Title Page

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Word count: 3663

Conflict of interest: KR has received consultancy, research and educational grants from Olympus, Pentax, Cook, Boston Scientific, Medtronics, ERBE. No conflicts of interest to report for the remaining authors.

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Abstract

Background and Objectives: Endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA) are effective treatments for dysplastic Barrett's esophagus (BE). This study evaluates efficacy, durability and safety in a single high-volume UK tertiary centre with 15-years' experience.

Methods: Prospective data from Nottingham University Hospitals 2004-2019 for endotherapy of dysplastic BE or intramucosal adenocarcinoma. Procedural outcome measures: complete resection, complications and surgery rates. Efficacy outcomes: complete remission of dysplasia (CR-D) and intestinal metaplasia (CR-IM), recurrence, treatment failure rates, durability of RFA, median follow up and tumour associated mortality.

Results: 319 lesions were resected. 671 RFAs were performed on 239 patients. Median age was 67(±9.5) years, male:female ratio was 5:1 and median BE length was C3(IQR:6) M6(IQR:5). The most common lesion was Paris IIa(64%) with a median size of 10mm(3-70). Final histology was adenocarcinoma in 50%. Complete resection rates were 96%. The multiband mucosectomy technique (91%) was most commonly used. The median number of RFA sessions was 3(IQR:2). The rates of CR-D and CR-IM were 90.4%% and 89.8% achieved after a median of 20.1(IQR:14) months. The most common complications: EMR was bleeding 2.2% and RFA was stricture (5.4%) requiring a median of 2 (range 1-7) dilatations. Median follow up post CR-IM/CR-D was 38 months(14-60). Metachronous lesions developed in 4.7% after CR-D and tumour related mortality was 0.8%. Dysplasia and intestinal metaplasia free survival at 5 years was 95% and 90% respectively.

Conclusions: BE endotherapy is minimally invasive, effective, safe and deliverable in a day-case setting.

Keywords:
Barrett's Esophagus; Dysplasia; Esophageal Cancer; Endoscopic Mucosal Resection; Radiofrequency Ablation

Introduction

Barrett's esophagus develops after longstanding gastro-esophageal reflux disease (GERD) leading to metaplastic transformation from squamous to columnar epithelium with intestinal metaplasia. [1] Barrett's esophagus has the potential to progress through dysplastic stages to adenocarcinoma. The incidence of adenocarcinoma is approximately 2% per year in the United States. [2] The overall annual malignant progression in Barrett's esophagus is approximately 0.22-0.33% per year [3, 4] but if invasive esophageal adenocarcinoma develops the 5-year survival rates are relatively poor at less than 13%. [5] Endotherapy is now the established standard of care for dysplasia and intramucosal adenocarcinoma in Barrett's esophagus with high success rates. [6] Tumors located in the mucosal layer (T1a) treated by endoscopic resection have a less than 2% rate of lymph node metastasis. It also offers similar survival benefits when compared to surgery with lower post-operative morbidity and mortality. [7, 8] Surgery is the main curative modality for submucosal (T1b) tumors as lymph node metastasis can be as high as 37% in T1b sm2/3 lesions. [9] However, the evidence for T1b sm1 tumours is less clear as they are often reported with sm2/3 lesions. [10] When T1b sm1 tumors are classified with low risk features such low depth of invasion, well to moderate differentiation and no lymphatic invasion then endoscopic treatment is a feasible alternative to surgery with two European studies reporting lymph node metastasis as low as 2% and 0% respectively. [11, 12]

Endotherapy in Barrett's esophagus aims to remove or ablate early neoplastic or dysplastic mucosa. Firstly, any focal dysplastic and early neoplastic lesions are delineated using a variety of advanced endoscopy imaging techniques and chromoendoscopy. Secondly, any focal lesions are resected. Thirdly, flat dysplasia without identifiable lesions and residual Barrett's mucosa is ablated. With the addition of acid suppression in the form of high dose proton pump inhibitors this results in regeneration of neo-squamous epithelium. Complications associated with EMR are rare but significant. These include perforations (<1%), hemorrhage (~5%) and stricture formation (but the majority can be treated with endoscopic dilatation). [13]

Two techniques that are used for EMR include multiband mucosectomy and cap assisted EMR methods. Both are equally effective in terms of complication rates and resection depth with success rates up to 98%. [14, 15] Subsequent RFA is needed to reduce the risk of meta- or synchronous dysplastic areas. The remaining Barrett's esophagus tissue is ablated by either thermal or cryotherapy devices. RFA is the most commonly used procedure to ablate remaining Barrett's esophagus. RFA is effective in treating flat dysplasia and intestinal metaplasia (IM). The complication rates are low but post procedure chest discomfort is the most common adverse event. 80-98% of dysplasia is eradicated by 12 months with reduced

adenocarcinoma rates when compared to surveillance. [6, 16, 17] Successful therapy is determined by the absence of intestinal metaplasia macroscopically and histologically confirmed complete remission of intestinal metaplasia (CR-IM).

Most single centres studies and smaller studies only report short-term efficacy and safety outcomes. Both procedures are known to be safe and effective in a short-term follow up but additional long-term data is needed. The aims of this study were to:
(a) Assess the clinical efficacy of endotherapy defined by CR-IM and CR-D (complete remission of dysplasia) rates. CR-IM and CR-D was defined as the complete histological eradication of intestinal metaplasia and dysplasia in all biopsies taken at 3- and 12-months post RFA treatment.
(b) Determine rates of esophageal tumour or metastatic adenocarcinoma of unknown primary associated deaths.
(c) Determine survival rates at 5 and 15 years
(d) Determine recurrence rates (defined as any patient with residual Barrett's esophagus or histology showing dysplasia after achieving CR-IM or CR-D)
e) Assess diagnostic yield of random biopsies from neosquamous mucosa and GEJ post RFA treatment. Also, to describe the rates of detection of recurrence by random biopsy and visible endoscopic lesions.
(f) Determine the procedural adverse event rates.

Methods

Study population and design

During a 15-year period between August 2004 and August 2019 patients (both local and from elsewhere in the East Midlands) referred to this tertiary centre with dysplastic Barrett's esophagus were prospectively collected and included in the analysis. Data was collected up to 2019 as after this period the tertiary service changed as one of the referral's centre set up a local Barrett's endotherapy service. This study was conducted as part of a service evaluation project (registration number:20-526C) thus formal ethical approval or written consent was not required. This study was reported according to observational study guidelines. [18]. All procedures were completed at Nottingham University Hospital NHS trust with expertise in the endoscopic management of Barrett's esophagus.

All adult patients referred to this tertiary centre for endotherapy for dysplastic Barrett's esophagus were included after MDT discussion. Inclusion criteria for EMR included; macroscopic dysplastic lesions, T1a submucosal tumors or T1b sm1 mucosal tumors with low-risk features [12]. Inclusion criteria for RFA included; all dysplastic Barrett's esophagus without visible lesions or residual dysplastic or non-dysplastic Barrett's esophagus post endoscopic resection. Exclusions included; squamous dysplasia, (≥T1b sm2), poorly differentiated (G3) or undifferentiated lesions (G4), those with vascular or lymphatic invasion or patients who underwent endoscopic submucosal dissection (ESD). Histological confirmation was required with no evidence of metastatic disease. Computer tomography

(CT) was carried out on all patients. Endoscopic ultrasound (EUS) was used if there was a suspicion of submucosal disease. Position emission tomography (PET) scans were used if there was any suspicion of disease not detected by CT. All patients agreed to attend regular appointments for treatment and surveillance procedures and written informed consent was obtained after receiving extensive information. Patient data was prospectively collected onto a detailed Excel spreadsheet and updated on a regular basis to include follow up information. Responsible clinicians were contacted if patients did not attend scheduled clinical appointments.

Procedures and protocols

Pharyngeal local anaesthetic spray Xylocaine (AstraZeneca, Luton, UK) and conscious sedation (with midazolam or diazemuls and pethidine) was used during these day-case procedures. Esophageal mucosa was washed with mucolytic mixture containing 100ml of water mixed with 2 ml of acetylcysteine (200 mg/ml, Parvolex, Celltech, UK) and 0.5 ml (40 mg/ml) dimethicone (Infacol, Forrest Laboratories, UK). Prior to endotherapy a full diagnostic assessment was carried out using high-definition white light, autofluorescence imaging (AFI) and narrow band imaging (NBI), (GIF-FQ260Z; Olympus Optical, Tokyo, Japan). Procedures were performed by expert endoscopists (KR, JO, AC, JDC) and by trainee fellows under supervision (including JW, JS). The principal investigator (KR) provided hands on training to ensure standardization of both RFA and EMR techniques. Barrett's segments and lesions were classified according to the Prague and Paris classifications respectively per procedure and patient. [19, 20]

The borders of lesions were marked by electrocautery snare. Resection was achieved by two methods. The first method using the multiband mucosectomy (MBM) technique (Duette; Cook Endoscopy, Limerick, Ireland/Captivator device (Boston Scientific Ltd): a pseudo polyp is created by suction then resected after deployment of a rubber band. This is then resected with a hot snare. This process is repeated until the lesion is completely resected. [21] The second method is termed the cap assisted EMR (EMR-C) technique (Olympus, Tokyo, Japan). A transparent cap is attached to gastroscope and the lesion is then raised with submucosal solution containing gelofusine and adrenaline or gelofusine alone. Once the lesion is lifted from the muscularis propria a snare closes around the tissue then is resected with the use of electrocautery. [14, 22] The EMR-C method was primarily used in the initial part of the study prior to the introduction of MBM technique. Lesions were either resected as single or piecemeal specimens with the goal of complete endoscopic resection (macroscopic complete resection). Resected sites were carefully examined for evidence of bleeding or perforations. Immediate bleeding was treated with snare tip coagulation or coagrasper hemostatic forceps (Olympus, Tokyo, Japan). Follow up was determined by histological findings. Invasive adenocarcinoma (T1b sm1-sm3 with high-risk features) was referred for esophagectomy or chemoradiotherapy if appropriate. (Figure 1)

Within 3 to 6 months patients were then treated with ablation (termed the RFA treatment stage). RFA was delivered using BARRX system bipolar electrodes on circumferential (Halo 360) or focal (Halo 60, Halo 90, Halo Ultra or through-the-scope TTS, Covidien, Dublin, Ireland) devices supplying thermal energy directly to mucosa. The choice of device was

determined by the length of Barrett's and the patient's tolerance. Ablative energy of 12J/cm^2 was delivered by both focal and balloon catheter respectively. Focal ablations with three consecutive ablations without cleaning were carried out. Circumferential ablation protocol included two ablations interrupted by a cleaning phase. Other techniques include argon plasma coagulation (APC) (ERBE Elektromedizin GmbH, Tübingen, Germany) for focal areas of residual Barrett's segments or islands. RFA sessions were repeated in 3-month intervals until Barrett's esophagus successfully eradicated. After both EMR and RFA patients were maintained on high dose proton pump inhibitor therapy twice a day and Ranitidine 300mg once at night for 14 days. (Figure 2)

The post RFA Barrett's esophagus follow up protocol comprised of an endoscopy with advanced imaging, biopsy at 3 months and 12 months after completion of RFA (termed the exit biopsy stage). During the exit biopsy stage, careful inspection with advanced imaging was carried out and then biopsies were taken according to a standard protocol. Four quadrant biopsies are taken from 1cm below GEJ, and every 2cm from the GEJ in the neosquamous esophagus (i.e., the original length of Barrett's). If any visible lesions were seen then target biopsy or EMR was carried out. If Barrett's mucosa was seen within the exit biopsy stage this was then treated with targeted biopsy excision, APC or RFA. If further therapy was needed during this initial 12-month period then the patient would undergo further biopsy post therapy (month 3 and 12) after the last therapy. If these two sets of biopsies show no IM or dysplasia then CR-IM and CR-D is achieved and the patient moves to the final stage in the treatment cycle (the surveillance stage). Patients then undergo annual surveillance (12 monthly) with the same standard biopsy protocol. If IM or dysplasia is detected after CR-IM/CR-D then this is then classed as recurrence. Any recurrent dysplasia or early neoplasia identified during follow up was treated according to multi-disciplinary team meeting consensus.

Adverse events were defined as early (0-48 hours) and delayed (> 48 hours). Major complications were defined as perforation, bleeding that required blood transfusion, repeat endoscopic/radiological or surgical intervention and hospital admission >24 hours. Minor complications included unplanned admission < 24 hours and intraprocedural bleeding that was successfully treated at index endoscopy. Delayed complications included symptomatic strictures that required dilatation.

Histological analysis

EMR specimens were attached to cork board with pins and placed in formalin by experienced nursing staff. Samples were then embedded in paraffin and cut into sections. Histological examination was performed by two expert pathologists independently. Any discrepancies were reviewed by a third pathologist. EMR neoplasm specimens were classified according to infiltration, depth, differentiation, lymphatic and vascular invasion and resection completeness. [23] Free resection margins were defined as peripheral and deep sites free of tumor. Biopsies were assessed for IM, buried Barrett's glands or neoplasia.

Statistical analysis

Analysis was performed with SPSS 23.0 (IBM, Armonk, NY, USA) statistical software. Mean (±SD) was used in variables with normal distribution and median (IQR 25–75%) used for variables with skewed distribution. Kaplan-Meier (KM) estimation over a 60-month (5 year) period was performed to assess patient survival after RFA treatment and recurrence of CR-IM and CR-D. Only patients who achieved CR-IM/CR-D were included in the KM analysis.

Results

Patient demographics

EMR was initially undertaken with curative intent on 221 patients. 38 (23.9%) of the adenocarcinoma patients had non curative diagnostic endoscopic therapy and of these 20 patients later underwent an esophagectomy. The remainder of patients either declined surgery or were deemed inoperable. A total of 239 patients (which included 183 of those who had EMR) underwent RFA. Figure 3 shows the flow diagram of patients in this study. 24.5% of patients were taking a form of anticoagulation or antiplatelet therapy. 11 (5%) and 4 (1.8%) of the EMR patients had stenosis and esophagitis at baseline respectively.

Histology characteristics

Prior to EMR the most common lesion was HGD in 152 (47.6%). The median distance of the lesion from the incisors was 35cm (IQR 5). A total of 319 lesions were resected. 52% of lesions were found at the 12 to 3 o'clock position. The median lesion diameter size was 10mm. 18% of lesions (21 LGD and 36 HGD) were upstaged to adenocarcinoma. Of the resected EMR specimens 128 (80.5%) had clear deep margins, 106 (66.7%) had clear peripheral margins and 148 (93.1%) had no lymphatic involvement. Table 1 details the baseline and histology characteristics of these patients.

The most common indication for RFA was HGD (46%) followed by post adenocarcinoma resection (32.2%) and LGD (21.8%). Table 2 details the baseline characteristics of the patients who underwent RFA.

EMR Procedure techniques

A high proportion of patients underwent the MBM technique (91.2%) without submucosal lifting (75.5%). Immediate minor bleeding or oozing was treated in 11.3% patients. En bloc resection was performed in 125 (39%) and piecemeal in 194 (61%) of lesions. APC was used in 6 (1.9%) of lesions to fulgurate any potential microscopic disease residual. A complete endoscopic resection was believed to be achieved in 305 (95.6%) of lesions. Table 3 details EMR technique.

RFA procedure technique

239 patients underwent RFA to eradicate remaining Barrett's mucosa to reduce the development of metachronous neoplasia. A total of 671 RFA sessions were undertaken. Halo 360 was the most commonly used device for the first session at 60% followed by Halo 90 for most successive sessions. See table 4. The median number of ablation sessions was 3 (range 1-9), dependent on patient's baseline maximal length of Barrett's mucosa. Other ablative techniques were used to eradicate small areas of Barrett's mucosa in 104 (43.5%) of patients. APC was used in the majority of cases (94, 39%) followed by excision biopsy (10, 4%). During the initial RFA treatment phases 31 (13%) developed metachronous lesions requiring EMR. Of these resected lesions 15 were adenocarcinoma (T1a=10, T1b=5), 11 HGD, 2 LGD and 6 NDBE. During the ablative phase, 30 (12.6%) had evidence of severe inflammation (Grade C/D esophagitis) at endoscopy which delayed RFA treatment. 3 patients underwent anti-reflux surgery during the ablative phase due to poor response to RFA.

Outcome measures

a) Clinical efficacy

CR-IM and CR-D rates were achieved in 89.8%% (95% CI 83-97) (149/166 patients) and 90.4% (95% CI 84-96) (150/166 patients) of patients respectively. The median treatment time (from 1st RFA session to confirmation of CR-IM/CR-D) was 20.1 (IQR:14) months. 6.7% (16 patients) did not achieve complete remission due to RFA failure (no endoscopic change in Barrett's length after three sessions) or abandonment. The main reasons for failure included poor squamous regeneration (10), failure of esophagitis healing post endoscopic treatment despite PPI therapy (2), unrelated carcinoma found (1) or the patient declining further treatment (3). In patients who failed RFA, the median length of Barrett's was C5M7 with a histology showing HGD and LGD. A further 16 patients (6.7%) were lost to follow up and 57 patients (23.8%) are still receiving treatment or were at the exit biopsy stage at the end of the study.

b) Tumour related deaths

There were 2 tumour related deaths during follow up (0.8%, 2/239 patients) and 13 non tumour related deaths (5.4%, 13/239 patients).

c) Survival rates

Of 150 patients who achieved CR-IM/CR-D, 6 died in the first 5 years of follow up (4%) – all from non-tumour related causes. In the cohort of patients who had achieved 5 years of follow up, the 5-year survival rate was 91.9 ±0.3% (Figure 4). The overall survival rates over

the 15-year study period was 82% with a median follow up of 38 months (14-60) post CR-IM/CR-D.

d) Recurrence rates

Recurrence of dysplasia (HGD/adenocarcinoma) was detected in 7 patients (4.7%, 95% CI 1-8) after CR-D during the follow up phase. The median time for recurrence was 14.9 months (95% CI 4-33) (Figure 5A). Majority of these lesions were found at the GEJ (6) and the rest in the distal 5cm of the esophagus (1). None of these patients developed lymph nodes on follow up EUS or CT scan. The majority were treated successfully with repeat endoscopic treatment but two had evidence of submucosal malignancy. One patient was successfully treated with esophagectomy and the other received chemotherapy. Two of these patients later achieved CR-D during the follow up.

Post RFA treatment, recurrent focal IM at GEJ (7) or tubular esophagus (3) was found in 10 patients. The recurrence rate after CR-IM was 6.7% (95% CI 3-10). The median time for recurrence was 16.6 months (95% CI 4-29) months (Figure 5B). These were treated with further ablation, APC or biopsy avulsion. The cumulative proportion of patients maintaining CR-D and CR-IM over 5 years was 95% ±0.02 and 90% ±0.04 respectively.

e) Diagnostic yield of random biopsies

The overall diagnostic yield of random biopsies for detecting dysplasia at GEJ and distal esophagus was 1.3% (2 out of 150 patients) and 0% (0 out of 150 patients) respectively. Two of these dysplasia recurrences were detected by random biopsies and five by target biopsies from visible endoscopic lesions. IM was detected in seven patients by random biopsies and three were endoscopically visible. The overall diagnostic yield of random biopsies for detecting IM at GEJ and the distal esophagus was 4% (6 out of 149 patients) and 0.7% (1 out of 149 patients) respectively. In one patient repeat sampling did not reproduce IM therefore, the sampling may have been from the cardia in error.

f) Procedural Adverse events

The overall early major EMR complication rate was 2.5%, which included one perforation that settled with endoscopic treatment and the patient was later discharged. Bleeding that required endoscopic intervention, and/or blood transfusion and hospitalisation was 2.2%. Other minor early complications requiring hospital admission included non-specific chest pain and one patient with an episode of atrial fibrillation (1.3%). 11 patients were admitted with a median length of stay of 1 day (range 0-8). Delayed complications of symptomatic strictures was 2.5% requiring a median of 1 dilatation (IQR: 1.25). There was no mortality associated with early or delayed complications. See Table 5.

There were no perforations related to RFA treatment. Bleeding rate was 0.8% and stricture rate requiring therapeutic dilatation was 5.4%. The median number of dilatations was 2 (range 1-7 dilatations). Two patients required a short admission with angina and

hypertension. Both patients settled with medication and made a full recovery. 8 patients had evidence of superficial mucosal lacerations at endoscopy. All settled without the need for endoscopic intervention or medical admission. See Table 6.

Discussion

This is the largest prospective single centre experience of endotherapy for early Barrett's associated neoplasia in the UK with a large number of patients with a median follow up of over 3 years. We provided further evidence that endotherapy and post treatment surveillance is effective to treat dysplastic Barrett's. Our data demonstrates comparable real-world outcomes to clinical trials and the UK registry. [24-27] This study demonstrates good clinical effectiveness and the important role of centralised specialist care alongside the real-world need to train future endoscopists in Barrett's management. Our study findings are generalisable to tertiary centre practice in the UK.

The majority of the study patients were ASA grade 1 and 2. The age and gender distribution was typical of Barrett's esophagus patient population in the UK. Adenocarcinoma was the most commonly resected lesion located in the 12 to 3 o'clock position in the distal oesophagus. Previous studies have described similar findings, thus highlighting the importance of detailed assessment of this area. [28, 29] Intraprocedural bleeding was an anticipated minor complication and was successfully treated in the majority of cases. The majority of lesions were resected by piecemeal but with this technique there is always the risk that the lateral margins affected by dysplasia may need repeated EMR sessions. This may increase the complication rate as previous EMR generates mucosal fibrosis and so hinders repeat procedures. However, there was no increase in complication rate in those who undergoing single session or repeat EMR during follow up period in this study.

The treatment pathway consisted of resection and ablation sessions lasting approximately 1 year. The combination of both techniques can achieve good success rates. EMR not only provides accurate histological assessments but also the removal of dysplastic lesions. Endoscopic therapy is recommended over surveillance or surgery for HGD and mucosal adenocarcinoma. [6] It also reduces the risk of recurrent dysplasia. A systematic review by Menon *et al* revealed mortality related to endoscopic therapy to be lower 0.04% when compared to surgery 1.2%. [8] RFA is also more cost effective than surgery. [30]

Approximately half of this cohort of patients had adenocarcinoma at baseline. 95% of patients who completed the planned treatment are dysplasia free. Eradication of dysplasia and intestinal metaplasia rates in this study were similar to previous international studies reported rates between 80% to 98%. [16, 27, 31, 32] Orman *et al* meta-analysis demonstrated high eradication of dysplasia rates with low recurrence during a 5-year follow up. [33] Long follow up and stringent post treatment biopsy could account for some of the recurrent IM seen in this data set. Some cases of recurrence IM were not reproduced in repeat biopsies suggesting sampling from the cardia with IM present. The presence of IM post treatment however can be considered a risk factor for recurrence or progression of dysplasia. Guarner-Argente *et al* reported recurrent neoplastic rates of 32% in individuals with persistent IM after ablation compared with 9% in those without. [34] The high rates of

eradication are likely due to the setting of an expert centre with all procedures performed by experienced endoscopists and the strict adherence to protocols. All patients underwent RFA until Barrett's mucosa was visibly eradicated and received high dose acid suppression (Omeprazole 40mg twice a day long-term and Ranitidine 300mg at night for 14 days). Aggressive acid suppression would also contribute to neo-squamous regeneration and lower complications.

This study provides a detailed account of procedures on a large cohort of patients in a UK tertiary centre. These results add much needed real-world clinical data as RCTs are not always generalizable to routine clinical practice. The presented clinical information is also useful for endoscopists and endoscopy units across the UK. The majority of literature in this field is retrospectively collected, therefore, this prospective registry is better suited to capturing more accurate data.

Predictors of RFA failure are known to be length of BE segment, evidence of reflux, hiatus hernia length, race, duration of dysplasia and age. [35-37] Patients whose Barrett's esophagus is complicated with multifocal dysplasia, ulcerations and nodules are also likely to require more treatment sessions and therefore, may have a higher failure rate. However, numbers were too small in this cohort to investigate these factors further. Most recurrences were detected at an early stage and managed with endoscopic treatment. Recurrence rates were in line with previous studies demonstrating the stability of neosquamous mucosa after RFA. [24, 27, 38-40] Recurrence occurred at GEJ or distal esophagus in line with a recently published multicentre study. [41] Post RFA malignancy could also indicate failure to identify lesions prior to therapy. These number of recurrences demonstrate the importance of high-quality endoscopic assessment during surveillance and benefits of further effective resection of visible lesions. Data from this report is in line with previously published large prospectively collected registry demonstrating that cancer advancement is low after endoscopic therapy and rescue surgery can still be performed if indicated. [27] This data and previous reports suggest response to RFA is durable over a median follow up period of 3 years.

This study also demonstrated detailed demographics of patients involved and a comprehensive account of practice in this tertiary referral centre. This real-world data demonstrates minimally invasive endotherapy is accurate for staging, safe, effective and can be delivered in a day-case setting. The large patient numbers and expertise within this centre is an ideal environment for specialist care and training. Significant complications such as perforation and bleeding were low. Minor complications such as strictures were successfully treated with endoscopic dilatation. The formation of strictures was more common in individuals who underwent both endoscopic therapies. Qumseya *et al's* systemic review and meta-analysis described complication events of 8.8%, with strictures the most frequent with rates of 5.6%. [42]

Strengths of this study included hands on training and supervision coordinated by a single clinical lead endoscopist. A specialist Barrett's team ensured the prospectively registration of study data and that the treatment protocol was adhered to. Prospective data collection in this way minimised the amount of missing data. All procedures were conducted in a

standardised way, with post RFA surveillance biopsies shown to accurately detect IM and dysplasia.

Other strengths include a number of practical outcome measures together with important detailed information about the logistical structure of the treatment pathways for the set-up of the Barrett's endotherapy service. This is important as results from multicentre studies are not always as uniform as single centres as protocols often vary. This study also has a large sample size and long duration of follow up. This study also provides one of the longest follow up periods post CR-D and CR-IM [17, 43] which is important as there is no clear consensus in the literature on the duration of follow up and biopsy protocol post endoscopic therapy. The initial guidance in this area was based on expert opinion and cohort studies. [44] RFA lowers the cancer risk so surveillance should not be the same as non-dysplastic Barrett's. Cotton *et al* investigated whether less intensive surveillance post ablation was possible using a validated statistical model which predicted the probability of developing recurrent neoplasm. The proposed surveillance for LGD was one then three years and for HGD/adenocarcinoma 3, 6 then 12 monthly following CRIM. The aim of this structure was to reduce surveillance but maintain low rates of recurrence. [45, 46] Our presented data supports their proposed follow up structure as most recurrences occurred in the first 24 months. Therefore, it may also be possible to review surveillance after 5 years in individuals who may be unlikely to benefit from further surveillance but more data is required.

Recurrent neoplasm developed at the GEJ and distal esophagus in our cohort, highlighting this area as high risk. [41] The baseline histology for these recurrences was HGD/adenocarcinoma. Our post ablation protocol included random biopsies from the GEJ and neosquamous tubular esophagus. The majority of recurrences were found on random biopsies in the GEJ. The implication of collecting samples from these areas over such a long follow up period supports the idea that only GEJ random sampling and targeted biopsies from visible lesions in the tubular esophagus is needed in post ablation surveillance. [47]

One limitation of this study was that only patients discussed at the specialist meetings and who were deemed medically fit and suitable for endoscopic therapy were included. This is likely to lead to selection bias and influence complication rates as they are likely to have better outcomes as the candidates are fit for surgery and/or intensive care admissions. The majority of patients were followed up post endoscopic therapy at this centre. Due to geographical logistics, 19 patients had to be followed up locally and 10 of these were lost to follow up. In specialist centres such as this surveillance is carried out by experienced endoscopists with access to expert pathologists and surgery. In comparison, follow up at non-specialist units is likely to have some impact on the procedure success rates.

Despite a long median follow up, there was also still a large group of patients (24%) under active endoscopic therapy or at the exit biopsy stage leading to possible selection bias as the longer the duration of treatment the higher the risk of treatment failure. However, this is difficult to avoid as this study is a snapshot of data from a database that is being updated regularly so there will always be patients requiring ongoing treatment. Other limitations include variable EMR methods, change in indications for RFA and change in practice over

the 15-year study period. Over the long study period, treatment protocols, endoscopic equipment and clinician experience have improved, possibly resulting in a positive bias on the outcome measures. Due to the service provision constraints of a busy endoscopy unit the proposed protocol for RFA of every 3 months was also sometimes difficult to achieve in a few cases. This cohort of patients has also been specially selected for suitability for endoscopic therapy and so are likely to account for a minority of esophageal cancer cases as the disease has been detected at an early stage. Therefore, the outcomes are likely to be more favourable. This study also highlights that the focus should still be on screening and early detection in a high-risk population as endoscopic treatment is highly effective. [48] Finally, endoscopies were conducted by experts, therefore, are unlikely to be generalizable to all endoscopists.

Conclusion

The use of endotherapy for dysplastic Barrett's leads to over 90% remission of dysplasia and IM and remains stable over period of 5 years. Dysplasia free survival at 5-years was 95%. This large prospective maintained series demonstrates minimally invasive, safe and effective treatments for Barrett's dysplasia is achievable in a day-case setting. EMR provides accurate local staging with the option of surgery for locally advanced disease. Stricture formation still remains the most common complication which is usually managed successfully with endoscopic dilatation. In addition, this tertiary centre provides a useful insight for service development allowing for further training and research opportunities.

Conflict of interest

KR has received consultancy, research and educational grants from Olympus, Pentax, Cook, Boston Scientific, Medtronics, ERBE. No conflicts of interest to report for the remaining authors.

Acknowledgments

Guarantor of the article: KR. Conception and study design: KR, JO, JRW. Study coordinator: JRW, JO. Endoscopy procedures: KR, JO, AC, JDC, JRW, JS. Histopathology assessment: PK. Data collection: JRW, JS. Source documents and data review: JO. Data analysis: DR, AL, JRW. Data interpretation: JRW, JO, KR. Manuscript writing: JRW. All the authors approved the final version of the manuscript.

Trainee fellows who also completed procedures with supervision and participated in data collection: George Anagnostopoulos, Rajvinder Singh, Manolis Telakis, Jayan Mannath, Sarmad Sami, Stefano Sansone, Sabina Beg and Mirela Pana.

JRW and KR research is supported by the National Institute for Health Research (NIHR), through Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

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