Cryoballoon ablation for treatment of patients with refractory esophageal neoplasia after first line endoscopic eradication therapy

Introduction
Barrett’s esophagus (BE) is a premalignant condition with metaplastic cells that can progress to esophageal adenocarcinoma. It is characterized by a change of normal squamous epithelial cells lining the esophagus to metaplastic columnar cells [1]. In most patients, BE only exists in the metaplastic stage without progression to dysplasia. Chronic exposure to acid reflux can result in epithelial cell inflammation and proliferation that can lead to the development of BE metaplasia and progression to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and invasive esophageal adenocarcinoma [2]. Incidence of esophageal adenocarcinoma has increased in recent years and despite advances in medical and surgical interventions, long-term survival remains poor [3, 4] with less than 20% of patients surviving at 5 years [5]. Surgical management of early esophageal neoplasia carries significant mortality rates [6–8]. In recent years there have been significant developments in minimally in-
vasive endoscopic eradication therapy (EET) of BE neoplasia with high eradication rates and a good safety profile.

Currently, endoscopic treatment of BE neoplasia consists of endoscopic resection (ER) of visible lesions for accurate staging and risk stratification of patients [9] followed by field ablation of remaining areas of flat BE to prevent the development of metachronous lesions [10]. The most commonly used and studied ablative modality is radiofrequency ablation (RFA), that utilizes pulsed radiofrequency energy to destroy superficial mucosal tissue with preservation of deeper tissue [11]. This technique has been shown to be effective in achieving CR-D and CR-IM; however it can result into pain, bleeding and stricture in the esophagus [12–14]. In a minority of patients, ablative therapy with RFA is ineffective and therefore alternative ablative techniques are warranted.

Recurrence of IM and dysplasia can occur after achieving CR-IM and therefore surveillance has been recommended. Data from the United States RFA registry noted a 20 % recurrence of BE over a follow-up period of 2.4 years and recurrence of dysplasia reported in 14 % of those who had BE recurrence [5]. A systematic review and meta-analysis by Krishnamoorthi et al, showed a recurrence rate for IM to be 7.1 % per patient year, 1.3 % for LGD and 0.8 % for HGD/EAC (after first line EET) [16].

BE refractory to endoscopic therapy has been documented in various studies with overall rate ranging from 2 % to 25 % [12, 17].

Treatment of BE neoplasia by endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) have shown to be effective and less invasive than surgical esophagectomy. Both techniques allow histological assessment of resected specimens that can be used to guide further therapy; however, these techniques require advanced training in endoscopic therapy with noticeable adverse events (AEs) such as bleeding (2.1 %), perforation (2.5 %–5 %), and stenosis (10 %).

A new treatment for esophageal neoplasia has been developed. Cryoablation with the Cryoballoon device (cryoballoon focal ablation system, Pentax Medical Inc) is a novel ablative therapy that uses cycles of freezing (with nitrous oxide at~80 °C) and thawing to induce cell death by intracellular and extracellular ice formation, leading to vascular injury, and ultimately apoptosis and cell death [18]. The technique may ablate deeper than RFA whilst preserving the extracellular matrix [19] and therefore may result into lower stricture rates and deeper tissue destruction [20]. In addition, recent studies have shown that cryoablation to be better tolerated by patients and to be less painful [21–23].

The aim of this study was to prospectively evaluate the feasibility of the focal cryoablation device for the treatment of areas of refractory esophageal neoplasia in patients who had undergone first line EET in a single high-volume tertiary referral center.

Patients and methods

Patients were treated by a single experienced endoscopist with several years’ experience in advanced endoscopic management of esophageal neoplasia including resection and ablative modalities.

Refractory esophageal neoplasia was defined as failure of three ablative procedures (argon plasma coagulation [APC] or RFA) in patients with BE neoplasia or failure of two ablative procedures (APC or RFA) with less than 50 % reduction of BE after the second ablation. Reduction in BE length was determined by measuring the remaining length of BE using the Prague classification.

The primary objectives were complete resolution of dysplasia (CR-D) and complete resolution of intestinal metaplasia (CR-IM) at 3-month follow-up endoscopy. Secondary objectives included the rate of stenosis, AEs and durability of disease reversal. Stenosis was defined as any stricture causing symptomatic dysphagia to solid and liquid and strictures preventing the passage of an adult gastroscope requiring endoscopic dilatation.

Inclusion criteria are 18 or older; previous receipt of first-line EET (ER and ablation with RFA or APC for at least three sessions excluding cryoablation) in patients with BE neoplasia with biopsy proven residual disease; persistence of flat areas of esophageal neoplasia after first-line EET confirmed by two expert pathologists; and in patients with IMC, no evidence of poorly differentiated malignancy, involvement of deep resection margin (i.e. T1b deep), or lymphovascular involvement on previous ER specimens.

Exclusion criteria were presence of esophageal stricture preventing the passage of a therapeutic gastroscope and deployment of the Cryoballoon ablation device; active gastrointestinal bleeding or perforations; active inflammation in the upper gastrointestinal tract; and presence of raised or high-risk lesion requiring endoscopic resection.

The requirement for baseline was persistent BE with LGD, HGD, or IMC.

Cryoablation device and endoscopic procedure

The cryoablation balloon system has two main components: The delivery catheter with a balloon probe (30 mm in length) and a handheld controller device for application of the cryogenic fluid with a small cylinder containing the nitrous oxide. The delivery catheter utilizes one balloon probe for all sizes of esophagi. The delivery catheter is introduced via the working channel of a therapeutic gastroscope (Pentax EG34-i10) and the balloon is inflated by the trigger on the foot pedal. The balloon is automatically inflated until it reaches the diameter of the treated esophagus, hence preventing over inflation and trauma to the wall of the esophagus. The inflated balloon is cooled by spraying nitrous oxide via the diffuser within the inflated balloon, which subsequently freezes the targeted mucosa to ~80 °C. The cryogenic spray covers an area of about 2 cm². Rotation of the diffuser within the balloon (360 degree), is controlled by the foot pedal, which allows targeting of specific areas of the mucosa following deflation of the balloon, the gas is aspirated back automatically into the hand...
held controller and condensed. The treated mucosa becomes erythematous immediately after deflation of the balloon, allowing the endoscopist clear visualisation of the treated segment of the mucosa.

Endoscopic therapy and follow up
The endoscopic procedure was performed under conscious sedation by the same gastrointestinal endoscopist. Refractory areas of BE were measured as per the Prague C & M classification and careful inspection for any visible raised lesions was first carried out. The refractory areas of BE were ablated for 10 seconds by the cryoballoon device. After each ablation, the adjacent area was subsequently ablated until all areas of visible BE including the gastroesophageal junction (GOJ) were treated. In patients with long-segment BE, there was a minimum overlapping area of cryoablation to ensure that all areas were treated adequately. Scraping of the ablated mucosa was not performed.

All patients received post-ablative care, which included high-dose acid suppressive medication (omeprazole 40 mg twice a day, ranitidine 300 mg in the evening and sucralfate liquid 2 g three times a day) and a liquid diet for 24 hours followed by a soft diet for 1 week. All patients received follow-up endoscopy at about 3 months post-cryoablation. At follow-up endoscopy, all treated area were inspected with white light endoscopy (WLE), virtual chromoendoscopy (Narrow Band Imaging [NBI]) or optical enhancement (OE) and chromoendoscopy (with acetic acid). All remaining areas of neoplasia were documented. In addition, presence of stenosis, if any was also documented. Biopsies were then taken from 1 cm below the GOJ, the GOJ and the remaining segment of BE at 2-cm intervals, including target biopsies from any suspicious areas (Fig. 1).

Biopsy specimen
All biopsy specimens were placed in formalin and fixed in paraffin and subsequently stained with haematoxylin and eosin. All our histological specimens were examined by the same two senior BE expert pathologist (MN, MJ) at University College London Hospital (UCLH).

Study approval and patient consent
This project was presented to the local Clinical Effectiveness Steering Group (CESG) at UCLH for approval as a new procedure. The CESG committee gave their final approval in June 2016 and subsequently patient recruitment started. Written informed consent was taken from all participating patients prior to the endoscopic therapy with cryoablation.
Statistical analysis

Statistical analysis was performed using the SPSS Statistics software (Version 25). Quantitative variables were expressed as median with range and qualitative variables were presented as percentages. This was a feasibility study and therefore sample size calculation was not performed. Kaplan–Meier analysis was used to determine the durability of CR-IM and CR-D post Cryoablation.

Results

A total of 18 patients with BE neoplasia (15 male, 3 female; median age 71.5, IQR 65–74), refractory to first-line EET were treated with cryoablation from June 2016 to March 2018 (▶Table 1 and ▶Table 2, ▶Fig. 3).

Baseline sequential EET included a combination of EMR and RFA in 13 patients (72 %) and RFA only in five patients (28 %) with BE neoplasia with a median length of dysplastic BE treated of 3 cm (IQR 3–4.25) (▶Table 3).

Successful ablation was achieved in 17 patients (94 %) with only one patient (5.5 %) receiving inadequate ablation with the Cryoballoon due to a tortuous and dilated esophagus, preventing adequate contact between the mucosa and the cryoballoon device.

A median of 11 ablations (IQR 9–16) were applied per patient. Each patient received only one session of cryoablation (▶Table 3). At follow-up endoscopy 3 months after treatment with cryoablation, CR-D was achieved in 78 % of patients (14/18) and CR-IM was achieved in 39 % of patients (7/18) (▶Table 4). Lack of response to Cryoablation was seen in one patient (5.5 %) with IMC and disease progression from LGD to HGD was confirmed in one patient (5.5 %) at 3-month follow-up endoscopy (▶Table 4). All patients with a remaining segment of BE (with IM or dysplasia) post-cryoablation received further endo-

▶Table 1 Baseline histology.

<table>
<thead>
<tr>
<th>Baseline histology prior to failed first-line EET</th>
<th>Baseline histology prior to Cryoballoon therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE neoplasia Low-grade dysplasia (LGD)</td>
<td>4 (22 %)</td>
</tr>
<tr>
<td>High-grade dysplasia (HGD)</td>
<td>6 (33 %)</td>
</tr>
<tr>
<td>Intramucosal carcinoma (IMC)</td>
<td>8 (44 %)</td>
</tr>
</tbody>
</table>

EET, endoscopic eradication therapy; BE, Barrett’s esophagus
scopic therapy with EMR, RFA or both, with the aim of achieving complete eradication of BE.

There were two (11%) reported esophageal strictures post-cryoablation, each requiring one successful endoscopic dilatation. There were no recorded complications or AEs.

Durability of disease reversal

Analysis of all patients post-endoscopic therapy with cryoablation showed that CR-D was maintained in 72% (13/18) and CR-IM in 33% (6/18) after a median follow-up of 19 months (IQR 13–28) (▶ Fig.4).

Discussion

Endoscopic treatment of early esophageal neoplasia has significantly developed in the past decade. The current consensus is to resect any visible lesions followed by ablative therapy using RFA or APC for BE neoplasia. Depressed lesions are associated with a high risk of submucosal invasion and would be under-treated by ablation.

RFA is safe and effective [12, 25, 26] for treatment of BE neoplasia. ET is also more cost-effective than surgery [27]; however, the treatment can be painful and risk of stenosis post-ET is not negligible [28], especially in patients who require circumferential ablation [29].

In various studies, the rate of recurrence of BE and BE neoplasia has been documented as ranging from 5% to 40%. Long-term surveillance is therefore needed to maintain remission and detect early recurrence of disease [30–33]. Non-compliance with endoscopic surveillance and failure to achieve complete remission at 12 months post-ET are predictors of progression [34]. In addition, a number of patients (2%–25%) [12, 17] will not respond to first-line EET, therefore, alternative rescue treatment modalities other than surgery are needed as some of these patient may not be suitable surgical candidates and surgery can be associated with mortality and morbidity rates that are not negligible [13, 35, 36]. Acid suppression is an im-

Table 2 Baseline histology with corresponding post-cryoablation histology at 3 months follow-up for all patients.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pre-EET histology</th>
<th>Pre-cryoablation histology</th>
<th>Post-cryoablation histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IMC</td>
<td>HGD</td>
<td>Normal squamous mucosa</td>
</tr>
<tr>
<td>2</td>
<td>HGD</td>
<td>HGD</td>
<td>Normal squamous mucosa</td>
</tr>
<tr>
<td>3</td>
<td>IMC</td>
<td>IMC</td>
<td>Normal squamous mucosa</td>
</tr>
<tr>
<td>4</td>
<td>IMC</td>
<td>HGD</td>
<td>Normal squamous mucosa</td>
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<tr>
<td>5</td>
<td>LGD</td>
<td>LGD</td>
<td>Normal squamous mucosa</td>
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<tr>
<td>6</td>
<td>LGD</td>
<td>LGD</td>
<td>Normal squamous mucosa</td>
</tr>
<tr>
<td>7</td>
<td>IMC</td>
<td>LGD</td>
<td>Normal squamous mucosa</td>
</tr>
<tr>
<td>8</td>
<td>LGD</td>
<td>LGD</td>
<td>IM only, no dysplasia</td>
</tr>
<tr>
<td>9</td>
<td>HGD</td>
<td>LGD</td>
<td>IM only, no dysplasia</td>
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<tr>
<td>10</td>
<td>HGD</td>
<td>HGD</td>
<td>IM only, no dysplasia</td>
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<tr>
<td>11</td>
<td>HGD</td>
<td>LGD</td>
<td>IM only, no dysplasia</td>
</tr>
<tr>
<td>12</td>
<td>LGD</td>
<td>LGD</td>
<td>IM only, no dysplasia</td>
</tr>
<tr>
<td>13</td>
<td>IMC</td>
<td>IMC</td>
<td>IM only, no dysplasia</td>
</tr>
<tr>
<td>14</td>
<td>HGD</td>
<td>LGD</td>
<td>IM only, no dysplasia</td>
</tr>
<tr>
<td>15</td>
<td>IMC</td>
<td>HGD</td>
<td>LGD</td>
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<tr>
<td>16</td>
<td>HGD</td>
<td>LGD</td>
<td>HGD</td>
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<tr>
<td>17</td>
<td>IMC</td>
<td>HGD</td>
<td>HGD</td>
</tr>
<tr>
<td>18</td>
<td>IMC</td>
<td>IMC</td>
<td>IMC</td>
</tr>
</tbody>
</table>

EET, endoscopic eradication therapy; IMC, intramucosal carcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

1 Patient received inadequate ablation with the Cryoballoon due to a tortuous and dilated esophagus.

18 Patients with treatment refractory BE neoplasia enrolled into this study:

(June 2016–March 2018)

• 13 (72%) patients had combination of EMR and RFA therapy prior to Cryoablative therapy
• 5 (28%) patients had RFA only prior to Cryoablative therapy

One session of Cryoablation (10 second ablations) applied:

• Under conscious sedation
• By the same GI endoscopist
• At a large volume tertiary referral centre

All patients received post ablative care:

• High dose acid suppressive medication (Omeprazole 40 mg bd, Ranitidine 300 mg nocte and Sucralfate liquid 2 g TDS)
• Liquid diet for 24 hours followed by soft diet for 1 week

All patients received follow up endoscopy at about 3 months post cryoablation:

• All treated area were inspected with WLE, NBI/OE and chromoendoscopy with acetic acid
• Biopsies were taken from 1 cm below the GOJ, the GOJ and the remaining segment of BE at 2 cm intervals (including target biopsies from any suspicious areas)

Fig. 3 Study flowchart.
important factor in treatment of patients with BE and refractory disease. GORD is associated with BE, therefore, controlling acid reflux is an essential part of treatment. Uncontrolled acid reflux is associated with persistent IM post-RFA. Persistent acid reflux is also associated with a higher mean number of RFA sessions needed to achieve CR-IM and recurrence of disease after EET [37, 38]. Challenging anatomy due to dilated and tortuous esophagus and strictures post-EET and presence of submucosal carcinoma has been shown to limit efficacy of endoscopic therapy and subsequently result in treatment failure and relapse [12].

Cryoballoon therapy using nitrous oxide as the cryogenic agent is a novel new therapy for management of early BE neoplasia which has been shown to be safe and effective with success rates comparable to that of RFA [22, 39]. In this single-center, prospective, feasibility cohort study, cryoablation with the Cryoballoon device appeared to be a viable treatment modality.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Baseline length of BE with corresponding number of cryoablations for each patient.</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>Gender</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
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<tr>
<td>2</td>
<td>M</td>
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<td>3</td>
<td>M</td>
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<td>4</td>
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<tr>
<td>18</td>
<td>M</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 4</th>
<th>Summary of results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical difficulty due to Anatomy</td>
<td>5.5% (1/18) Tortuous and dilated esophagus</td>
</tr>
<tr>
<td>Stenosis</td>
<td>11% (2/18)</td>
</tr>
<tr>
<td>No response</td>
<td>5.5% (1/18) 1 case with IMC</td>
</tr>
<tr>
<td>Progression</td>
<td>5.5% (1/18) Progressed from LGD to HGD</td>
</tr>
<tr>
<td>CR-D</td>
<td>78% (14/18)</td>
</tr>
<tr>
<td>CR-IM</td>
<td>39% (7/18)</td>
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</tbody>
</table>

IMC, intramucosal carcinoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; CR-D, complete remission of dysplasia; CR-IM, complete remission of intestinal metaplasia

Fig. 4 Kaplan-Meier curve showing the durability of disease reversal in all patients with BE neoplasia, treated with Cryoballoon therapy.
in patients with BE neoplasia refractory to sequential first-line EET.

In this study, CR-D and CR-IM could be achieved in patients who previously did not respond completely to standard first-line EET. We were able to achieve these eradication rates (CR-D: 78% and CR-IM: 39% in patient with BE) with only one session of cryoablation in treatment-refractory patients with a wide range of pre-cryoablation pathologies including LGD, HGD and IMC.

We were also able to demonstrate durability of disease reversal with 72% of patients (13/18) with BE neoplasia maintaining CR-D and 33% of patients (6/18) maintaining CR-IM after a median follow-up of 19 months (IQR 13–28).

Our data are in line with previously published series (CR-D achieved in 75%-88% of patients)[17, 23,40]. A recent meta-analysis by Visrodia et al analyzed 11 studies with 148 patients with BE treated with cryotherapy for persistent dysplasia or IM after RFA. CR-D was achieved in 76.0% (95% CI, 57.7–88.0) and CR-IM in 45.9% (95% CI, 32.0–60.5) of patients [41].

We have also shown that cryoablation is safe with an acceptable stricture rate. The documented symptomatic stricture rate from several major studies on BE endotherapy range from 2.1% to 14% [13, 29,42] requiring a median of two to four dilatations post-endotherapy. Despite circumferential ablation of the GOJ in all patients and a pre-ablation EMR rate of 71%, we were able to show a stricture rate of 11%, which is comparable to that reported in similar studies [39, 43,44].

The benefit of cryoablative therapy over RFA is due to intrinsic and technical differences between the two modalities. The rapid freeze and thaw cycles delivered by cryotherapy achieves a greater depth of tissue penetration with relative preservation of tissue architecture [45]. Cryotherapy is minimally destructive to the structural components of tissue, such as collagen, whereas heat-based ablation techniques like RFA, irreversibly destroy proteins and therefore affect the architecture of the collagen matrix [20]. The effects of cryoablation are dose-dependent. Overlap of ice patches on adjacent treated sites may result in higher application of cryogen and deeper injury and subsequent stricture development [43]. The Cryoballoon pressure is regulated by the controller to 3.5-147 psi per square inch (psi), which is significantly lower than dilating balloons, which exert pressures of 44 to 147 psi [46]. Procedure times for cryoballoon ablation are short and the portability and ease of use of the Cryoballoon ablation device is appealing.

Our data suggest that Cryoballoon ablation is a promising treatment for refractory BE neoplasia. Our study showed that this technique is relatively easy and quick without serious AEs. It allows treatment of large circumferential areas in the esophagus as well as small islands. Several studies in BE neoplasia [23] and other fields of medicine have shown that cryoablation is less painful [47,48]. Pain perception was not formally assessed in this study, but previous studies have shown that the cooling process may have an anaesthetic effect [49] by reducing or blocking nerve conduction and, therefore, less postprocedural discomfort than that seen with RFA [47]. In addition, vasoconstrictive blood vessels as a result of the cooling process may reduce development of edema and release of painful inflammatory mediators [50].

There were some limitations to this study. First, there was a small sample size and patients were treated in a single high-volume tertiary referral center with no control group, which was due to only a small number of treatment-refractory patients with residual disease in our hospital. An increase in the number of patients may alter the results achieved. In addition, it may have been possible for patients with long segments of BE refractory to RFA sessions to achieve CR-IM if further RFA therapy sessions were utilized, therefore, cryoablation may have never been required. The median segment of treated BE was 3 cm and the efficacy of cryoablation on long segments of BE refractory to EET is yet to be studied.

There was no formal assessment of pain perception and use of analgesia among patients participating in this study.

There was only a relatively short follow-up period after treatment, which is important taking into account the late recurrence of disease reported in major studies. This has, therefore, limited the conclusions regarding the risk of progression or recurrence in this high-risk group of patients.

Side-by-side ablation for 10 seconds of a large segment of BE may be time-consuming. Our study did not formally assess the duration of the procedures.

Finally, analysis for determinants for successful ablation and for complications was not performed.

Conclusion
In conclusion, cryoablation is a promising treatment for patients with BE neoplasia refractory to first-line EET. The CR-D and CR-IM rates achieved in this study and the encouraging safety profile show that it may be an alternative therapeutic modality for those that are not suitable for RFA or in cases where RFA was not successful.

Longer-term follow-up is needed to determine complete remission durability for cryoablation with application to larger/circumferential areas to determine efficacy and stricture rate. Further studies to illicit the effects of two or more sessions of cryoablation with randomized controlled trials and comparison with RFA are recommended.

Competing interests

The authors declare that they have no conflict of interest.

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