NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia

Barrett's oesophagus refers to changes in the cells lining the lower part of the oesophagus (the gullet). The first sign of change is called Barrett's oesophagus with no dysplasia, meaning that the cells are no longer 'normal' but there is no evidence of dysplasia (abnormal cells). The cells may then develop an abnormality called low-grade dysplasia. The changes may lead to cancer. In endoscopic radiofrequency ablation, the abnormal cells are destroyed by a coil-like device inserted through the mouth and into the oesophagus.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in November 2013.

Procedure name

- Endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia

Specialist societies

- British Society of Gastroenterology
- The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.

Description

Indications and current treatment

Barrett's oesophagus is a precancerous condition characterised by abnormal replacement of the squamous epithelium of the lower oesophagus by a type of columnar epithelium resembling that in the stomach and intestine.

In some patients, Barrett's oesophagus may progress through a series of stages to oesophageal adenocarcinoma – a cancer with a poor prognosis. These intermediate stages are graded into low-grade and high-grade dysplasia according to the degree of abnormal cellular architecture.

The risk of progression to oesophageal adenocarcinoma for any individual with Barrett's oesophagus is difficult to predict accurately. In general, the risk of cancer is highest for patients with high-grade dysplasia, lower for patients with low-grade dysplasia, and lowest for patients with no dysplasia (also referred to as intestinal metaplasia – a change from epithelium that is normal for this site but with no evidence of dysplasia). Accurate classification of Barrett's oesophagus into these distinct histopathological types is difficult; there is the possibility of diagnostic misclassification because of biopsy sampling error and subjective biopsy interpretation. Strategies for addressing this include multiple biopsy sampling, diagnosis on at least 2 occasions, confirmation by 2 specialist histopathological experts and confirmation by an independent pathologist external to the original institution each time – all in the context of a multidisciplinary team.

The main risk factor for developing Barrett's oesophagus is a history of reflux of acid and bile into the oesophagus. Reflux commonly produces symptoms of heartburn but it can be asymptomatic.

The management of Barrett's oesophagus is determined by the type of dysplasia present. In Barrett's oesophagus with no dysplasia or low-grade dysplasia, periodic endoscopic surveillance and repeat biopsies may be considered, with the aim of early detection of progression to high-grade dysplasia or cancer. If high-grade dysplasia or early cancer (carcinoma in situ) is detected, then treatment is recommended. If the disease is superficial (confined to the mucosa), treatment can usually be done endoscopically.

Endoscopic treatments for Barrett's oesophagus aim to destroy the Barrett's epithelium, leaving a surface that is subsequently replaced with a normal squamous epithelium. If the disease is flat, then it is generally ablated using one of several possible modalities, such as photodynamic therapy, argon plasma coagulation, laser ablation, cryotherapy or multipolar electrocoagulation. If there are visible abnormalities, such as nodules or ulcers, then those areas are usually removed by endoscopic resection.

What the procedure involves

The procedure is usually carried out with the patient under conscious sedation, in an outpatient setting. Using endoscopic visualisation, an appropriately sized radiofrequency ablation (RFA) probe attached to an endoscope is inserted into the oesophagus and advanced to the target area. Controlled pulses of radiofrequency energy are delivered, which cause thermal ablation of a thin epithelial layer in the affected areas. A circumferential ablation catheter is usually used for primary treatment, whereas a focal ablation catheter is used for remaining patches of Barrett's epithelium in any subsequent treatments. RFA can also be used after performing endoscopic resection to remove larger, superficial abnormal areas. If follow-up high resolution endoscopy and re-biopsy show residual Barrett's changes, repeat treatment can be done using RFA.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia. Searches were conducted of the following databases, covering the period from their commencement to 25-11-2013: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with Barrett's oesophagus with low-grade dysplasia or no dysplasia.
Intervention/test	Endoscopic radiofrequency ablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 815 patients from 3 randomised controlled trials (RCTs)[1,2,3], and 9 case series[4–12].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details

Studies of patients with low-grade dysplasia

Shaheen NJ (2009)[1], (2011)[2]

(AIM Dysplasia Trial)

RCT

USA (19 centres)

Recruitment period: not reported

Study population: patients with non-nodular dysplastic BO (confirmed with endoscopy); 64 with LGD and 63 HGD

n=**127 (64 LGD of which 42 RFA, 22 sham) (63 HGD)**

Age: range 41 to 80 years in LGD

Sex: 86.6% male (RFA: 83.3%, sham: 93%)

Patient selection criteria: between 18 and 80 years, length of BO <8 cm. Exclusion criteria: Pregnant women, patients with active oesophagitis or stricture precluding endoscope passage, history of oesophageal cancer or varices, uncontrolled coagulopathy or <2-year life expectancy.

Technique: upper endoscopy, oesophageal intubation with study catheter, and measurement of oesophageal diameter in all

Key efficacy findings

Number of patients analysed: **RCT 64 LGD, of which 42 RFA, 22 sham at 12 months;**

Crossover cohort: RFA: LGD 52 at 2 years (including 16 sham crossover) and 32 at 3 years follow-up.

Patients in the treatment group with residual BO at 2-, 4- and 9-month follow-up were treated with a focal ablation device HALO[90]. There were mean 3.5 treatments per patient.

Complete eradication of IM or dysplasia at 12-month follow-up[1]

Determined by quadrant biopsies taken every 1 cm of BO segment with the worst histological grade used as overall histological grade.

Outcome	Intervention (%)	Sham (%)	p value
Eradication of IM (LGD patients)	81.0 (34/42)	4.5 (1/22)	<0.001
Eradication of dysplasia (LGD patients)	90.5 (38/42)	22.7 (5/22)	<0.001

(all values are based on ITT analysis)

Complete eradication of IM or dysplasia at 2- and 3-year follow-up in RFA group (including crossover patients)[2]

Outcome	2 Years % (n)	3 Years % (n)
CE-D (LGD patients)	98 (51/52)	100 (32/32)

Key safety findings

***Complications* in RFA LGD and HGD group** (including crossover patients, n=119, 58 LGD, 61 HGD)

Complications	% (n)
Serious adverse events (probably associated with procedure) 1 upper gastrointestinal haemorrhage in a patient being treated by antiplatelet therapy for heart disease (treated endoscopically) 1 overnight hospitalisation for new chest pain 8 days after RFA (outcome not reported) 1 overnight hospitalisation for nausea and chest discomfort immediately after RFA (outcome not reported)	3.4 (4/119)
Oesophageal stricture* (treated with endoscopic dilation, in mean 2.6 sessions)	7.6 (9/119)
Perforations or procedure related deaths	0

*defined as endoscopically identified narrowing with/without dysphagia.

Pain scores (at 1-day follow-up)

This was measured on a VAS from 0 to 100 with higher scores meaning more pain. Below is the score and interquartile range of chest pain 1 day after the operation:

	RFA	Sham

Comments

Follow-up issues:

- In the RCT, 8% (5/64) LGD patients (in both RFA and sham arms) were lost to follow-up within 1 year (with RFA: 2 withdrew consent, 1 died from an unrelated cause; with sham: 2 withdrew consent).
- At 2-year follow-up (after sham crossover to RFA), 12% (7/59) LGD patients were lost to follow-up (with RFA: 1 withdrew consent, with sham 3 withdrew consent, 3 had HGD at 1 year and moved to HDG arm), 52 analysed.
- At 3-year follow-up, 1 patient in LGD group had no CR-IM at 2 years and was ineligible for further study extension, 51 entered extended study, and 32 patients completed 3-year follow-up.

Study design issues:

- Multicentre RCT of 127 patients referred to tertiary centers; computer-generated randomisation was 2:1 and stratified according to grade of dysplasia (LGD or HGD) and length of BO (<4 cm or 4–8 cm).
- Manufacturer managed the database during trial, which was transferred to the authors at the end of the trial, concealed for analysis (so it appears they were

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Study details	Key efficacy findings	Key safety findings	Comments

Study details

patients. In intervention group, entire BO was ablated with HALO^{360} system (BÂRRX Medical) twice at 12 J/cm^2 and 40 W/cm^2 at 3 cm increments, if necessary; all patients received twice daily 40 mg of esomeprazole for 12 months.

16 LGD patients in sham groups crossed over to RFA at 12 months. Patients were followed for 2 years after initial RFA. Those who achieved CR-IM at 2 years or salvaged with an additional RFA after failing to achieve CR-IM at 2 years were eligible to enter a trial extension of additional 3 years. 40 mg twice daily esomeprazole was given throughout trial.

Follow-up: **12 months in RCT**;

3.05 years (mean) in crossover patients (extended to 5 years for patients with eradication of IM at 2 years).

Conflict of interest/source of funding: this review was supported by BÂRRX Medical and medication was supplied by AstraZeneca

Key efficacy findings

CE-IM (LGD patients)	98 (51/52)	NR

Kaplan–Meier analysis showed complete eradication of dysplasia in >85% of patients and IM in >75% without maintenance RFA in the whole cohort.

Progression of dysplasia at 12 months[1]

	Intervention (%)	Sham (%)	p value
LGD to HGD	4.8 (2/42)	13.6 (3/22)	0.33
LGD to cancer	0 (0/42)	0 (0/22)	n/a

Disease progression at 2.05 years (mean) in RFA group (including crossover patients)[2]

4.2% (5/119) patients had disease progression (3 from LGD to HGD, 1 from LGD to EAC, 1 HGD to EAC). The annual rate of overall neoplastic progression was 1 per 73 patient years (1.37%/patient-years). And an annual rate of progression to EAC of 1 per 181 patient years, or 0.55 per patient per year. For patients with LGD, the annual rate of overall disease progression was 1 per 49 patient years, or 2.04% per patient per year and the annual rate of progression to EAC was 1 per 197 patient years, or 0.51% per patient per year.

Recurrence[2]

14 patients who achieved CE-IM reported recurrence of BO after 1 year, half of these occurred in patients with 'normal or irregular z-line'. Of these, 4 demonstrated subsquamous intestinal metaplasia (SSIM), 8 reported CE-IM after single additional RFA, 5 had no further RFA, 1 treatment was ongoing.Rate of oesophageal adenocarcinoma was 1 per 181 patient years (0.55%/patient years) in the whole cohort.

Key safety findings

No. of patients	81	40
Median VAS	23 (0–51)	0 (0–0)
LGD patients	40	20
LGD median VAS	26 (4–48)	0 (0–0)
LGD median VAS	22 (0–57)	0 (0–0)

Buried metaplasia

At baseline, 25.2% of the patients had evidence of subsquamous intestinal metaplasia (20.6% of those with HGD and 29.7% of those with LGD). At 12 months, subsquamous intestinal metaplasia occurred in 5.1% of the patients in the ablation group and in 40.0% of those in the control group ($p<0.001$).

No cancer-related mortality or morbidity was reported.

Comments

blinded, but this is not explicitly stated).

- Standard treatment protocol, standardised biopsy procedures with large samples taken and samples analysed by a central laboratory.
- All patients lost to follow-up as 'failed' in ITT analysis.

Study population issues:

- 11 patients in RCT had previous EMR (7 RFA, 4 sham). Of the 119 patients in crossover study, 58 had LGD and 61 had HGD. 80% of the LGD patients were male with a mean age of 65 years.
- 4/39 of the sham patients developed adenocarcinoma before 1 year outcomes and were not eligible for crossover.
- The sham group had a higher rate of progression to cancer than previous studies. The authors suggest it may be because of more rigorous biopsies, more patients with HGD, and the fact that patients in this study were recruited from tertiary centres so may not reflect progression in the population.

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Study details

Nadine Phoa K (2014)[3]

(SURF Trial)

RCT (multicentre)

Europe (5 countries)

Recruitment period: 2007-2011

Study population: patients with BO with confirmed diagnosis of LGD

n=**136 (68 RFA vs 68 control-endoscopic surveillance)**

Age: 63 years (mean)

Sex: RFA: 55%, control: 61% male

Patient selection criteria: patients with BO containing LGD on endoscopy (and biopsy) within the previous 18 months

Exclusion criteria: prior endoscopic treatment for BO, history of HGD or adenocarcinoma, active secondary malignancy, life-expectancy <2 years, age <18 or >85 years.

Technique: RFA group treated with circumferential (HALO^{360}) or a focal ablation (HALO^{90}). Subsequent sessions every 3 months, until complete eradication. If residual columnar epithelium persisted, a single session of endoscopic resection or argon plasma coagulation was used in 5 (7%) and 12 (18%) of

Key efficacy findings

Number of patients analysed: **136 (68 RFA vs 68 control)**

Rate of neoplastic progression during 3-year follow-up

Outcome	RFA group % (n=68) with event	Control group % (n=68) with event	Risk difference (95% CI)	P value
Progression to HGD or adenocarcinoma	1.5 (1/68)*	26.5 (18/68)^	25 (14.1 – 35.9)	<0.001
Progression to adenocarcinoma	1.5 (1/68)	8.8 (6/68)	7.3 (0.0– 14.7)	0.026

* treated with endoscopic resection, achieved complete eradication of dysplasia

^ 1 underwent oesophagectomy, 2 had endoscopic surveillance,15 had endoscopic resection/RFA.

Complete eradication of metaplasia or dysplasia

Outcome	RFA % (n=68)	Control % (n=68)	Risk difference (95% CI)	P value
Complete eradication of dysplasia at end of treatment	93 (63/68)*			

Key safety findings

Complications in RFA group

Adverse events	% (n)
Abdominal pain 4 days after ablation (hospitalised and treated with analgesics)	1 (1/68)
Small mucosal laceration during ablation (no intervention required, procedure completed)	4 (3/68)
Retrosternal pain 3 weeks after focal ablation (resolved with analgesics)	1 (1/68)
Oesophageal stricture requiring dilation (median 1)	12 (8/68)

There were no adverse events in control patients.

Bleeding 7 days after endoscopic resection for a visible lesion (LGD) before first ablation was reported in 1 patient (patient hospitalised dilated for stricture and developed fever and chills) treated with antibiotics.

Comments

Follow-up issues:

- Few patients lost to follow-up (7 in RFA group and 8 in control group).

Study design issues:

- Patients randomly assigned in a 1:1 ratio, randomisation was sequentially numbered and concealed from trial staff.
- The data and safety monitoring board recommended early termination of the trial (after second interim analysis) because of superiority of ablation for the primary outcome and concerns about patient safety.
- Centralised expert pathology review.

Study population issues:

The 2 groups were similar at baseline.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments

ablation patients. Patients received proton pump inhibition, H_2-receptor antagonist and sucralfate suspension for 2 weeks after each endoscopy performed annually. Control group patients underwent endoscopy at 6 and 12 months, and annually until 3 years.

Follow-up: **3 years**

Conflict of interest/source of funding: funded by Dutch Digestive Diseases Foundation, Covidien GI Solutions. Covidien provided ablation devices and access to a central electronic data management system.

Complete eradication of IM at end of treatment	88 (60/68)*			
Complete eradication of dysplasia during follow-up^	98.4 (62/63)*	28(19/68)	70.5 (59.4–81.6)	<0.001
Complete eradication of IM during follow-up^	90 (54/60)*	0 (0/68)	90 (82.4–97.6)	<0.001

* Including 1 patient who died of metastasised lung carcinoma after the second ablation treatment and 1 patient who had cancer diagnosed after the 4th ablation session as failures for complete eradication of dysplasia IM.

^ If, at any follow-up endoscopy biopsies showed IM or LGD, this was considered a failure for persistence of complete eradication during follow-up.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments
Sharma (2009)[4] **Case series** USA Recruitment period: 2006–2007 Study population: patients with LGD or HGD n=**63 (39 with LGD, 24 with HGD)** Median age: 71 years Sex: 90.5% male Patient selection criteria: patients with dysplasia confirmed by 2 independent pathologists; patients with a history of prior ablative therapy for BO were excluded Technique: use of HALO^{360} at 12 J/cm^2 (each area treated twice); HALO^{90} for focal ablation, if needed (each area received 4 applications of energy); esomeprazole was given until metaplasia was eradicated. Median follow-up: **24 months** Conflict of interest/source of funding: Mayo Clinic where these were performed has received grants from BÂRRX Medical for trials involving ablation of BO.	Number of patients analysed: **38 LGD** Focal ablation was used for ablation of residual BO in the last study year. The study does not report the distribution of patients treated by either circumferential, focal ablation or both types of ablation. ***Complete response at last follow-up (median 24 months)***[2] A CR was defined as an absence of metaplasia or dysplasia in all biopsies. **LGD % (n=38)** CR (eradication of)-IM: 86.8% (33/38)[3] CR (eradication of)-dysplasia: 94.7% (36/38) [2] This figure was written as 24 months in text and 23 months in a table. [3] 10 patients achieved complete response with a single ablation session; of 5 with a partial response, 3 had metaplasia only and 2 had possible dysplasia.	***Complications in patients with LGD*** There were 2 minor events: - 1 had minor self-limited bleeding that did not require intervention - 1 patient with a history of severe peptic stricture had a mild symptomatic stricture after the first ablation but this was treated successfully with balloon dilation. **Buried columnar glands** No buried glands were detected.	**Follow-up issues**: • 1 patient with LGD was not available for follow-up biopsy (no more details reported). • Biopsies were completed at 3-month intervals and every 1 cm of BO. **Study design issues**: • All consecutive patients treated at the Mayo Clinic in Arizona. • Patients had a median of 1 circumferential and 1 focal ablation sessions. 51% (20/39) patients had combination of focal and circumferential ablation. **Study population issues**: • There may be an overlap of patients with Fleischer (2008). **Other issues:** Data on HGD patients, not an indication for this overview, are not presented here.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details

Studies of patients with no dysplasia

Sharma VK (2007)[5], Fleischer (2008, 2010)[6, 7]

Case series (2 phases)

USA

Recruitment period: 2003–2009

Study population: patients with 2–6 cm of BO with histologically confirmed intestinal metaplasia without dysplasia

n=**102 (dosimetry phase I 32, effectiveness phase II 70)**

Mean age: 56 years

Sex: 79% male in phase II

Patient selection criteria: Phase I and II: 18–75 years, diagnosis of BO (without dysplasia), with histopathological confirmation within 6 months, BO length 2–3 cm (dosimetry phase) 2–6 cm (effectiveness phase).

Phase II: patients with CR-IM at 2.5-year follow-up were eligible for 5-year biopsy.

Technique: after proximal extent of BO confirmed by endoscopy, HALO^{360} system (BÂRRX Medical) used at 10 J/cm^2, delivered twice for all patients (dosimetry cohort: 6–12 J/cm^2). Esomeprazole 40 mg given twice daily for 1 month, and 40 mg daily

Key efficacy findings

Number of patients analysed: **102 (32 in dosimetry phase and 70 in effectiveness phase)** with mean

1.5 circumferential ablation procedures

95% (59/ 62) patients positive for metaplasia at 12 months were treated with mean 1.9 focal ablations.

Treatment response:

Dosimetry study, 12-months follow-up, n=31

BO eradication response rate	Per protocol	ITT
Complete (100%)	61% (19/31)	59% (19/32)
Partial (50–99%)	26% (8/31)	25% (8/32)
No response 90–5%)	16% (5/31)	16% (5/32)

CR-IM (defined as negative biopsy in all specimens) **in effectiveness phase.**

		% with CR/BO eradication (n)	
Follow-up	**n**	Per protocol	ITT
12 months	69	70 (48/69)	69 (48/69)
30 months (with focal ablation)[5]	61	98 (60/61)	97 (60/61)
5 year[6]	50	92 (46/50)	

CR-IM after single session salvage focal RFA

8% (4/50) patients who had focal NDBO at 5 years had a single session of RFA 1 month after biopsy, and all were CR-IM at subsequent re-biopsy 2 months after RFA.

All patients had CR-IM at either the 5-year biopsy or after a single salvage focal ablation.

Key safety findings

Complications in dosimetry phase

	First treatment % (n=32)	**Repeat treatment % (n=26)**
Mucosal scarring (resolved at 3 and 12 months)	3 (1/32)	4 (1/26)
Chest pain	9 (3/32)	
Linear mucosal injury	3 (1/32)	
Fever		12 (3/26)
Hypotension (sedation related)		4 (1/26)
Nausea (sedation related)		4 (1/26)
Abdominal pain/constipation		4 (1/26)

Events not dose related, transient and resolved spontaneously. 1 of the 3 fever events occurred 42 days after treatment but was unrelated to the procedure (time of occurrence for other events not reported).

Complications in effectiveness phase (both first and second treatments) after circumferential ablation reported in 26.7% (16/70) patients at 2.5 years follow-up[5]

	Treatment sessions % (n)
Total	**22 (24/106)**
Fever	2 (2/106)
Chest/throat pain	8 (9/106)
Linear mucosal injury	1 (1/106)
Mild bleeding	1 (1/106)

Comments

Follow-up issues:

- In phase I, 1 patient chose not to continue follow-up.
- In phase II, 69 and 61 patients were available for follow-up at 1 and 2.5 years (3 could not be located, 1 moved, 1 had financial constraints, 3 had no metaplasia at 1 year so chose not to continue.) At 5 years' follow-up, of 70 original participants, 20 patients were excluded because they: were unable to be located (n=3), withdrew consent (n=3), declined follow-up (n=12), died (n=1) and developed intestinal metaplasia (n=1).

Study design issues:

- 5–8 centre prospective case series
- Recruitment of patients not described.
- ITT analysis for 12-month follow-up attributed a 'no response' outcome for patients not available for follow-up.
- 26 patients in the dosimetry study and 36 patients in the effectiveness study had a second procedure as BO was detected at 1- and 3-month follow-up.

Study population issues:

- The authors presented characteristics between those who completed 12-month follow-up and those who remained in the study. There did not appear to be differences in sex, age, body weight, BO length or presence of

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<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>for 1 year. All patients assessed by endoscopy and biopsy at 1- and 3-month follow-up per protocol.

Phase II: Focal ablation with HALO^{90} (BÂRRX Medical) used at 12 J/cm ^{2} and 40 W/cm^{2} at 1-year follow-up in those with positive Barrett's or columnar lined oesophagus; 40 mg of esomepraxole given daily for 30 months to control reflux for 2.5 years of study. 40 mg of esomepraxole daily for 2 months was given before 5-year visit.

If NDBO was identified at 5-year follow-up, focal RFA was performed 1 month later and re-biopsy 2 months later to assess histological response[6].

Follow-up: 5 years (50 patients)
2.5 years (61 patients; 69 completed 12 months of follow-up)

Conflict of interest/source of funding: study was supported by by a grant from BÂRRX Medical and supported by AstraZeneca.</td>
<td>CR-IM Kaplan–Meier survival analysis

The probability of maintaining CR-IM for at least 4 years after first durable CR-IM was 0.91 (95% CI 0.77 to 0.97), whereas the mean duration of CR-IM was 4.22 (SE 0.12) years.</td>
<td>
<table>
<tr><td>Mucosal scarring</td><td>1 (1/106)</td></tr>
<tr><td>Transient airway obstruction</td><td>1 (1/106)</td></tr>
<tr><td>Nausea related to sedation</td><td>8 (8/106)</td></tr>
<tr><td>Hypotension related to sedation</td><td>1 (1/106)</td></tr>
</table>
All outcomes were transient and resolved completely.
There were 4 events in 3 (4.9%) patients after 115 focal ablations (at 2.5 years follow-up)
<table>
<tr><th></th><th>No. of patients</th></tr>
<tr><td>Chest pain</td><td>1</td></tr>
<tr><td>Nausea or vomiting</td><td>2</td></tr>
<tr><td>Sedation-related hypotension</td><td>1</td></tr>
</table>
There were no strictures at 2.5 and 5 years follow-up.
6% (3/50) patients had erosive oesophagitis at 5-year follow-up.
1 patient reported a globus sensation 1 week after 5-year salvage focal ablation, which resolved without intervention.

Buried columnar glands

No buried glands or dysplasia were detected.
</td>
<td>hiatal hernia.
Other issues:
Fleischer et al. (2008, 2010) report the 2.5- and 5-year follow-up, of the effectiveness phase, of a trial described by Sharma et al. (2007) with 1-year follow-up.
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Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details

Studies of patients with both low-grade and no dysplasia

Lyday WD (2010)[8]

Case series (Multicentre-Registry)

USA

Recruitment period: 2004–2008

Study population: patients with confirmed IM with/without dysplasia on biopsy of a BO.

BO length : mean 3 cm in both cohorts

n=**429 (ND-IM 326, ID 12, LGD 52, HGD 39)**

Age: cohort A – mean 59 years, cohort B-mean 60 years

Sex: cohort A – 71% male, cohort B – 91% male

Patient selection criteria: patients who underwent RFA and had histological confirmation of IM with/without dysplasia.

Exclusion criteria: patients with invasive cancer and negative margins

Technique: stepwise RFA (primarily ablation with circumferential RFA, secondary with focal RFA as necessary at 40 W/cm^2, 10 or 12 J/cm^2) with follow-up endoscopies and oesophageal biopsies every 2–4 months. EMR was done >8 weeks

Key efficacy findings

Number of patients analysed: **Cohort A 338 patients biopsied once after initial treatment** (ND-IM 255, IND 10, LGD 42, HGD 31), **cohort B 137 patients biopsied at least once after 1 year** (ND-IM 110, IND 4, LGD 13, HGD 10)

Histological complete response

	Cohort A^ (median follow-up 9 months)	**Cohort B^^ (median follow-up 20 months)**
CR-D*, % (n)	89 (74/83)	100 (27/27)
CR-IM in dysplasia patients % (n)	63 (52/83)	78 (21/27)
Overall CR-IM** % (n)	72 (244/338)	77(105/137)
CR-IM in ND-IM patients % (n)	75 (192/255)	76 (84/110)
CR-IM in LGD % (n)	71 (30/42)	85 (11/13)
CR-D in LGD % (n)	95 (40/42)	100

*CR-D (defined as all biopsies negative for Indefinite dysplasia [IND], LGD, HGD at last biopsy session)

** CR-IM (defined as all biopsies negative for IM at last biopsy session)

^ Cohort A included patients with at least 1 biopsy session after initial treatment

^^ cohort B patients with at least 1 biopsy session >1 year after initial treatment

Treatment failure was reported in 3 patients (0.9%) in cohort A within 2–4 months of primary RFA (1

Key safety findings

Safety cohort (all patients n=429)

No serious adverse events (bleeding, perforation, death)

Adverse event	**% (n)**
Stricture (resolved with dilation, mean 3)	2.1 (9/429)
Transient bradycardia during endoscopy	0.7 (3/429)
Superficial mucosal injury during endoscopy (no intervention needed)	0.2 (1/429)
Mild fever (postop day 1, managed with antibiotics, resolved in 48 hours)	0.2 (1/429)
Bloody tinged mucus vomit (observed in recovery room, discharged without complication)	0.2 (1/429)
Mild self-limiting bleeding during endoscopy	1 (4/429)

No buried glands were detected on follow-up biopsies.

Comments

Follow-up issues:

- Patients in cohort B had longer follow-up than cohort A.
- Authors state that it is unclear what percentages of patients were lost to follow-up and what percentage had incomplete follow-up because of timing.
- Authors state that greater attrition of failures before inclusion in the longer-term cohort could have resulted in over-estimates of complete response rates for cohort B and partly contribute to the greater efficacy seen in this group.

Study design:

- Retrospective multicentre study in 4 community-based gastroenterology practices.
- Diagnosis was confirmed by independent pathologists.
- 788 RFA procedures were done, 429 were primary and 359 were secondary.
- Biopsy acquisition methodology, treatment and follow-up biopsy sessions were not standardised. Patients had a mean 1.8 (in cohort A) and 2.1 (in cohort B) RFA procedures and a median of 1 follow-up biopsy session (in cohort A) and 2 sessions (in cohort B) after last treatment.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments
before ablation in 7 patients. Follow-up: **median 9 months (Cohort A); median 20 months (cohort B)** Conflict of interest/source of funding: 1 author gives lectures and conducted teaching sessions on behalf of BÂRRX Medical.	from LGD to IMC, 1 from HGD to IMC and 1 from HGD to T1sm1 oesophageal adenocarcinoma). In cohort B 1 patient (0.7%) with non-dysplastic-IM (ND-IM) did not achieve CR-IM by 1 year and then showed LGD.		

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments
Krost RJ (2013)[9] **Case series (single centre)** USA Recruitment period: 2007–2011 Study population: follow-up of successfully ablated patients during a phase II clinical study of RFA for BO by endoscopic and histological surveillance **n=53 (40 NDBO, 4 LGD, 4 HGD, 4 IND, 1 adenocarcinoma)** Age: median 59 years Sex: 64% (37/53) males Patient selection criteria: Technique: RFA and surveillance. Patients underwent scheduled endoscopic follow-up according to rigorous protocol depending on patients' pre-ablation histological diagnosis. Recurrence was confirmed histologically by a systematic biopsy protocol (4 quadrant biopsies). PPI dose was maintained at a level that provided relief from reflux symptoms. **Follow-up: median 18 months (range 3–50 months)** Conflicts of interest/source of funding: none	Number of patients analysed: **53** 151 follow-up endoscopies were performed (1–5 per patient) and 2492 biopsies evaluated, of which 604 (24%) were from the gastro-oesophageal junction. **Recurrence of BO** (defined as recurrence of a grossly visible columnar lining within the tubular oesophagus with histological confirmation of IM) 26% (14/53) 3 distinct patterns after successful initial ablation: 1. <u>visible recurrence in the tubular oesophagus</u> in 6% (3/53) patients who had NDBO before ablation. In all cases, active oesophagitis and biopsies confirmed IM; timing not clearly described 2. <u>buried glands</u> (defined as glandular epithelium present underneath stratified squamous epithelium) detected in 6% (3/53) patients (2 NDBO and 1 HGD before ablation) (all endoscopically invisible) 3. <u>intestinal metaplasia at the gastro-oesophageal junction</u> (with a squamous lined tubular oesophagus) in 19% (10/53) patients (9 NDBO and 1 HGD before ablation). **Post-ablation gastro-oesophageal reflux control** 64% (34/53) were maintained on elevated PPI dose used for ablation. 28% (15/53) PPI dose reduced to less than they were taking before ablation. 8% (4/53) had fundoplication and hiatal hernia repair (2 after successful ablation, 1 before ablation and 1 after a failed ablation). **Dysplasia or cancer was not detected at follow-up.**		**Study design:** • Majority of the patients had NDBO. • 1 adenocarcinoma was removed using EMR before ablation. • Patients with IM of the gastro-oesophageal junction without a columnar lined oesophagus were not included in this study. Those identified at follow-up did not undergo further ablation because they did not meet the definition of BO when the protocol was written. • Hiatal hernia repair and fundoplication were done at investigators' discretion but were symptom directed. **Other** • The median length of initial columnar segment was 3 cm and median hiatal hernia size was 2 cm.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments
Santos RS (2010)[10] **Case series (retrospective)** USA (2 centres) Recruitment period: 2006–2008 Study population: with symptomatic GERD and Barrett's metaplasia or LGD **n=14 (NDBO 11, LGD 3)** Age: median 60 years Sex: 71% (10/14) male Technique: RFA (with HALO^{360} or 90) initially performed, and if BO present, retreated 1 more time, and ARS (fundoplication) undertaken after 6 weeks. Repeat RFA was done after 3 months if necessary. Patients with giant hiatal hernias had fundoplications before RFA and RFA given after 3 months. **Median follow-up: 17 months** Conflicts of interest/source of funding: none	Number of patients analysed: **14** Mean number of ablation procedures: 2.6 (range 1–6) Mean length of BO decreased from 6.2 to 1.2 cm after treatment (p=0.001) Before treatment, 93% (13/14) patients had circumferential BO, and after treatment only 1 patient had BO (P=0.001). Histological severity decreased significantly (p=0.003), mean grade from 2.2 to 1.5. After combined treatment, there were 50% (7/14) patients with persistent Barrett's metaplasia and 50% (7/14) with complete resolution of Barrett's metaplasia. The number of RFA treatments was significantly associated with success (p<0.05). Patients receiving 3 or more RFA treatments had complete resolution of Barrett's metaplasia.	**Complications after ARS (perioperative):** 1 pneumonia after repair of giant hiatal hernia 1 atrial fibrillation (resolved in hospital). **Complications of RFA** 1 patient had mild dysphagia 2 months after ablation, requiring dilation.	**Study design:** • Small sample size • 1 patient had a large hiatal hernia. • EMR both before and after ARS was done in 4 patients. • 3 patients underwent endoscopic fundoplication, 11 had laparoscopic fundoplication. • Histological findings graded as 1 to 5, with 1 representing normal mucosa and 5 cancer.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments
Goers TA (2011)[11] **Case series (retrospective)** **USA** Recruitment period: January 2008 to December 2009 Study population: with GORD scheduled for ARS because of failure/dislike of medical therapy with confirmed BO; and considered failures to ablate because of anatomical distortion of the oesophagus. **n=10 (7 NDBO, 3 LGD)** Age: mean 58 years Sex: 70% (7/10) male Mean length of BO: 6.4 cm. Technique: endoscopic RFA (using HALO^{360} (8) or HALO^{90} (2) at 10/12 J/cm^2. After ablation, hiatal hernia repair and laparoscopic fundoplication was performed. PPI were given. **Follow-up: mean 17 months (range 7–28 months)** Conflicts of interest/source of funding: none	Number of patients analysed: **10** Mean number of ablations: 4.39. 60% (6/10) patients had major hiatal hernias. **Resolution of BO** 60% (6/10) patients had 100% resolution at post-operative endoscopy after concomitant treatment. 40% (4/10) patients had >50% resolution and had subsequent ablation. At follow-up endoscopy, 3 had residual BO and further ablation resulted in complete control and 1 patient had columnar epithelium with no IM at 24 months' follow-up. All patients were free of BO at last follow-up. **Symptomatic evaluation** Symptomatic results showed that 4 patients had substantial dysphagia to solids and other symptoms were minimal.	**Complications due to RFA** 1 stricture (noted on first endoscopy at day 48 for mild solid food dysphagia) (treatment details not reported). 1 perforation 1.5 cm within the proximal RFA field (noted 6 weeks postoperatively because of report of a food impaction). Further details not reported. **Complications of fundoplication** 1 patient reported heartburn in the long term.	**Follow-up issues** • 8 patients completed 1-year follow-up and 4 completed 24-month follow-up. **Study design:** • Patients with HGD were excluded. • Standardised gastrointestinal assessment tool was used. • 1 patient had oesophagitis at diagnosis. • 7 patients had multiple pre-procedure ablations because of persistent BO. 3 new patients with BO had ARS because of failed medical therapy.

Abbreviations used: ARS, antireflux surgery; BO, Barrett's oesophagus; CI, confidence interval; CR, complete response; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IM, intestinal metaplasia; IND, indefinite dysplasia; NDBO, non-dysplastic Barrett's oesophagus; ND-IM, non-dysplastic intestinal metaplasia; ITT, intention to treat; LGD, low-grade dysplasia; PPI, proton pump inhibitor; RCT, randomised controlled trial; RFA, radiofrequency ablation; VAS, visual analogue scale

Study details	Key efficacy findings	Key safety findings	Comments
Haidry R et al (2013)[12] United Kingdom (19 centres) **HALO RFA Registry** July 2008- August 2012. n= 335 patients with BO and neoplasia (72% [241/335] with HGD, 24% [82/335] with intramucosal cancer, **4% [12/335] with low-grade dysplasia** Mean age, 69 years; Sex: 81%(271/335) male Inclusion criteria: patients referred for ablative management of dysplastic BO, older than 21 years with no contraindications to endoscopy were included. Technique: nodules were removed by EMR and patients underwent RFA every 3 months until all areas of BO were ablated or cancer developed. Biopsies collected 12 months after first RFA. **Follow-up (mean, 27 months).** Conflicts of interest/source of funding: 1 author received grant support from BARRX Medical Inc and Covidien plc.	**Low-grade dysplasia** 12 patients in the registry underwent ablation for LGD. 83% (10/12) achieved CR-D and have no dysplasia at their most recent follow-up (mean, 27 months).		Only outcomes of patients with BO with LGD from this large series of patients in UK have been reported here.

Efficacy

Low-grade dysplasia

Complete response

A randomised controlled trial of 127 patients with non-nodular dysplastic Barrett's oesophagus (64 with low-grade dysplasia and 63 with high-grade dysplasia) compared radiofrequency ablation plus endoscopic surveillance against endoscopic surveillance alone (sham procedure). Among patients with low-grade dysplasia (n=64; 42 treated by radiofrequency ablation, 22 treated by sham procedure), complete eradication of dysplasia was reported in 91% (38/42) of patients treated by radiofrequency ablation, compared with 23% (5/22) treated by sham procedure at 12-month follow-up. Eradication of intestinal metaplasia was reported in 81% (34/42) of patients with low-grade dysplasia who received RFA compared with 4.5% (1/22) of patients who received a sham procedure ($p<0.001$ for all)[1]. Patients randomised to the sham procedure were offered crossover to radiofrequency ablation after 12 months. After crossover, complete eradication of all dysplasia and intestinal metaplasia was reported in 98% (51/52) of patients with low-grade dysplasia at 2-year follow-up. At 3-year follow-up, dysplasia was eradicated in 100% (32/32) of patients[2].

An RCT of 136 patients with low-grade dysplasia comparing RFA (n=68) against endoscopic surveillance (control, n=68) reported that the low-grade dysplasia patients treated with RFA were less likely to progress to high-grade dysplasia or adenocarcinoma (2% [1/68] compared with 27% [18/68], $p<0.001$) of patients in the control group, and less likely to progress to adenocarcinoma (2% [1/68] compared with 9% [6/68], $p=0.026$) of patients in the control group at 3-year follow-up. At the end of the treatment, complete eradication of dysplasia and intestinal metaplasia occurred in 93% (63/68) and 88% (60/68) of patients respectively in the RFA group (data not given for the control group). During follow-up, complete eradication of dysplasia and metaplasia was maintained in 98% (62/63) and 90% (54/60) of patients respectively compared with 28% (19/68) ($p<0.001$) and 0% ($p<0.001$) of patients respectively in the control group[3].

A case series of 63 patients (39 with low-grade dysplasia, 24 with high-grade dysplasia) reported complete response of intestinal metaplasia in 87% (33/38) of patients with low-grade dysplasia and complete response of dysplasia in 95% (36/38) of patients with low-grade dysplasia at a median follow-up of 24 months[4].

Prevention of progression to cancer

The RCT of 127 patients reported less progression from low-grade dysplasia to high-grade dysplasia in patients treated with RFA (5% [2/42]) compared with those treated by a sham procedure (14% [3/22], $p=0.33$) at 12-month follow-up. No patients with low-grade dysplasia progressed to cancer in either the

intervention or the sham group[1]. In the crossover study, Kaplan– Meier analysis showed that dysplasia remained eradicated in more than 85% of patients and intestinal metaplasia in more than 75% without maintenance RFA[2].

No dysplasia

Complete response

A case series of 102 patients with no dysplasia (32 in a dosimetry phase and 70 in an effectiveness phase) reported complete eradication of metaplasia and dysplasia in 59% (19/32) of patients in a dosimetry phase and 69% (48/70) of patients in an effectiveness phase at 12-month follow-up (results were based on intention-to-treat analysis)[5]. In the effectiveness phase study at 30 months' follow-up, after additional focal ablation in patients with endoscopic and histological evidence of intestinal metaplasia at 12-month biopsy, complete response of intestinal metaplasia was achieved in 97% (60/61) of patients[6]. At 5-year follow-up, 92% (46/50) of these patients demonstrated complete response of intestinal metaplasia, whereas 8% (4/50) of patients had non-dysplastic intestinal metaplasia and were treated with single salvage focal ablation after 1 month and achieved complete response of intestinal metaplasia at subsequent 2-month biopsy[7].

A case series of 429 patients in the mixed-grade dysplasia group reported that in cohort A (n=338) complete response of intestinal metaplasia and complete response of dysplasia were achieved in 72% (224/338) and 89% (74/83) of patients respectively at a median follow-up of 9 months. Subgroup analysis reported that complete response of intestinal metaplasia was achieved in 75% (192/255) of patients with non-dysplastic intestinal metaplasia and 63% (52/83) of patients with dysplasia, and complete response of dysplasia in 89% (74/83) of patients. In cohort B (n=137), complete response of intestinal metaplasia and complete response of dysplasia were achieved in 77% (105/137) and 100% (27) of patients respectively at a median follow-up of 20 months. Subgroup analysis reported that complete response of intestinal metaplasia was achieved in 76% (84/110) of patients with non-dysplastic intestinal metaplasia and 78% (21/27) in patients with dysplasia[8].

Recurrence

A case series of 53 patients (40 non-dysplastic Barrett's oesophagus) reported that recurrent or persistent intestinal metaplasia was detected in 26% (14/53) of patients in 3 different forms. These included visible recurrence in the tubular oesophagus in 6% (3/53) of patients with non-dysplastic Barrett's oesophagus, buried glands (defined as glandular epithelium present underneath stratified squamous epithelium) in 6% (3/53) of patients (2 non-dysplastic Barrett's oesophagus and 1 high-grade dysplasia before ablation) and intestinal metaplasia at the gastro-oesophageal junction (with a squamous lined tubular

oesophagus) in 19% (10/53) of patients (9 non-dysplastic Barrett's oesophagus and 1 high-grade dysplasia before ablation)[9].

Low-grade dysplasia and no dysplasia (concomitant treatments)

A case series of 14 patients (11 non-dysplastic Barrett's oesophagus, 3 low-grade dysplasia) treated with concomitant RFA and anti-reflux surgery (fundoplication) reported that 50% (7/14) of patients achieved complete resolution of Barrett's metaplasia at a mean follow-up of 17 months[10].

A case series of 10 patients (7 non-dysplastic Barrett's oesophagus and 3 low-grade dysplasia) treated with concomitant RFA and laparoscopic reflux surgery (fundoplication) reported 100% Barrett's oesophagus resolution at a mean follow-up of 17 months[11].

Safety

Perforation

Perforation of the oesophagus (measuring 1.5 cm) within the proximal RFA field (noted 6 weeks postoperatively because of a report of 'a food impaction') was reported in 1 patient in a case series of 10 patients. Further details were not reported[11].

Gastrointestinal hemorrhage

Gastrointestinal haemorrhage was reported in 1 patient being treated by antiplatelet therapy for heart disease in the RFA group in the randomised controlled trial of 127 patients. This was treated endoscopically[1].

Oesophageal stricture

Oesophageal strictures were reported in 12% (8/68) of patients treated with RFA (time of occurrence not reported) in the randomised controlled trial of 136 patients: all were successfully treated with endoscopic dilatation (in median 1 session)[3].

Oesophageal strictures were reported in 7.6% (9/119) of patients treated with ablation (time of occurrence not reported) in the crossover cohort study of 119 patients[2]. This is a follow-up of a multicentre randomised sham controlled trial of 127 patients[1]. All were successfully treated with endoscopic dilatation (in mean 2.6 sessions).

A mild symptomatic stricture after primary circumferential ablation successfully treated with balloon dilation in a patient with low-grade dysplasia and a history of a severe peptic stricture was reported in the case series of 63 patients[4].

Strictures were reported in 2% (9/429) of patients (in 788 procedures) in a registry of the 429 patients in the mixed-grade dysplasia group. All strictures resolved with a median 3 dilations[8].

Erosive oesophagitis

Erosive oesophagitis (transient and resolved completely) was reported in 6% (3/50) of patients at 5-year follow-up in a case series of 70 patients[7].

Chest pain

Overnight hospitalisation for new chest pain was reported in 1 patient (8 days after procedure) in the RFA group in the randomised controlled trial of 127 patients (outcome not reported)[1]. Chest pain (transient and resolved spontaneously) was reported in 8% (9/106) of procedures in the case series of 70 patients[5].

Nausea and discomfort

Hospitalisation for nausea and chest discomfort immediately after RFA was reported in 1 patient in the crossover cohort study of 119 patients (outcome not reported)[2]. Nausea related to sedation (that resolved spontaneously) occurred in 8% (8/106) of procedures in the case series of 70 patients[6].

Fever

Fever (transient and resolved completely) was reported in 2% (2/106) of procedures undertaken in the case series of 70 patients[6].

Validity and generalisability of the studies

- Two studies presented data for patients with only low-grade dysplasia, 2 studies included patients with non-dysplastic Barrett's oesophagus and a few other studies included patients at various stages of Barrett's oesophagus.
- The evidence included in this overview includes 1 RCT of low-grade dysplasia patients comparing the procedure with a sham group and 1 RCT comparing the procedure with endoscopic surveillance. There are no studies comparing this treatment with alternative treatments. All other studies included were case series with short- to medium-term follow-up.
- Some studies used focal ablation if residual metaplasia or dysplasia was detected at follow-up.
- Two studies with very few patients were on concomitant treatments (RFA and anti-reflux surgery).

- There appears to be some duplication of patients reported in some of the included studies.

Existing assessments of this procedure

British Society of Gastroenterology

The British Society of Gastroenterology guidelines (2013) on the diagnosis and management of Barrett's oesophagus and related early neoplasia included the following recommendations for management of dysplasia or early cancer:

Indefinite for dysplasia

Patients with a diagnosis of indefinite for dysplasia should be managed with optimisation of antireflux medication and repeat endoscopy in 6 months. If no definite dysplasia is found on subsequent biopsies, then the surveillance strategy should follow the recommendation for non-dysplastic Barrett's oesophagus (Recommendation grade C: evidence obtained from expert committee reports, or opinions or clinical experience of respected authorities in the absence of directly applicable clinical studies).

Low-grade dysplasia

Management of low-grade dysplasia is unclear in view of limited data about the natural history. It is essential that the diagnosis is confirmed by 2 pathologists, and patients should be surveyed endoscopically at 6-monthly intervals. Currently, ablation therapy cannot be recommended routinely until more data are available (Recommendation grade C).

All patients with dysplasia or early cancer, for whom therapy is considered, should be discussed with a specialist multidisciplinary team for oesophago-gastric cancer. This team should include an interventional endoscopist, upper gastrointestinal cancer surgeon, radiologist and a gastrointestinal pathologist (minimum standard) (Recommendation grade C).

Patients with dysplasia or early cancer should be informed of treatment options and have access to consultation with all specialists as required (Recommendation grade C)[13].

Blue Cross and Blue Shield of Alabama

The Blue Cross and Blue Shield of Alabama policy statement (2013) recommends that for patients with low-grade dysplasia, the benefit of RFA is less certain, because the rate of progression to cancer is variable in the literature. There are no high-quality trials that treat patients with an initial diagnosis of low-grade dysplasia and report improved outcomes. However, based on the available evidence, specialty society guidelines, and the results of clinical vetting, it is

possible to define a population with a higher risk of progression by having the initial low-grade dysplasia diagnosis confirmed by an additional pathologist who is an expert in gastrointestinal pathology. In this subpopulation of patients with low-grade dysplasia, it is likely that the benefit of treatment outweighs the risk. As a result, RFA of low-grade dysplasia may be considered medically necessary when the initial diagnosis of low-grade dysplasia is confirmed by an expert in gastrointestinal pathology.

Non-dysplastic Barrett's oesophagus has a relatively low rate of progression to cancer. Although available research reports that non-dysplastic metaplasia can be eradicated by RFA, the risk/benefit ratio and the net effect on health outcomes is uncertain. It is possible that the risk of RFA exceeds the benefit in this population, owing to the low underlying rates of progression and the reported rates of oesophageal strictures after RFA. For patients with non-dysplastic BE, it cannot be concluded that the benefit of RFA outweighs the risk, and therefore RFA is considered investigational for this population[14].

The Blue Cross and Blue Shield of Alabama Technology Evaluation Center (TEC) (2010) assessment of RFA plus surveillance versus surveillance alone in the treatment of non-dysplastic or low-grade dysplastic Barrett's esophagus reported that the available evidence is insufficient to show that RFA plus surveillance achieves a better net health outcome than surveillance alone among patients with non-dysplastic or low-grade dysplastic Barrett's esophagus. The body of evidence on disease progression is too small and of a too short duration to permit conclusions about the effects of RFA on this outcome among patients with non-dysplastic or low-grade dysplastic Barrett's esophagus[15].

American Gastroenterological Association

The American Gastroenterological Association Medical Position Statement (2011) on the management of Barrett's esophagus recommends that endoscopic RFA should also be a therapeutic option for treatment of patients with confirmed low-grade dysplasia. Although endoscopic eradication therapy is not suggested for the general population of patients with Barrett's esophagus in the absence of dysplasia, they suggest that RFA, with or without endoscopic mucosal resection, should be a therapeutic option for select individuals with non-dysplastic Barrett's esophagus who are judged to be at increased risk for progression to high-grade dysplasia or cancer, but that specific criteria that identify this population have not been fully defined at this time[16].

Medical Services Advisory Committee (MSAC) Australia

The Medical Services Advisory Committee (MSAC)'s assessment on the safety and effectiveness of RFA for Barrett's oesophagus with low-grade dysplasia, high-grade dysplasia and early intramucosal cancer (2010) concluded that RFA was safe for the treatment of Barrett's oesophagus with dysplasia and/or early IMC, with few major complications after multiple treatment sessions. Most

adverse events were minor and resolved with no intervention. Lack of comparative data prevented the direct comparison of RFA with the specified comparators in patients with low-grade dysplasia, high-grade dysplasia and intramucosal cancer. As a result, it reported that conclusions cannot be drawn as to whether RFA is safer, and as effective or more effective, than surveillance or argon plasma coagulation in patients with low-grade dysplasia [17].

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Minimally invasive oesophagectomy. NICE interventional procedure guidance 407 (2011). Available from http://guidance.nice.org.uk/IPG407 This replaces previous guidance on Thoracoscopically assisted oesophagectomy. NICE interventional procedure guidance 189 (2006).
- Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia. NICE interventional procedure guidance 355 (2010). Available from http://guidance.nice.org.uk/IPG355
- Photodynamic therapy for Barrett's oesophagus. NICE interventional procedures guidance 350 (2010). Available from http://guidance.nice.org.uk/IPG350 This replaces previous guidance on Photodynamic therapy for Barrett's oesophagus. NICE interventional procedure guidance 82 (2004).
- Epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedure guidance 344 (2010). Available from http://guidance.nice.org.uk/IPG344 This guidance is currently under review and is expected to be updated in 2014. For more information, see http://guidance.nice.org.uk/IPG344
- Photodynamic therapy for early-stage oesophageal cancer. NICE interventional procedure guidance 200 (2006). Available from http://guidance.nice.org.uk/IPG200

Clinical guidelines

- Ablative therapy for the treatment of Barrett's oesophagus. NICE clinical guideline 106 (2010). Available from http://guidance.nice.org.uk/CG106

Pathway

- Barrett's oesophagus. NICE Pathway (2012)

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Professor Hugh Barr, Dr Laurence Lovat, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; Dr Pradeep Bhandari, British Society of Gastroenterology.

- Two specialist advisers perform this procedure regularly and 1 has performed it at least once.
- The specialist advisers had a range of opinions about the procedure's status: 1 considered it to be an established procedure, whereas 1 thought it to be novel and of uncertain safety and efficacy, and 1 thought it a minor variation of an existing procedure.
- All advisers stated that less than 10% of specialists are engaged in this area of work.
- Comparators listed include surveillance endoscopy and argon plasma coagulation.
- Theoretical and anecdotal adverse events listed include bleeding, perforation, stricture, laceration, chest and back pain, and dysphagia.
- Key efficacy outcomes include eradication of dysplasia, eradication of intestinal metaplasia, eradication of Barrett's oesophagus, quality of life and development of cancer. Two advisers stated that there is uncertainty whether the procedure is effective and will prevent cancer. One adviser stated that large studies with longer-term follow-up are needed. One adviser stated that there are major issues about the correct diagnosis of low-grade dysplasia and non-dysplasia.
- The procedure should be performed in specialist centres with access to the full spectrum of therapeutic endoscopies, support facilities (in case of complications) and cancer network multidisciplinary teams to discuss cases.
- Training should involve hands-on courses, mentoring at a specialist centre and regularly performing complex therapeutic upper gastrointestinal endoscopy,

advanced endoscopic imaging, endoscopic ultrasound, endoscopic resection, radiofrequency ablation and lesion recognition.

- There is a UK National HALO Patient Registry (with 20 centres and over 800 patients) for Barrett's oesophagus. There are not many patients with low-grade dysplasia and almost none with non-dysplastic Barrett's oesophagus. The majority have high-grade dysplasia or intramucosal cancer.
- One adviser stated that there are some slight variations in practice in terms of energy delivered but these are minor details. One adviser stated that the evidence on low-grade dysplasia is building up and needs more studies.
- Two advisers stated that the likely speed of diffusion is slow but 1 adviser stated that it will be adopted widely by all specialist centres in the UK. Another adviser stated that if approved for low-grade dysplasia, the number of patients treated will increase significantly. He also stated that the cost-benefit ratio is unlikely to support the approval for non-dysplastic dysplasia but suggests that there may be specific groups (for example, people with a strong relevant family history) in whom there might be a case for treatment.
- Specialist advisers had a range of opinions about the potential impact of this procedure on the NHS ranging from major to minor impact.

Patient commentators' opinions

NICE's Public Involvement Programme sent 18 questionnaires to 2 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 2 completed questionnaires. The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

- Ongoing studies:
  - NCT01360541: Radiofrequency ablation versus endoscopic surveillance in the management of low-grade dysplasia in Barrett's oesophagus: multicentre randomised controlled trial, location: France, sample size:

120 patients, start date: 2010, completion date: 2018, primary outcome: prevalence of low-grade dysplasia 3 years after randomisation (study currently recruiting patients).

- NCT00848237: UK National HALO Patient Registry: Ablation of Barrett's esophagus – a multicentre patient registry, study type: interventional, location: USA, patients: patients with Barrett's esophagus (non-dysplastic intestinal metaplasia, low-grade dysplasia and high-grade dysplasia), sample size: 10,000 patients, start date: 2007, completion date: 2014, primary outcomes: clearance rate for Barrett’s oesophagus, intestinal metaplasia and dysplasia, subsquamous intestinal metaplasia at 1 year, adverse event incidence and quality of life at 12 months.
- ISRCTN93069556: UK National HALO Patient Registry (with 20 centres): A national patient registry for radiofrequency ablation (RFA) for Barrett’s oesophagus: a UK prospective multicentre trial with long-term follow-up on radiofrequency ablation of Barrett’s columnar lined oesophagus and squamous dysplasia, sample size: 1000 patients, start date: 2008, completion date: 2018, principal investigators: Dr LB Lovat and Professor SG Bown, funded by BAARX Medical Inc (USA).

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3. Nadine Phoa K, van Vilsteren FGI, Weusten B LAM, Bergman J et al (2014). Radiofrequency ablation reduces neoplastic progression in patients with Barrett's oesophagus and low-grade dysplasia: A randomised, controlled trial**.** *JAMA*; 311(12):1209-1217.

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6. Fleischer DE, Overholt BF, Sharma VK et al. (2008) Endoscopic ablation of Barrett's oesophagus: a multicentre study with 2.5-year follow-up. Gastrointestinal endoscopy 68: 867–76.

7. Fleischer DE, Overholt BF, Sharma VK et al. (2010). Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 42 (10): 781–789.

8. Lyday WD, Corbett FS, Kuperman DA et al. (2010). Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. Endoscopy 42 (4): 272–278.

9. Korst RJ, Santana-Joseph S, Rutledge JR et al. (2013). Patterns of recurrent and persistent intestinal metaplasia after successful radiofrequency ablation of Barrett's esophagus. Journal of Thoracic & Cardiovascular Surgery 145 (6): 1529–1534.

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11. Goers TA, Leao P, Cassera MA et al. (2011). Concomitant endoscopic radiofrequency ablation and laparoscopic reflux operative results in more effective and efficient treatment of Barrett esophagus. Journal of the American College of Surgeons 213 (4): 486–492.

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17. Gurgacz S, Church J, Cameron A et al. (2010). Radiofrequency ablation for Barrett's oesophagus with dysplasia MSAC Application 1143, Assessment Report. Commonwealth of Australia, Canberra, ACT.

Appendix A: Additional papers on endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Caillol F, Bories E et al (2012). Radiofrequency ablation associated to mucosal resection in the oesophagus: experience in a single centre. Clinics & Research in Hepatology & Gastroenterology 36 (4) 371-377.	Comparative study EMR+RFA (n=16: 13 HGD, 3 LGD) vs RFA alone (n=18: 14 LGD, 3ND, 1 HGD) Group 1: Mean follow-up was 15 months Group 2: Mean follow-up was 10 months	In group 1, high-grade dysplasia (HGD) was eradicated in 12 cases (92%), low-grade dysplasia (LGD) in 3 cases (100%). Complete response occurred in 9 cases (56%), partial response in 100% of cases. In group 2, HGD was eradicated in 1 patient (100%), LGD in 3 patients (64%). A complete response was achieved in 8 patients, partial response in 4 cases (77%).. The complication rate for groups 1 and 2 was of 18% and 10% respectively. No complication prevented completion of treatment or continued monitoring. Recurrence was 5% in both groups. RFA associated with EMR is feasible, offering probably better results and a very important advantage: a more complete histology before follow-up. Our results show effective treatment of BO and associated dysplasia with a low rate of complication.	2 groups had different numbers of BD grading patients. Not a useful comparison.
Curvers WL, ten Kate FJ, Krishnadath KK, et al (2010). Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. American Journal of Gastroenterology 105 (7) 1523-1530.2010.		LGD in BE is an overdiagnosed and yet underestimated entity in general practice. Patients diagnosed with LGD should undergo an expert pathology review to purify this group. In case the diagnosis of LGD is confirmed, patients should undergo strict endoscopic follow-up or should be considered for endoscopic ablation therapy.	Natural history of LGD
Das A, Wells C et al (2009). An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. Endoscopy 41 (5) 400-408.		Within the limits of the model, ablation for nondysplastic Barrett's oesophagus is more cost-effective than endoscopic surveillance. Clinical trials of ablative therapy in nondysplastic Barrett's oesophagus are needed to establish its effectiveness in reducing cancer risk.	costs
Dulai PS, Pohl H, et al (2013). Radiofrequency ablation for long- and ultralong-segment Barrett's esophagus: a	Case series (retrospective review) n=72 (34 ULSBE, 38	Eradication rates for dysplasia (90% vs 88%, P = 1.0) and intestinal metaplasia (IM) (77% vs 82%, P = .77) were similar. ULSBE patients required more overall (P < .01) and circumferential (P < .01) RFA;	Efficacy results presented for mixed indications

comparative long-term follow-up study. Gastrointestinal Endoscopy 77 (4) 534-541.2013.	LSBE) LGD=9 ND =9 RFA	however, stricture rates were identical (14%). There was no dysplasia recurrence, and IM recurrence was similar (ULSBE, 23%; LSBE, 16%; P = .52). At 3 years, IM remained eradicated in 65% of ULSBE and 82% of LSBE, without maintenance RFA. On multivariate regression analysis, increasing Barrett's length was associated with a reduced likelihood for eradicating IM (odds ratio 0.87; 95% CI, 0.75-1.00), but not dysplasia (odds ratio 1.13; 95% CI, 0.95-1.35)	
Eldaif SM, Lin E, Singh KA et al. Radiofrequency ablation of Barrett's esophagus: short-term results. Annals of Thoracic Surgery 87 (2) 405-410.410.	Case series n=27 (no dysplasia, 2 LGD) Follow-up = 8 weeks	Short term results shows that RFA for BE I safe and effective and achieves 100% replacement of intestinal metaplasia. No mortality, dysphagia or strictures at follow-up.	Larger studies with longer follow-up included in table 2.
Ertan A, Zaheer I et al (2013). Photodynamic therapy vs radiofrequency ablation for Barrett's dysplasia: Efficacy, safety and cost-comparison. World Journal of Gastroenterology 19 (41) 7106-7113.2013.	Comparative study PDT (33 HGD) vs 53 RFA (47 LGD, 6 HGD)	One patient with PDT had an oesophageal perforation and was managed with non-surgical measures and no perforation was seen with RFA. PDT was 5 times more costly than RFA at our institution. The 2 groups were not randomized and had different BD grading are the limitations of the study. RFA had higher rate of CR-D without any serious adverse events and was less costly than PDT for endoscopic treatment of BD.	2 groups had different BD grading. not a useful comparison.
Fleischer DE, Odze R et al (2010). The case for endoscopic treatment of non-dysplastic and low-grade dysplastic Barrett's esophagus. [Review]. Digestive Diseases & Sciences 55 (7) 1918-1931.	Review	Currently, there is no type of treatment for dysplastic or non-dysplastic BE that achieves a complete response in 100% of patients, eliminates all risk of developing cancer, results in zero adverse events, is less expensive in terms of absolute costs than surveillance, is durable for 20+ years, or eliminates the need for surveillance. Regardless, RFA shows established safety, efficacy, durability, and cost-effective profiles that should be considered in the management of patients with non-dysplastic or low-grade dysplastic BE.	Review- opinion article
Fernandez-Esparrach, G. and Panes J Radiofrequency ablation for nondysplastic Barrett's esophagus: to treat or not to treat? Gastroenterology 140 (7) 2130-2132.2132.			Summary and comment on Felischer 2010 and reply by authors.

Fischer-See S, Lenglinger J, Reza, A et al (2013). Effect of radiofrequency ablation (RFA) for the elimination of Barrett's esophagus. European Surgery - Acta Chirurgica Austriaca.Conference: 54th Annual Meeting of the Austrian Society of Surgery Vienna Austria.Conference Start: 20130530 Conference End: 20130601.Conference Publication: (var.pagings).45 (pp S125-S126), 2013.Date of P (var.pagings) S125-S126.2013.	Conference abstract n=127 NDBE=124 LGD=3 RFA (26 had antireflux surgery before RFA)	Severe procedure related complications (n = 5/161; 3.1 %) included 1 perforation, which were successfully repaired by Nissen fundoplication and stenting; and 1 pulmonary embolism, 1 cardiac arrhythmia, 2 cases of pleuritis, which were managed by conservative therapy. Follow up (15 days-1 year) included 107 persons. NDBE was eliminated in 71.7 % (76/107), 84.1 % (90/107), and 86.9 % (93/107) after 1,2, and 3 RFA treatment sessions, respectively. LGD + NDBE was eliminates in all 3 LGD positive persons after 3 RFA sessions. No patient progressed to dysplasia or cancer	Larger studies included in table 2. Safety outcomes covered already.
Force S D. and Miller DL. (2008). Esophageal radiofrequency ablation for the treatment of intestinal metaplasia, low grade dysplasia, and high grade dysplasia. [Review] [10 refs]. Seminars in Thoracic & Cardiovascular Surgery 20 (4) 305-309.	Review on technique, clinical studies and recommendations	Radiofrequency ablation (RFA) has more recently been studied to eradicate IM and dysplasia of the oesophagus. This manuscript will review the technique, clinical results, and recommendations for RFA	Reports mixed indications. Not systematic review.
Gray NA, Odze RD, and Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. [Review]. American Journal of Gastroenterology 106 (11) 1899-1908.1909.	Systematic review PDT , RFA for BE PDT 22 papers RFA 18 papers	9 articles describing 34 patients with neoplasia appearing in buried metaplasia (31 after PDT). 5 articles describing a baseline prevalence of buried metaplasia (before ablation) ranging from 0% to 28%. In 22 reports on PDT for 953 patients, buried metaplasia was found in 135 (14.2%); in 18 reports on RFA for 1,004 patients, buried metaplasia was found in only 9 (0.9%). A major problem limiting the conclusions is that they do not describe how frequently biopsy specimens contained sufficient subepithelial lamina propria to be informative for buried metaplasia. Endoscopic ablation can bury metaplastic glands with neoplastic potential but, even without ablation, buried metaplasia often is found in areas where Barrett's epithelium abuts squamous epithelium. Buried metaplasia is reported less frequently after RFA than after PDT. However, available reports do not provide crucial information on the adequacy of biopsy specimens and, therefore, the frequency and importance of buried metaplasia after endoscopic ablation remain unclear.	Reports frequency buried metaplasia. Although results are reported separately for PDT and RFA, RFA analysis included studies of various histology grading. Relevant large studies from this review are included in table 2. Others in Appendix A.

Gurgacz S, Church J et al (2010). Radiofrequency ablation for barrett's oesophagus with dysplasia (Structured abstract). Health Technology Assessment Database (4).	HTA report reviews safety and effectiveness of RFA for patients with BO with LGD, HGD, and IMC.	safety: 5 studies, suggest RFA is safe. 23 complications occurred in 411 patients after multiple treatment sessions, most were minor resolved without intervention. Efficacy: 6 studies, comparative analysis from 1 RCT found that CR-IM rates lower in control LGD group (4%) compared to RFA group (81%).CR-D rates was also lower in the control group (23% vs 90%). EMR was done in 20, all achieved complete eradication at 24 months.	Results reported separately for each group. Included in existing assessments.
Gaddam S, Muthusamy R, and Sharma P (2011). The controversy regarding ablation for Barrett's esophagus without dysplasia. [Review]. Current Opinion in Gastroenterology 27 (4) 368-373.	Review	Recent studies have shown endoscopic ablation therapies to be relatively safe and effective in the eradication of NDBE. It is possible that if future data can affirmatively answer some of these questions, ablation of NDBE would be reasonable in selected patients; however, until then, a wait and watch approach is likely to be the best option for most low-risk patients	Discusses management options, gaps and challenges.
Hernandez JC, Reicher S, Chung D et al. (2008) Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia. Endoscopy 40:388-392.	Case series n = 10 (7 non-dysplastic, 2 LGD, 1 HGD) Follow-up = 12 months (range 3-38 months)	Complete eradication of BO in 7 patients and partial in 3. Buried metaplasia in 10% patients was found and successfully re-ablated.	Larger studies in table 2.
Hur C, Choi SE et al (2012). The cost effectiveness of radiofrequency ablation for Barrett's esophagus. Gastroenterology 143 (3) 567-575.		By using updated data, initial RFA might not be cost effective for patients with BE without dysplasia, within the range of plausible rates of progression of BE to EAC, and be prohibitively expensive, from a policy perspective. RFA might be cost effective for confirmed and stable LGD. Initial RFA is more effective and less costly than endoscopic surveillance in HGD.	costs
Jo Y. (2012). New consensus on the management of Barrett's dysplasia and early stage esophageal adenocarcinoma: Limited evidence, but best available guidance. Journal of Neurogastroenterology and Motility.18 (4) 455-456.		Consensus guideline focused on HGD and oesophageal adenocarcinoma rather than low-grade dysplasia. In addition it has new informative statements updated from previous guideline for BE.	Summary on guidelines and comment
Korst RJ. and Lee BE (2012). The use of radiofrequency ablation for patients with nondysplastic Barrett's esophagus. Journal of Thoracic & Cardiovascular Surgery			Letter to editor

143 (4) 992-993.			
Klaus Mönkemüller, MD, PhD. Radiofrequency Ablation for Barrett Esophagus With Confirmed Low-Grade Dysplasia. *JAMA*. 2014;311(12):1205 doi:10.1001/jama.2014.2512			Editorial on low grade dysplasia.
Max Almond L (2013). Management controversies in Barrett's oesophag. J Gastroenterol	Systematic review on current management of dysplastic BE and IMC with attention to areas of controversy.	A significant body of evidence exists to support early endoscopic therapy for high-grade dysplasia (HGD). Although not supported by randomised controlled trial evidence, endoscopic therapy is now favoured ahead of oesophagectomy for most patients with HGD. Focal intramucosal (T1a) carcinomas can be managed effectively using endoscopic and surgical therapy, however surgery should be considered the first line therapy where there is submucosal invasion (T1b). Treatment of low-grade dysplasia is not supported at present because of widespread over-reporting of the disease. The role of surveillance endoscopy in non-dysplastic Barrett's remains controversial.	Areas of clinical controversy discussed.
Menon D, Stafinski T, Wu H et al (2010). Endoscopic treatments for Barrett's esophagus: a systematic review of safety and effectiveness compared to esophagectomy. [Review].BMC Gastroenterology 10 111.	Systematic review on all endoscopic treatments. Includes RFA (16 studies) with/without dysplasia.	Some radiofrequency ablation (RFA) or argon plasma coagulation (APC) studies (used in multiple sessions) reported rates of almost 100% for complete eradication of dysplasia. Endoscopic treatments offer safe and effective alternatives to oesophagectomy for patients with Barrett's oesophagus and high-grade dysplasia. Unfortunately, shortcomings in the published studies make it impossible to determine the comparative effectiveness of each of the endoscopic treatments	Results of mixed indications.
Okoro NI, Tomizawa et al (2012). Safety of prior endoscopic mucosal resection in patients receiving radiofrequency ablation of Barrett's esophagus. Clinical Gastroenterology & Hepatology 10 (2) 150-154.	Comparative case series (retrospective analysis) Group 1, n=44 (EMR before RFA) vs group 2, n=46 (RFA alone) Only 3 LGD in group 1 and 13 in group 2. 2 ND in group 1 and 25 in group 2.	Compared incidence of complications and histological outcomes between groups. Stricture rates were 14% in group 1 and 9% in group 2 (odds ratio, 1.53; 95% confidence interval [CI], 0.26-9.74). The rates of CR-IM were 43% in group 1 and 74% in group 2 (odds ratio, 0.33; 95% CI, 0.14-0.78). The rates of complete resolution of dysplasia were 76% in group 1 and 71% in group 2 (odds ratio, 1.28; 95% CI, 0.39-4.17). The adjusted odds ratio for CR-IM in group 1 (adjusting for age, segment length, and grade of dysplasia) was 0.50 (95% CI, 0.15-1.66) Stricture rates among patients who receive only RFA are comparable to those of patients who had prior EMR. EMR appears safe to perform before	Comparison of outcomes in the 2 treatments groups provided for mixed indications. Breakdown of initial and final pathology available for 2 groups but not useful to make any judgement as very small sample size in 1 group compared to the other.

		RFA.	
Orman ES, Kim H P et al. Intestinal metaplasia recurs infrequently in patients successfully treated for Barrett's esophagus with radiofrequency ablation. American Journal of Gastroenterology 108 (2) 187-195.196.	Case series (retrospective) n=262 RFA for dysplastic BE or IMC follow-up=397 days	In patients with BE and dysplasia or early cancer who achieved CE-IM, BE recurred in 5%/year. Patient characteristics did not predict recurrence. Subjects undergoing RFA for dysplastic BE should be retained in endoscopic surveillance	Pre-treatment histology grading not clear.
Pouw RE, Gondrie JJ, Sondermeijer CM et al. (2008) Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. Journal of Gastrointestinal Surgery 12:1627–1636.	Case series (2 no dysplasia, 10 LGD, 32 HGD) n = 44 Median follow-up: 21 months	97.7% (43) of patients had eradication of metaplasia and dysplasia after a median of 1 circumferential ablation and 2 focal ablation sessions at median 21 months of follow-up. no recurrences of dysplasia.	Results for ND, LGD, HGD not reported separately.
Pouw RE, Gondrie JJ et al. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. Journal of Gastrointestinal Surgery 12 (10) 1627-1636.1636.	Case series n=44 2 LGD, 12 HGD, 16 IMC Follow-up =21 months	CR-IM 40/44 (91%). 4 required EMR 1 circumferential and 2 halo sessions. Adverse events: non transmural laceration-3, dysphagia 4, fever-1, chest pain-2, superficial mucosal laceration 1.	Efficacy results for mixed indications
Pouw RE, Visser M, Odze RD et al (2014). Pseudo-buried Barrett's post radiofrequency ablation for Barrett's esophagus, with or without prior endoscopic resection. Endoscopy 46 (2) 105-109.	Histological evaluation in 69 Barrett's patients treated with RFA Frequency of buried glands in biopsies obtained after RFA compared with biopsies from normal squamous epithelium.	A total of 2515 biopsies were obtained from neosquamous epithelium during follow-up post-RFA. Buried glands were found in 0.1 % of biopsies from endoscopically normal neosquamous epithelium. However, when small islands of columnar mucosa were biopsied, buried glands were detected in 21 % of biopsies.	Not sure if patient population had low grade dysplasia or no dysplasia Barrett's oesophagus.
Roorda AK, Marcus SN, and Triadafilopoulos G. (2007) Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia. Diseases of the Esophagus 20:516-522.	Case series n = 13 (3 HGD, 4 LGD, 6 non-dysplastic) Follow-up = mean 12 months	Mean 1.4 ablations with no serious adverse events. Complete eradiation of BO in 46% (6/13) and of dysplasia in 71% (5/7) No buried intestinal metaplasia	Larger studies in table 2.
Rees Jonathan RE, Lao-	Systematic	Ablative therapies have an increasing	Includes medical

Sirieix et al (2010). Treatment for Barrett's oesophagus. Cochrane Database of systematic Reviews (1)	Review of pharmacological, surgical and endoscopic treatments for dysplasia and non dysplastic BE and prevention of progression to adenocarcinoma. RCTs only.	role in the management of dysplasia within Barrett's and current data would favour the use of RFA compared with photodynamic therapy. RFA has been shown to yield significantly fewer complications than photodynamic therapy and is very efficacious at eradicating both dysplasia and Barrett's itself. However, long-term follow-up data are still needed before radiofrequency ablation can be used in routine clinical care without the need for very careful post-treatment surveillance.	surgical and endoscopic treatments. 1 study on RFA for LGD (Shaheen 2009) included in table 2.
Sharma VK, Kim HJ, Das A et al. (2008) A prospective pilot trial of ablation of Barrett's esophagus with low-grade dysplasia using stepwise circumferential and focal ablation (HALO system). Endoscopy 40:380-387.	Prospective case series n = 10 (LGD) Follow-up = 2 years	At follow-up, there was a complete response for dysplasia in all and complete response for intestinal metaplasia in 9 (90%). CR-D 100% No strictures or buried intestinal metaplasia. 1 coffee ground emesis, no intervention required.	Efficacy results for mixed indications Larger studies in table 2.
Sharma P, Falk GW et al (2009). Management of nondysplastic Barrett's esophagus: where are we now? [Review] American Journal of Gastroenterology 104 (4) 805-808.2009.		No proof that any strategy will decrease the cancer risk of patients with BE without dysplasia. Endoscopic surveillance can be performed as suggested by the American College of Gastroenterology. In the clinical setting, endoscopic ablation of nondysplastic BE cannot be recommended at this time.	Review-opinion article
Shaheen NJ. and Frantz DJ (2010). When to consider endoscopic ablation therapy for Barrett's esophagus. [Review] [34 refs]. Current Opinion in Gastroenterology 26 (4) 361-366.		The excellent efficacy, side-effect profile, and cost-effectiveness appear to make RFA the intervention of choice in cases of high-grade dysplasia. RFA for low-grade dysplasia may be of value in young patients and/or those with long segment or multifocal disease. Treatment of nondysplastic Barrett's oesophagus is of uncertain value. PDT appears to have a higher stricture rate and to be more expensive than RFA.	Review- Not systematic but opinion article
Shaheen NJ, Peery AF, Hawes RH et al (2010). Quality of life following radiofrequency ablation of dysplastic Barrett's esophagus. Endoscopy 42 (10) 790-799.	Analysed changes in QoL in the AIM Dysplasia Trial (RCT) 10-item questionnaire was completed by patients at baseline and 12 months. 127 patients were randomized to RFA (n=84) or sham (n=43). Of those randomized,	At baseline, most patients reported worry about oesophageal cancer (71% RFA, 85% sham) and oesophagectomy (61% RFA, 68% sham). Patients also reported depression, impaired QoL, worry, stress, and dissatisfaction with the condition of their oesophagus. Compared with the sham group, patients treated with RFA had significantly less worry about oesophageal cancer (P=0.003) and oesophagectomy (P=0.009). They also had significantly reduced depression (P=0.02), general worry about the condition of their oesophagus (P<=0.001), impact on daily QoL (P=0.009), stress (P=0.03), dissatisfaction with the condition of their oesophagus (P<=0.001), and impact on	Results not stratified according to dysplasia grading.

	117 patients completed the study to the 12-month end point.	work and family life (P=0.02). study reporting significant advantages favouring radiofrequency ablation over sham on 8 of 10 instrument subscales.	
Semlitsch T, Jeitler K et al (2010). A systematic review of the evidence for radiofrequency ablation for Barrett's esophagus. [Review]. Surgical Endoscopy 24 (12) 2935-2943.	Systematic review BE and metaplasia or dysplasia with/without EMR follow-up= 12 months	radiofrequency ablation with the HALO system could be a promising method associated with a low complication rate, low risk of stricture formations, and a minor probability of buried glands. To evaluate the potential benefit at a higher level of evidence, randomized controlled trials (RCTs) involving a direct comparison with other more established endoscopic methods such as photodynamic therapy are necessary	Includes all histological types of dysplasia (HGD, LGD, ND, IMC). Relevant large and longer follow-up studies included in table 2, others in Appendix A.
Vahabzadeh B, Rastogi, A et al (2011). Use of a plastic endoprosthesis to successfully treat esophageal perforation following radiofrequency ablation of Barrett's esophagus. Endoscopy 43 (1) 67-69.	Case report	Procedural complication identified immediately and treated endoscopically with stent placement. The patient was successfully treated with conservative measures and surgical intervention was avoided.	Pre-treatment histology not clear.
Vassiliou MC, von Renteln D et al (2010). Treatment of ultralong-segment Barrett's using focal and balloon-based radiofrequency ablation. Surgical Endoscopy 24 (4) 786-791.	Case series n=25 6LGD, 15 HGD, 3 IMC Follow-up= 20.3 months	CR-IM 11/14 (79%), CR-d 13/14 (93%). Self-limiting haemorrhage 1, stricture 1-required dilation, postprocedural nausea 2. Two patients regressed from HGD to IM, and 1 patient with IMC had residual HGD and was treated with repeat EMR. The number of ablations in this group was 2.5	Efficacy results for mixed indications
Velanovich, V (2009). Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: initial results and lessons learned. Surgical Endoscopy 23 (10) 2175-2180.	Case series n=66 LGD/HGD Follow-up=12 months	CR-IM=79% CR-D=89% strictures-4.	Efficacy results for mixed indications
Veeramachaneni, N (2011). Radiofrequency ablation for nondysplastic Barrett's esophagus: should we do it, because we can? Journal of Thoracic & Cardiovascular Surgery 142 (5) 1173-1174.			Commentary
Wani S, Puli SR et al (2009).Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: A meta-analysis and systematic review. American Journal of	Systematic review and meta-analysis Determines cancer incidence in BE patients after ablation	Compared to historical reports of the natural history of BE, ablation may be associated with a reduction in cancer incidence, although such a comparison is limited by likely heterogeneity between treatment and natural history studies. The greatest benefit of ablation was observed in BE patients with HGD.	Reports cancer incidence, all endoscopic therapies included.

Gastroenterology.104 (2) (pp 502-513), 2009.Date of Publication: February 2009. (2) 502-513.	therapy vs no ablation (surveillance).		
Wani, S (2012). Management of low-grade dysplasia in Barrett's esophagus. [Review]. Current Opinion in Gastroenterology 28 (4) 370-376.	Review	Eradication of LGD and intestinal metaplasia can be achieved by radiofrequency ablation as demonstrated in a randomized controlled trial. Although treatment appears to be durable for up to 3 years, progression to HGD and EAC can occur, highlighting the need for close endoscopic surveillance even after EET.	Discusses the various controversies that surround the management of LGD
Xie X, McGregor M, and Dendukuri N (2009). Radiofrequency ablation for treatment of Barrett's esophagus: A systematic review and cost analysis (Structured abstract). Health Technology Assessment Database (4)	Systematic review on RFA for BE patients with HGD and cost analysis of RFA and esophagectomy.	There is sufficient evidence to conclude that RFA is highly effective for extensive high grade oesophageal dysplasia (for at least 2 years) and safer than oesophagectomy. Compared to oesophagectomy RFA is less costly.	Data on LGD from 1 RCT (Shaheen 2009) is included in table 2.

Appendix B: Related NICE guidance for endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia

Guidance	Recommendations
Interventional procedures	**Minimally invasive oesophagectomy. NICE interventional procedure guidance 407 (2011)** This document replaces previous guidance on thoracoscopically assisted oesophagectomy (interventional procedure guidance 189) 1.1 Current evidence on the efficacy and safety of minimally invasive oesophagectomy (MIO) is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit with local review of results. 1.2 Patient selection should be done by a multidisciplinary team specialising in the management of oesophageal cancer. 1.3 MIO is a technically challenging procedure, which should only be carried out by surgeons with special expertise and specific training. They should perform their initial operations with an experienced mentor. 1.4 Clinicians should enter details about all patients undergoing MIO onto the National Oesophago-gastric Cancer Audit (www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/cancer). **Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia. NICE interventional procedure guidance 355 (2010)** 1.1 Current evidence on the efficacy of endoscopic submucosal dissection (ESD) in patients with oesophageal adenocarcinoma or high-grade dysplasia in Barrett's oesophagus is limited in quantity and there are safety concerns specifically regarding the risk of oesophageal perforation. Therefore, in these patients, the procedure should only be used in the context of research. 1.2 Current evidence on the efficacy of ESD in patients with oesophageal squamous carcinoma or squamous dysplasia is limited. This evidence is mostly from Japan where the epidemiology of oesophageal cancer is different from the UK. There are safety concerns specifically regarding the risk of oesophageal perforation. Therefore, in these patients, the procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.3 Clinicians wishing to undertake ESD for oesophageal squamous carcinoma or squamous dysplasia should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended.

	• Audit and review clinical outcomes of all patients having ESD for oesophageal squamous carcinoma or squamous dysplasia (see section 3.1). 1.4 Patient selection should be carried out by an upper gastrointestinal cancer multidisciplinary team. 1.5 The procedure is technically challenging and should be carried out only by clinicians with specific training in the technique. 1.6 NICE encourages further research into the procedure. Studies should define clearly the type, grade and stage of cancer or dysplasia being treated. Efficacy outcomes should include adequacy of resection and the proportion of patients free from local recurrence. Safety outcomes should include perforation and stricture, and the consequences of these complications. **Photodynamic therapy for Barrett's oesophagus. NICE interventional procedures guidance 350 (2010)** This document replaces previous guidance on photodynamic therapy for high-grade dysplasia in Barrett's oesophagus (interventional procedure guidance 82). 1.1 Current evidence on the efficacy of photodynamic therapy (PDT) for patients with Barrett's oesophagus with high-grade dysplasia (HGD) is adequate, provided that patients are followed up in the long term. There are no major safety concerns, although there is a risk of oesophageal stricture, and photosensitivity reactions are common. This procedure may be used in patients with Barrett's oesophagus with HGD provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Current evidence on the efficacy and safety of PDT in patients with Barrett's oesophagus with either low-grade dysplasia (LGD) or no dysplasia is inadequate in quality and quantity, and the balance of risks and benefits is not clear. Therefore, for these patients, the procedure should be used only with special arrangements for clinical governance, consent and audit or research. 1.3 Clinicians wishing to undertake PDT in patients with Barrett's oesophagus with either LGD or no dysplasia should take the following actions. Inform the clinical governance leads in their Trusts. Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. Audit and review clinical outcomes of patients with Barrett's oesophagus other than HGD having PDT (see section 3.1). 1.4 Patient selection should be carried out by a multidisciplinary team experienced in the management of the condition. 1.5 PDT for Barrett's oesophagus should only be carried out by endoscopists with specific training in this procedure.

	Epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedure guidance 344 (2010) This document replaces previous guidance on circumferential epithelial radiofrequency ablation for Barrett's oesophagus (interventional procedures guidance 244). Further recommendations have been made as part of the clinical guideline on Barrett's oesophagus – ablative therapy published in August 2010, as follows: *Consider using radiofrequency ablation alone or photodynamic therapy alone for flat high-grade dysplasia, taking into account the evidence of their long-term efficacy, cost and complication rates.* Clinical and cost-effectiveness evidence was reviewed in the development of this guideline which has led to this more specific recommendation. More information is available from http://guidance.nice.org.uk/CG106. The IP guidance on epithelial radiofrequency ablation for Barrett's oesophagus remains current, and should be read in conjunction with the clinical guideline. This guidance is currently under review and is expected to be updated in 2014. For more information, see http://guidance.nice.org.uk/IPG344 1.1 Current evidence on the efficacy of epithelial radiofrequency ablation (RFA) in patients with Barrett's oesophagus with high-grade dysplasia (HGD) is adequate, provided that patients are followed up in the long term. There are no major safety concerns. Therefore this procedure may be used in patients with Barrett's oesophagus with HGD provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Current evidence on the efficacy and safety of epithelial RFA in patients with Barrett's oesophagus with either low-grade dysplasia (LGD) or no dysplasia is inadequate in quality and quantity, and the balance of risks and benefits is not clear. Therefore, in these patients, this procedure should be used only with special arrangements for clinical governance, consent and audit or research. 1.3 Clinicians wishing to undertake epithelial RFA in patients with Barrett's oesophagus with either LGD or no dysplasia should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of patients with Barrett's oesophagus with LGD or no dysplasia having epithelial RFA (see section 3.1). 1.4 Patient selection for epithelial RFA for Barrett's oesophagus should be done by a multidisciplinary team experienced in the management of Barrett's oesophagus. 1.5 Epithelial RFA for Barrett's oesophagus should only be carried out by

	endoscopists with specific training in this procedure. 1.6 NICE encourages further research into epithelial RFA for Barrett's oesophagus. This should address the balance of risks and benefits of the procedure in patients with Barrett's oesophagus and either LGD or no dysplasia, and long-term outcomes in patients with Barrett's oesophagus of any histological type. **Photodynamic therapy for early-stage oesophageal cancer. NICE interventional procedure guidance 200 (2006)** 1.1 Current evidence on the safety of photodynamic therapy (PDT) for early-stage oesophageal cancer appears adequate. PDT appears efficacious in reducing tumour bulk in carefully selected patients with small early-stage tumours. However, the current evidence is of poor quality and relates only to short-term outcomes; it is therefore not adequate to support the use of this procedure without special arrangements for consent, audit and clinical governance. 1.2 Clinicians wishing to undertake PDT for early-stage oesophageal cancer should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having PDT for early-stage oesophageal cancer (see section 3.1). 1.3 Further research will be useful, and clinicians are encouraged to enter patients into well-designed trials and to collect longer-term follow-up data. The Institute may review the procedure upon publication of further evidence.
Clinical guidelines	**Barrett's oesophagus: ablative therapy for the treatment of Barrett's oesophagus. NICE clinical guideline106 (2010)** Key principles of care 1.1.1 All treatments for high-grade dysplasia and intramucosal cancer in Barrett's oesophagus should be performed by specialist oesophago-gastric cancer teams with the experience and facilities to deliver the treatments recommended in this guideline. Endoscopic therapies 1.1.2 Consider offering endoscopic therapy as an alternative to oesophagectomy to people with high-grade dysplasia and intramucosal cancer (T1a), taking into account individual patient preferences and general health. Endoscopic therapy is particularly suitable for patients who are considered unsuitable for surgery or who do not wish to undergo oesophagectomy. Endoscopic mucosal resection 1.1.3 Consider using endoscopic mucosal resection alone to treat localised lesions.

	1.1.4 Use circumferential endoscopic mucosal resection with care because of the high incidence of stricture formation. 1.1.5 If residual or recurrent disease is suspected, consider additional or repeated therapy with appropriate follow-up using: • endoscopic mucosal resection with further pathological assessment **or** • ablative therapy (radiofrequency ablation or photodynamic therapy) **or** • endoscopic mucosal resection and ablative therapy (radiofrequency ablation, argon plasma coagulation or photodynamic therapy). Ablative therapies 1.1.6 Consider using radiofrequency ablation alone or photodynamic therapy alone for flat high-grade dysplasia, taking into account the evidence of their long-term efficacy, cost and complication rates.[1] 1.1.7 Do not use argon plasma coagulation, laser ablation or multipolar electrocoagulation alone, or in combination with each other, unless as part of a clinical trial. Endoscopic mucosal resection in combination with ablative therapies 1.1.8 If using endoscopic mucosal resection, consider following with an additional ablative therapy (radiofrequency ablation, argon plasma coagulation or photodynamic therapy) to completely remove residual flat dysplasia, taking into consideration the side-effect profiles[1]. Patient and carer support and information 1.1.9 Give patients verbal and written information about their diagnosis, available treatments, patient support groups and the uncertainty of the long-term outcomes of ablative therapies. Give patients time to consider this information when making decisions about their care. 1.1.10 Discuss the multidisciplinary team's views on the range of appropriate treatments with the patient. 1.1.11 Offer patients the opportunity to see the same specialist healthcare team more than once to agree treatment. 1.1.12 Advise patients who have endoscopic therapy that they will need lifelong care and repeated endoscopies. [1] Recommendation linked to IPG344 and IPG350.
Pathway	Barrett's oesophagus. NICE Pathway, October 2012

Appendix C: Literature search for endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	19/03/2014	Issue 3 of 12, March 2014	22
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	19/03/2014	Issue 3 of 12, March 2014	7
HTA database (Cochrane Library)	19/03/2014	Issue 3 of 12, March 2014	11
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	19/03/2014	Issue 3 of 12, March 2014	47
MEDLINE (Ovid)	19/03/2014	1946 to March Week 1 2014	30
MEDLINE In-Process (Ovid)	19/03/2014	March 18, 2014	35
EMBASE (Ovid)	19/03/2014	1974 to 2014 Week 11	56
PubMed			
JournalTOCS	19/03/2014	-	0

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE Strategy:

1 Catheter Ablation/ (20902)
2 (Cathet* adj4 ablat*).tw. (7043)
3 ((needle* or electrode* or heat*) adj4 ablat*).tw. (1028)
4 (Radiofrequen* adj4 ablat*).tw. (10989)
5 (Radio frequen* adj4 ablat*).tw. (670)
6 (Radio-frequen* adj4 ablat*).tw. (670)
7 (RF adj4 ablat*).tw. (2132)
8 RFA.tw. (3100)
9 (Radio* adj4 frequenc* adj4 ablat*).tw. (690)
10 (thin* adj4 layer* adj4 ablat*).tw. (11)
11 (Endoscop* adj4 ablat* adj4 therap*).tw. (120)
12 (circumferen* adj4 ablation*).tw. (326)
13 Esophagoscopes/ (714)
14 Esophagoscope*.tw. (151)
15 ((circumferen* adj4 balloon* or radiofrequen* or radio-frequen*).tw. (23497)

16 c-rfa.tw. (19)
17 (circumferen* adj4 rfa).tw. (9)
18 or/1-17 (35709)
19 exp Barrett Esophagus/ (6319)
20 (Barrett* adj4 (esophagus* or oesophagus* or syndrome* or metaplasia)).tw. (6366)
21 (intestin* adj4 metaplas*).tw. (4395)
22 CELLO.tw. (216)
23 (column* adj4 lin* adj4 esophag*).tw. (321)
24 (column* adj4 lin* adj4 oesophag*).tw. (121)
25 CLO.tw. (2321)
26 Epithelium/su (378)
27 (esophag* adj4 epithel*).tw. (2244)
28 (oesophag* adj4 epithe*).tw. (523)
29 Esophagus/ab (1653)
30 (abnormal* adj4 (esophag* or oesophag*)).tw. (1628)
31 (dysplas* adj4 (esophag* or oesphag*)).tw. (1159)
32 (low-grade* adj4 dysplas*).tw. (1467)
33 no dysplasia.tw. (259)
34 without dysplasia.tw. (466)
35 NDBE.tw. (8)
36 LGD.tw. (337)
37 or/19-36 (20450)
38 HALO 360.tw. (4)
39 HALO 90.tw. (5)
40 Barrx.tw. (8)
41 (Stellartech adj4 coagulation adj4 system).tw. (0)
42 or/38-41 (14)
43 18 and 37 (416)
44 42 or 43 (419)
45 animals/ not human/ (3968230)
46 44 not 45 (407)