NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus

Squamous dysplasia is abnormal cells on the inside lining of the oesophagus (gullet). Itmay 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 December 2013.

Procedure name

- Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus

Specialist societies

- British Society of Gastroenterology
- Association of upper Gastrointestinal Surgeons of GB and Ireland.

Description

Indications and current treatment

Squamous dysplasia of the oesophagus consists of flat premalignant epithelial lesions that may progress to squamous cell carcinoma. Histological features of squamous dysplasia include cellular disorganisation, loss of polarity and downward growth of the epithelium. Cytological abnormalities include hyperchromasia, increased nucleus: to cytoplasm ratio and mitotic activity. The World Health Organization's (WHO) histologic classification of gastrointestinal tumours refers to squamous dysplasia as squamous intra-epithelial neoplasia (defined as non-invasive cytological or architectural alterations that may lead to development of invasive cancer) and categorises it as either low- or high-grade. Low-grade squamous neoplasia is associated with a low risk of progression to invasive squamous cell carcinoma. Histological and cytological changes are moderate and involve the lower half of the epithelium. High-grade intraepithelial neoplasia carries a higher risk of progression to invasive squamous cell carcinoma .Abnormalities involve the upper half of the epithelium, and cytological changes are greater than those in low-grade intraepithelial neoplasia.

Squamous cancer of the oesophagus can be treated by surgery (oesophagectomy) or chemoradiotherapy or a combination of these methods. When the disease is detected at an earlier pre-invasive stage such as carcinoma in situ or high-grade dysplasia then endoscopic treatment is possible. Methods include removal by endoscopic mucosal resection or endoscopic submucosal dissection, and ablation using photodynamic therapy, argon plasma coagulation, laser ablation, cryotherapy, multipolar electrocoagulation or radiofrequency ablation.

What the procedure involves

The aim of endoscopic radiofrequency ablation is to destroy squamous dysplasia in order to allow re-epithelialisation with normal squamous epithelium.

The procedure is usually carried out with the patient under conscious sedation, in an outpatient setting. The area of squamous dysplasia is visualised using an endoscope. Spraying the oesophageal lining with a dye called Lugol's iodine is performed first in order to locate areas of dysplasia that can be difficult to find. An appropriately sized radiofrequency ablation probe attached to the 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 layer of cells in the affected areas. A circumferential (360^{o}) ablation catheter is usually used for primary treatment whereas a focal ablation (90^{o}) catheter can be used for remaining patches of squamous dysplasia in any subsequent treatments. Radiofrequency ablation can also be used after performing endoscopic mucosal resection to remove larger, superficial abnormal areas. If follow-up

endoscopy and re-biopsy show residual changes, repeat treatment can be done using radiofrequency ablation.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus. Searches were conducted of the following databases, covering the period from their commencement to 4-12-2013: 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 squamous dysplasia of the oesophagus.
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 62 patients from 3 case series.

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 squamous dysplasia of the oesophagus

Abbreviations used: CR-D, complete reversal of squamous dysplasia; EMR, endoscopic mucosal resection; ESCN, early esophageal cell neoplasia; ESCC, esophageal squamous cell carcinoma; GI: gastrointestinal; IEN, intraepithelial neoplasia; MGIN, moderate grade squamous intraepithelial neoplasia; HGIN, high grade squamous intraepithelial neoplasia; RFA, radiofrequency ablation; SCC, squamous cell carcinoma; USLs, unstained lesions;

Study details	Key efficacy findings	Key safety findings	Comments
Bergman JJ (2011)[1] **Case series** China (single centre) Recruitment period: October 2008- April 2009 Study population: patients with early esophageal cell neoplasia (ESCN) defined as moderate and high grade squamous intraepithelial neoplasia (MGIN, HGIN) and early flat type (0-11b) esophageal squamous cell carcinoma (ESCC). n = **29** (with MGIN 18, HGIN 10, or ESCC 1) Age: mean 60.3 years Sex: 48% (14/29) male Patient selection criteria: at least 1 USL ≥3cm containing MGIN, HGIN or early flat (type 0-IIb) ESCC, USL-bearing esophagus ≤12cm, no lymphatic invasion or metastatic disease on EUS (all patients) or CT of the chest and upper abdomen (HGIN and ESCC patients) Exclusion: prior endoscopic resection or ablation/radiation or surgery, stricture, or any non-flat mucosa, oesophageal dilation in past 12 months, history of non-SCC of oesophagus, or ESCC (any stage). Technique: Esophageal unstained lesions (USLs) were identified using Lugol's chromoendoscopy. Primary circumferential RFA (HALO^{360}) creating a continuous treatment area including all USLs. At 3-month intervals thereafter, chromoendoscopy with biopsies, followed by focal RFA (HALO^{90}) of USLs, if present. Follow-up: **12 months** Conflict of interest/source of funding: funded by BARRX Medical, USA; and in part by intramural Research Program of the NIH, National Cancer Institute.	Number of patients analysed: **29** Length of treatment area: mean 8.2 cm. Length of unsustained lesions: mean 6.2 cm. **Complete response (CR) at 12 months** (defined as absence of MGIN, HGIN or ESCC from any biopsy in treatment area) 97% (28/29) patients achieved CR at 12-month follow-up endoscopy (4 LGIN, 24 no IEN). **Complete response at 3 months** 86% (25/29) patients achieved CR at 3-month follow-up (1 LGIN, 24 no IEN). **Neoplastic progression** (defined as detection of ESCN of a more severe histological grade) No neoplastic progression was reported at 12-month follow-up. Patient with treatment failure (residual disease) at 12 months had EMR for unifocal disease with clear resection margins.	**Adverse events** No serious adverse events such as perforation, infection, bleeding or death. Mucosal laceration after sizing (required no intervention) was reported in 1 patient. Stricture reported in 14% (4/29) patients after primary ablation (resolved with dilation). Post-ablation symptoms peaked on day 1 and returned to 0 by day 8 after primary ablation and returned to 0 by day 4 after focal ablation.	**Study design issues**: • Prospective cohort study. • Small sample size. • All patients had 2 applications of energy at primary ablation with and without coagulum clearance between ablations and different dose regimens (12J/cm2 or 10J/cm2) were used. • A data and safety monitoring committee monitored the study. • Diagnosis by 2 expert independent GI pathologists blinded to the study. • Chinese classification of squamous neoplasia used. • Post-ablation symptoms monitored using a daily diary assessing chest pain, dysphagia, throat pain, odynophagia and abdominal pain at baseline for 14 days on a visual analogue scale (0-100) with100 representing severe symptoms. **Study population issues**: • Only 1 patient with flat type ESCC included.

Abbreviations used: CR-D, complete reversal of squamous dysplasia; EMR, endoscopic mucosal resection; ESCN, early esophageal cell neoplasia; ESCC, esophageal squamous cell carcinoma; GI: gastrointestinal; IEN, intraepithelial neoplasia; MGIN, moderate grade squamous intraepithelial neoplasia; HGIN, high grade squamous intraepithelial neoplasia; RFA, radiofrequency ablation; SCC, squamous cell carcinoma; USLs, unstained lesions;

Study details	Key efficacy findings	Key safety findings	Comments
Haidry RJ (2013)[2] **Case series** (national registry) United Kingdom Recruitment period: January 2008- March 2013 Study population: patients with squamous high grade dysplasia (HGD) and oesophageal ESCC (T1a) confined to the mucosa n = **20** (with HGD 12, ESCC 8) Age: mean 71.6 years Sex: 20% (4/20) male Patient selection criteria: patients with endoscopic and histological diagnosis of squamous HGD or ESCC confirmed by 2 independent expert GI histopathologists prior to embarking on endotherapy. Technique: a single RFA delivered circumferentially (HALO^{360}) in 16 patients with multifocal dysplasia (limited to median 5cm) or focally (HALO^{90}) in 4 patients with unifocal dysplasia (limited to 1cm) at 12 Jcm^2. At 3-month intervals thereafter, enhanced imaging, chromoendoscopy done and biopsies were reviewed by GI histopathologists. All patients had proton pump inhibitors, co-codamol, and discharged same day after review. Patients with residual disease had ongoing endotherapy after MDT discussion. Follow-up: **median 24 months (n=10)** Conflict of interest/source of funding: part funding from Department of Health's NIHR Biomedical Research Centres funding scheme.	Number of patients analysed: **20** **Complete reversal of squamous dysplasia (CR-D) at 12 months** 50% (10/20) of patients achieved CR at 12-month follow-up endoscopy after a mean 1.5 RFA treatment. 80% (8/10) patients with CR-D were free of dysplasia at a median follow-up of 24 months. **Recurrence** 20% (2/10) of patients had a recurrence after initial successful RFA. 1 progressed to invasive cancer and the other had multifocal low grade dysplasia (LGD). Patient had 4 further RFA procedures but still had LGD at 41-month follow-up. **Progression to cancer** 30% (6/20) patients (4 after first RFA treatment and 2 at 1-year follow-up) progressed to invasive cancer. Using Kaplan Meier analysis, the risk of progression to invasive disease in all 20 patients is 26% at 18-month follow-up. 20% (4/20) of patients had residual dysplasia at 12 months. 1 patient had surgery to remove dysplasia, 2 had further RFA treatments and were free of disease and 1 was lost to follow-up.	**Adverse events** — % (n) Bleeding at follow-up endoscopy after biopsies following iodine application. Treated with adrenaline injection, discharged next day (not RFA-related). — 10 (2/20) Superficial oesophageal tear (after sizing prior to circumferential ablation). Procedure discontinued and focal ablation was used. — 5 (1/20) Endoscopic dilatations for moderate oesophageal stricturing after circumferential ablation (2 needed single dilation, while other 2 needed serial dilations with a median of 4 per patient for symptomatic dysphagia): — 20 (4/20)	**Follow-up issues**: • 1 patient lost to follow-up. **Study design issues**: • Prospective cohort study from 8 tertiary referral centres. • Small sample size. • Only patients who completed treatment protocol were included in the study. • Standardised treatment protocol for 12 months. • Development of invasive cancer was defined as treatment failure. **Study population issues**: • Visible lesions removed by EMR before RFA treatment in 25% (5/20) of patients and 6 EMR procedures and 4 patients after initial treatment. • 8 patients with ESCC included.

Abbreviations used: CR-D, complete reversal of squamous dysplasia; EMR, endoscopic mucosal resection; ESCN, early esophageal cell neoplasia; ESCC, esophageal squamous cell carcinoma; GI: gastrointestinal; IEN, intraepithelial neoplasia; MGIN, moderate grade squamous intraepithelial neoplasia; HGIN, high grade squamous intraepithelial neoplasia; RFA, radiofrequency ablation; SCC, squamous cell carcinoma; USLs, unstained lesions;

Study details	Key efficacy findings	Key safety findings	Comments
van Vilsteren (2011)[3] **Case series** The Netherlands Recruitment period: March 2007 to December 2009 Study population: patients with at-least 1 USL of the oesophagus using Lugol's chromoendoscopy and squamous HGIN/ESCC upon biopsy. n = **13** (10 HGIN, 3 ESCC) Age: median 65 years Sex: 8/13 male Patient selection criteria: at-least 1 USL upon endoscopy with Lugol's staining, squamous HGIN/ESCC upon biopsy of >1 USL, flat (type0-IIb), slightly elevated (type0-IIa), slightly depressed (type0-IIc) USLs according to Paris classification of early gastrointestinal neoplasia, in type0-IIa/IIc lesion EMR>8weeks before RFA, EMR specimens demonstrating, t1m3, negative margins, <T1m2 before RFA, no lymphatic /vascular invasion, no metastasis, informed consent. Technique: RFA with/without prior endoscopic resection. EMR (with ER-cap technique or multiband mucosectomy) was done in nonflat USL. After 2 months, eligible patients had RFA using halo360 at 12J/cm2. For small USLs focal ablation was used at 15J/cm2. Patients were given oral esomeprazole 40mg and sucralfate 5ml for 14 days after EMR/RFA. After initial RFA, endoscopy and biopsies repeated at 2-3 months interval. If negative biopsies, follow-up was done at 6 months and annually thereafter. **Follow-up: median 17 months** Conflicts of interest: none	Number of patients analysed**: 13** Median length of USL was 4 cm and 50% of circumference. **CR-D** (defined as absence of LGIN,HGIN ESCC on all biopsies at 2 months after last treatment) 100% complete response with a median of 2 treatments per patient and remaining disease free at 17-month follow-up.	**Death:** 1 patient died from an unrelated cause (hepatocellular carcinoma) 8 months after reaching CR for neoplasia. **Severe complication** 1 patient (with a narrowed oesophagus after EMR) had an oesophageal perforation and mediastinal abscess 2 days after dilation for a stenosis that developed at 12 days after RFA. This was managed with a covered stent and percutaneous drainage. After removal of the stent a new stenosis was observed distally. This resolved after 12 dilations, intra-lesional corticosteroid injection and incisional therapy. **Moderate complications** 2 strictures in 2 patients resolved after dilations (both related to EMR and 1 developed dysphagia, 1 stenosis). **Mild complications (asymptomatic, required no intervention)** Mucosal laceration (at the endoscopic resection scar) -2 Submucosal hematoma (asymptomatic, needing no intervention) -1	**Study design issues**: • Prospective cohort study from 2 tertiary referral centres. • Small sample size. • Histological evaluation done by experienced pathologists using WHO classification. • Several adjustments were made to the treatment protocol and regimen over the study period. In total12 circumferential ablation and 12 focal RFA sessions were performed. **Study population issues**: • Heterogeneous cohort of patients in terms of histology. • 69% (9/13) required EMR (median 1 resection per patient) at baseline for visible lesions before RFA treatment.

Efficacy

Complete response

A case series of 29 patients (18 with moderate-grade squamous intra-epithelial neoplasia, 10 with high-grade squamous intra-epithelial neoplasia and 1 with early squamous cell carcinoma) treated with radiofrequency ablation reported that 86% (25/29) of patients had a complete response at 3 months and 97% (28/29) had a complete response at 12-month follow-up[1].

A case series of 20 patients (12 with squamous high-grade dysplasia and 8 with early squamous cell carcinoma confined to the mucosa) treated by radiofrequency ablation reported that 50% (10/20) of patients there was no complete reversal dysplasia at 12 months after a median of 1 treatment. Of these patients 80% (8/10) remained dysplasia free at a median follow-up of 24 months[2].

A case series of 13 patients (10 high-grade squamous intra-epithelial neoplasia, 3 oesophageal squamous cell carcinoma) reported that 100% of patients achieved a complete response after a median of 2 radiofrequency ablation sessions and remained disease free at 17-month follow-up[3].

Recurrence

The case series of 20 patients reported that 20% (2/10) of patients had a recurrence after initial successful radiofrequency ablation. In 1 patient this progressed to invasive cancer. The other patient had multifocal low-grade dysplasia and after 4 further radiofrequency ablation procedures still had low-grade dysplasia at 41-month follow-up[2].

Progression to cancer

The case series of 29 patients reported that there was no neoplastic progression (defined as detection of early oesophageal cell neoplasia of a more severe histological grade) at 12-month follow-up[1].

The case series of 20 patients reported that 30% (6/20) of patients progressed to invasive squamous cell cancer (defined as infiltration into the submucosal layer or beyond) at 1-year follow-up[2].

Safety

Oesophageal perforation

One patient (with a narrowed oesophagus after endoscopic mucosal resection) had an oesophageal perforation and a mediastinal abscess that developed 2 days after dilation for a stenosis and 12 days after radiofrequency ablation in a case series of 13 patients. This was managed with a covered stent and

percutaneous drainage. After removal of the stent a new stenosis was observed distally. This resolved after 12 dilations, intra-lesional corticosteroid injection and incisional therapy[3].

Strictures

Oesophageal strictures were reported after circumferential radiofrequency ablation in 20% (4/20) and 14% (4/29) of patients in the case series of 20 and 29 patients. Two strictures (both related to endoscopic mucosal resection and 1 developed dysphagia, 1 developed stenosis) were reported in 2 patients in the case series of 13 patients. Both resolved after dilations[3]. All strictures resolved with endoscopic dilations[1, 2].

Bleeding

Bleeding at follow-up endoscopy after biopsies (not related to radiofrequency ablation) was reported in 10% (2/20) patients in the case series of 20 patients. Patients were treated with adrenaline injection and discharged next day[2].

Superficial esophageal tear

Superficial esophageal tear (after sizing before circumferential ablation) was reported in 1 patient in the case series of 20 patients. The procedure was discontinued and focal ablation was used[2].

Other

Submucosal hematoma (asymptomatic, needing no intervention) was reported in 1 patient in the case series of 13 patients[3].

Mucosal laceration after sizing was reported in 1 patient in the case series of 29 patients. This needed no intervention[1]. Mucosal laceration (at the endoscopic resection scar) was reported in 2 patients in the case series of 13 patients. Both needed no therapy[3].

Validity and generalisability of the studies

- Data on the safety and efficacy of radiofrequency ablation for squamous dysplasia are limited; only 3 prospective case series with few patients were included.
- Patients with early squamous cell carcinoma were also included in the 3 case series because the procedure is relevant in these patients.

- There is lack of long-term follow-up.
- Treatment protocols and the number of ablations varied in the published studies. Two studies used various ablation energy settings.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

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

- 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
- 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).
- 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. Clinical Guideline106 (August 2010) Available from http://guidance.nice.org.uk/CG106

Pathway

- Barrett's oesophagus. NICE Pathway, October 2012 (http://pathways.nice.org.uk/pathways/barretts-oesophagus)

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.

Prof Hugh Barr, Dr Laurence Lovat, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; Dr Krish Ragunath, British Society of Gastroenterology.

- Two specialist advisers perform this procedure regularly and 1 has performed it at least once.
- Two specialist advisers considered the procedure to be novel and of uncertain safety and efficacy while 1 thought it is a variation of an existing procedure.
- All advisers stated that fewer than 10% of specialists are engaged in this area of work.
- One adviser stated that there is no standard practice (comparator) to this procedure, while 2 advisers listed comparator procedures as endoscopic mucosal resection, argon beam coagulation, photodynamic therapy, laser therapy, oesophagectomy, radiotherapy and chemotherapy.
- Theoretical adverse events listed include bleeding, perforation, stricture, laceration, chest and back pain, dysphagia, odynophagia, complications of sedation and progression to cancer.
- Anecdotal adverse events reported include dysphagia, odynophagia, laceration, stricture, post-radiofrequency ablation cancer (pop-up lesions).
- Key efficacy outcomes include eradication of squamous dysplasia and reduction in development of squamous carcinoma of the oesophagus. Two advisers stated that there is uncertainty whether the procedure is effective and will prevent cancer. One adviser stated that there is uncertainty around what

proportion of patients will be cured and when endoscopic resection should be carried out.

- The procedure should be performed in specialist centres with access to the full spectrum of therapeutic endoscopies, support facilities in case of complications and a cancer network multidisciplinary team to discuss cases.
- Training should involve 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 register with fewer than 30 patients with squamous dysplasia (results have been reported in this overview).
- One adviser stated that the optimal power setting and technique for treating squamous dysplasia is still evolving. Another stated that the likely speed of diffusion is slow but 2 advisers stated that if effective the procedure will be adopted by all specialist centres in the UK.
- Specialist advisers had a range of opinions about the potential impact of this procedure on the NHS; 2 considered it to have a minor impact while 1 considered it to be major.

Patient commentators' opinions

NICE's Public Involvement Programme sent 7 questionnaires to 2 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 3 completed questionnaires.

Issues for consideration by IPAC

- Ongoing study:
  ISRCTN93069556: UK HALO Registry (with 20 centres): a national patient registry for radiofrequency ablation 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).

References

1. Haidry RJ, Butt MA et al (2013) Radiofrequency ablation for early oesophageal squamous neoplasia: outcomes from United Kingdom registry. World J Gastroenterol. 2013 September 28; 19(36): 6011-6019. http://www.wjgnet.com/1007-9327/full/v19/i36/6011.htm

2. Bergman JJ, Zhang YM et al (2011). Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus. Gastrointestinal Endoscopy 74 (6) 1181-1190.

3. van Vilsteren FG, Alvarez Herrero L, et al (2011). Radiofrequency ablation for the endoscopic eradication of esophageal squamous high grade intraepithelial neoplasia and mucosal squamous cell carcinoma. Endoscopy; 43: 282-290.

Appendix A: Additional papers on endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus

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
Pouw RE et al (2008). Successful balloon-based radiofrequency ablation of a widespread early squamous cell carcinoma and high-grade dysplasia of the esophagus: a case report. Gastrointestinal Endoscopy 68 (3) 537-541.	n=1 (66 years) Balloon-based RFA for 5-mm large, flat-type ESCC with surrounding HGD in the oesophagus FU: 4 months	Complete endoscopic and histological eradication of HGD and ESCC without adverse events such as dysphagia or esophageal narrowing.	Case report
Zhang YM, Bergman JJ et al (2010). Radiofrequency ablation for early esophageal squamous cell neoplasia. Endoscopy 42 (4) 327-333.			Abstract and full article not available. Relevant article included in table 2.
JM Dunn, S Thorpe, M Novelli, SG Bown, L Lovat Radiofrequency Ablation for the Treatment of Squamous High Grade Dysplasia of the Oesophagus- First Reported Series. Gastrointestinal Endoscopy, Volume 69, Issue 5, April 2009, Page AB255.			Proceedings paper

Appendix B: Related NICE guidance for endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus

Guidance	Recommendations
Interventional procedures	**Photodynamic therapy for Barrett's oesophagus. NICE interventional procedures guidance 350 (2010). Replaces NICE interventional procedure guidance 82 (2004).** 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. **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. **Epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedure guidance 344 (2010).** 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. **Minimally invasive oesophagectomy. NICE interventional procedure guidance 407 (2011) Replaces NICE interventional procedure guidance 189 (2006).** 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.
Clinical guidelines	**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 squamous dysplasia of the oesophagus

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/12/13	Issue 12 of 12, December 2013
Database of Abstracts of Reviews of Effects – DARE (CRD website)	04/12/13	Issue 12 of 12, December 2013
HTA database (CRD website)	04/12/13	Issue 12 of 12, December 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/12/13	Issue 12 of 12, December 2013
MEDLINE (Ovid)	04/12/13	1946 to November Week 3 2013
MEDLINE In-Process (Ovid)	04/12/13	December 03, 2013
EMBASE (Ovid)	04/12/13	-
PubMed	-	-
BLIC	-	-

Trial sources searched on 25/11/2013:

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 25/11/213:

- National Institute for Health and Clinical Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites <<add details>>
- General internet search

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

MEDLINE search strategy

1 Carcinoma, Squamous Cell/
2 Esophageal Neoplasms/
3 (((Earl * adj 4 Squamous* or Esophag* or Oesophag*) adj4 (neoplas* or cancer* or dysplas* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw.
4 (Neoplast* adj4 barrett* adj4 (esophag* or oesophag* or epithelium* or syndrome* or metaplasia*)).tw.
5 ESCN.tw.
6 ESCC.tw.
8 LGIN.tw.
9 MGIN.tw.
10 HGIN.tw.
11 or/1-10
12 Catheter Ablation/
13 (Cathet* adj4 ablat*).tw.
14 ((needle* or electrode* or heat*) adj4 ablat*).tw.
15 (Radiofrequen* adj4 ablat*).tw.
16 (Radio frequen* adj4 ablat*).tw.
17 (Radio-frequen* adj4 ablat*).tw.
18 (RF adj4 ablat*).tw.
19 RFA.tw.
20 (Radio* adj4 frequenc* adj4 ablat*).tw.
21 (thin* adj4 layer* adj4 ablat*).tw.
22 (Endoscop* adj4 ablat* adj4 therap*).tw.
23 (circumferen* adj4 ablation*).tw.
24 ((circumferen* adj4 balloon*) or radiofrequen* or radio-frequen*).tw.
25 c-rfa.tw.
26 (circumferen* adj4 rfa).tw.
27 or/12-26
28 HALO 360.tw.
29 HALO 90.tw.
30 Barrx.tw.
31 (Stellartech adj4 coagulation adj4 system).tw.
32 or/28-31
33 11 and 27
34 32 or 33
35 animals/ not human/
36 34 not 35