Radiofrequency ablation compared with argon plasma coagulation after endoscopic resection of high grade dysplasia or T1 adenocarcinoma in Barrett's Esophagus: a randomised pilot study (BRIDE). NCT01733719

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Keywords

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Abstract

Background and aims: Endoscopic resection (ER) is safe and effective for Barrett's esophagus (BE) containing high grade dysplasia (HGD) or mucosal adenocarcinoma (T1A); risk of metachronous neoplasia is reduced by ablation of residual BE using radiofrequency ablation (RFA) or argon plasma coagulation (APC). These have not been directly compared. We aimed to recruit up to 100 patients with BE and HGD or T1A confirmed by ER over 1 year in 6 centres in a randomized pilot study.

Methods: Randomisation was 1:1 to RFA or APC (4 treatments allowed at 2 month intervals); recruitment, retention, clearance of neoplasia, clearance of benign BE, adverse events, healthcare costs and quality of life (QoL) using EQ-5D, EORTC QLQ-C30, OES18 were assessed up to the end of the trial at 12 months.

Results: Of 171 patients screened, 76 were randomized to RFA (n=36) or APC (n=40); mean age was 69.7, 82% male. BE was <5cm (n=27), 5-10cm (n=45) and >10cm (n=4). Sixty-five patients completed the trial. At 12 months, neoplasia clearance was RFA 79.4 % and APC 83.8 % (OR 0.7; 95%CI 0.2-2.6); BE clearance was RFA 55.8% and APC 48.3% (OR 1.4, 95%CI 0.5-3.6). 6.1% (RFA) and 13.3% (APC) had buried BE glands. Adverse events and QoL scores were similar, but RFA cost £21,147 more per case than APC.

Conclusion: This pilot suggests similar efficacy and safety but a cost difference favouring APC. A fully powered non-inferiority trial is appropriate to confirm these findings.

Take home message

Endoscopically identifiable high grade dysplasia and intramucosal adenocarcinoma arising in Barrett's esophagus are best treated by endoscopic resection, but neoplasia recurs in up to 30%.

Ablation of the remaining Barrett's epithelium reduces this risk; the best current evidence relates to radiofrequency ablation (RFA).

For the first time, RFA has been compared with argon plasma coagulation (APC) in a randomised multicentre pilot study in which clearance of neoplasia, safety and quality of life appear similar after 1 year with both techniques but APC is more than 80% cheaper.

Introduction and background

Barrett's esophagus (BE) is metaplasia of esophageal squamous to columnar epithelium[1] carrying a risk of progression to adenocarcinoma,[2] via low and high grade dysplasia (HGD). Most cancers are advanced at diagnosis, with 5-year survival of 15 % in England and Wales.[3] If early stage (T1) cancer or HGD is diagnosed, the prognosis is considerably better. Endoscopic therapy is the treatment of choice for patients with Barrett's related early neoplasia (HGD or T1a adenocarcinoma)[4] given its better safety profile and similar efficacy compared to esophagectomy.[5] The most important element of endoscopic therapy is endoscopic resection (ER) which targets macroscopically visible lesions, providing accurate staging information[6, 7] and successful management.[8, 9] However, ER only targets visible abnormalities, leaving BE in which neoplasia could recur.[10] Metachronous neoplasia occurs in up to 30% of residual BE after ER,[10] but not if all BE is removed by stepwise repeated ER, though oesophageal stenosis is frequent (>80% in a recent randomized trial [RCT]).[11] Ablative techniques, including thermal methods such as argon plasma photocoagulation (APC)[12-14] and radiofrequency ablation (RFA),[15, 16] offer an alternative strategy. Both are effective in case series and RCTs, with the strongest evidence for RFA. Shaheen, in a multicentre RCT comparing RFA with sham, found dysplasia clearance at one year of 81% in patients with HGD.[17] Large prospective series have shown similar results.[18-20] Efficacy of APC in clearance of dysplastic and non-dysplastic BE has been demonstrated in small case series,[12-14, 21, 22] and recently in a RCT comparing APC with surveillance of residual BE after ER for HGD or intramucosal cancer: metachronous lesions occurred in 3% after APC compared with 36% after 24 months' surveillance.[23] RFA has been more extensively investigated,[17, 20, 24, 25] and has a standardised methodology developed from in-vitro and animal studies[26], allowing a predictable burn depth,[27] and extensive clinical experience from UK and US registries has shown a good safety profile.[18, 19, 28, 29] APC is cheaper and widely available but is less standardised.

RFA and APC have not been compared directly by RCT in patients with BE early neoplasia. We performed a randomized pilot study of the two techniques comparing neoplasia clearance, BE eradication, recruitment, retention and health economic analysis.

Methods

Trial design

BRIDE (Barrett's Randomised Intervention for Dysplasia by Endoscopy) is a multi-centre pilot study investigating patients with BE and HGD or T1a adenocarcinoma randomized to up to four treatments every two months with APC or RFA after initial ER. All trial endoscopists had previously attended accredited training courses in the use of Barrx™ RFA and practiced at recognized RFA centres. The technique for APC ablation was standardised at a meeting of trial endoscopists prior to trial commencement, using videotaped procedures illustrating a systematic APC ablation protocol.

Participants

Six English tertiary referral centres for esophagogastric cancer participated. Inclusion criteria: age 18–85, histology: HGD or T1a cancer with a maximum depth of invasion on ER of T1m3, endoscopic ultrasound and CT or PET-CT scan negative for locally advanced or metastatic disease (for histologically proven invasive cancer only).

Exclusion criteria: histology more than T1m3, poorly differentiated histology, lymphatic or vascular invasion, short tongues (<2 cm) of BE completely removable by ER, no localised endoscopically identifiable abnormality, prior esophageal endoscopic therapy other than ER, existing stricture not dilatable to a level suitable for endoscopic treatment, history of mediastinal radiation, esophageal surgery (except fundoplication without complication), esophageal varices or coagulopathy.

Potential participants identified at upper gastrointestinal cancer multidisciplinary team (UGICMDT) meetings before ER (or after ER if done up to 6 months previously) were invited to participate.

Subjects could be randomized before ER if a resectable visible lesion had been identified to maximise recruitment by allowing patients referred from distant hospitals to be entered without an additional visit, although subsequent advanced histology required withdrawal prior to ablation intervention in 2 patients in the APC arm (see results). Patients who agreed to enter the trial were provided with a participant information leaflet and written consent was obtained.

Randomisation

Recruited participants underwent 1:1 randomisation into 2 groups: ER plus RFA or ER plus APC. The method of randomisation was permuted blocks stratified by centre and by the length of Barrett's epithelium (<5cm, 5-10cm, >10cm), with variable block sizes. Allocation concealment was achieved by the use of an online randomisation system provided by a third party (Sealed Envelope Ltd), in which the randomisation lists were hidden from the user.

Interventions

All patients received high dose (twice daily) proton pump inhibitors; ER was performed at entry if not done within the previous 6 months. If the latter, at initial trial endoscopy either further ER if appropriate or mapping biopsies were permitted but not APC or RFA. ER aimed to resect all visible lesions regardless of extent, including visible lesions at any subsequent treatment sessions; we did not limit ER size. All units used high definition endoscopes, processors and screens (5 units used Olympus H260 or 260Z, all with narrow band imaging). The remaining unit used Pentax 7000 Epki - i10 with iScan.

ER was by either 'cap and snare' (Olympus Optical Co. Ltd., Tokyo, Japan) after submucosal lifting injection or Duette 'band and snare' (Cook Ireland Ltd, Ireland);[30] unfavorable ER histology resulted in withdrawal. If a stricture occurred, dilatation was allowed at any session to allow treatment.

For RFA, either circumferential balloon HALO ablator (Barrx Medical, Sunnyvale, California) at a 12 J setting after initial sizing balloon or focal HALO 90 ablator (Barrx) at a 15J setting were used at the local investigator's discretion; HALO 60, Ultra or TTS ablators were allowed if thought appropriate. The originally described technique of ablation (double for focal ablators), cleaning and further ablation were used with both the balloon and focal ablators, using the same techniques and power settings as the EURO-1 and EURO-2 studies led by the Amsterdam group.[25, 31]

For APC, an axial firing APC catheter was used with gas flow of 2L/ minute. Forced 60W setting was used with ERBE ICC 200 or pulsed 50W setting with ERBE Vio (ERBE Electromedizin, GmbH,Tubingen, Germany), depending on equipment available at each site. Ablation was carried out using a stroking technique, with the tip of a forward-firing APC catheter protruding approximately 1 cm beyond the endoscope, which was withdrawn from distal to proximal, starting at the junction of BE with the longitudinal gastric folds. Up to 60% of the circumference was treated in any one session, using endoscope torque to treat successive radial segments. The same APC settings were used for focal treatment of islands or tongues of BE. Use of a distal endoscopic attachment cap was optional. For both ablation techniques, repeated treatment of the gastroesophageall junction was emphasized during the initial standardisation meeting of endoscopists at the start of the trial.

At 12 months, diagnostic high-resolution endoscopy was performed with targeted biopsies of any macroscopically abnormal areas and 4 quadrant biopsies at 2 cm intervals, including at the gastroesophageal mucosal junction, of the area still containing BE or of neo-squamous epithelium, using standard biopsy forceps with a 6-7mm open span and the 'turn and suck' technique. Trial biopsies were only required at exit from the trial. No ablation was offered as part of the trial at this time point, though after study completion, patients continued endoscopic treatment (ER and/or ablation) at the local investigators' discretion, aiming to achieve complete BE clearance.

Pathology

ER specimens and follow up biopsies were reported by 2 expert gastrointestinal pathologists, according to Royal College of Pathology Guidelines for double reporting of gastrointestinal dysplasia, with additional pathology review for the UGICMDT meeting.

Outcomes

Primary outcomes measured at 12 months were: recruitment, retention, and clearance of HGD or cancer (dysplasia clearance). Secondary outcomes were: clearance of histological intestinal metaplasia (IM), complications, quality of life (QoL) at 0, 6 and 12 months measured using the EORTC QoL Questionnaire version 3.0 (EORTC QLQ-C30), module QLQ-OES18 to assess oesophageal-specific aspects of QoL and general QoL using EQ-5D;[32-35] healthcare costs were calculated using patient-reported resource utilization (hospital admission, ER visits, healthcare professional visits, medication use) collected at each visit, endoscopy costs (healthcare professional time-adjusted salaries, medication, endoscopy disposables, costs of salvage treatment such as endoscopic dilatation, additional endoscopies, chemoradiotherapy or surgery) and procedure duration. To assess tolerance of the procedures, patients were telephoned 1 week after each intervention to ask about chest pain (yes/no) and dysphagia (yes/no).

Statistical considerations

Sample size

This was a pilot study not powered to make formal comparisons between intervention groups. The target recruitment was up to 100 patients (50 patients per arm). Each of the six centres would expect to see between 15-20 new patients per year, and there was a 12-month period of recruitment.

Statistical analysis

Clinical outcomes are presented by treatment group using descriptive statistics (number and percentage for binary and categorical measures; mean and standard deviation, or median with minimum and maximum for continuous measures). Odds ratios (ORs), and 95% CIs are presented to estimate relative efficacy of the 2 ablative modalities. QoL measures were presented by intervention group at baseline, 6 and 12 months with results summarised graphically to examine effects over time. As this is a pilot study in preparation for a non-inferiority trial, for which the usual analysis uses the per protocol population rather than the intent to treat population, results are presented for all randomized participants for whom we have outcome data. The safety analysis population included all participants who started treatment in either arm. Student's t tests or Chi squared tests were used as appropriate to compare baseline demographic data.

Ethics

This study received ethical approval from the Leicester Central NRES Committee, East Midlands REC ref: 12/EM/0445 approved 19/12/2012. ClinicalTrial.gov NCT01733719 registered 27/11/2012; recruitment started 04/05/2013, ended 02/05/2014, and trial end 02/11/15.

Results

Primary outcomes

Recruitment and retention

171 patients were screened for inclusion over 12 months, of which 64/171 (37%) were ineligible: too old (3), previous ablation (4), BE <2 cm (7), LGD only on ER (4), HGD with no visible lesion for ER (13), no ER due to scar (1), multiple strictures requiring weekly dilatation (1), >T1m3 cancer (12) and reason not specified (19). Seventy six of those 107 eligible (71%) agreed to participate.

Reasons for non-inclusion were by patient choice in the remaining 31/152 (20%): 3 wanted RFA, 2 had severe co-morbidity, 1 declined any ablation, 7 not interested in research, and no reason given in 16.
Baseline characteristics and stratification of the included subjects are summarized in Table 1.
Figure 1 shows patient flow through the study. Of 40 randomized to APC, 31 had outcome data including one withdrawn early for more invasive disease; retention was 77.5%. However, 3 did not start treatment, due to withdrawal of consent (1), and cancer >T1m3 after ER (2). Among those starting treatment, 3 withdrew consent, 1 discontinued due to unrelated comorbidities and 2 developed strictures requiring more frequent endoscopies.
Of 36 randomized to RFA, 34 had outcome data including one withdrawn early for more invasive disease; retention was 94.4%. One patient discontinued due to unrelated comorbidities, and 1 had no exit biopsy.

Clearance of dysplasia (HGD/cancer) at 12 months (Table 2)

In the APC arm, 30/31 received all allocated treatment, with an average of 3.4 APC sessions. Twenty-six were clear of cancer or HGD, giving dysplasia clearance of 83.9%. Four had ongoing HGD at 12 months, and 1 exited the trial early with cancer >T1m3.
In the RFA arm, 34 received an average of 3.2 RFA sessions. Twenty-seven were clear of cancer or HGD, so dysplasia clearance was 79.4%. Four had ongoing HGD, 2 ongoing cancer at 12 months (1 subsequently successfully managed with ER, and one with ESD then surgery), and 1 early trial exit with cancer >T1m3.
Rates of dysplasia clearance, stratified according to BE length, are shown in Table 3.

Secondary outcomes

Clearance of benign Barrett's epithelium

Defined as absence of histological IM (IM at cardia with no visible BE was not regarded as failure but this was only detected in 2 patients, both receiving RFA), 15/31 patients (48.4%) in the APC arm and 19/34 patients (55.9%) in the RFA arm had BE clearance at 12 months (Table 2). BE clearance stratified by initial length is shown in Table 4.

Buried glands

Thirty patients had outcome data for histology in the APC arm and 33 in the RFA arm. Four of 30 (13.3%) in the APC arm had buried glands compared to 2 of 33 (6.1%) in the RFA arm at 12 months. All buried glands were detected only among patients who had not achieved complete clearance of BE. No buried neoplasia occurred.

Complications

Five of 37 who received at least 1 APC treatment developed symptomatic strictures requiring dilatation (13.5 %), compared with 3 of 36 patients receiving at least 1 RFA treatment (8.3%). However, 2 of the patients developing strictures in the APC group did so after initial ER and before APC was administered. Therefore 3 developed strictures after APC was started (8.1%). There were 5 gastrointestinal bleeds in each arm, 2 (5.4%) requiring admission after APC and 1 (2.8%) after RFA. One patient (2.8%) had an ER-related perforation in the RFA arm managed endoscopically and went on to complete the trial. One patient in the RFA arm had sedation-related syncope post-endoscopy, requiring admission. There were no deaths.

Quality of life

QoL scores using EQ-5D and QLQ-C30 were similar in both arms at 6 and 12 months as shown in Figure 2. Oesophageal-specific symptoms (QLQ-OES18 has 4 domains: reflux, chest pain, dysphagia and eating) improved to a similar extent after both treatments at 12 months compared with baseline. Dysphagia and chest pain are shown in Figure 2. Tolerance of the procedures assessed by telephone interview 1 week after each intervention appeared similar for APC and RFA (table 5), with slightly more chest pain and dysphagia (mostly transient) reported at some time points (visits 3-5) with RFA.

Duration of procedure and healthcare costs

Mean time for procedural completion from time of intubation was lower with APC (24 minutes) compared with RFA (30 minutes). Figure 3 shows the mean duration of procedures during the trial, which reduced with time, presumably due to progressive reduction in BE extent.
Complete data on health service utilization was available for all 76 patients in the trial and endoscopy resource use data was available for 49 patients (25 APC and 24 RFA). There was a substantial cost difference of more than £20,000 in procedural costs as shown in Table 6 with RFA being costlier. There were slightly higher healthcare costs for APC treated patients, although procedural costs dominate.

Discussion

Effectiveness and safety of endotherapy in reducing neoplasia recurrence in patients with Barrett's related early neoplasia has been demonstrated in randomized trials comparing RFA to sham,[17] surveillance[36] and stepwise radical endoscopic resection,[11] and comparing APC to surveillance.[23] BRIDE is the first randomized trial comparing RFA with APC after ER for Barrett's early neoplasia. It was designed as a pilot study to examine recruitment, retention, estimation of comparative efficacy of the 2 interventions and healthcare resource utilisation. The study has some limitations: first, patients were recruited from the UK only, affecting generalisability of the results. Second, some outcome data was missing, reducing accuracy of assessment. Third, small numbers recruited with longer BE (>10 cm) limit what can be learnt with regards to potential differences in efficacy in very long segment BE.
Seventy-six patients were recruited over one year from six centres, comprising 71% of those eligible to participate. The retention rate amongst those who did enrol was 77.5% and 94.4% in the APC and RFA arms respectively. More patients discontinued in the APC arm, including 2 withdrawn before receiving ablation due to advanced histology after initial ER, 2 due to strictures requiring frequent dilatations, 4 by 'patient choice' (non-attendance, moving out of area and choice not to have APC: some misunderstood randomisation and had been expecting RFA) and 1 due to severe unrelated co-morbidity, compared to 1 withdrawn from RFA due to severe unrelated co-morbidity. Thus, although retention was less in the APC group, there is no single explanation related to treatment, but the drop-out rate is concerning if it reflects lower patient acceptability (which was not apparent from our quality of life measurements).
Being a pilot study, no formal comparison between groups has been made, but our data reveal similar rates of dysplasia clearance after APC or RFA, with 26/31 (83.8%) receiving APC clear of dysplasia at 12 months compared with 27/34 (79.4%) using RFA. Dysplasia clearance at 12 months beyond the end of the BRIDE trial was not a pre-specified secondary outcome, but we collected this data showing that 5 in the APC group with cancer/dysplasia on exit received further endotherapy (3/5 became dysplasia free), so dysplasia clearance at 24 months is 29/31 (93.5%) for APC, compared to 30/34 (88.2%) for RFA (6 of 7 with ongoing cancer/dysplasia continued endotherapy, with 3/6

dysplasia -free at 24 months). Comparable dysplasia clearance at 12 months with each technique appears robust at 24 months.
In comparison, the UK RFA registry included patients with intramucosal cancer or HGD, reporting 77% dysplasia clearance in the earlier report (2008-2012)[18] to 90 % more recently (2011-2013).[19] Lower dysplasia clearance in the first report is attributed to less use of ER in the first period.[18, 19] Patients were allowed up to 6 RFA treatments during 2008-12 and up to 5 during 2011-13 compared to 4 in BRIDE. All centres and endoscopists involved in BRIDE are part of the UK RFA registry group. However, registry patients include those with or without visible lesions, and not all had ER; elimination of bias is difficult in a registry.
In a RCT of RFA versus sham, Shaheen reported 90% dysplasia clearance (per protocol) for the HGD group using RFA,[17] but did not study BE with adenocarcinoma; patients were limited to 4 RFA interventions in one year, and BE length was <8cm,[17] whereas we allowed >10 cm; longer BE length is associated with reduced dysplasia clearance[18].
Manner investigated APC compared with surveillance in BE after ER for early neoplasia, allowing up to 7 APC sessions compared with 4 in our study. After APC, 97% were free of dysplasia at 24 months.[23] In the EURO-II study, up to 5 RFA treatments were allowed, together with 'escape' ER and up to 2 APC treatments for residual BE, resulting in dysplasia clearance of 92%,[31] similar to our 24-month outcomes.
We determined dysplasia clearance according to initial BE length (Table 3). Overall, APC and RFA show similar dysplasia clearance in BE <5cm and 5-10cm groups, suggesting APC efficacy in longer segment BE, although the longest segments (>10 cm) are under-represented in BRIDE. Using RFA, Herrero[37] demonstrated neoplasia clearance in 83% of BE >10cm.
Criteria for BE clearance vary: Shaheen[17] required biopsy evidence of absent IM, while Gupta required both no visible BE and no IM.[38] Manner defined clearance as $\geq$90% macroscopic ablation of the previous BE.[23] In the EURO-II study, failure of BE clearance was defined as visible BE containing IM on biopsy, but IM at a normal appearing cardia was not regarded as failure,[31] similar to our definition.

BE clearance was similar in both groups (48.4% for APC, 55.9% for RFA), both showing reduction of BE length at 12 months (Table 4). Gupta followed 592 patients treated with RFA, reporting 26% BE clearance at 1 year, 56% at 2 and 71% at 3 years.[38] Our BE clearance for RFA is lower than Shaheen using RFA (77% at 1 year),[17] and Manner using APC (79% at 2 years),[23] but clearance was defined differently than for BRIDE. Patients in our study had longer BE at baseline, with mean length 6.2 cm (maximum 20) in BRIDE compared with 4.6 cm (maximum 8) in the HGD group in Shaheen.[17] Manner allowed up to 7 APC treatments, compared to 4 for BRIDE. In the EURO-II study, better clearance of BE (93%) was achieved with up to 5 RFA treatments and "escape" treatment using up to 2 APC and 1 ER for residual islands.[31] We might have found better BE clearance with more ablations (as did Gupta[38] with RFA).

Concern exists around BE glands with neoplastic potential buried under neo-squamous epithelium. The risk for different ablative therapies is unclear:[39, 40] buried glands occur under squamous mucosa close to BE before treatment,[17, 41] but APC may leave buried glands in up to 40% of treated patients.[42, 43] We found a lower rate of buried glands (13.3%) after APC, though lower still with RFA (6.1%) as previously reported.[41]
Symptomatic stricture dilatation was required in 13.5% after APC (although 2 occurred after initial ER before APC was used) and 8.3% after RFA. Stricture rate in a RCT using APC was 9%,[23] and for RCTs using RFA 6-12%,[17, 31] comparable to our study. The TREAT-BE consensus quality standards for BE endotherapy proposes tracking and documentation of adverse events though not actually agreeing benchmark rates[44]. Stricture rate is an important consideration in comparing 2 ablation

techniques, though it was acknowledged by the TREAT-BE panel that ER plays a major role in this[44]. Hybrid-APC may reduce stricture rate (only 1 of 50 patients – 2%) by creating a submucosal fluid cushion.[45] APC and RFA were otherwise comparable with similar complication rates, and both were associated with similar scores for general quality of life measures (EQ-5D, QLQ-C30) and esophageal specific measures (QLQ-OES18) throughout the trial.

APC is considered more time-consuming than RFA, especially for longer BE.[46] Our data suggests that APC took, on average, less time than RFA. Whether this stands true for very long BE >10 cm or not cannot be determined due to small numbers with >10 cm BE: intuitively it seems likely that more APC sessions might be required in long segment BE than with circumferential balloon RFA. The length of time for RFA can be reduced by omitting the cleaning phase,[24, 47] but there are concerns about higher stricture rate using the simplified regimen with the new combined sizing/treatment system (Barrx™ 360 Express).

Cost utility modelling analyses comparing ablation to esophagectomy for HGD favour RFA[48] though these models only consider costs of ablation using RFA. In our study, the average cost for ER followed by APC (£3,985) was considerably lower than for RFA (£25,417), a difference dominated by higher procedural costs for RFA. Cost difference is an important outcome, since both techniques may offer similar safety and efficacy. In England and Wales, the National Oesophago-Gastric Audit found 930 cases of BE HGD over 2 years (2012-14),[49] which could translate into a cost saving of £9,965,880 per year if endotherapy including APC instead of RFA were to have been used in all cases – this does not include cases of T1a cancer or LGD potentially suitable for endotherapy.

This pilot warrants a fully powered non-inferiority RCT comparing neoplasia clearance with APC or RFA. The low stricture rate with hybrid APC[50] suggests this should be the comparator with RFA using the optimal regimes for focal and 360 Express RFA that are currently being established. Patients could also be included with confirmed low grade dysplasia,[36] biopsy-only detected HGD (no visible lesion for ER), 'good prognosis' T1sm1 tumours[50] and no upper age limit (85 in BRIDE). This would have increased those eligible by at least 32 in our screened cohort. If these findings are replicated then cost difference would make a strong case for change in practice.

Conclusion

This is the first reported randomized trial to compare APC with RFA in the treatment of patients with Barrett's and early neoplasia after ER. The preliminary results in this pilot study show similar dysplasia clearance, safety and QoL for RFA and APC, but a substantial difference in cost favoring APC; these findings should be tested in an adequately powered non-inferiority trial.

Figures

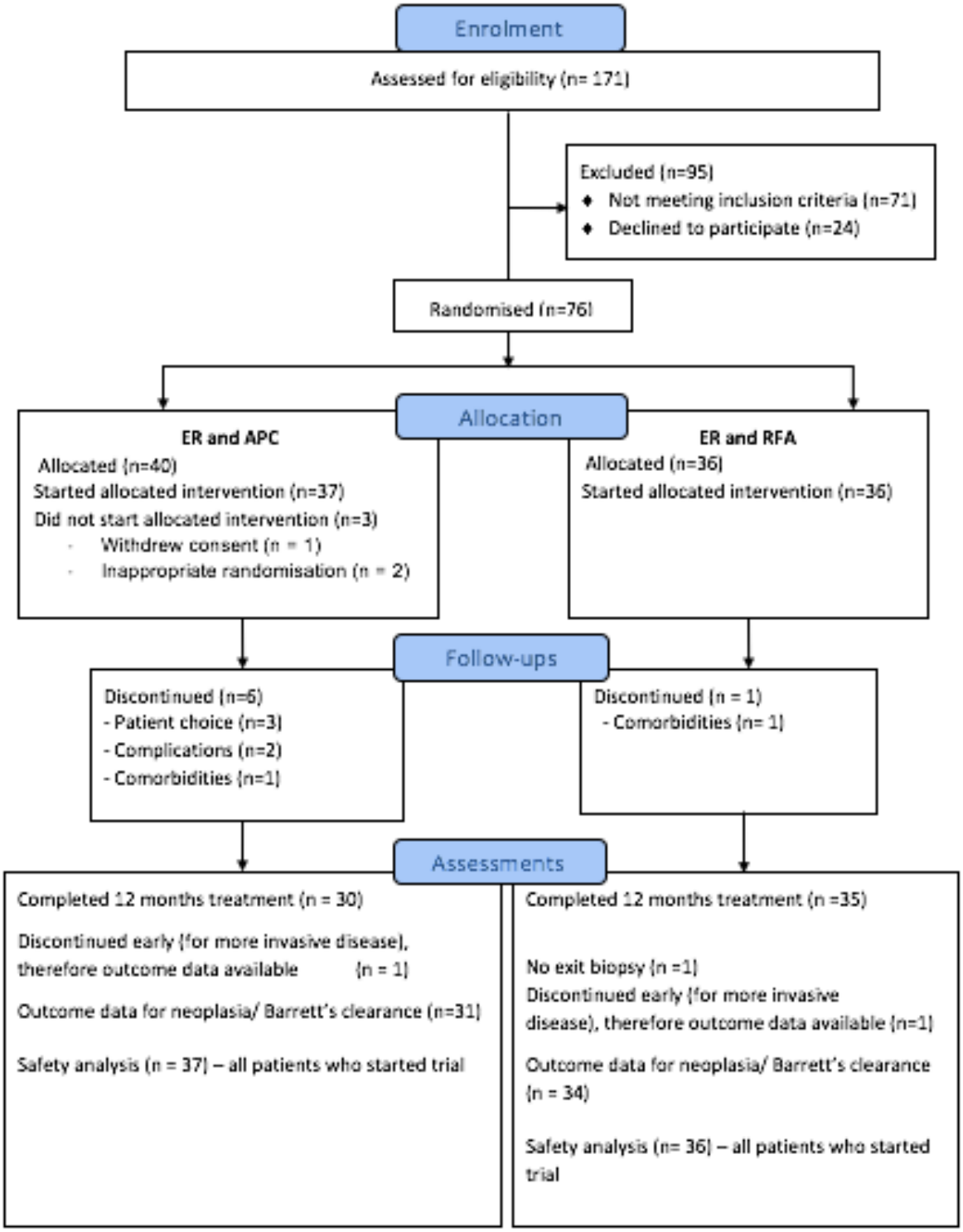


Figure 1: CONSORT diagram

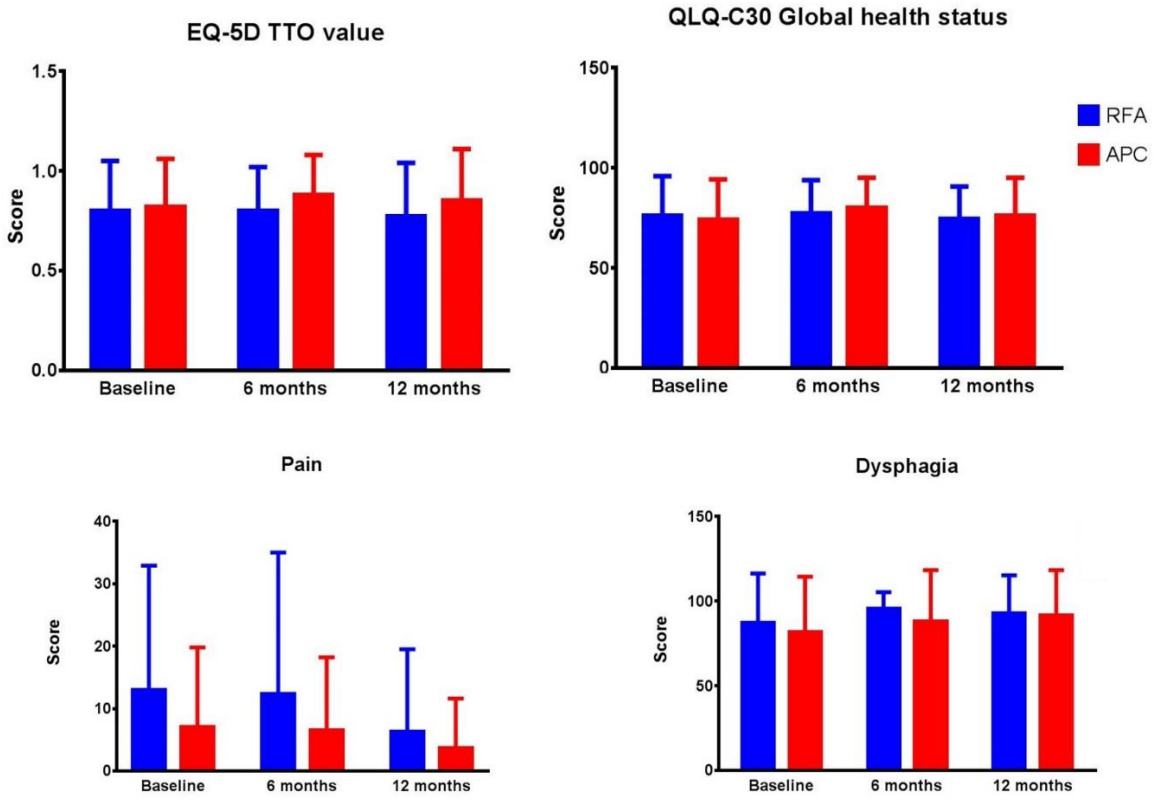
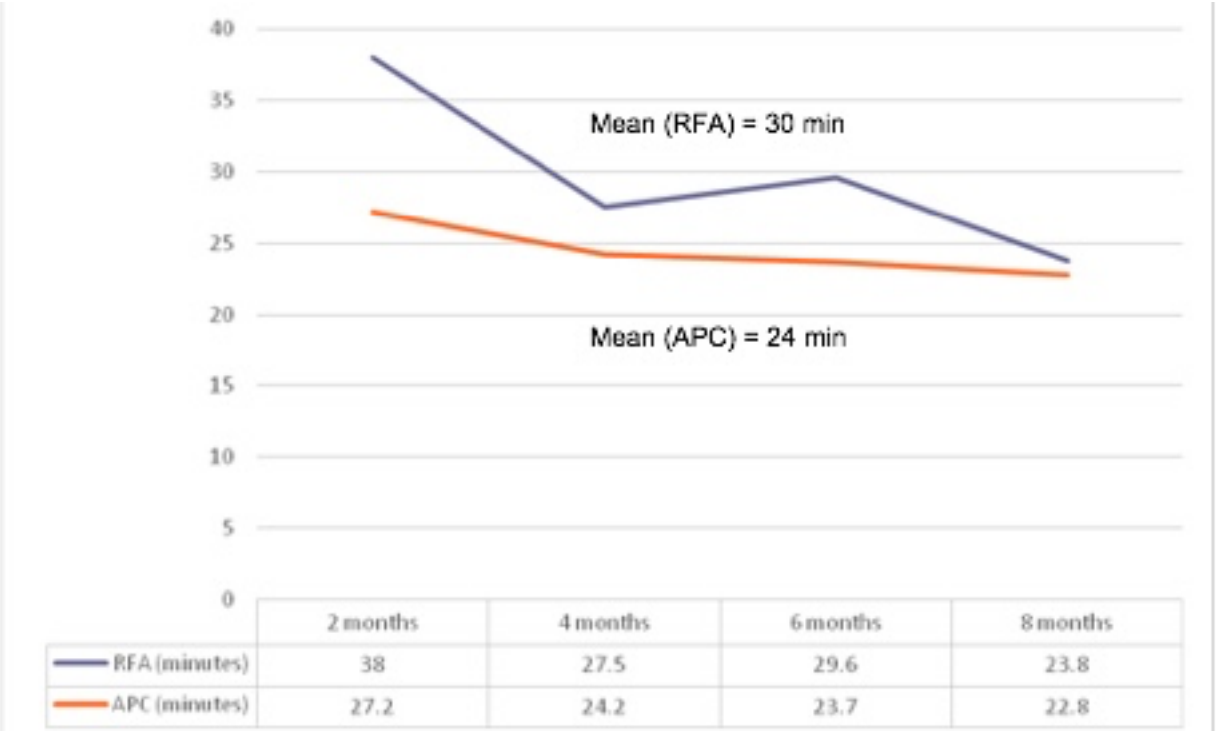


Figure 2- Mean Quality of Life scores. For EQ-5D, QLQ-C30 and pain, the lower the score, the better the QoL. For dysphagia, the higher the score, the better the swallowing ability. The error bars represent 1 standard deviation.



	2 months	4 months	6 months	8 months
RFA (minutes)	38	27.5	29.6	23.8
APC (minutes)	27.2	24.2	23.7	22.8

Figure 3 - Mean duration of ablation procedures over time

Tables

Baseline Characteristic	ER and APC (40 patients)	ER and RFA (36 patients)	
Age (years) Mean (SD)	71.0 (8.1)	68.2 (10.2)	p = 0.18
Sex, no. (%) Male Female	36 (90.0) 4 (10.0)	28 (77.8) 8 (22.2)	p= 0.44
BMI (kg/m^2) Mean (SD)	28.1 (4.4)	28.3 (3.9)	p= 0.72
Maximal (M) & Circumferential (C) BE length (cm) Mean (SD)	M 6.2 (3.4) C 4.1 (3.8)	M 5.6 (2.3) C 3.3 (2.8)	p= 0.3 p= 0.19
BE length, no. (%) <5 cm 5-10 cm >10 cm	12 (30.0) 25 (62.5) 3 (7.5)	15 (41.7) 20 (55.6) 1 (2.8)	p= 0.43
Histology, no. (%) High Grade Dysplasia T1 Adenocarcinoma	29 (72.5) 11 (27.5)	29 (80.6) 7 (19.4)	p= 0.41

Table 1 - Baseline Characteristics of patients enrolled into the study

Outcomes and analysis *	APC N/ Total with outcome data (%)	RFA N/ Total with outcome data (%)	Odds Ratio (95% Confidence Interval)
Clearance of dysplasia (HGD or cancer)	26/31 (83.9)	27/34 (79.4)	0.7 (0.2 - 2.6)
Clearance of BE on endoscopy	15/31 (48.4)	19/34 (55.9)	1.4 (0.5 – 3.6)
IM at cardia with no visible BE	0/31 (0)	2/34 (5.9)	

Table 2 - Clinical outcomes at 12 months (including all patients who started treatment and have outcome data available at 12 months)*

Length of Barrett's (cm)	Intervention (total with outcome data)	Clearance of dysplasia N (%)
Less than 5	ER/ APC (n = 9)	9 (100)
	ER/ RFA (n= 14)	12 (85.7)
5 to 10	ER/ APC (n= 20*)	15 (75.0)
	ER/ RFA (n=19**)	15 (78.9)
More than 10	ER/ APC (n=2)	2 (100)
	ER/ RFA (n=1)	0 (0.0)

Table 3 – Clearance of dysplasia rates by initial length of BE at 12 months
** including one patient in APC group who developed more invasive disease during trial*
*** including one patient in RFA group who developed more invasive disease during trial*

Length of Barrett's (cm)	Intervention (total with outcome data)	Histological clearance of IM N (%)	Median length of BE (min, max) cm	
			T = 0	T = 12
Less than 5	ER/ APC (9)	7 (77.8)	4 (3, 4)	0 (0, 1)
	ER/ RFA (14)	9 (64.3)	4 (2, 4)	0 (0, 2)
5 to 10	ER/ APC (20)	7 (35.0)	6 (5, 10)	1 (0, 6)
	ER/ RFA (19)	10 (52.6)	6 (5, 10)	0 (0, 8)
More than 10	ER/ APC (2)	1 (50.0)	15 (11, 20)	3 (0, 9)
	ER/ RFA (1)	0 (0)	11*	10*

Table 4 – Clearance of Barrett's at 12 months by stratification length
** Single datum value*

	% reporting chest pain		% reporting dysphagia	
	APC	**RFA**	**APC**	**RFA**
Baseline	16.7	16.7	11.1	16.7
Visit 2	45.5	42.9	36.4	35.7
Visit 3	28.6	37	25	44.4
Visit 4	28.6	30	42.9	30
Visit 5	12	25	24	39.3

Table 5. Proportion of patients reporting chest pain or dysphagia (mostly transient) at telephone interview 1 week after each intervention

	RFA mean cost	**APC mean cost**	**Mean difference**
Procedural cost	£25,217	£3,985	£21,232
Healthcare cost	£298	£383	£-85
Total cost	£25,515	£4,368	£21,147

Table 6 – Cost comparisons between RFA and APC

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