%) with a mean circumferential length of 9.33cm and mean maximal length of 10.83cm. Of these 12 patients, eight patients were referred with HGD and four patients referred with LGD. One patient had persistent intestinal metaplasia after seven RFA treatment sessions, three patients had persistent intestinal metaplasia after six treatment sessions and eight patients had persistent intestinal metaplasia after four treatment sessions.

Age and gender

After univariate analysis, there were no statistical difference between the GR and PR groups in terms of mean age (74 years compared to 73 years, $p=0.98$). Similarly, gender did not make a significant difference between GR and PR, (male gender 86% vs 85%, $p=0.897$ respectively).

Length

GR had a shorter mean circumferential length as well as a shorter mean maximal length than PR, (3.3cm vs 8.3cm, $p<0.0001$) and (4.8cm vs 8.7cm, $p<0.0001$) respectively (Fig 1).

Hiatus hernia

Most patients in both groups had a hiatus hernia, (GR group 96% v PR group 95%, $p=0.859$). The mean size of hiatus hernia between the two groups were also similar (6 cm in GR group v 5cm in the PR group, $p=0.4623$).

Endoscopic evidence of reflux oesophagitis

There was a higher proportion of patients in the PR group with endoscopic evidence of reflux oesophagitis compared to the GR group; 12 (44%) vs 20 (16%), $p=0.001$, respectively (Fig 2). There was no difference in the number of patients with histological evidence of inflammation between the two groups. Endoscopic evidence of reflux oesophagitis includes any patchy, striated, erosions or confluent defects in the squamous epithelium, neosquamous epithelium or within the Barrett's mucosa.

Most advanced histology of Barrett's oesophagus at referral.

After full assessment of histology by our expert gastrointestinal pathologist, there were no difference in the proportion of patients with low grade dysplasia (LGD) between GR and PR, 48 (38%) vs 10 (37%) $p=0.622$. Similarly, the proportion of patients with HGD and intramucosal carcinoma (IMC) between GR and PR were similar, 60 (48%) vs 15 (56%) and 17 (14%) vs 2 (7%), $p=0.622$ respectively.

Predictors of poor response to RFA.

Univariate analysis detected three factors which are associated with a poor response to RFA; circumferential length, maximal length and endoscopic evidence of reflux

oesophagitis despite twice a day PPI therapy. After multivariate analysis, these factors maintain their significant associations with a poor response to RFA (Fig 3).

Discussion

Our study shows that Barrett's segment length and endoscopic evidence of reflux oesophagitis are associated with a poor response to RFA. This is important as reflux oesophagitis is a modifiable factor, hence should be treated aggressively in patients undergoing RFA. Our results are comparable to the findings of Van Vilsteren et al., who also demonstrated that endoscopic evidence of reflux oesophagitis is associated with a poor response to RFA, in their study of 278 patients from 14 centres [14].

In addition, Krishnan et al. in their 37 patient cohort study found that length, size of hiatus hernia and uncontrolled acid reflux on 24 hr impedance pH testing was associated with poorer response to RFA(16). Our results did not show an association between size of hernia and response to RFA. This may be due to a difference in RFA protocols, as Krishnan's study patients all received circumferential RFA with HALO³⁶⁰ as initial treatment, whereas we used either focal or circumferential RFA based on the extent of the Barrett's segment and the operator's discretion. There may be a poorer response associated with large hiatus hernias due to poor tissue apposition when performing circumferential RFA with HALO³⁶⁰.

We relied on endoscopic signs of reflux oesophagitis to identify ongoing gastro-oesophageal reflux despite minimum of twice daily PPI. Although we did not perform 24 hr impedance or pH testing, which may have missed ongoing but non-erosive reflux, our findings indicate that endoscopic oesophagitis is a strong predictor of poor response to RFA. These findings suggest that endoscopic findings without the need for pH testing is adequate for most patients undergoing RFA, though there may be a role for pH testing in a minority of patients with poor response to RFA but without oesophagitis.

Our treatment regime ensures that all patients with dysplasia are on high dose 40mg PPI twice a day prior to commencement of RFA therapy. Acid suppression was further up titrated with ranitidine 300mg nocte followed by 1g sucralfate four times daily if patients are still symptomatic or have endoscopic evidence of reflux oesophagitis on subsequent endoscopies. This regime may not be adequate given there are still a subset of patients with a poor response to RFA. In Van Vilsteren's protocol, all patients were on esomeprazole 40mg twice daily, with 300mg of ranitidine at night and sucralfate suspension 5ml four times daily for 14 days after every treatment session. Despite this aggressive acid suppression therapy, 15% of the poor responders still had endoscopic signs of active reflux disease(17).

We have altered our treatment protocol after this study. Currently, if there is endoscopic evidence of LA grade B reflux oesophagitis or higher, we will not commence RFA therapy until resolution of reflux oesophagitis. Repeat gastroscopy will be performed

every 6 weeks with escalation of acid suppression therapy until LA grade A reflux oesophagitis or lower is achieved. If this is not achieved despite maximal medical therapy, then the patient will have a pH study and manometry in preparation for anti-reflux surgery if deemed an appropriate surgical candidate.

Fundoplication prior to RFA is safe(18, 19). Currently there is no recommendation in the literature which addresses the concept of routine fundoplication to control severe reflux prior to RFA. There have been case studies which have demonstrated the success of complete eradication of dysplasia and intestinal metaplasia in patients with severe reflux by fundoplication prior to RFA(20), however Shaheen et al in their large registry of 5537 patients receiving RFA showed that the 301 patients with prior fundoplication have similar efficacy and adverse event rates compared to those on medical therapy alone(18).

It is extremely important to control reflux oesophagitis prior to RFA, given the potential poor prognosis if dysplastic Barrett's oesophagus is allowed to progress to invasive cancer. We suggest aggressive acid suppression prior to RFA, if this is not achieved with maximal medical therapy; then anti reflux surgery should be considered. There may be a role for future large randomised control studies aiming to risk stratify and identify those who may benefit most from a potential anti-reflux surgery prior to RFA.

Conclusion

In conclusion, our data suggests that the length of Barrett's oesophagus and endoscopic evidence of reflux oesophagitis are associated with poor response to RFA for patients with dysplastic Barrett's oesophagus. This illustrates the importance of aggressive acid suppression prior to RFA therapy, including consideration of anti-reflux surgery if maximal medical therapy fails.

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	Good Responders n= 125	Poor Responders n= 27	P value
Circumferential Length (cm)	3.3	8.3	<0.0001
Maximal Length (cm)	4.8	8.7	<0.0001
Presence of Hiatus Hernia (%)	96%	95%	0.859
Size of Hiatus Hernia mean (cm)	6	5	0.4623
Endoscopic evidence of reflux oesophagitis n(%)	20 (16%)	12 (44%)	0.001
Most advance pathology at referral (LGD) n(%)	48 (38%)	10 (37%)	0.622
Most advance pathology at referral (HGD) n(%)	60 (48%)	15 (56%)	0.622
Most advance pathology at referral (IMC) n(%)	17 (14%)	2 (7%)	0.622

ANS_15687_Fig 3.JPG

Factors that predict a poor response to radiofrequency ablation for Barrett's oesophagus with dysplasia.

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