Radiofrequency ablation for Barrett's oesophagus with dysplasia

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Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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A new treatment option for the removal of Barrett's mucosa is the endoscopic circumferential HALO^{360} (balloon catheter) or focal HALO^{90} (flat plate catheter) radiofrequency ablation (RFA) system. The purpose of RFA is to thermally destroy the diseased mucosa via radiofrequency energy, allowing for the re-epithelialisation with healthy squamous epithelium (NICE 2010, Rees et al 2010, Shaheen et al 2009). Radiofrequency ablation treatment is generally provided as a day procedure performed by a gastroenterologist under conscious sedation in an outpatient setting.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) was engaged to conduct a systematic review of the literature and an economic evaluation of RFA for Barrett's oesophagus (BO) with dysplasia. An Advisory Panel with expertise in this area then evaluated the evidence presented and provided advice to MSAC on the safety, effectiveness and cost-effectiveness of RFA for BO with dysplasia.

MSAC's assessment of radiofrequency ablation for Barrett's oesophagus with dysplasia

Clinical need

Australian data has identified an increase in the frequency of diagnosis of BO from 2.9 to 18.9 per 1000 endoscopies between 1992 and 2002 (Kendall and Whiteman 2006). According to the Australian Institute of Health and Welfare (AIHW 2010) data 10,160 principle diagnoses of BO were recorded in 2007-08; however, this data is not reported according to the severity of disease or level of dysplasia. There is limited data available regarding the prevalence of BO in Australia. A United States population-based study estimated the prevalence of BO to be 18 per 100,000; however, autopsy studies found the condition to be 21 times more prevalent than estimated (Schulz et al 2000). BO is diagnosed in approximately 10 per cent to 15 per cent of patients with gastro-oesophageal reflux disease (GORD) undergoing endoscopy (AIHW 2010).

This assessment reviews the safety and effectiveness of RFA for patients with BO with low-grade dysplasia (LGD), high-grade dysplasia (HGD) and early intramucosal cancer (IMC).

Significant patient overlap between studies has reduced the amount of literature available for the safety and efficacy analysis within this assessment. In addition, reporting of mixed

patient populations with inappropriate patient groups further decreased the amount of literature available for inclusion. In total, four studies had to be excluded due to cited patient overlap.

Safety

A total of five studies (one randomised controlled trial (RCT) comparing RFA to a sham procedure) were included for the safety analysis. The limited literature currently available suggests RFA for BO with dysplasia and early IMC is safe. A total of 23 complications occurred in 411 patients included in this assessment, following multiple treatment sessions with RFA. Most adverse events were minor and resolved without additional intervention.

Effectiveness

Histological eradication of intestinal metaplasia and dysplasia

A total of six studies were included in the effectiveness analysis. The limited literature suggests RFA is effective for achieving histological eradication of intestinal metaplasia (IM) and dysplasia at a mucosal level. The complete histological eradication of intestinal metaplasia (CR-IM) across all included studies ranged from 54 per cent (Ganz et al 2008) to 91 per cent (Pouw et al 2008). The comparative effectiveness data available from the one RCT (Shaheen et al 2009) included found the CR-IM rates were lower in the control group (4% LGD and 0% HGD respectively), than those of the RFA group (81% LGD and 74% HGD). Additionally, the complete histological eradication of dysplasia (CR-D) rate was also lower in the control group (23%) compared to the RFA group (90%) for patients with LGD. Escape endoscopic mucosal resection due to failure of RFA to achieve histological eradication of IM was performed in 20 (of 411) patients, with results reported in 15 out of the 20 patients. Of those reported, all achieved complete eradication of IM on long-term follow-up (24 months). Additional RFA treatment sessions were required in 5 (of 411) patients.

Disease progression and evidence of subsquamous intestinal metaplasia

Evidence of subsquamous IM was found in five patients (Pouw et al 2008 and Shaheen et al 2009) treated with RFA, of which four occurred in the study by Shaheen et al (2009). This higher rate of subsquamous IM reported in Shaheen et al (2009) may have been identified due to the more rigorous endoscopic work up and follow-up throughout the study.

Economic considerations

The objective of this section was to conduct an economic evaluation of the therapeutic use of RFA in BO with dysplasia. Following advice from the Advisory Panel, it was decided that the treatment of HGD and LGD would be considered separately.

Given there was sufficient evidence of the superior effectiveness of RFA in treating LGD compared to surveillance, a full cost-utility analysis of RFA for the treatment of LGD was undertaken. A decision analytic model was developed to estimate the incremental cost per quality adjusted life year (QALY) of using RFA over surveillance.

Based on a number of estimates and assumptions:

- For LGD, replacing surveillance with RFA would yield an additional benefit of 0.129 QALYs at an additional cost of $10,175. This gave an incremental cost-effectiveness ratio (ICER) for RFA compared to surveillance of $78,975 per QALY.

- The main drivers of the cost-effectiveness result are the probability of eradication of LGD after treatment with RFA, the probability of progressing to cancer from LGD and the cost of RFA.

- In the sensitivity analysis, if the frequency of surveillance is reduced after eradication of low-grade or HGD, the resulting ICER is $71,075.

There was insufficient comparative evidence to undertake a full cost-effectiveness analysis of RFA for the treatment of HGD. A cost analysis was conducted to compare the annual cost of treating HGD with RFA, oesophagectomy, endoscopic mucosal resection (EMR) or argon plasma coagulation (APC).

- Based on an estimated prevalence of 100 cases of HGD, if direct replacement of RFA occurred for oesophagectomy the overall cost savings would be $1,214,588. If RFA was used to treat 100 patients instead of EMR or APC, there would be a total additional cost of $778,156 or $606,155 respectively.

- The cost analysis assumes that RFA, EMR, APC and oesophagectomy are identical in terms of effectiveness and does not take into account any reduction in quality of life that may occur post-surgery with oesophagectomy (for example). Individual patient characteristics may mean that all four treatment options are not interchangeable.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of radiofrequency ablation (RFA), which is a therapeutic device for Barrett's oesophagus (BO) with dysplasia and early IMC. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine, general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for RFA for BO with dysplasia and early IMC.

Background

BO is defined as 'the displacement of the squamocolumnar junction proximal to the gastroesophageal junction with the presence of columnar intestinal metaplasia containing goblet cells', and is a risk factor for oesophageal adenocarcinoma. (Ajumobi et al 2009, Wang and Sampliner 2001). Gastro-oesophageal reflux disease (GORD) is a risk factor for BO and plays an important role in the genesis of the condition (Franchimont et al 2003). Other risk factors for BO include age of onset of GORD symptoms, duration of GORD symptoms, obesity, race and hereditary risk factors (Schulz et al 2000, Sharma et al 2009).

A healthy oesophagus is lined with thin, flat, tile-like squamous epithelial cells. Exposure to stomach acid, particularly as a result of GORD, causes irritation and acts as a noxious stimulus, resulting in metaplasia typical of BO. Metaplasia is the transdifferentiation of the squamous epithelial cells into columnar epithelial cells (Kumar et al 2005). Additionally, metaplasia can progress to dysplasia which is characterised by the presence of immature epithelial cells due to the lack of cell differentiation, and often occurs in a patchy, irregular fashion usually invisible at endoscopy (Van Laethem et al 2001). This change is indicative of the early neoplastic process which can result in adenocarcinoma. Histologically, dysplasia is defined as unequivocal neoplastic alteration of the epithelium not invading the lamina propria and is characterised by cytologic and architectural disarray (Van Laethem et al 2001).

Dysplasia is categorised into three groups: negative, indefinite and positive. The latter comprises low-grade dysplasia (LGD) and high-grade dysplasia (HGD). The cancer risk in LGD is not well-defined but is smaller than that associated with HGD. While most patients with BO do not develop adenocarcinoma in their lifetime, research indicates that HGD, in particular, can progress to cancer (Attwood et al 2003). Adenocarcinoma in BO develops from non-dysplastic metaplasia, followed by increasing grades of dysplasia and eventually adenocarcinoma (Hage et al 2005, Shaheen et al 2009).

The accurate diagnosis of dysplastic BO is an important step in the treatment algorithm. Clinical opinion indicates that multiple biopsies should be taken, and that a consensus on the diagnosis should be reached by two expert pathologists, ideally with an interest in conditions of the upper gastrointestinal (GI) tract. Any disagreement should be addressed by involving a third pathologist in the final decision.

BO prevalence in males is twice that of females and is diagnosed in approximately 10 per cent to 15 per cent of all patients with GORD who are undergoing endoscopy (Sharma et al 2009). It is rare in childhood; the estimated mean age of development is about 40 years, although the mean age at diagnosis is often about 60 years (Terano et al 2002). Australian data suggests that the prevalence of BO has been increasing in recent decades (Kendall, 2006). Many patients develop BO as a result of long-term chronic GORD and these symptoms are ongoing. Barrett's metaplasia alone seldom impacts on patient quality of life (QoL); sufferers often have comorbidities that may affect QoL, including reflux, obesity and smoking-related symptoms. In contrast, patients presenting with oesophageal cancer or HGD typically come to endoscopic detection with persistent heartburn, regurgitation, difficult and/or painful swallowing, recurrent vomiting, persistent weight loss or a sensation of fullness during consumption of food.

Current treatment options include the use of acid-suppressive medications, a range of endoscopic therapies such as endoscopic mucosal resection (EMR), thermal ablation, argon plasma coagulation (APC), electro-coagulation, photodynamic therapy (PDT), and surgery (oesophagectomy).

Acid-suppressing medications and anti-reflux surgery treat the underlying reflux disease, and are not used as primary treatments for BO. The most common acid-suppressing medications are proton pump inhibitors (PPI) including omeprazole, esomeprazole, lansoprazole and pantoprazole. H_2 antagonists may also be used including ranitidine, cimetidine and famotidine.

In the absence of HGD, the management of BO is usually conservative, and includes acid-suppressing therapy and regular endoscopic surveillance.

The development of HGD generally triggers a more aggressive therapeutic approach because of the increased risk of developing adenocarcinoma. Oesophagectomy is the traditional treatment of choice, but has a high morbidity and significant mortality.

Endoscopic ablative techniques are methods of treating patients with BO with HGD and early IMC, avoiding the need for an oesophagectomy. Such treatments have included EMR, PDT and APC. These treatments have significant limitations with regard to practical application and long-term treatment outcomes. The technique of RFA (RFA) is potentially a significant step forward in the endoscopic management of these patients, as it seems to overcome some of the significant shortfalls of previous endoscopic techniques.

Clinical need / burden of disease

On the basis of endoscopically diagnosed cases, the prevalence of BO was estimated to be 18 per 100,000 in a US population-based study (Schulz et al 2000). In autopsy material, however, this condition was found to be 21 times more prevalent, suggesting a considerable underestimation of the prevalence of BO in clinical studies (Schulz et al 2000). BO is diagnosed in approximately 10 per cent to 15 per cent of patients with GORD who are undergoing endoscopy, and has a prevalence of 5.6 per cent in patients without chronic reflux symptoms (Sharma 2009). Australian data has identified an increase in the frequency of diagnosis of BO from 2.9 to 18.9 per 1000 endoscopies between 1992 and 2002 (Kendall and Whiteman 2006). In addition, according to clinical advice from the Advisory Panel, it is estimated that 100 cases of HGD are diagnosed Australia wide per annum (I Brown [Queensland Health] 2010, pers. comm., 5 August).

The Australian Institute of Health and Welfare (AIHW) data regarding the number of principle diagnoses of BO and GORD in the Australian Hospital System are listed below in Table 1; however, this data does not distinguish patients according to severity of the disease (AIHW 2010). In addition, clinical expert opinion suggests that this may be an underestimate of the number of principle diagnoses of BO, as many patients would be diagnosed in outpatient clinics. Additionally, the diagnosis of BO with dysplasia and early IMC suffers from difficulty regarding the reproducibility of results. Finally, in those patients with BO the development of dysplasia is ongoing and therefore regions of dysplasia have the tendency to develop at different locations as well as spontaneously regress in other regions, constantly modifying the location of the diseased tissue.

Table 1 AIHW principal diagnosis using ICD10-AM, Australia, 2007-08

ICD10-AM	Description	Number of separations as values
K22.7	Barrett's oesophagus	10,160
K22.8	Other specified diseases of the oesophagus	2,274
K22.9	Other diseases of the oesophagus, unspecified	177

Note: Data was not categorised according to severity of the disease, and no data could be obtained for early intramucosal cancer (AIHW 2010).

Radiofrequency ablation

A new option for the removal of Barrett's mucosa is the circumferential HALO^{360} (balloon catheter) or focal HALO^{90} (flat plate catheter) RFA system. The HALO^{360} enables circumferential ablation (usually the initial treatment of choice), whilst the HALO^{90} is used for focal ablation (subsequent treatments). RFA treatment is generally a day procedure performed by a gastroenterologist under conscious sedation in an outpatient setting.

The purpose of RFA is to thermally destroy the diseased mucosa, allowing for re-epithelialisation with healthy squamous epithelium (NICE 2010c). Initially, a sizing balloon is used to measure the diameter of the oesophagus whilst the patient is under conscious sedation. Then an appropriately sized radiofrequency balloon catheter is introduced over a guidewire in a side-by-side manner with an endoscope (Shaheen et al 2009). The catheter's balloon is then inflated and radiofrequency energy applied, circumferentially ablating the epithelium of the oesophagus to less than one millimetre (Shaheen et al 2009). The ablated epithelium is then removed by the clinician using irrigation, suction and light pressure (Shaheen et al 2009). Once dysplasia has progressed to adenocarcinoma, invading deep layers (lamina propria or beyond), then the HALO system is not indicated (Shaheen et al 2009, Sharma et al 2008). Rather, an oesophagectomy is the treatment of choice to ensure no potentially malignant cells remain in any cell layer (Rees et al 2010).

The HALO^{90} RFA system enables focal ablation of short segments of BO via attachment to the distal end of an endoscope. The HALO^{90} system can also provide secondary treatment following ablation with the HALO^{360} device and radiofrequency energy is applied in the same manner.

Current reimbursement arrangements

Currently there are four Medicare Benefits Schedule (MBS) listings for RFA procedures (MBS 2009). Notably, no procedures involve the use of the HALO^{360} or HALO^{90} device. In addition there is no present indication for RFA for the upper GI tract. The current MBS indications for RFA are described in Table 37 in Appendix C.

In addition, RFA for treatment of BO is currently funded by the Victorian Health Department for use at the Royal Melbourne and St Vincent's Hospitals (State Government of Victoria Department of Human Services 2009). Data from this patient population are not yet available.

Marketing status of the technology

The current Therapeutic Goods Administration (TGA) listings for HALO^{360} or HALO^{90} equipment are described in Table 2.

The current Food and Drug Administration (FDA) listings for HALO^{360} or HALO^{90} are described in Table 3.

Table 2 Items relating to radiofrequency ablation listed by the TGA

ARTG number	ARTG label name	Date approved	Indication
140709	Device Technologies Australia Pty Ltd – Catheter, gastrointestinal balloon	20/06/2007	A thin, flexible tube with an inflatable balloon at its distal tip used to widen and size the oesophagus for endoscopic ablation procedures. This is a single use device.
140684	Device Technologies Australia Pty Ltd – HALO system – Electrosurgical unit, endotherapy	20/06/2007	A dedicated electrosurgical unit specifically designed for use in combination with endoscopes and dedicated endotherapy instruments during endotherapy. This unit is specially designed for the purpose of generating high frequency energy used in conjunction with an endoscopic electrode to perform high frequency endotherapy inside the body via an endoscope or endoscopic system. Endoscopic ablation generator.
140685	Device Technologies Australia Pty Ltd – Electrode, electrosurgical, active, hand-controlled, single use	20/06/2007	An electrical conductor intended to provide an electrical connection (possibly in conjunction with a cable) between the output terminals of an electrosurgical generator and a patient at which an electrosurgical effect is intended. Ablation catheter for coagulation of the bleeding and non-bleeding sites in the gastrointestinal tract. The electric power switch for this device is an integral part of the electrode, allowing its operation by the surgeon's hands. This device is single use.

ARTG, Australian Register of Therapeutic Goods. (TGA 2010)

Table 3 Items relating to radiofrequency ablation listed by the FDA

FDA number	FDA label name	Date approved	Indication
K060169	Barrx Medical's HALO^{90} Coagulation System	21/04/2005	The HALO^{90} Coagulation System is indicated for use in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to, the oesophagus. Indications include oesophageal ulcers, Mallory-weiss tears, arteriovenous malformations, angiomata, barrett's oesophagus, dieulafoy lesions and angiodysplasia.
K083711	Barrx Medical's HALO^{360+} Ablation Catheter	02/02/2009	The HALO^{360+} Ablation Catheter is indicated for use in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to, the oesophagus. Indications include oesophageal ulcers, Mallory-weiss tears, arteriovenous malformations, angiomata, barrett's oesophagus, dieulafoy lesions and angiodysplasia.

FDA, Federal Drug Administration. (FDA 2010)

Existing procedures

Traditionally conservative therapy has been employed for non-dysplastic or low-grade dysplastic BO and involves acid suppressive therapies and surveillance (Sharma 2009). Acid-suppressive medical therapy includes pharmacological intervention with PPIs or anti-reflux surgery. The most common anti-reflux surgery is laparoscopic fundoplication and involves construction of a new anti-reflux barrier preventing reflux of gastric contents into the oesophagus. Fundoplication is useful for patients whose reflux symptoms are not adequately controlled by pharmacological therapy, resulting in regurgitation of weakly acidic chyme or bile.

Surveillance is commonly indicated for patients with BO to monitor disease progression and facilitate early detection of new lesions following therapeutic intervention (Rees et al 2010). However, surveillance lacks sufficient evidence regarding the prevention of early detected dysplastic Barrett's mucosa lesions (Sharma 2009). In addition, many authors debate the appropriate time interval for surveillance. Guidelines published regarding the frequency of endoscopy should consider the monetary burden such procedures contribute to the health care system (Fernando et al 2009, Lalwani 2008, Sharma 2009).

Oesophagectomy has traditionally been the primary treatment of HGD and adenocarcinoma (Bennett et al 2009). There are two types of oesophagectomy, namely transhiatal and transthoracic, and the two differ with respect to the incisions made and the way the oesophagus is mobilised. The removed section of diseased oesophagus can be replaced with the stomach or a colonic conduit (Lalwani 2008). Oesophagectomy has a high morbidity rate of approximately 30 per cent to 50 per cent and complications include, but are not limited to cardiac (arrhythmias), pneumonia, anastomotic leak, stricture and reflux (Fernando et al 2009, Lalwani 2008, Sharma 2009). Mortality has been reported to lie within 1 per cent to 10 per cent (Fernando et al 2009, Lalwani 2008, Sgourakis 2010, Sharma 2009). In Australia, high volume centres generally quote mortality figures around 2 per cent (Kendall and Whiteman 2006). In 2006, NICE published guidance on 'Thorascopically assisted oesophagectomy' (NICE 2010b). Indications assessed included adenocarcinoma, BO with HGD or severe benign disease. Two comparative studies (thorascopically-assisted compared with open oesophagectomy)

and th'ree large case series were included in the assessment. NICE concluded that the evidence supported the use of thoracoscopically-assisted oesophagectomy for the assessed indications (NICE 2010b). The guidance also acknowledged that the procedure was technically demanding and that surgeons undertaking the procedure should have special expertise in laparoscopic and thoracoscopic surgical techniques.

Alternative endoscopic therapies have been developed to offer a less invasive approach to treatment, and may be used where lesions are confined to the mucosal tissue. These include EMR, APC and PDT and currently none are funded under the Medicare Benefits Schedule (MBS) (MBS 2009). Notably, current literature regarding the safety and effectiveness of these procedures, including randomised controlled trials (RCTs), reports the majority of patients treated as diagnosed with non-dysplastic BO. As this patient population was deemed outside the scope of this assessment, drawing comparisons between treatment modalities in contrast to RFA is difficult.

EMR is a procedure similar in intent to the surgical resection of a lesion; however, it is performed endoscopically, minimising the invasiveness of the intervention. There are three main techniques, namely, the strip biopsy, cap-assisted and suck-and-ligate methods (Conio et al 2006). The approach selected depends on the characteristics of the lesion as well as the preference of the endoscopist. Endoscopic mucosal resection can also be used diagnostically as a staging tool to determine the grade of cancer/dysplasia present at the lesion site, and especially the depth of invasion, as the removal of the entire lesion enables a full histological analysis (Conio et al 2006, Moss et al 2009). EMR is generally considered to be the most common endoscopic treatment for BO both in Australia and worldwide (Lord R [St Vincent's Hospital] 2010, personal communication, 5 August). Due to its usefulness for staging, EMR is usually used as part of surgical treatment for BO, and may be associated with any other endoscopic approach or oesophagectomy. EMR is not currently reimbursed by Medicare (MBS 2009).

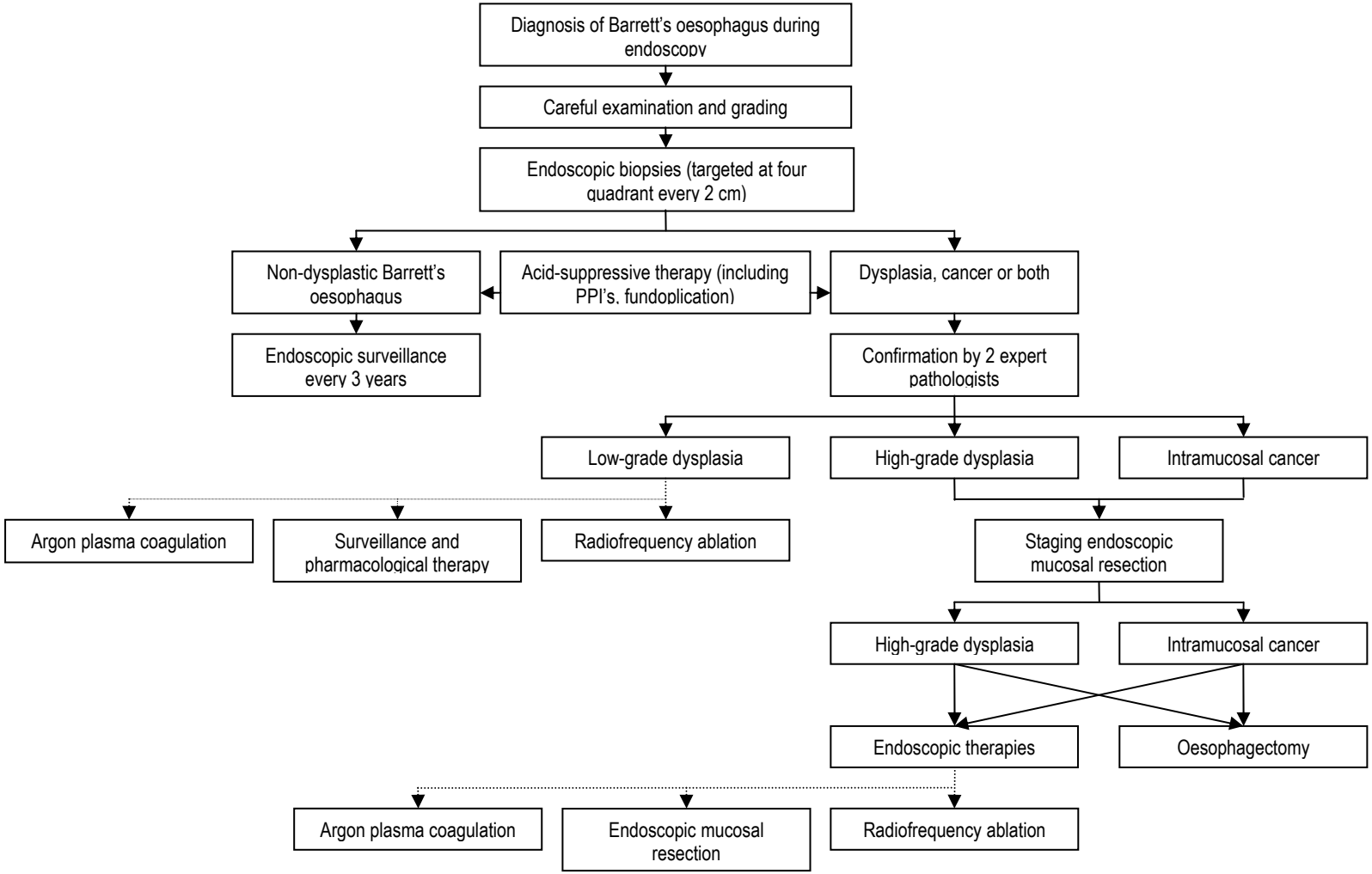
The APC device is a development of multipolar electrocoagulation. It uses a high frequency monopolar current conducted to target tissues via ionised argon gas to achieve tissue ablation (MSAC 2008). The depth of ablation lies between 2 millimetres and 3 millimetres, decreasing the risk of perforation or haemorrhage. Due to the limitations of the technique, APC is usually restricted to small areas of abnormal cells. Compared to RFA, APC does not ablate cells to a controlled depth, increasing the risk of stricture or perforation. A previously published RCT by Ackroyd et al (2004) comparing APC to surveillance in patients with IM; reported complete regression of BO in 58 per cent (11/19) of patients compared to 15 per cent (3/20) in the surveillance group at one year follow-up ($P<0.01$). In August 2010, NICE published guidance on 'ablative therapy for the treatment of BO' including three studies in the assessment (NICE 2010a). Recommendations instructed that APC should not be used to treat BO unless as part of a clinical trial.

Photodynamic therapy is an ablative technique employing photosensitising agents which are ingested by the patient (MSAC 2008). The agent is preferentially taken up by dysplastic and cancerous cells of the oesophagus, but is also taken up by other cells within the body. Using endoscopy, a laser-light is pointed at the area of the oesophagus undergoing treatment, resulting in the targeted formation of cytotoxic reactive oxygen species, leading to cell necrosis (Hage et al 2004, Kelty et al 2004, MSAC 2008, Ragunath et al 2005). However, the complications of PDT have limited its benefit for Australian patients, as exposure to light (particularly sunlight) can cause serious adverse reactions for many days following treatment (Rees et al 2010). Two studies by Overholt et al (2005,

2007) reported a photosensitivity reaction rate of 69 per cent. In a meta-analysis conducted by Li et al (2008) contrasting APC with PDT found a decreased rate of reduction in BO area of 27.5 per cent compared to 59 per cent with APC in patients with IM (P=0.0008) (Hage et al 2004, Kelty et al 2004, Li et al 2008, Ragunath et al 2005). However, Li et al (2008) did not state at which time point during follow-up these results were recorded. Finally, NICE published guidance regarding the use of PDT for BO (NICE 2010a) which included one RCT and 10 case series. Results of the assessment recommended that PDT should not be used unless part of a clinical trial.

Relevant existing MBS procedures and their associated cost(s) are listed in Table 35 in Appendix C. Relevant AIHW data reporting the number of oesophagectomy procedures in Australian hospitals is listed in Table 36 in Appendix C.

Figure 1 Clinical decision tree for radiofrequency ablation in Barrett's oesophagus with dysplasia



Outcome measurement tools

The primary outcome, namely, the histological eradication of BO and dysplasia is determined by biopsy of the oesophagus following RFA. The 'gold standard' of biopsy technique is the method of taking four-quadrant biopsies every 1–2 centimetres, conducted with high resolution narrow band imaging. Additionally, direct biopsy of visible abnormalities should also be conducted following treatment. All specimens should be fixed in formalin, stained with haematoxylin and eosin and interpreted by a pathologist with experience in GI pathology using standardised criteria, in order to obtain accurate and reproducible results. In cases in which dysplasia is diagnosed a consensus of two pathologists is recommended. If necessary a third pathologist may be required to address any disagreement. To determine the secondary outcome, disease progression, scheduled biopsies should be performed every 3–6 months according to this technique throughout the duration of follow-up.

In addition, the four quadrant every 1–2 centimetres technique should be employed in the diagnosis of BO prior to treatment with RFA. Specimens should also be reviewed by a central pathologist (or consensus of two expert GI pathologists) to ensure standardisation of diagnosis.

Approach to assessment

Review of literature

The PICO (population, intervention, comparator, outcome) criteria were developed with the assistance of the Advisory Panel (see Table 4, Table 5, Table 6). These three tables were developed to reflect the three different patient populations as identified through the clinical decision pathway. The criteria outlined in these tables assisted in specifying the search strategy.

The Advisory Panel were of the opinion that the approach and criteria represented in Shaheen et al (2009) was the gold standard and could be adopted for this assessment.

Table 4 PICO criteria and clinical questions for radiofrequency ablation in Barrett's oesophagus with low-grade dysplasia

Population	Patients with BO, with LGD
	All patients should be adults over 18 years of age
Intervention	Radiofrequency ablation with the HALO^{360} and HALO^{90} RFA devices
Comparators	Surveillance and pharmacological therapy
	Argon plasma coagulation (APC)
Outcomes	*Effectiveness*
Primary	The proportion of patients which achieved histological eradication of dysplasia (CR-D), confirmed by biopsy
	The proportion of patients which achieved histological eradication of IM (CR-IM), confirmed by biopsy
Secondary	The proportion of patients who had progression of dysplasia (including LGD, HGD and early IMC) to adenocarcinoma
	The proportion of biopsy samples at last follow-up that were free from IM
	The proportion of patients with buried glands at last follow-up
	All patient-related outcomes
	Technical outcomes
	Safety
	Complication/adverse event rates
	Mortality
	Perforation
	Thermal injury
	Stricture
	Oedema
	Haemorrhage
	Dysphagia
	Buried or subsquamous BO

BO, Barrett's oesophagus; LGD, low-grade dysplasis; HGD, high-grade dysplasia; IM. intestinal metaplasia; IMC, intramucosal cancer.

Clinical questions

Is RFA as safe, or safer than *surveillance or APC* for BO with LGD?

Is RFA as effective, or more effective than *surveillance or APC* for BO with LGD?

If RFA is as effective, or more effective than *surveillance or APC* for BO with LGD, is it cost effective?

Table 5 PICO criteria and clinical questions for radiofrequency ablation in Barrett's oesophagus with high-grade dysplasia

Population	Patients with BO, with HGD
	All patients should be adults over 18 years of age
Intervention	Radiofrequency ablation with the HALO^{360} and HALO^{90} RFA devices
Comparators	Oesophagectomy
	Argon plasma coagulation (APC)
	Endoscopic mucosal resection (EMR)
Outcomes	*Effectiveness*
Primary	The proportion of patients which achieved histological eradication of dysplasia (CR-D), confirmed by biopsy
	The proportion of patients which achieved histological eradication of IM (CR-IM), confirmed by biopsy
Secondary	The proportion of patients who had progression of dysplasia (including LGD, HGD and early IMC) to adenocarcinoma
	The proportion of biopsy samples at last follow-up that were free from IM
	The proportion of patients with buried glands at last follow-up
	All patient-related outcomes
	Technical outcomes
	Safety
	Complication/adverse event rates
	Mortality
	Perforation
	Thermal injury
	Stricture
	Oedema
	Haemorrhage
	Dysphagia
	Buried or subsquamous BO

BO, Barrett's oesophagus; LGD, low-grade dysplasis; HGD, high-grade dysplasia; IM. intestinal metaplasia; IMC, intramucosal cancer.

Clinical questions

Is RFA as safe, or safer than *oesophagectomy or APC or EMR* for BO with HGD?

Is RFA as effective, or more effective than *oesophagectomy or APC or EMR* for BO with HGD?

If RFA is as effective, or more effective than *oesophagectomy or APC or EMR* for BO with HGD, is it cost effective?

Table 6 PICO criteria and clinical questions for radiofrequency ablation in early intramucosal adenocarcinoma

Population	Patients with BO, with early intramucosal cancer (IMC)
	All patients should be adults over 18 years of age
Intervention	Radiofrequency ablation with the HALO^{360} and HALO^{90} RFA devices
Comparators	Oesophagectomy
	Endoscopic mucosal resection (EMR)
	Argon plasma coagulation (APC)
Outcomes	*Effectiveness*
Primary	The proportion of patients which achieved histological eradication of dysplasia (CR-D), confirmed by biopsy
	The proportion of patients which achieved histological eradication of IM (CR-IM), confirmed by biopsy
Secondary	The proportion of patients who had progression of dysplasia (including LGD, HGD and early IMC) to adenocarcinoma
	The proportion of biopsy samples at last follow-up that were free from IM
	The proportion of patients with buried glands at last follow-up
	All patient-related outcomes
	Technical outcomes
	Safety
	Complication/adverse event rates
	Mortality
	Perforation
	Thermal injury
	Stricture
	Oedema
	Haemorrhage
	Dysphagia
	Buried or subsquamous BO

BO, Barrett's oesophagus; LGD, low-grade dysplasis; HGD, high-grade dysplasia; IM. intestinal metaplasia; IMC, intramucosal cancer.

Clinical questions

Is RFA as safe, or safer than *oesophagectomy or APC or EMR* for BO with early IMC?

Is RFA as effective, or more effective than *oesophagectomy or APC or EMR* for BO with early IMC?

If RFA is as effective, or more effective than *oesophagectomy or APC or EMR* for BO with early IMC, is it cost effective?

Literature sources and search strategies

Relevant electronic databases were searched to identify relevant studies and reviews for the period between database inception and 29 April 2010. Searches were conducted via PubMed, EMBASE, the Cochrane Library, Current Contents and York CRD. The search terms used included MeSH terms and textwords and were designed to be broad in order to capture all available, relevant literature:

Population

Oesophageal neoplasm*, Esophageal neoplasm*, Oesophageal cancer*, Esophageal cancer*, Oesophageal tumour, Esophageal tumour, Oesophageal tumor, Esophageal tumor, Oesophageal oncolog*, Esophageal oncolog*, Oesophageal carcin*, Esophageal carcin* (combined with or).

AND: above terms plus Barrett oesophagus (MeSH term) OR Barret* (keyword) OR Esophageal neoplasms (MeSH term).

Intervention

Radiofrequency ablation (MeSH term), Radiofrequenc* (keyword), Radiofrequency ablat* (keyword), RFA (keyword), HALO (keyword), HALO* (keyword), Barrx (keyword) (combined with or).

Population and Intervention results were then combined with AND.

Note: (* represents a truncation – takes into account different spelling)

The Advisory Panel deemed a literature search for comparators or outcomes irrelevant to this assessment.

The search terms for accessing the available health technology assessment (HTA), systematic reviews and guidelines were:

Barretts, Barrets, Barret*, Oesophagus, Esophagus, HALO, Radiofrequency ablation, radiofrequency ablat*, RFA.

Health technology assessments (HTAs), systematic review and guideline databases searched conducted on the 24th June 2010 included Cochrane, NICE, clinicaltrials.gov, ANZCTR, TRIP, SIGN, York CRD, AHTA, Centre for Clinical Effectiveness (Monash University), AETMIS, AHFMR, CADTH, CAHSPR, CHEPA, CHSPR, HUI, ICES, IHE, MHLTC-MAS, NZHTA, NCCHTA, NHS CRD, AHRQ, HSPH-CUAR and VATAP. For further details regarding the list of HTA websites searched see Appendix F: Electronic databases searched.

Inclusion criteria

The detailed inclusion criteria which were applied to all retrieved studies are in Table 7.

Table 7 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	*Effectiveness:* systematic reviews and clinical studies including randomised and non-randomised comparative studies and case series will be included. Non-systematic reviews, case reports, letters, editorials, and animal, in-vitro and laboratory studies will be excluded. *Safety:* systematic reviews and clinical studies including randomised and non-randomised comparative studies, case series and case reports will be included. Non-systematic reviews, letters, editorials, and animal, in-vitro and laboratory studies will be excluded.
Patient	Male or female patients diagnosed with Barrett's oesophagus with LGD, HGD or early intramucosal cancer were included. Male or female patients with Barrett's oesophagus with intestinal metaplasia or invasive adenocarcinoma were excluded.
Intervention	Radiofrequency ablation, circumferential (HALO^{360}) and focal (HALO^{90})
Comparator	Patients with Barrett's oesophagus with LGD: surveillance and pharmacological therapy, APC Patients with Barrett's oesophagus with HGD: EMR, APC, oesophagectomy Patients with Barrett's oesophagus with intramucosal cancer: EMR, APC, oesophagectomy
Outcome	*Effectiveness:* Histological eradication of intestinal metaplasia, LGD, HGD and intramucosal cancer. Secondary outcome included prevention of disease progression.
Language	Non-English articles will be excluded unless they appear to provide a higher level of evidence than English language articles. Translation of such articles will significantly increase the timeframe of the review.

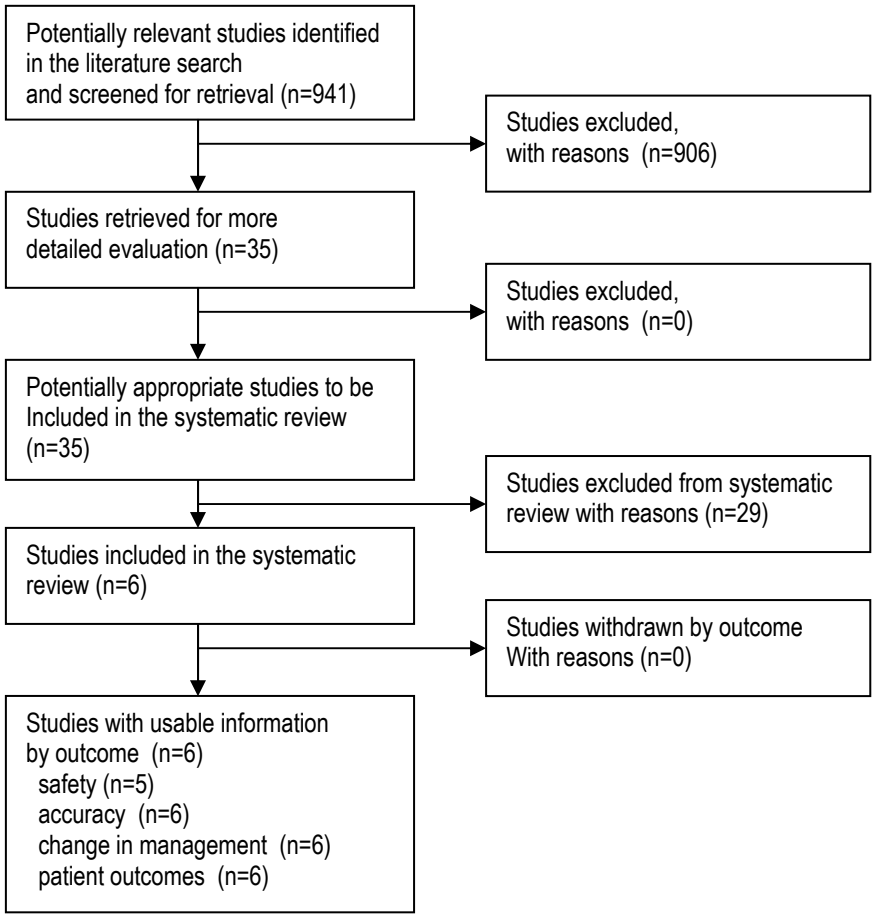
BO, Barrett's oesophagus; LGD, low-grade dysplasis; HGD, high-grade dysplasia; IMC, intramucosal cancer; APC, argon plasma coagulation; EMR, endoscopic mucosal resection.

Literature databases

Initial eligibility on the basis of the collated study citations was conservatively determined by one reviewer (i.e. if unclear from the abstract, or if the reviewer was unsure, the full text paper was ordered). One reviewer then assessed each of the retrieved full text articles for eligibility, with another assessing those over which there was doubt. When consensus could not be reached, a third reviewer independently assessed the paper in question and the majority decision prevailed. A list of studies which met the inclusion criteria but were subsequently excluded from the report is provided at Appendix H. The bibliographies of all included studies were hand-searched for any relevant references which may have been missed through the literature searching (pearling).

Quorum flowchart

Figure 2 Summary of the process used to identify and select studies for the review



Adapted from Moher et al (1999)

Included studies

The studies identified as fulfilling the review inclusion criteria, stratified by the levels of evidence (Merlin et al 2009), are listed in Appendix E. Those studies which did not meet inclusion criteria were listed in Appendix H: Excluded studies, along with the reason for exclusion.

Data extraction

Data were extracted by one researcher and checked by a second using standardised data extraction tables developed a priori. Data were only extracted and reported if stated in the text, tables, graphs of figures of the study, or if they could be accurately extrapolated from the data presented.

Description and methodological quality of included studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (Merlin et al 2009). These dimensions (Table 8) consider important aspects of the

evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 8 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design*
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

*See Table 9

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 9.

Table 9 Designations of levels of evidence* according to type of research question (including table notes) (Merlin et al 2009)

Level	Intervention §
I *	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial † Cohort study Case-control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study ‡ Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.
§ Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000).
† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C).
‡ Comparing single arm studies i.e. case series from two studies.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.
Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence.

Expert advice

An Advisory Panel with expertise in gastroenterology and upper GI surgery was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for Advisory Panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Appraisal of the evidence

Appraisal of the evidence was conducted in 3 stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

The NHMRC evidence hierarchy provides a ranking of various study designs (levels of evidence) by the type of research question being addressed (see Table 9)

Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000). This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al 2001).

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and *P*-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). Studies need to be appropriately assessed to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

For intervention studies of intervention name it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95 per cent confidence interval included only clinically important effects.

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

- the evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients
- the consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction i.e. homogenous or heterogenous findings
- the potential clinical impact - appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test
- the generalisability of the evidence to the target population
- the applicability of the evidence - integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 10) (NHMRC 2008).

Table 10 Body of evidence assessment matrix

Body of evidence Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Adapted from (NHMRC 2008)

Results of assessment

Descriptive characteristics of the included studies

Six studies were identified for inclusion in this assessment, five for safety and six for efficacy analysis for the treatment of BO with LGD, HGD or IMC. One RCT, Shaheen et al (2009), was identified for inclusion and compared RFA to a sham procedure. The remaining five studies were case series, designated as level IV evidence. Ganz et al (2008) was the only study not to report safety outcomes, as all other studies reported both safety and effectiveness outcomes. Ganz et al (2008) was the only study that did not use the HALO[90] device, all other included studies used both devices (HALO[360] and HALO[90]).

Table 11 Included studies

Study ID	Country	Sponsored by Barrx	Potential patient overlap	n	FU (mo)	Losses to FU	LGD	HGD	IMC
RCT									
Shaheen et al 2009	USA	✓	x	127	12	7	✓	✓	-
Case Series									
Pouw et al 2008	Netherlands	✓	✓	44	21 (med)	NR	✓	✓	✓
Sharma et al 2009	USA	✓	✓	63	24	1	✓	✓	-
Sharma et al 2008	USA	✓	✓	10	24	None	NR	NR	NR
Ganz et al 2008	USA	✓	✓	142	12	50	-	✓	-
Vassiliou et al 2010	Canada	NR	x	25	11	None	✓	✓	✓

n, number of patients; FU, follow-up; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal cancer; NR, not reported; med, median.

Critical appraisal

The descriptive characteristics of the included studies are outlined above in Table 11 and include one RCT (Shaheen et al 2009) and five case series. Four studies were conducted in the United States of America, one in the Netherlands and one in Canada. Notably, four out of the five studies were sponsored by the manufacturer, Barrx. In addition, a total of 58 patients (out of 411 patients) included in this assessment were lost to follow-up. The minimum and maximum length of follow-up was 11 months and 24 months respectively. Considering the relevant patient outcomes include disease progression to cancer, this duration of follow-up is relatively short. The study population varied in size, from 10 (Sharma et al 2008) to 127 (Shaheen et al 2009) patients. The mean age and male to female ratio were similar between the studies included as outlined below in Table 12. For study inclusion, three of the six studies authors required patients to have endoscopically visible lesions.

Patient populations were similar between all studies (Table 12). Each study included a range of severity of BO, including IMC. Circumferential and focal ablation (HALO[360]

and HALO[90] respectively) were commonly used together as part of the treatment regiment.

Randomised control trial (RCT)

The RCT by Shaheen et al (2009) conducted RFA versus a sham procedure on 127 patients with LGD and HGD. Of the 127 recruited patients (intention-to-treat) 117 completed treatment as per the protocol. Detailed study inclusion and exclusion criteria are outlined below in Table 13.

Allocation

Allocation was via concealed computer-generated block-randomisation with a 2:1 ratio RFA to a sham procedure. Randomisation was stratified according to the grade of dysplasia and length of BO as viewed on endoscopy. At the completion of the study the patient database was analysed by an independent study statistician with concealment of study group assignments. Shaheen et al (2009) does not state whether patients were masked to the procedure; however, detailed procedural techniques were included.

Diagnosis and pathological analysis

Baseline pathology diagnosis was confirmed for each patient using an independent review process of oesophageal body biopsies by two pathologists, one of whom was an expert in GI histopathology and BO. In the case of discordance a consensus committee review involving at least three pathologists was utilised to arrive at a final worst histological grade.

Outcomes

Primary and secondary outcomes were reported with 12-month follow-up according to the level of dysplasia. The study population for the primary intention-to-treat analysis included all patients who underwent randomisation. A second per-protocol analysis was performed in patients who completed the 12-month follow-up visit in order to account for those patients lost to follow-up. Adverse events were not reported according to the level of dysplasia, nor was the incidence of subsquamous IM at 12-month follow-up. In addition, cancer prevention was not an end point and the number of cancers reported in the patient cohort was small in comparison to the previously documented natural history of BO.

Follow-up

Seven patients were lost to follow-up and reasons included withdrawal of consent (n=6; intervention: 2 LGD, 2 HGD; control: 2), and co-morbidities (n=1 Parkinson's disease). Patients lost to follow-up were regarded as having had a failure of treatment for the primary outcomes. Notably, the length of follow-up was too short to detect the development of cancer.

Statistical analysis

Power calculations were reported to ensure that sufficient participants were recruited to enable statistical significance to be reached for the primary outcomes. Power calculations were performed for the primary outcome variables with the use of estimates from cohort studies of ablative therapy and reports of the natural history of dysplastic BO. Authors

assumed that 30 per cent of the patients in the control group would have no dysplasia at one-year follow-up and that 5 per cent would have no IM. The study was designed to have statistical power of no less than 80 per cent to detect a difference of 50 per cent in the proportion of patients with complete regression of dysplasia and a difference of 45 per cent in the proportion of patients with complete regression intestinal metaplasia (CR-IM) between the ablation group and the control group. This was determined by a two-sided test with a significance level of 0.05; and calculations allowed for a dropout rate of 15 to 20 per cent. Fisher's exact test and Student's t-test were used to compare baseline variables and differences in eradication of dysplasia and IM at 12 months. Due to non-normal distribution, chest-pain scores were compared with the use of the Wilcoxon rank-sum test and medians were reported. Logistic regression was used to assess predictors of response to therapy. No subgroup or ancillary analyses were carried out.

Case series

Three of the five included case series reported prospective consecutive patient enrolment (Pouw et al 2008, Sharma et al 2009, Ganz et al 2008), whilst Vassiliou et al (2010) reported retrospective data collection. The patient population included in the case series ranged from 10 to 142 patients and age ranged from 66 to 79 years of age (see Table 12). Exclusion criteria was not reported in three of the five case series (see Table 13). Vassiliou et al (2010) permitted previous ablative treatment, which was noted for patients on study entrance.

Safety and efficacy data was available in all studies except Ganz et al (2008), where safety data was not reported. In addition, Ganz et al (2008) excluded 50 patients from the efficacy analysis due to development of adenocarcinoma within three months of primary ablation with the HALO^{360} device, as this was deemed as prevalent cancer.

Sharma et al (2008) included 10 patients, but did not report the number of patients in each population. Therefore safety and efficacy outcomes are not stratified according to severity of disease.

Duplication of results and patient overlap

There were a large number of studies excluded from this assessment, and reasons included cited patient overlap, incorrect indication and not meeting the inclusion criteria outlined in the PICO criteria (see Table 4, Table 5 and Table 6).

Significant patient overlap occurred between Pouw et al (2008), Pouw et al (2009), Gondrie et al (2008a), Gondrie et al (2008b) and Beaumont et al (2009). Pouw et al (2008) was included as it contained four prospective consecutive patient cohorts, whilst all other studies either reported one, two or three of the same patient cohorts. Thus only the most up-to-date paper containing the largest number of patients was included in this assessment.

There is possible patient overlap between Sharma et al (2008) and Sharma et al (2009); however, no specific overlap has been cited by the authors and both studies are reported separately.

For a table outlining studies with significant patient overlap and reasons for exclusion see Table 41 in Appendix H: Excluded studies.

Table 12 Patient demographics

Study ID	n	Gender (m/f)	Mean age (sd) [range]	Length of BO (cm)	LGD	HGD	IMC	EMR	HALO 360	HALO 90
RCT										
Shaheen et al 2009	127	110/17	65.9±1.4	<8cm	62	63	-	11	3.5[a]	
Case Series										
Pouw et al 2008	44	35/9	68	7	3[b]	12[b]	16[b]	31	1	2
Sharma et al 2009	63	57/6	71[43-83]	LGD 4 [1-13] HGD 6 [1-12]	39	24	-	2	1	1
Sharma et al 2008	10	9/1	66.9±11.4[48-79]	4.4±1 [3-6]	NR	NR	NR	NR	2	1
Ganz et al 2008	Safety n=142 Effic n=92	125/17	Safety cohort (n=142):68 Efficacy cohort (n=92):67	6	0	142	-	24	1	-
Vassiliou et al 2010	25	22/3	66	10	6	15	3	3[c]	1	0-1

a, total ablations involving the HALO^{360} and HALO^{90}; b, this is the grade of dysplasia of 31/44 before EMR prior to RFA. The worst histological grade of BO after any EMR but prior to the first ablation procedure (for all 44 patients) was HGD n=32, LGD n=10 and IM=2; c, all 3 patients had IMC. n, number of patients; sd, standard deviation; BO, Barrett's oesophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal cancer; EMR, endoscopic mucosal resection; RCT, randomised controlled trial; Effic, Efficacy.

The inclusion and exclusion criteria for study entrants into each study included in this review are outlined below in Table 13.

Table 13 The inclusion/exclusion criteria for study entrants

Study	L of E	Design	Inclusion	Exclusion
Shaheen et al 2009	II	RCT; 2:1 randomisation stratified according to level of dysplasia	Patients aged 18-80 years and who had endoscopically evident, non-nodular, dysplastic BO of no more than 8 cm in length. Patients with HGD required negative results on EUS for lymphadenopathy and oesophageal wall abnormalities within 12 months before enrolment. Previous EMR was permissible 8 weeks or more before study entry if subsequent endoscopy showed non-nodular dysplasia.	Pregnancy, active oesophagitis or stricture precluding the passage of the endoscope, a history of oesophageal cancer, oesophageal varices, uncontrolled coagulopathy, or a life expectancy of less than two years as judged by the site investigator.
Pouw et al 2008	IV	Case Series Consecutive	Patients aged 18-85 years with endoscopically visible BO≤12cm with HGD or EAC diagnosed at 2 separate endoscopies by an experienced gastrointestinal pathologist.	Histological evaluation of the specimens from patients with prior EMR could not show vertical resection margins positive for cancer, deep submucosal invading cancer, poorly or undifferentiated cancer or the presence of lymphatic/vascular invasion. Patients with oesophageal stenosis at baseline and/or invasive cancer in biopsies obtained after EMR but prior to RFA were also excluded.
Sharma et al 2009	IV	Case series Consecutive	All consecutive patients undergoing ablation of BO with HGD from March 2006 to February 2007 and of BO with LGD from June 2006 to October 2006 were included.	NR
Sharma et al 2008	IV	Case series NR	Patients 18 years of age or older; histopathological diagnosis of intestinal metaplasia containing LGD demonstrated on the last 2 sequential biopsy sessions in the 2 years prior to enrolment. Biopsies were obtained while on adequate proton pump inhibitor (PPI) therapy. An independent review of the histology slides used for inclusion eligibility was performed by 2 pathologists at the institution who were blinded as to the baseline diagnosis. Enrolment required concordance for LGD.	Oesophageal stricture or varices; oesophagitis; any history of HGD or cancer involving the oesophagus; prior oesophageal surgery except fundoplication; and prior radiation therapy; ablative therapy; or EMR involving the oesophagus.
Ganz et al 2008	IV	Case series Consecutive	Adults with 1. a baseline finding of endoscopically identifiable BO 2. histologic evidence of HGD in biopsy specimens obtained from the BE region 3. confirmation of HGD by a second expert pathologist at the same institution 4. eligibility for EMR if indicated 5. eligibility for ablative therapy (no varices or no prior oesophageal radiation therapy or surgery other than fundoplication).	NR
Vassiliou et al 2010	IV	Case series Retrospective	Patients with BO measured to be 8 cm or longer at the time of their first ablation. All degrees of dysplasia including IMC. Previous endoscopic ablative treatment or EMR was noted.	NR

RCT, randomised controlled trial; BO, Barrett's oesophagus; LGD, low-grade dysplasis; HGD, high-grade dysplasia; IMC, intramucosal cancer; APC, argon plasma coagulation; EMR, endoscopic mucosal resection; L of E, Level of evidence.

As the RFA ablation depth is restricted to the mucosa, it is important that detailed endoscopic and regional diagnostic techniques are employed to exclude pre-existing and prevalent adenocarcinoma prior to ablation, in order for accurate reporting of treatment outcomes. The detailed diagnostic methodology of all studies is outlined below in Table 14. Regional radiological tests such as computed tomography (CT) scan and endoscopic ultrasound (EUS) were commonly undertaken to exclude the presence of regional cancer metastases.

Table 14 Procedural details

Study ID	Diagnostic method(s)	EMR	Type of anaesthesia	Number of HALO^{360} applications	Number of HALO^{90} applications
RCT					
Shaheen et al 2009	NR	11	CS, GA[b]	3.5[a]	
Case series					
Pouw et al 2008	2 HR E with NBI, EUS, CT	31	CS	1	2
Sharma et al 2009	E, EUS, CT, fine needle aspiration of suspicious lymphnodes	2	CS	1	1
Sharma et al 2008	NR	NR	NR	2	1
Ganz et al 2008	E, EUS, CT, fine needle aspiration of suspicious lymphnodes	24	CS, GA	1	-
Vassiliou et al 2010	4Q 1-2cm, HR E with NBI	3	CS, GA	1	0-1

a, total ablations involving the HALO^{360} and HALO^{90}; b, GA was used in patients who experienced considerable discomfort at anaesthetists discretion. RCT, randomised controlled trial; 4Q, four quadrant biopsy; E, endoscopy; NBI, narrow band imaging; HR, high resolution; CT, computed tomography scan; EUS, endoscopic ultrasound; CS, conscious sedation; GA, general anaesthesia; NR, not reported.

The average number of HALO^{360} applications was 1.2, whilst the average number of HALO^{90} applications ranged from 0.8 to 1 application. Conscious sedation was the most common form of anaesthesia and endoscopy was conducted to confirm the initial patient diagnosis in all studies that reported the diagnostic method.

Is it safe?

A total of five studies met inclusion criteria for the assessment of treatment safety. There were a total of four adverse events (AEs) in Shaheen et al (2009), three in the intervention group and one in the control group (see Table 15). Two of the three incidents of chest pain recorded in the intervention group resolved without sequalae. There was one incident of GI haemorrhage (intervention group) requiring platelet therapy and the patient recovered without any additional episodes.

Table 15 Adverse events following treatment with RFA

Study	N	Adverse event	n	Incidence (%)	Outcomes
RCT					
Shaheen et al 2009	127				
Intervention	84	GI haemorrhage	1	1	Patient on platelet therapy
		Chest pain	2	2	Resolved without sequalae
Control	43	Death	1	2	Death due to unrelated cause
Case series					
Pouw et al 2008	44	Non-transmural laceration	3	7	All patients remained asymptomatic and no therapeutic interventions required as laceration occurred on EMR scar
		Dysphagia	4	9	All required endoscopic dilation
		Fever	1	2	Conservative treatment and analgesics
		Chest pain	2	5	Conservative treatment and analgesics
		Superficial mucosal laceration	1	2	All at previous EMR site followed by negative contrast study
Sharma et al 2009	63	Haemorrhage	1	2	Self limiting; patient was on platelet therapy; no intervention required
		Stricture	1	2	Patient has baseline history of peptic stricture; treated successfully with balloon dilation
Sharma et al 2008	10	Coffee ground emesis	1	10	Single episode; no intervention required
Vassiliou et al 2010	25	Haemorrhage	1	2	Self limiting
		Stricture	2	8	Required dilation
		Postprocedural nausea	2	8	No intervention reported

Note: it is possible that some adverse events considered minor may not have been reported by some authors. Ganz et al (2008) did not report safety outcomes. N, number of patients; n, number of adverse events; RCT, randomised controlled trial.

No safety outcomes were reported according to patient population in any of the studies included. The most common adverse event (AE) as outlined in Table 15 and Table 16 was chest pain and dysphagia. The lowest and highest rate of AE incidence was GI haemorrhage (Shaheen et al 2009) and coffee ground emesis (Sharma et al 2008) respectively. Notably, the single incidence of coffee ground emesis occurred in Sharma et al (2008) where only 10 patients were included.

Pouw et al (2008) reported that the three non-transmural lacerations and one superficial mucosal laceration following RFA occurred on a previous EMR scar. In addition, the single patient who developed stricture in Sharma et al (2009) had a history of peptic

stricture, indicating prior EMR may predispose some patients to stricture or lacerations upon application of RFA.

Pouw et al (2008), Sharma et al (2009) and Vassiliou et al (2010) reported successful dilation procedures in all patients who developed stricture following RFA (3/411 patients).

The total complication rate across the studies reporting AEs was 9 per cent (23/269 patients). In contrast the overall complication rate of all the included studies was 6 per cent (23/411 patients) (Table 16).

Table 16 Summary of adverse events over entire assessment population

Adverse event	Total
Chest pain	4
Dysphagia	4
Stricture	3
Haemorrhage	3
Nausea/emesis	3
Non-transmural laceration	3
Superficial mucosal laceration	1
Fever	1
Death[a]	1
Total (of 269 patients)[b]	23 (9%)
Total (of 411 patients)[c]	23 (6%)

a, death due to unrelated cause; b, number of patients where safety outcomes were reported, excludes Ganz et al (2008) where safety outcomes were not reported; c, number of patients from all included studies.

Summary of safety

The limited literature available reports RFA to be safe for the treatment of BO with dysplasia and/or early IMC, with few major complications following multiple treatment sessions. Most adverse events were minor and resolved with no intervention.

Lack of comparative data prevented the direct comparison of RFA to the specified comparators in patients with LGD, HGD and IMC. As a result, conclusions cannot be drawn as to whether RFA is safer than surveillance or APC in patients with LGD. In addition, limitations in the literature also prevented the comparison of the safety of RFA to APC, EMR or oesophagectomy for patients with HGD and IMC.

Is it effective?

A total of six studies were included in the effectiveness analysis, including one RCT (Shaheen et al 2009). Two studies reported effectiveness results according to patient populations (Shaheen et al 2009, Sharma et al 2009), whilst the remaining four reported all populations as a single cohort (Ganz et al 2008, Pouw et al 2008, Sharma et al 2008, Vassiliou et al 2010). The effectiveness of RFA for BO can be categorised into primary and secondary outcomes (Table 4, Table 5, Table 6).

Primary outcomes

Primary efficacy outcomes involve the histological eradication of BO IM and dysplasia. Shaheen et al (2009) defined primary effectiveness outcomes as:

- the proportion of patients with LGD, HGD or early IMC which achieved complete histological eradication of dysplasia (CR-D), confirmed by biopsy following RFA application
- the proportion of patients who achieved CR-IM, confirmed by biopsy following RFA application.

Secondary outcomes

Secondary efficacy outcomes as defined by the Advisory Panel and Shaheen et al (2009) included:

- the proportion of patients who had progression of dysplasia (including LGD, HGD and early IMC) to adenocarcinoma
- the proportion of biopsy samples at last follow-up that were free from IM
- the proportion of patients with buried glands at last follow-up.

The efficacy results are outlined below in Table 17, Table 18 and Table 19.

Complete eradication of IM in all ablation patients (intention-to-treat) was 77 per cent (65/84), compared to 2 per cent (1/43) in the control group (Shaheen et al 2009). At 12-month follow-up the incidence of subsquamous IM was 5 per cent (4/84) for the ablation group and 40 per cent (17/43) in the control group (Shaheen et al 2009). In addition, disease progression (for all levels of dysplasia) was 4 per cent (3/84) in the ablation group contrasted with 16 per cent (7/43) in the control group (P=0.03) (Shaheen et al 2009).

Table 17 Efficacy results low-grade dysplasia

Study ID	N	LGD	Primary outcome Histological eradication	*P*-value	FU (mo)
RCT					
Shaheen et al 2009	127				
Intervention	84	42	CR-IM 81% (34/42) CR-D 90% (38/42)	*P*<0.001	12
Control	43	22	CR-IM 4% (1/22) CR-D 23% (5/22)	*P*<0.001	12
Case series					
Sharma et al 2009	63	39	CR-IM 87% (33/39)		24

N, number of patients, LGD, low-grade dysplasia; FU, follow-up; RCT, randomised controlled trial; CR-IM, complete response (eradication) of intestinal metaplasia; IND, indefinite for dysplasia; AC, adenocarcinoma; EMR, endoscopic mucosal resection; a, *P*<0.001; b, *P*=0.04 for all patients

The rate of CR-IM is higher (81%) in the intervention group compared to the control group (4%) (*P*<0.001) (Shaheen et al 2009). The incidence of subsquamous IM (also known as buried glands) is higher in the control group than the intervention group, suggesting the intervention is not associated with a higher rate of subsquamous IM in patients with LGD (Shaheen et al 2009). Secondary outcomes reported by Sharma indicate that following RFA 3/39 patients had residual IM without dysplasia, 2/39 indefinite for dysplasia and 1/39 had adenocarcinoma. The patient with adenocarcinoma required EMR and at 24-month follow-up had achieved CR-IM. Additionally, Sharma et al (2009) reported no buried glands, indicating a lower incidence rate than the control group in Shaheen et al (2009). The total rate of disease progression is also higher in the control group (16%) compared to the intervention group (4%; *P*<0.001), indicating RFA is effective in decreasing the rate of disease progression in patients with LGD and HGD.

Table 18 Efficacy results high-grade dysplasia

Study ID	N	HGD	Primary outcome histological eradication	*P*-value	FU (mo)
RCT					
Shaheen et al 2009	127				
Intervention	84	42	CR-IM 74% (31/42)	*P*<0.001	12
Control	43	21	CR-IM 0% (0/21)	*P*<0.001	12
Case Series					
Sharma et al 2009	63	24	CR-IM 67% (16/24); CR-D 79%(19/24)		24

N, number of patients; HGD, high-grade dysplasia; p-value, power value; FU, follow-up; mo, months; RCT, randomised controlled trial; CR-IM, complete response (eradication) intestinal metaplasia; CR-D, complete response (eradication) dysplasia; EMR, endoscopic mucosal resection.

The patterns of results for both primary and secondary outcomes for patients with HGD were similar to those with LGD; with the rate of CR-IM higher (74%) in the intervention group compared to the control group (0%) in Shaheen et al (2009) (*P*<0.001). Similarly, the incidence of subsquamous IM is lower in the intervention group compared to the control group and Sharma et al (2009) reports no incidence of buried glands. Sharma et

al (2009) reports disease progression in 2/24 patients, both requiring escape EMR for nodular IMC three months after treatment with RFA. Results at 24-month follow-up revealed that both patients achieved CR-IM.

Table 19 Efficacy results mixed indications

Study ID	N	LGD	HGD	IMC	Primary Outcome Histological Eradication	FU (mo)	Notes
Case series							
Pouw et al 2008	44	3	12	16	CR-IM 40/44 (91%)	21[a]	n=4 required escape EMR (MBM technique); 1 HALO ^{360}and 2 HALO^{90} sessions
Sharma et al 2008	10	NR	NR	NR	CR-IM 9/10 (90%); CR-D 10/10 (100%)	24	n=1 not CR-IM received EMR for focal resection of nodule; CR-D and CR-IM achieved at 24 months
Ganz et al 2008	142	0	142	-	CR-HGD 85/92 (92%); CR-D 77/92 (84%), CR-IM 50/92 (54%)	12	Only 92/142 assessed for efficacy
Vassiliou et al 2010	25	6	15	3	CR-IM 11/14 (79%), CR-D 13/14 (93%)[b]	20.3	n=1/13 HGD had residual dysplasia on EMR n=2/3 require additional ablations ongoing

a, median; b, this value has been calculated as Vassiliou et al 2010 did not report this value as a cumulative patient proportion; N, number of patients (total); LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal cancer; FU, follow-up; mo, months; CR-IM, complete response (eradication) intestinal metaplasia; CR-D, complete response (eradication) dysplasia; CR-HGD, complete response (eradication) high-grade dysplasia; EMR, endoscopic mucosal resection; MBM, multi-band mucosectomy.

The CR-IM rates for studies not reporting results according to the level of dysplasia range from 54 per cent (Ganz et al 2008) to 91 per cent (Pouw et al 2008). As the number of patients in each population is not recorded it is difficult to draw conclusions regarding the effectiveness of RFA in achieving CR-D.

Ganz et al (2008) reports an unusually low rate of CR-IM, and this may be due to a slight difference in procedural technique. Ganz et al (2008) performed successive ablations in an incremental fashion, in order to prevent overlap between BO segments. In contrast, all other authors ensured overlap between BO segments when applying RFA to guarantee that there were no islands of BO to which RFA was not applied.

Evidence of subsquamous IM at follow-up was identified in a total of 22 patients included in this assessment. However 17 of the 22 patients were in the control group of Shaheen et al (2009) and therefore did not receive RFA. Of those who did receive RFA only 5 of 22 patients developed subsquamous IM (Pouw et al 2008 and Shaheen et al 2009).

Patients who received EMR prior to RFA

Five studies conducted EMR prior to RFA in order to remove nodular HGD, ensuring RFA was applied to a flat mucosa (see Table 38 and Table 39; Appendix G: Additional Tables). Subgroup analysis was carried out by Ganz et al (2008), assessing the difference in histological eradication of IM in patients who received prior EMR compared to those who did not. There was no statistically significant difference in the rate of histological eradication of IM or dysplasia and the results were as follows: Complete histological eradication IM (CR-IM), EMR 62.5 per cent, no EMR 53 per cent; complete histological

eradication dysplasia (CR-D), EMR 81 per cent, no EMR 80 per cent; complete histological eradication HGD (CR-HGD), EMR 87.5 per cent, no EMR 9 per cent.

Summary of effectiveness

The limited literature suggests RFA is effective for achieving histological eradication of IM and dysplasia at a mucosal level.

CR-IM across all studies included ranged from 54 per cent (Ganz et al 2008) to 91 per cent (Pouw et al 2008) as outlined in Table 17, Table 18 and Table 19. The lowest rate of histological eradication of dysplasia (CR-D) was 79 per cent (Sharma et al 2009) and the highest was 100 per cent (Sharma et al 2008).

Notably, in the RCT (Shaheen et al 2009) the CR-IM and CR-D rates were lower in the control group (57% and 59% respectively) than those of the RFA group (98% and 99%) ($P<0.001$).

Escape EMR due to failure of RFA to achieve histological eradication of IM was performed in 20 (of 411) patients, with results reported in 15 out of the 20 patients. Of those reported all achieved CR-IM on long-term follow-up (24 months). Additional RFA treatment sessions were required in five (of 411) patients.

Evidence of subsquamous IM was found in five patients treated with RFA (Pouw et al 2008 and Shaheen et al 2009), of which four occurred in the study by Shaheen et al (2009). This higher rate of subsquamous IM may have been identified due to the more rigorous endoscopic work up and follow-up throughout the study.

Additionally, lack of comparative data prevented the direct comparison of the clinical effectiveness of RFA in patients with LGD, HGD and IMC. As a result, conclusions cannot be drawn as to whether RFA is as effective, or more effective than surveillance or APC in patients with LGD. In addition, limitations in the literature also prevented the comparison of the safety of RFA to APC, EMR or oesophagectomy for patients with HGD and IMC.

Discussion of systematic reviews and HTAs

HTA reports

Two health technology assessment reports were found on RFA for treatment of BO. The one published RCT by Shaheen et al (2009) was included in both assessments, with the authors relying on this data as the core evidence for the recommendations. In addition, both assessments included six single cohort case series, and neither excluded studies according to cited patient overlap.

The California Technology Assessment Forum (CTAF 2010) reviewed the scientific literature on the safety and efficacy of RFA for the treatment of dysplastic BO from 1966 till January 2010. Only prospective studies, measuring clinical outcomes in humans that were published in English as peer-reviewed articles were included. A total of six prospective uncontrolled studies (Gondrie et al 2008a, Gondrie et al 2008b, Pouw et al 2009, Fleischer et al 2008, Sharma et al 2009, Hernandez et al 2008) and one RCT by Shaheen et al (2009) were retrieved. Of the uncontrolled studies, most were small (10-24 patients) with a follow-up of 12 months to 2.5 years. Notably, Gondrie et al (2008a), Gondrie et al (2008b) and Pouw et al (2009) have been excluded from this MSAC assessment due to cited patient overlap between studies. In addition, Fleischer et al (2008) and Hernandez et al (2008) were also excluded as they included patients with IM, which was outside the scope of this MSAC assessment. Three studies reported inclusion criteria of IM; in two of the studies it was unclear as to whether any dysplasia was present. The CTAF concluded that (particularly in patients with HGD) RFA compared with other treatment alternatives achieves short-term histological eradication of dysplasia with a significantly lower complication rate (CTAF 2010).

The second technology assessment was conducted by the Technology Assessment Unit of the McGill University Health Centre (MUHC) (2009). The assessment involved a systematic review of the literature specifically on the safety and effectiveness of RFA for patients with HGD, including a cost comparison of RFA with esophagectomy. The inclusion criteria were limited to RCTs and cohort studies whose full text was published in peer-reviewed journals before 3 September 2009. One RCT and six single arm cohort studies and one economic study published in English and French languages were identified for inclusion. Despite the lack of long-term follow-up data MUHC concluded that RFA is a highly effective treatment for extensive, high grade oesophageal dysplasia (for at least two years) and considerably safer than oesophagectomy. Compared to oesophagectomy, RFA was deemed less costly and more efficient, both per treatment session and according to the recurring budget impact for the clinic. Based on the assessment findings the committee strongly recommended that RFA for HGD be funded by MUHC; however, this decision should be updated in two years to account for the paucity of follow-up data.

Guidelines

Guidelines on the treatment of Barrett's oesophagus which discuss the use of RFA have been published by three groups – The Society of Thoracic Surgeons, The American College of Gastroenterology and The National Institute for Health and Clinical Excellence (NICE). The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines briefly discuss RFA of BO in their guidelines for surgical treatment of GORD. According to their website, The American Gastroenterological Association intends to produce guidelines for the management of BO in 2010.

The Society of Thoracic Surgeons guidelines for Barrett's with HGD state that RFA may be effective for ablation of HGD, but suggest that further trials are needed before this can be recommended in preference to currently available ablative therapies (Fernando et al 2009).

The American College of Gastroenterology published updated guidelines for the diagnosis, surveillance and therapy of BO (Sampliner et al 2008). They state that therapy choice for patients with HGD is dependent on local expertise, both endoscopic and surgical as well as the patient's age, comorbidity and preference. In addition, they state that oesophagectomy is no longer the necessary treatment response.

NICE has published an interventional procedure guideline (244) on epithelial RFA for BO (May 2010). NICE included one RCT (Shaheen et al 2009) and one large case series (Ganz et al 2008) outlining the safety and efficacy of patients treated with RFA who had BO with HGD only (both of which are included in this MSAC assessment). Due to the lack of comparative data, NICE conducted their own indirect comparison of PDT to RFA using a common control group. RCTs with inappropriate control groups were treated as single arm cohort studies and consequently compared to the control group NICE assembled. However, the method by which anomalies in the baseline patient characteristics were overcome was not described. NICE declared that the results of the two studies (Shaheen et al 2009 and Ganz et al 2008) recommended RFA to be offered routinely as a treatment option in the United Kingdom (UK) health care system. However, this recommendation was given provided gastroenterologists and upper GI surgeons monitored the results of the procedure adequately, as long-term follow-up data was currently lacking in the literature.

NICE has also published guidance on 'ablative therapy for the treatment of BO' (CG106, August 2010). Three studies were included in the assessment of APC, and eleven studies (one RCT, ten case series) for PDT. Recommendations regarding RFA were the same as previously published guidance (IPG244), as no additional studies were included. In addition, NICE recommended that APC, laser ablation and multipolar electrocoagulation alone or in combination with each other, should not be used, unless as part of a clinical trial.

Systematic literature reviews

Four reviews have been written on the treatment of BO. Two of these are systematic reviews with meta-analyses (Li et al 2008; Wani et al 2009) and two Cochrane reviews were available.

The systematic review by Li et al (2008) evaluated different treatment modalities, including medical, surgical and endoscopic, for BO. The authors did not state specific inclusion criteria regarding the histology of the patient population. Only RCTs in which patients had been randomly assigned to two or more treatment groups and in whom BO had been validated by pathology were included. Further inclusion criteria included clearly defined primary outcome(s). No studies reporting outcomes of RFA for BO were included, as Shaheen et al (2009) was published after this review had been completed. A total of thirteen studies were retrieved, with three trials comparing PDT to PPI, one RCT comparing APC to surveillance and four trials comparing APC to PDT. The studies investigating PDT (compared to PPI) (Ackroyd et al 2000, Overholt et al 2005, Overholt et al 2007) reported a 30 per cent to 70 per cent reduction in BO area in patients with IM or LGD only (no HGD) ($P<0.001$) and the occurrence of cancer was 15 per cent in the

PDT group compared to 29 per cent in the PPI group (P=0.006). However, Overholt et al (2005 and 2007) also found the photosensitivity reaction rate to be 69 per cent in patients receiving PDT, presenting a significantly higher complication rate compared to RFA. The one study reporting APC (compared to PPI and surveillance) (Ackroyd et al 2004) achieved complete regression of BO in 58 per cent (11/19) of patients, compared to 15 per cent (3/20) in the control group at one-year follow-up (P<0.01). The meta-analysis conducted by Li et al (2008) into the effectiveness of APC compared to PDT included three RCTs and revealed a significant difference in the incidence of complete ablation of BO. In APC patients 59 per cent achieved CR-IM compared to 27.5 per cent in the PDT group (P=0.0008), showing APC is more effective than PDT.

The objective of the other systematic review by Wani et al (2009) was to determine the cancer incidence in BO patients after ablative therapy and compare these rates to cohort studies of BO patients not undergoing ablation. Ablative modalities included APC, multipolar electrocoagulation (MPEC), PDT, laser and RFA, and results were not reported separately according to modality. For inclusion patients required histologically proven BO with or without dysplasia and results were reported according to disease severity. Randomised controlled trials and uncontrolled trials on patients that had undergone ablative endoscopic therapy were included. One study by Sharma et al (2007) was retrieved reporting the outcomes of RFA on patients with IM without dysplasia.

Cochrane reviews

The first Cochrane review identified, 'Treatment for Barrett's oesophagus', evaluated several types of treatment modalities for patients with endoscopically and histologically diagnosed BO of varying grades of disease severity (Rees et al 2010). The interventions included: pharmacological therapy (either alone or in combination), anti-reflux surgery and endoscopic therapies including thermal methods (APC, MPEC, laser therapy, RFA and cryotherapy), chemical methods (PDT) and mechanical methods (EMR and ultrasonic surgical aspiration). In addition, any endoscopic therapy in combination with either pharmacological therapy or anti-reflux surgery was evaluated. Similarly, Shaheen et al (2009) was the only RCT published on RFA. The overall conclusion from the review was that RFA appeared to be the most successful therapy to date for patients with early cancer, or severe (high-grade) dysplasia in BO.

The second Cochrane review, titled 'Surgical versus radical endotherapies for early cancer and HGD in Barrett's oesophagus', included patients of any age found to have a histologically confirmed diagnosis of early neoplasia (HGD or early cancer) as a result of BO disease progression or squamous cell carcinoma (Bennett et al 2010). Endoscopic modalities under review included APC, PDT, MPEC, laser therapy, cryotherapy and RFA. However, no studies met inclusion criteria and therefore no conclusions or recommendations could be synthesised for this report.

APC comparative studies

Four peer-reviewed comparative studies have been published reporting the effectiveness of APC, with only Ragunath et al (2005) including patients with BO with dysplasia only (Ackroyd et al 2004, Hage et al 2004, Kelty et al 2004, Ragunath et al 2005). Three studies compared APC to PDT, namely, Hage et al (2004), Kelty et al (2004) and Ragunath et al (2005). Ragunath et al (2005) performed APC on patients with LGD and reported 6/13 patients (46%) who achieved eradication of dysplasia at 12-month follow-up. The results of Ackroyd et al (2004) are reported above as this study was included in

the systematic review by Li et al (2008), and included patients with IM and LGD (LGD n=2/20). Hage et al (2004) and Kelty et al (2004) only included patients with BO without dysplasia, which is outside the scope of this assessment.

Other relevant considerations

Expert opinion

Expert clinicians on the Advisory Panel were available to provide comment on a number of issues regarding BO, including diagnosis, prevalence and incidence, treatment with RFA, comparators and follow-up.

Diagnosis

Expert clinicians concurred that the diagnosis of BO should be conducted by the four quadrant every two centimetres method and that the final diagnosis of BO should be reached via the agreement of two expert GI pathologists. The use of EMR as a diagnostic staging tool is advantageous when determining the extent of diseased oesophagus.

Prevalence

Currently there is lack of prevalence and disease progression data for BO and IMC worldwide. The prevalence of BO with HGD included in this assessment was estimated via personal communication between expert clinicians on the Advisory Panel (Brown and Whiteman 2010). Lack of disease progression data has made estimation of the number of BO patients in Australia who may need access to RFA treatment difficult.

RFA

Clinicians with experience using the RFA procedure indicated that use of the device was simple and quick. An additional benefit of RFA highlighted by the Advisory Panel was that it was a day procedure of minimal invasiveness, decreasing the risk of complications and providing a convenient alternative to oesophagectomy.

Comparators

Whilst EMR was considered a comparator for this assessment, expert clinicians highlighted that EMR is commonly used to remove nodular sections of BO prior to RFA, as RFA can only be applied to flat sections of BO. Clinicians also indicated that EMR is commonly used as a staging tool prior to RFA. Despite a number of studies included in this assessment not reporting the use of EMR prior to RFA in this fashion, clinicians indicated many gastroenterologists commonly conduct this procedure.

It was highlighted that oesophagectomy is a highly invasive procedure with a high complication rate. Clinicians indicated that it is not uncommon for patients to spend up to two weeks in the intensive care unit (ICU) following surgery. Additionally, removal of the diseased section of the oesophagus leads to further reflux and therefore recurrence of BO. As a result many patients following surgery continue to suffer the symptoms of reflux and BO.

Clinicians indicated that whilst still utilised overseas, PDT experiences little use in the Australian health care system, as high ultra-violet light exposure in the Australian climate leads to a high rate of photosensitivity complications.

Consumer implications and other considerations

Traditionally, treatment selection for patients with BO has been based on the severity of disease, as patients lie within two distinct categories. Those with the less severe form of BO require routine endoscopic examinations (known as conservative surveillance) and administration of medicines to control their reflux symptoms. In contrast, those patients with the more severe form of the disease traditionally required a surgical procedure known as oesophagectomy. This is open surgery, whereby an upper GI surgeon removes the diseased section of the oesophagus.

For patients with the more severe form of BO, RFA provides a less invasive form of therapy as it is not a surgical procedure. Instead, destruction of the diseased tissue is achieved via placing the RFA device directly down into the oesophagus. Compared to traditional therapy (oesophagectomy), BO patients treated with RFA experience fewer complications. In addition, the treatment is generally provided in an outpatient setting as a day procedure, providing additional convenience to the patient.

RFA also provides a curative treatment option for patients with the less severe form of BO, who traditionally would not receive treatment at the site of the disease. There are also other less invasive options (than surgery) currently available (APC, EMR and PDT). These endoscopic approaches may be used in combination with each other.

Oesophagectomy is a highly invasive procedure which requires lengthy recovery. Whilst removal of the diseased oesophagus is curative, people who have had an oesophagectomy have an increased chance of developing BO as they no longer have the anatomical structures in place to prevent the reflux of stomach acid. As a result, they have a higher chance of developing cancer in the future. This affects patient quality of life, as they must continue to live with the side effects of surgery, and the knowledge that they may develop cancer in the future.

In contrast, RFA preserves the anatomical structures which prevent reflux, decreasing the probability of patients developing BO and/or cancer in the future.

What are the economic considerations?

Economic evaluation of new health care technologies is important when determining whether the new initiative offers additional benefits and at what cost. Economic evaluations are able to determine whether the new initiative is dominated by (or dominates) the existing technology, such that the costs are higher (lower) and the effectiveness is less (greater). Economic evaluation is particularly important where the new initiative offers health benefits at additional costs. Within a constrained health care budget, determining the additional cost that would be paid for a given health gain is important when ascertaining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to determine the incremental effectiveness, which is the additional benefits associated with the new technology relative to current practice. The second step is to determine the incremental costs, which is the difference in costs between the new initiative and current practice. Finally the incremental cost-effectiveness ratio (ICER) can be calculated using the following ratio:

$$ICER = \frac{Cost_{New} - Cost_{Comparator}}{Effectiveness_{New} - Effectiveness_{Comparator}}$$

To allow comparison of effectiveness across interventions and/or across settings, it is preferable for an economic evaluation to take the form of a cost-utility analysis. This analysis generates an ICER as described which can then be compared to a threshold, or range of thresholds, to determine whether the health system should invest in the new technology. The most common generic outcome measure is the quality-adjusted life year (QALY). This is a measure of effectiveness which combines morbidity and mortality dimensions into one composite measure of outcome. The use of cost-utility analysis, while preferable to disease-specific outcome measure, is reliant on the existence of appropriate published data.

Where the new technology demonstrates equal effectiveness to the existing technology (i.e. it is non-inferior) then a cost-minimisation approach is warranted.

Objective

The objective of this section is to conduct an economic evaluation of the therapeutic use of RFA for BO with dysplasia. Following advice from the Advisory Panel, it was decided that the treatment of HGD and LGD would be considered separately. The comparators for LGD and HGD are:

- For LGD the most appropriate comparator is surveillance.
- For HGD the most appropriate comparators are oesophagectomy, APC and EMR.

Search strategies

As described in the 'approach to assessment', a search strategy was developed to systematically identify studies in which RFA was used.

Databases of peer-reviewed literature including Medline, PubMed, CINAHL and Cochrane have been searched. The bibliographies of all retrieved publications were hand-searched for any relevant references missing in the database search. Web-based searches included the Internet engines 'Google' and 'Google scholar'.

In addition to the search terms described in the 'approach to assessment' section, Cost$ or Econ$ were added. This was to identify any published cost-effectiveness analysis. The inclusion and exclusion criteria remained the same.

Background – evidence of cost-effectiveness

There have been a number of published cost-effectiveness analyses of RFA for the management of patients with BO.

The most recent by Boger et al (2010) was a UK-based cost-utility analysis comparing RFA to oesophagectomy for the management of HGD. The results of this analysis demonstrated that RFA would cost £1902 (~A$3,120)[1] less than immediate oesophagectomy and result in 0.4 more QALYs. There was an 85 per cent probability that RFA remained cost effective at a willingness to pay threshold of £20,000–30,000. There are a number of limitations with this study. Firstly, the effectiveness data was not based on direct comparative evidence. This is due to the lack of randomised controlled trials comparing RFA directly with oesophagectomy, as noted previously in this report. Secondly, in the Markov model HGD and adenocarcinoma are combined into a single state and the transition probability to HGD from LGD or Barrett's no dysplasia is identical, which seems unlikely in real life. Despite this, the study was well designed and used a probabilistic sensitivity analysis approach to estimate the uncertainty.

Another analysis undertaken in the United States by Inadomi et al (2009) constructed a Markov model to simulate a cohort of patients with BO with HGD, LGD or no dysplasia. Four different ablation techniques were compared: RFA, APC, MPEC and PDT. The model for HGD compared endoscopic surveillance, immediate ablation followed by endoscopic surveillance and oesophagectomy. The model for LGD compared no intervention, endoscopic surveillance and the four different ablation techniques.

Based on a cohort of 50-year-old patients, for HGD the results demonstrate that the incremental ICER of RFA relative to surveillance is US$5,830 (~A$7,350)[2] per QALY. The sensitivity analysis suggests that RFA is the most cost-effective ablation strategy as long as the proportion of patients with residual HGD after RFA is less than 17 per cent. For LGD, RFA followed by surveillance in patients whom metaplasia persists after ablation dominated all other interventions. A limitation of this model was the choice of

[1] Average exchange rate for 2010 from the RBA where A$1=GBP£0.584665

[2] Average exchange rate for 2009 from the RBA where A$1=US$0.79273

utility values. The model used a utility value of 1 for Barrett's without dysplasia, LGD and HGD. Given that the cohort in the model had a mean age of 50, providing full health to this population may be too high. For example the UK population norm for someone aged 50 is 0.84 for males and 0.85 for females (Kind et al 1999).

A technology assessment by the McGill University Health Centre conducted a cost analysis of RFA for BO. The estimated cost of using RFA (2 procedures with Halo^{360} and one procedure with Halo^{90}) was C$11,208 (~A$12,489)[3] compared to C$13,788 (~A$15,364) for oesophagectomy. Overall if seven cases were treated by RFA instead of oesophagectomy, the cost savings was approximately C$18,060 (~A$20,124) annually. It was recommended that due to paucity of follow-up data, the report should be followed up in two years time.

A National Institute for health and Clinical Excellence (NICE 2010c) guideline report conducted a cost-utility analysis of RFA (NICE 2010c). The model was run with a cohort of 60-year-old patients for 50 years. The results demonstrate that endoscopic resection and RFA compared to no surveillance had an ICER of £13,893 per QALY (~A$23,762)[4]. Also, endoscopic resection and RFA had the least uncertainty of being cost-effective and an 18 per cent probability of being the optimal choice.

Rationale for the cost-effectiveness analysis

There was sufficient evidence to conduct a full cost-effectiveness analysis of RFA for the treatment of LGD. A decision analytic model was developed which provides a framework for decision making under conditions of uncertainty. The economic evaluation will aim to estimate the incremental cost-effectiveness of RFA compared to surveillance.

There was insufficient comparative evidence to support a full cost-effectiveness analysis of RFA for the treatment of HGD. Therefore the aim of the economic evaluation was to calculate the cost of providing RFA compared to oesophagectomy, APC and EMR for the treatment of patients with HGD in BO.

Low-grade dysplasia

Economic model

A state transition Markov model was developed for estimating the costs and benefits of using RFA compared to surveillance in LGD.

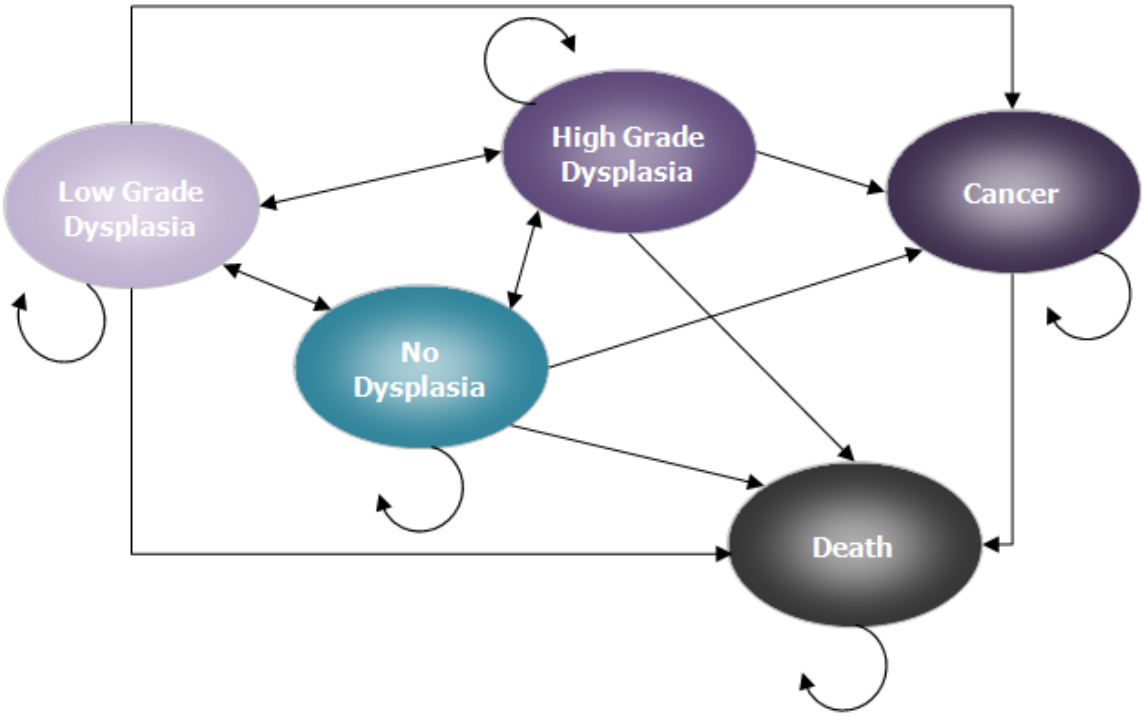
Markov models are based on a series of mutually exclusive disease states that a patient can occupy at any point in time. Instead of disease progression being modelled by movement along a large number of possible pathways, as in a decision tree, a more complex prognosis can be produced as a set of possible transitions between these disease states. Time elapses explicitly in a Markov model, and is represented by a patient occupying a given disease state for a discrete time period (or cycle). The length of each cycle depends upon the disease and intervention under investigation, and can range from

[3] Average exchange rate for 2009 from the RBA where A$1=CDN$0.897443

[4] Average exchange rate for 2010 from the RBA where A$1=GBP£0.584665

a month to a year. The speed at which a patient moves between states in the model is determined by a set of transition probabilities. Costs and outcomes are incorporated into these models as a mean value per state per cycle. Expected values are calculated by adding the costs and outcomes across states and weighting these according to the time the patients is expected to be in each state. The structure of the model is shown in detail in Figure 3.

Figure 3 Markov model for low-grade dysplasia



Main assumptions in the model

- The starting age of the model cohort is 60 years, which is the average age of those diagnosed with BO. The model follows the cohort for their lifetime or until 100 years of age.
- The cycle length of the model is one year and transition to another state can only happen once in that year. Half-cycle correction is applied to the cycle length.
- All of the cohort begin the first cycle in the low dysplasia state.
- Death is a terminal state and incurs no cost or quality of life.
- Quality of life does not differ by age, but by disease state.
- The MBS fee for RFA is based on item 30479. This price is uncertain since the final fee is yet to be determined.
- The effectiveness of RFA is taken from a study by Sheehan et al. For the purposes of the economic model, it was assumed that the sham procedure would be equivalent to surveillance only.

- The increased effect of RFA relative to surveillance occurs each time someone is treated with RFA in the LGD state.

- Individuals that move to the HGD state are assumed to be treated with RFA in both the RFA and surveillance arms.

- A health care perspective is adopted. All future costs and benefits are discounted to their present value using a rate of 5 per cent.

Estimate of effectiveness

The estimate of effectiveness of RFA used in the model was taken from a study by Shaheen et al (2009) as discussed previously in the effectiveness section. This RCT compared RFA to a sham procedure in patients with both low grade and HGD. For the purposes of the economic model, it was assumed that the sham procedure would be equivalent to surveillance only. Using an intention-to-treat analysis, the results demonstrate that complete eradication of dysplasia occurred in 90.5 per cent of those in the RFA group, compared to 22.7 per cent of those in the control group ($P<0.001$).

Estimate of costs

The estimated costs of RFA and surveillance were taken from a number of sources. These included: the MBS, Australian Refined Diagnostic Related Group (AR-DRG) (version 5.1 round 11 – Private and Public), manufacturer's costs and the median charged Medicare fee. Resource use and MBS item numbers were determined by the Advisory Panel.

Average costs per procedure

MBS items

The MBS item fees, which represent the Australian Government contribution to each procedure, were obtained from MBS online (Table 20). The patient usually receives a reimbursement of 75 per cent of the schedule fee for inpatient services and 85 per cent for outpatient services. Consequently the benefit amount and not the full Medicare schedule fee were used in the model. Using the full fee would double count some of the copayment contribution.

Average copayments

Average copayments were provided by the Department of Health and Ageing. The copayment component is calculated as the MBS fee charged minus the MBS benefit paid plus any additional specialist fees. The copayment may not be the exact patient contribution, since it may also include some insurance contribution (up to 25% of the MBS fee). To avoid double counting, the 25 per cent insurance contribution is not included as a separate cost. The copayments are calculated as averages of all procedures claimed under the item number. Consequently, there may be a degree of heterogeneity, therefore the accuracy of the copayment is dependent on the other procedures that are also claimed under the same item number.

Table 20 MBS item numbers, fees and copayments

MBS item	Item #	MBS fee	MBS benefit*	Copayment
Initiation of anaesthesia	20740	$95.25	$81.00	$49.53
Oesophagoscopy	30473	$170.40	$144.85	$43.45
Endoscopy	30479	$458.05	$389.35	$81.67

* All of these items are undertaken as outpatient procedures. Therefore 85% of the scheduled fee is reimbursable and any extra will contribute to the extended safety net. MBS., medicare benefits schedule.

Capital costs

The capital cost of RFA included the following items: a generator, sizing balloon and ablation catheter for the Halo^{360} and a generator and ablation catheter for the Halo^{90}. All costs were provided by Device Technologies Australia Pty Ltd. The following costs were obtained for the Halo^{360}: $46,200 for the generator, $869 for the sizing balloon and $2,739 for the catheter. The costs for the Halo^{90} were as follows: $20,790 for the generator and $1,800 for the catheter.

The average capital cost contribution per patient was based on the following assumptions: a six-year -ife of the machine, an average 40 procedures per machine per year and discounted at 5 per cent. This gives an average capital cost per procedure of $275 and $248 for Halo^{360} and Halo^{90}, respectively.

Cost of treatment of low-grade dysplasia (RFA vs surveillance)

The estimated average cost of RFA compared with surveillance can be seen in Table 21. On average each patient receiving RFA will receive one procedure with the Halo^{360} and two procedures with the Halo^{90} along with one additional oesophagoscopy in the first year of treatment. By comparison, those in the surveillance arm will receive two endoscopies each year.

Table 21 Calculation of average costs for RFA and surveillance in low-grade dysplasia

	Unit cost	RFA		Surveillance	
		Units	Total	Units	Total
Equipment					
Halo 360	$275	1	$275		
Sizing balloon	$869	1	$869		
Ablation catheter	$2,739	1	$2,739		
Halo 90	$248	2	$495		
Ablation catheter	$1,800	2	$3,600		
Operational					
Radiofrequency ablation (MBS based on 30479)	$389	3	$1,168		
MBS 30479 copayment	$82	3	$245		
Initiation of anaesthesia (MBS 20740)	$81	3	$243		
MBS 20740 copayment	$50	3	$149		
Oesophagoscopy (MBS 30473)	$145	1	$145	2	$290
MBS 30478 copayment	$43	1	$43	2	$87
Initiation of anaesthesia (MBS 20520)	$81	1	$81	2	$162
MBS 20520 copayment	$50	1	$50	2	$99
Total consumables			$7,979		$0
Total MBS benefits			$1,637		$452
Total patient out-of-pocket			$487		$186
Total cost in low-grade dysplasia			$10,102		$638

MBS., medicare benefits schedule

Cost of high-grade dysplasia

It is assumed in the model that patients who transition to HGD will incur a cost of treating the HGD. In this model, all patients with HGD are treated with RFA, irrespective of if they are in the RFA or surveillance arms (see costing in the HGD section for full breakdown of costs).

Cost of cancer

An average lifetime cost of cancer was incurred as an individual progressed into the oesophageal adenocarcinoma state. This cost is an estimate of the average lifetime treatment costs of the cancer. Due to the high mortality rate with oesophageal cancer and the focus on the upfront costs of RFA versus surveillance, a detailed breakdown of the costs of different therapies used to treat oesophageal cancer was not modelled specifically, such as chemotherapy and oesophagectomy. The total lifetime treatment cost of oesophageal cancer was sourced from the AIHW report on health system expenditures on cancer and other neoplasms in Australia for 2000-01.[5] The estimate of $30,808 was inflated by using the AIHW health index[6] and an estimated lifetime cost of $46,886 was used in the model.

Cost estimates in the model

The frequency of surveillance endoscopies was provided by the Advisory Panel. For individuals with LGD under the surveillance regimen, two regular oesophagoscopies

[5] http://www.aihw.gov.au/publications/hwe/hsecna00-01/hsecna00-01.pdf

[6] Estimated as an average inflation rate of 0.0366 per year since 2000-01 extrapolated to 2009-10 from the Health Expenditure Australia 2007-08 report.

would be performed annually. For those treated with RFA, one oesophagoscopy would be required in the first year of treatment, then two endoscopies for the next five years followed by one endoscopy each year thereafter. Those with HGD would have one oesophagoscopy in the first year of treatment, followed by four oesophagoscopies in the year following RFA treatment, two oesophagoscopies each year for the next four years then one oesophagoscopy for each year thereafter.

Table 22 summarises the surveillance schedule following treatment used in the model.

Table 22 Surveillance base case

	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8+
No dysplasia (previously low grade)	2	2	2	2	2	1	1	1
LGD with surveillance	2	2	2	2	2	2	2	2
LGD eradicated with RFA	1	2	2	2	2	2	1	1
HGD eradicated with RFA	1	4	2	2	2	2	1	1

LGD, low grade dysplasia; HGD, high grade dysplasia; Y, year.

It is worth noting that these surveillance intervals are based on current clinical recommendations and may represent a higher estimated cost of RFA than required in the long term. It is likely that these surveillance intervals may decrease over time once a patient has been confirmed of having complete eradication of BO. The Advisory Panel noted that the required frequency of surveillance is still not known due to a lack of published literature and further evidence is required. In practice, once the patient has been confirmed BO eradicated, surveillance would be decreased. As recommended a sensitivity analysis was conducted using surveillance intervals for LGD following eradication with RFA as follows:

- every six months for first two years
- one yearly for three years
- one every two or three years thereafter.

Table 23 provides an estimate of the average costs per cycle used in the LGD Markov model. All costs are the total average cost for a patient in a year, depending on what health state they reside. The costs vary depending upon the time since treatment. For example, an individual previously treated with RFA who currently has no dysplasia will receive two endoscopies per year for the first six years and one endoscopy per year thereafter. Tunnel states were used to capture this timing issue. Tunnel states are commonly used in Markov models so memory can be integrated into the model. The model assigned the cost based on the number of years since treatment.

Table 23 Costs used in the model

Description	Treatment	Cost ($AU)	Assumption
Cost of LGD using RFA	Year 1	$10,102	3 x RFA + 1 x surveillance
Cost of LGD using RFA	Year 2-6	$638	2 x surveillance
Cost of LGD using RFA	Year 7+	$319	1 x surveillance
Cost of LGD using surveillance	Year 1-6	$638	2 x surveillance
Cost of no dysplasia	Year 1-5	$638	2 x surveillence
Cost of no dysplasia	Year 6 +	$319	1 x surveillance
Cost of HGD	Year 1	$10,102	3 x RFA + 1 x surveillance
Cost of HGD	Year 2	$1,276	4 x surveillance
Cost of HGD	Year 3-6	$638	2 x surveillance
Cost of HGD	Year 7+	$319	1 x surveillance
Lifetime cost of cancer	Year 1+	$46,886	See "cost of cancer" section

LGD, low grade dysplasia; HGD, high grade dysplasia

Model Inputs

Health State Utilities

The utility values used in the model were based on a study by Somerville et al (2008). The utility estimates were obtained from the NHS Value of Health Panel, who are trained in standard gamble techniques to express preferences in relation to short descriptions of health states. These values will be tested in sensitivity analysis.

Table 24 Utility values used in the model

Description	Value	Source
Utility of Barrett's with no dysplasia	0.813	Somerville et al (2008)
Utility of Barrett's with LGD	0.813	Somerville et al (2008)
Utility of Barrett's with HGD	0.813	Somerville et al (2008)
Utility of Barrett's with oesophageal adenocarcinoma	0.675	Somerville et al (2008)

LGD, low grade dysplasia; HGD, high grade dysplasia

Transition probabilities

The transition probabilities used in the Markov model were obtained from a variety of sources (published literature and ABS life tables). All of the transition probabilities were adjusted to estimate the one-year probability of moving into a different disease state. Table 25 summarises these estimates. The transition probabilities are the same for the RFA and surveillance arms except for the transition from LGD to no dysplasia. For RFA, the rate of eradication of LGD was 90.5 per cent compared with 22.7 per cent in the control group (Shaheen et al). The eradication of HGD was assumed to be 81 per cent following RFA treatment (Shaheen et al). This rate was applied to both the RFA and surveillance arms of the model.

Table 25 Transition probabilities

One-year probability	Value	Source
LGD progressing to HGD	0.0345	Somerville et al (2008)
LGD progressing to cancer	0.011	Sharma et al (2009)
HGD progressing to cancer	0.064	Rastogi et al (2008)
HGD regressing to LGD	0.048	Somerville et al (2008)
Eradication of HGD using RFA	0.810	Shaheen et al (2009)
No dysplasia progressing to LGD	0.0289	Somerville et al (2009)
No dysplasia progressing to HGD	0.010	Inadomi et al (2009)
No dysplasia progressing to cancer	0.005	Inadomi et al (2009)
LGD to no dysplasia (surveillance)*	0.227	Shaheen et al (2009)
Eradication of LGD using RFA**	0.905	Shaheen et al (2009)
Probability of death from cancer	0.290	various sources[7]
Probability of death from 'all causes'	age dependent	ABS life tables

*This rate is applied on the low-grade dysplasia arm.
**This rate is applied on the low grade RFA arm.
LGD, low-grade dysplasia; HGD, high-grade dysplasia; RFA, radiofrequency ablation

Cost-effectiveness results

For the base case analysis, those who receive RFA for LGD accrue on average 10.178 QALYs and their lifetime treatment costs, including RFA, surveillance and cancer costs is $23,400. For the surveillance group an average 10.079 QALYs are accrued and the lifetime treatment cost is $13,225. This gives an additional benefit of 0.129 QALYs in the RFA group at an additional cost of $10,175 per patient. This yields an incremental ICER for RFA compared to surveillance of $78,975 per QALY (Table 26).

Table 26 Summary of cost-utility analysis for RFA

Procedure	Total cost ($)	Total QALYs	Incremental cost	Incremental QALYs	ICER ($/QALY)
Surveillance	$13,225	10.049			
RFA	$23,400	10.178	$10,175	0.129	$78,975

RFA, radiofrequency ablation.

[7] The probability of cancer was estimated from taking the ratio of the 5-year survival rate of stomach cancer to oesophageal cancer in the UK and applying that to the 5-year survival rate from Australia for stomach cancer, as no 5-year survival rate was available for oesophageal cancer. This was then transformed into a one-year probability of death due to oesophageal cancer.
http://www.statistics.gov.uk/downloads/theme_health/cancer-survival-Eng-2001-2006.pdf
http://www.aihw.gov.au/publications/can/cspia-cdf-82-04/cspia-cdf-82-04.pdf

Sensitivity analysis

Treatment of RFA

In the base case scenario, it is assumed that everyone would be treated with RFA in the LGD arm. Those not successfully eradicated would remain under surveillance. However, if an individual transitions into low grade from any other the other states, they are treated with RFA in the first year they enter the LGD state. The resulting ICER was $78,975 per QALY.

Two scenarios were tested in the sensitivity analysis. The first assumed that those in LGD are only treated once with RFA in the first year and then receive surveillance for any subsequent years. The resulting ICER is $71,959 per QALY. The second scenario assumed that patients would be treated with RFA every year until total eradication of dysplasia occurred. The ICER for this scenario was $79,284 per QALY.

Frequency of surveillance

In the base case scenario, the frequency of surveillance after eradication of LGD was based on conservative estimates. If surveillance is reduced to every six months for the first two years, the one yearly for three years and then one every three years thereafter, the ICER is reduced to $71,075 per QALY.

Univariate

A univariate sensitivity analysis was conducted to test the assumptions and the robustness of the model parameters. The parameters were tested using a confidence interval if available and if unavailable, using an estimate of the range. For the costs of procedures, all costs were halved and doubled to see the effect in the model. The sensitivity analysis was conducted on the following parameters:

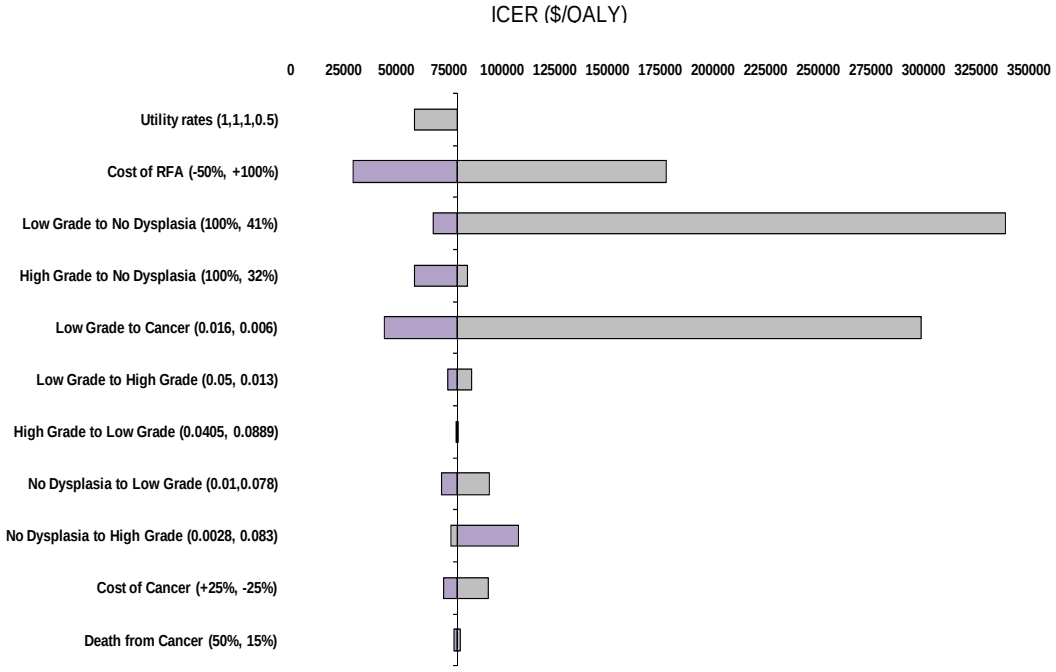
- utility values
- cost of RFA
- eradication rates of dysplasia when using RFA
- progression of LGD to HGD or cancer
- progression of no dysplasia to low grade or HGD
- regression of HGD to low grade or no dysplasia
- the lifetime cost of cancer
- probability of dying from oesophageal adenocarcinoma.

The results of this one-way analysis are presented as a tornado diagram in Figure 4. The vertical axis on the graph represents the base case ICER of RFA versus surveillance which is $78,975 per QALY. The bars to the left of the vertical axis represent a reduction in the ICER based on the lower confidence interval (i.e. first value in the brackets) and the bars to the right represent an increase in the ICER based on the upper confidence interval (second value in the brackets).

The probability of eradication of LGD and the progression from LGD to cancer have the largest effect on the ICER. In the sensitivity analysis the cost of RFA was doubled and reduced in half. As expected, increasing the cost of RFA increases the ICER. Reducing the rate of eradication of LGD following RFA also increases the ICER. This would be expected as these are the main inputs into the model. The parameters that had little effect on the ICER include: death rate from oesophageal cancer, regression of high

grade to low grade, the lifetime cost of cancer and the rates of no dysplasia progressing to LGD or HGD. The rate of LGD progressing to cancer also significantly impacted the ICER as the cancer state is the only state where there is a reduction in quality of life. Therefore, if fewer patients progress into the cancer state, there is not a significant health benefit of RFA over surveillance.

Figure 4 One-way sensitivity analysis



Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was also undertaken. In PSA a distribution is estimated for each of the parameters in the model, either based on confidence intervals, standard errors or the total number of participants in a trial. By assigning distributions to the model parameters, a Monte Carlo simulation with 1,000 draws can be performed to reflect the joint parameter uncertainty. Table 27 shows the distributions for all the transition probabilities and utility values included in the model. A gamma distribution was applied to all costs to account for any uncertainty around the cost estimates used in the model. A gamma distribution is constrained at zero, which best represents costs. As the costs estimated are based on the costing from this report, no standard error was calculated; therefore, the standard error was set to equal the mean.

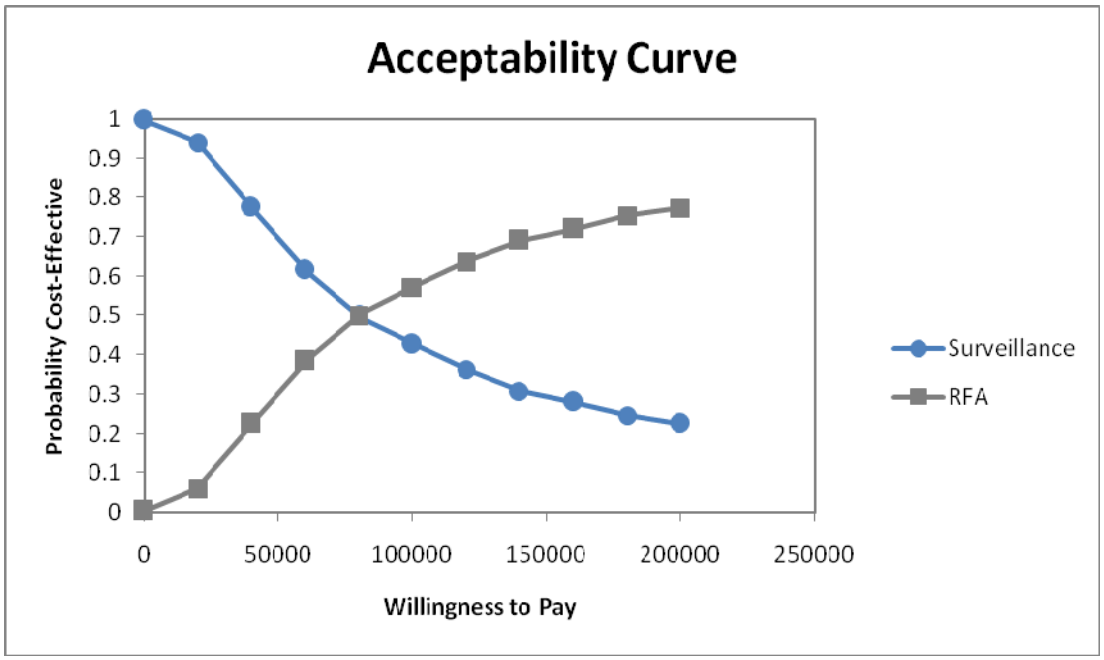
Table 27 Transition probabilities (PSA)

One year probability	Value	Standard Error	Distribution
LGD progressing to HGD	0.0345	0.00944	Beta
LGD progressing to cancer	0.0110	0.00255	Beta
HGD progressing to cancer	0.0640	0.03827	Beta
HGD regressing to LGD	0.0480	0.01235	Beta
HGD regressing to no dysplasia	0.1900	0.08561	Beta
No dysplasia progressing to LGD	0.0289	0.01735	Beta
No dysplasia progressing to HGD	0.0010	0.00804	Beta
No dysplasia progressing to cancer	0.0050	0.00140	Beta
Eradication of LGD using RFA	0.9050	0.01735	Beta
Eradication of LGD using surveillance	0.2270	0.02046	Beta
Probability of death from cancer	0.2900	0.01020	Beta
Utility no dysplasia	0.8125	0.025	Beta
Utility LGD	0.8125	0.025	Beta
Utility HGD	0.8125	0.025	Beta
Utility of cancer	0.6750	0.032	Beta

LGD, low-grade dysplasia; HGD, high-grade dysplasia; RFA, radiofrequency ablation

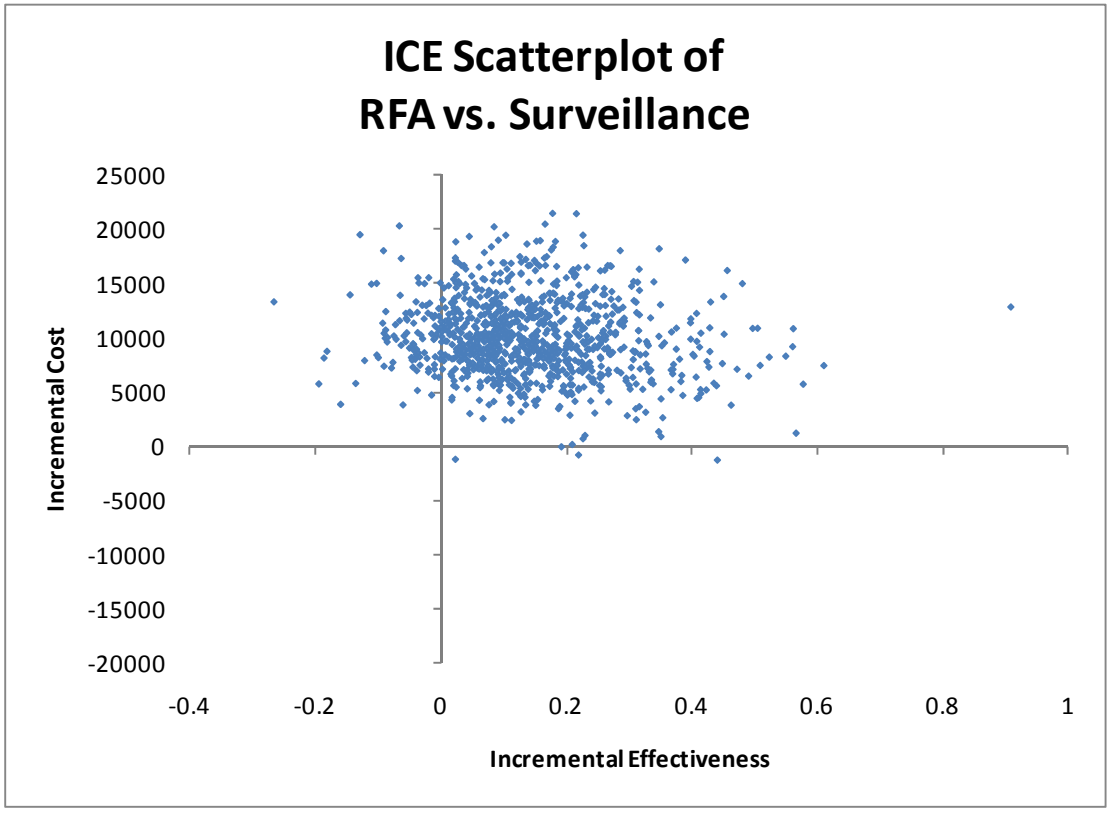
The cost-effectiveness acceptability curve demonstrates the probability of RFA being cost effective across a range of willingness to pay thresholds (Figure 5). At low willingness to pay thresholds surveillance is probably the most cost-effective options. The probability of RFA being more cost effective than surveillance occurs after a willingness to pay of approximately $50,000 per QALY. As can be seen by Figure 5, the probability of RFA being the most cost-effective treatment compared with surveillance is around 50 per cent once the ICER reaches approximately $80,000 per QALY.

Figure 5 Probability of RFA being cost effective compared to surveillance



A Monte Carlo microsimulation was also generated taking 1,000 draws randomly from the distributions around each of the parameters in the model. Figure 6 shows the scatter plot generated from this simulation. The scatter plot shows each of the 1,000 possible ICERs that are obtained when sampling all of the distributions. The simulation demonstrates that the point estimates for RFA are denser in the quadrant with higher effectiveness and higher cost (represented by the north-east quadrant).

Figure 6 PSA – Monte Carlo simulation



Financial implications

To estimate the cost per annum of providing RFA instead of surveillance the number of patients with BO was estimated from two different sources. The first method used the rate of 18 per 100,000 of the population as an estimate of the prevalence of BO. (Schultz et al 2000). Based on this rate, the estimated number of cases of BO is 3,988. Another source estimated the 10 year risk of BO of those in their early 30's at 1 per cent and those in their 70's at 0.1 per cent. Converting these rates into a one-year probability and applying this to the Australian population based on the same age brackets, gives an estimated number of BO cases as 4,103.

It was estimated that a further 10 per cent of those with BO have either LGD or HGD, resulting in 399 cases of LGD/HGD. The Advisory Panel advised that of these, 100 cases would be HGD. Given this breakdown, the financial implications use an estimate of 100 cases of HGD and 299 cases of LGD.

The AIHW Interactive National Hospital Morbidity Datacubes also has the number of separations for BO for 2007-08 as 10,160. This number, however, would include those patients with multiple procedures. Therefore the previous estimate (~4000) will be used to estimate the financial impact. It should be noted, however, that the majority of patients who are diagnosed with BO are non-dysplastic and would not be considered for any of the procedures discussed.

Another method is to estimate the number of cases of LGD and HGD per year, by estimating the prevalence of BO from the number of GORD cases treated. The Advisory Panel estimated that 10 per cent to 15 per cent of patients treated for GORD have BO. The number of GORD patients treated was taken from an AIHW report for 2006-07.[8] Therefore of the 61,049 treated for GORD, approximately 6105 have BO..This would result in 611 cases of LGD/HGD, resulting in an estimated 510 cases of LGD after accounting for the 100 estimated cases of HGD.

For the purposes of this report, the first estimate will be used in the financial implications.

Table 28 Financial Implications of low-grade dysplasia per annum

	RFA	Surveillance
Total cost per patient	$10,102	$638
Number of patients	299	299
Breakdown of financial implications:	0	0
Consumables	$2,385,652	$0
MBS Items	$489,433	$135,058
Patient out-of-pocket	$145,487	$55,602
Total financial implications	$3,030,973	$191,597
Incremental costs:		
Consumables		$2,385,652
MBS Items		$354,375
Patient out-of-pocket		$89,885
Total cost		$2,829,912

MBS., medicare benefits schedule

As can be seen in Table 28, the majority of the additional cost of RFA is due to the high consumables costs. The additional cost of treating the estimated 299 cases of LGD would be $2,829,912 compared to surveillance. This estimate, however, does not take into account any incremental gain in effectiveness from using RFA versus surveillance. As the cost-utility model demonstrated, surveillance will accrue downstream costs due to

[8] http://www.aihw.gov.au/publications/gep/gep-24-10721/gep-24-10721-c16.pdf

the lower rates of eradication of dysplasia. Both of the treatments will have lifetime costs that include hospital costs for surveillance, RFA of high dysplasia and treatment of oesophageal adenocarcinoma.

High-grade dysplasia

Economic model

As previously mentioned, there were insufficient data to support the superior effectiveness of RFA over oesophagectomy, APC or EMR for HGD. Because of the lack of evidence supporting improved effectiveness (clinical or procedural) of RFA, for the purpose of this cost-analysis the assumption is that clinical outcomes are identical between RFA and the comparators.

Estimate of costs

The estimated costs were taken from a number of sources. These included the Medicare Benefits Schedule (MBS), Australian Refined Diagnostic Related Group (AR-DRG) (version 5.1 round 12 – Private and Public), manufacturers' costs and the median charged Medicare fee.

Resource use and MBS item numbers were determined by the Advisory Panel.

Average costs per procedure

The MBS item fees and co-payment contributions were obtained from the MBS (Table 29).

Table 29 MBS item numbers, fees and copayments

MBS item	Item #	MBS fee	MBS benefit*	Copayment
Arterial blood gas	11503	$133.40	$100.05	$57.11
ICU attendance (first day)	13870	$348.40	$261.30	$149.07
ICU attendance	13873	$258.45	$193.85	$103.86
Pre-anaesthesia consultation	17610	$41.35	$31.05	$45.92
Infusion during anaesthesia	18222	$36.25	$27.20	$23.38
Initiation of anaesthesia	20500	$285.75	$214.35	$1,149.56
Initiation of anaesthesia**	20740	$95.25	$81.00	$49.53
Administration of blood	22002	$76.20	$57.15	$81.04
Bronchial blocker	22008	$76.20	$57.15	$87.47
Blood pressure monitoring	22012	$57.15	$42.90	$66.86
Respiratory function test	22018	$133.40	$100.05	$128.93
Central line	22020	$76.20	$57.15	$86.38
Arterial line	22025	$76.20	$57.15	$89.18
Intrathecal or epidural injection	22031	$95.25	$71.45	$126.17
Laparotomy	30375	$501.50	$376.15	$145.18
Oesophagoscopy	30473	$170.40	$144.85	$43.45
Oesophagoscopy (EMR)**	30478	$236.25	$200.85	$69.55
Endoscopy (APC)**	30479	$458.05	$389.35	$81.67
Oesophagectomy	30535	$1,632.35	$1,224.30	$1,138.16
Operative feeding jejunostomy	31462	$501.50	$376.15	$149.63
Parenteral nutrition	34538	$262.05	$196.55	$131.92
Thoracotomy	38418	$922.10	$691.60	$509.58
Thoracoscopy	38436	$240.30	$180.25	$74.39
Dilation of stricture	41819	$335.75	$251.85	$240.91
Assistance	51303	†		$329.19
ECG	55113	$230.65	$173.00	$101.86
CT scan	56101	$230.00	$172.50	$92.37
Chest X-ray	58503	$47.15	$35.40	$25.61
Barium swallow	58912	$110.25	$82.70	$53.95
Full blood count	65070	$17.05	$12.80	$7.20
Group and hold	65096	$41.30	$31.00	$18.93
Electrolyte	66512	$17.80	$13.35	$7.49

* The MBS benefit is 75% of the MBS fee for inpatient services and 85% for outpatient services.
** These MBS items are undertaken in the outpatient setting and therefore will contribute to the extended safety net.
† Assistance is calculated as 1/5th of the schedule fee for associated MBS items greater than $527.65.
ICU, intensive care unit; EMR, endoscopic mucosal resection; APC, argon plasma coagulation; ECG, electrocardiogram; CT scan, computed tomography scan; MBS., medicare benefits schedule.

Capital costs

As with LGD, the capital costs of RFA include a generator, sizing balloon and ablation catheter for the Halo^{360}. A separate generator and ablation catheter is also required for the Halo^{90}. All costs were provided by Device technologies Australia Pty Ltd. The capital costs for APC were sourced from a previous MSAC review (MSAC 1106), which evaluated endoscopic APC of GI bleeding and oesophageal stents.

The average capital cost contribution per patient was based on the following assumptions: a six-year-life of the machine, an average 40 procedures per machine per

year and discounted at 5 per cent. This gives an average capital cost per procedure of $275 and $248 for Halo^{360} and Halo^{90}, respectively.

Hospital stay

The average per diem cost for hospitalisation for an oesophagectomy was derived from the AR-DRG information for DRG G03B (version 5.1 round 12 – Private and Public). This DRG is for stomach oesophageal and duodenal procedures without malignancy with catastrophic or severe complications. The Advisory Panel indicated that the estimated hospital stay for a patient following an oesophagectomy would be approximately 10 days. The hospital stay was estimated as the overhead and direct cost of ward nursing and hotel divided by the average length of stay. A cost for intensive care was also included in the model, which is estimated from the critical care overhead and direct costs from DRG G03B.

Complication costs

Costs incurred due to complication post surgery were included in the model for oesophagectomy. It was assumed that approximately 20 per cent of patients would be treated for stenosis, 5 per cent for anastomic leak and a further 5 per cent would require a blood transfusion. These costs were based on the most appropriate MBS item which would cover these complications.

Table 30 Calculation of average annual costs for endoscopic therapies for high-grade dysplasia

	Unit Cost	RFA		EMR		APC	
		Units	Total	Units	Total	Units	Total
Equipment							
Halo[360]	$275	1	$275				
Sizing balloon	$869	1	$869				
Ablation catheter	$2,739	1	$2,739				
Halo[90]	$248	2	$495				
Ablation catheter	$1,800	2	$3,600				
Capital cost APC	$299					3	$1,017
Disposable probe	$300					3	$900
Consumables	$400			3	$1,200		
Operational							
Radiofrequency ablation (MBS based on 30479)	$389	3	$1,168				
MBS 30479 copayment	$82	3	$245				
Oesophagoscopy (MBS 30473)	$145	1	$145	1	$145	1	$145
MBS 30473 copayment	$43	1	$43	1	$43	1	$43
Oesophagoscopy (MBS 30478)	$201			2	$402		
MBS 30478 copayment	$70			2	$139		
Endoscopy (MBS 30479)	$389					3	$1,168
MBS 30479 copayment	$82					3	$245
Initiation of anaesthesia (MBS 20740)	$81	4	$324	3	$243	4	$324
MBS 20740 copayment	$50	4	$198	3	$149	4	$198
Total consumables			$7,979		$1,200		$1,917
Total MBS benefits			$1,637		$790		$1,637
Total patient out-of-pocket			$487		$331		$487
Total cost of RFA in HGD			$10,102		$2,321		$4,041

RFA, radiofrequency ablation; MBS., medicare benefits schedule.

Table 31 Calculation of average annual costs for oesophagectomy in high-grade dysplasia

	Unit cost	Units	Total
Equipment			
Stapler	$435	1	$435
Reloads	$244	5	$1,220
Central line (BA049)	$180	1	$180
Pre operational			
Anaesthesia consult (MBS 17610)	$31	1	$31
MBS 17610 copayment	$46	1	$46
Chest X-ray (MBS 58503)	$35	5	$177
MBS 58503 copayment	$26	5	$128
ECG examination (MBS 55113)	$173	1	$173
MBS 55113 copayment	$102	1	$102
Respiratory function test (MBS 22018)	$100	0.5	$50
MBS 22018 copayment	$129	0.5	$64
Full blood count (MBS 65070)	$13	10	$128
MBS 65070 copayment	$7	10	$72
Electrolyte count (MBS 66512)	$13	7	$93
MBS 66512 copayment	$7	7	$52
Blood group and hold (MBS 65096)	$31	1	$31
MBS 65096 copayment	$19	1	$19
Arterial blood gas (MBS 11503)	$100	10	$1,001
MBS 11503 copayment	$57	10	$571
Blood pressure monitoring (MBS 22012)	$43	5	$215

MBS 22012 copayment	$67	5	$334
Operational			
Oesophagectomy (MBS 30535)*	$1,224	1	$1,224
MBS 30535 copayment	$1,138	1	$1,138
Initiation of anaesthesia (MBS 20500)	$214	1	$214
MBS 20500 copayment	$1,150	1	$1,150
Assistance (MBS 51303)	$245	1	$245
MBS 51303 copayment	$329	1	$329
Insertion of central line (MBS 22020)	$57	1	$57
MBS 22020 copayment	$86	1	$86
Insertion of arterial line (MBS 22025)	$57	1	$57
MBS 22025 copayment	$89	1	$89
Intrathecal or epidural injection (MBS 22031)	$71	1	$71
MBS 22031 copayment	$126	1	$126
Operative feeding jejunostomy (MBS 31462)*	$188	1	$188
MBS 31462 copayment	$150	1	$150
Bronchial blocker (MBS 22008)	$57	1	$57
MBS 22008 copayment	$87	1	$87
Infusion during anaesthesia (MBS 18222)	$27	1	$27
MBS 18222 copayment	$23	1	$23
Laparotomy (MBS 30375)*	$94	1	$94
MBS 30375 copayment	$145	1	$145
Oesophagoscopy (MBS 30473)	$145	2	$290
MBS 30473 copayment	$43	2	$87
Initiation of anaesthesia (MBS 20740)	$81	2	$162
MBS 20740 copayment	$50	2	$99
Hospitalisation (Ward nursing+hotel)	$518	10	$5,179
Post-operational			
Intensive care (ICU)	$1,832	2	$3,664
ICU attendance first day (MBS 13870)	$261	1	$261
Co-payment (MBS 13870)	$149	1	$149
ICU attendance subsequent days (MBS 13873)	$194	1	$194
Co-payment (MBS 13873)	$104	1	$104
Chest physiotherapy (1 week)	$416	1	$416
Barium swallow (MBS 58912)	$83	1	$83
MBS 58912 copayment	$54	1	$54
Heparin injection (2x daily)	$11	10	$110
Dietician (3 visits)	$203	1	$203
*Complications***			
Dilation of stricture	$701	0.2	$140
Anastomic leak-radiological	$4,682	0.03	$140
Anastomic leak-clinical	$10,763	0.02	$215
Blood transfusion	$299	0.05	$15
Total consumables			$1,835
Total MBS benefits			$15,105
Total patient out-of-pocket			$5,308
Total cost of oesophagectomy			$22,248

* The multiple services rule applies to these items, in which the fee for the first procedure is calculated as100% of the Schedule fee, the second procedure 50% of the Schedule fee and 25% of the Schedule fee for all procedures thereafter.

**A full breakdown of the complications and MBS codes can be found in Appendix G. ICU, intensive care unit; ECG, electrocardiogram; CT scan, computed tomography scan; MBS., medicare benefits schedule.

Average costs of each procedure

The total estimated first-year-cost of RFA, oesophagectomy, EMR and APC in BO with high dysplasia is: $10,102, $22,248, $2,321 and $4,041, respectively. This represents a cost saving of $12,146 when using RFA as opposed to oesophagectomy. However, the incremental cost of RFA relative to EMR and APC is $7,782 and $6,062, respectively.

Table 32 Incremental cost of first year of treatment of high-grade dysplasia

	RFA	Oesophagectomy	EMR	APC
Total consumables	$7,979	$1,835	$1,200	$1,917
Total MBS items	$1,637	$15,105	$790	$1,637
Total patient out-of-pocket	$487	$5,308	$331	$487
Total cost per procedure	$10,102	$22,248	$2,321	$4,041
Incremental cost		-$12,146*	$7,782	$6,062

* The negative number denotes a cost saving. RFA, radiofrequency ablation; EMR, endoscopic mucosal resection; APC, argon plasma coagulation; MBS, medicare benefits schedule.

The main difference between the costs of the endoscopic procedures is the high cost of the consumables, which is the driver of the cost of RFA compared to the other treatment options. The generator, sizing balloon and catheters represent over 75 per cent of the total treatment cost of RFA. Even if the number of RFA procedures per patients is reduced (e.g. 2 instead of 3 procedures), RFA still remains a higher incremental cost than both EMR and APC.

Implication to the extended Medicare safety net

All MBS items for RFA, EMR and APC are performed in the outpatient setting. Therefore any out-of-pocket cost associated with these items will contribute towards the Extended Medicare Safety Net (EMSN). The total out-of-pocket costs for these items is below the $1126 threshold ($562.90 for concession card holders). Consequently, out-of-pocket contributions procedures relating to BO are unlikely to impact upon the EMSN.

Financial implications

As discussed in the LGD section, the number of estimated cases of HGD was 100 cases in Australia, based on expert opinion. Table 33 demonstrates the financial implications of treating these 100 cases with RFA instead of oesophagectomy, EMR or APC.

Table 33 Financial implications

	RFA	Oesophagectomy	EMR	APC
Total cost per patient	$10,102	$22,248	$2,321	$4,041
Estimated usage	100%	100%	100%	100%
Number of patients	100	100	100	100
Breakdown of financial implications:				
Consumables	$797,877	$183,500	$120,000	$191,722
MBS Items	$163,690	$1,510,545	$78,955	$163,690
Patient out-of-pocket	$48,658	$530,768	$33,114	$48,658
Total financial implications	$1,010,225	$2,224,813	$232,069	$404,070
Incremental costs:				
Consumables		$614,377	$677,877	$191,722
MBS Items		-$1,346,855	$84,735	$163,690
Patient out-of-pocket		-$482,110	$15,544	$48,658
Total cost		-$1,214,588*	$778,156	$606,155

* The negative number denotes a cost saving. RFA, radiofrequency ablation; EMR, endoscopic mucosal resection; APC, argon plasma coagulation; MBS, medicare benefits schedule.

As can be seen in Table 33, if direct replacement of RFA occurred for oesophagectomy in HGD, the overall cost savings would be $1,214,588. If RFA was used to treat 100 patients instead of EMR or APC, there would be an incremental cost of $778,156 or $606,155, respectively.

Other cost considerations

The analysis thus far has demonstrated that if RFA is used as a direct replacement for oesophagectomy there will be a cost savings, but if it replaces EMR or APC there will be an increase in cost. However, depending on the severity of the disease or a patient's individual characteristics, direct replacement may not be appropriate in all cases.

The analysis assumes that RFA, EMR, APC and oesophagectomy are identical in terms of effectiveness. However, the following factors should be considered: comparing oesophagectomy does not take into account any reduction in quality of life that may occur post-surgery; and individual patient characteristics may mean that all four treatment options are not suitable (i.e. they are not interchangeable).

Finally, funding of the RFA disposable catheter should be considered. The catheter cannot be funded by the MBS and may not be suitable for the prostheses and devices list. If this were the case the patient would be responsible for the additional cost.

Discussion

Limitations of the evidence

Conclusions determined in this assessment are limited by the evidence available. Only one level II RCT was available for inclusion, limiting the comparison of RFA to existing procedures such as APC, EMR and oesophagectomy. In addition, a large number of studies had to be excluded due to cited patient overlap, to prevent duplication or misrepresentation of results. However, in some studies it was unclear whether patient overlap was present, providing a possible source of evidence inconsistency. Many studies did not meet the inclusion criteria outlined in the PICO criteria, and reported pooled results for mixed indications. A full list of excluded studies and reasons for exclusion are outlined in Appendix H.

All studies included reported clinically relevant outcomes including complete histological eradication of IM and dysplasia, disease progression (number of patients and level of diagnosed and recurrent dysplasia), as well major and minor adverse events. Relevant adverse events included chest pain, stricture, haemorrhage, fever and dysphagia.

Validated outcome assessment tools were utilised in the studies included. These included histological confirmation of regression of IM and dysplasia as well as the absence of subsquamous IM.

The length of follow-up ranged from 11 to 24 months in the included studies. However, this length of follow-up is insufficient to determine the long-term success rate of RFA, as one of the secondary outcomes is disease progression (to cancer), which would occur over a number of years. In cases where recurrence occurred within the follow-up period of the study, the level of dysplasia and choice of corrective intervention was reported.

Many authors were personally funded or employed by Barrx, with additional funding provided to cover the costs of the research. In addition, the RCT by Shaheen et al (2009) was funded by Barrx, who also managed the patient database. This may have introduced biases in study design, patient selection and reporting of outcomes across the included studies.

Clinical need and burden of disease

Difficulty was encountered in determining the prevalence of BO with dysplasia in the Australian population. AIHW data reported the principle diagnosis of BO in the Australian hospital system; however, this data was not separated by the level of dysplasia. In addition, expert clinical advice indicated that this may be an underestimate of the total number of BO cases Australia-wide as many patients are diagnosed in an outpatient clinic. Consequently, it is difficult to estimate how many Australians would require treatment with RFA. Additionally, there is currently no literature published reporting the progression rate of patients from LGD to HGD and IMC. Expert clinical opinion also supported this finding and consequently economic modelling factored lack of reliable progression rate data into the Markov model included in this assessment.

Definition of the target population was determined a priori, impacting on the generalisability of the literature selected for inclusion. High-grade dysplasia was identified

as the target population for this assessment; however, the literature did not reflect this selection. Many authors selected LGD as the target population of choice, with few including patients with HGD. In addition, many authors treated patients with IM, identified as outside the scope of this assessment. Consequently, these studies could not be included as it was unclear which patients achieved the corresponding safety and effectiveness results. Identification of this issue within the literature may be indicative of a potential for patient leakage within the Australian health care system.

Existing procedures

The diffusion and use of EMR and APC was difficult to determine, as both treatments can be used as palliative or curative treatments. Consequently, identifying and isolating an equivalent alternative clinical regiment already utilised by gastroenterologists and upper GI surgeons was difficult. In addition, current MBS item numbers do not prescribe specific indications for the use of existing treatments including APC and EMR, and therefore did not provide an accurate estimate of the number of procedures currently conducted for treatment of BO with dysplasia.

Safety and effectiveness

The reporting of the safety and effectiveness results for mixed patient populations was of greatest concern in the safety and effectiveness sections, as it made it difficult to identify differences in safety and effectiveness between patient populations.

Additionally, the clinical impact of the safety and effectiveness results of RFA can be assigned as moderate for patients with LGD and substantial for patients with HGD and IMC. This is due to the differences in the risk of complication and disease progression between these patient populations. Traditionally patients suffering from LGD would be placed on treatments associated with low complication rates, namely, pharmacological intervention and surveillance. In contrast, patients with HGD would typically receive oesophagectomy, presenting a high complication rate and a greater risk of disease progression. Consequently, RFA provides a less invasive treatment modality with a lower complication rate, offering a substantial difference in possible patient management for patients with HGD.

Table 34 provides an overall evaluation of the body of evidence for RFA treatment for patients with BO with dysplasia.

Table 34 Completed body of evidence assessment matrix for RFA treatment for patients with BO with dysplasia

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base				level IV studies, or level I to III studies with high risk of bias
Consistency		most studies consistent and inconsistency may be explained		
Clinical impact		substantial	moderate	
Generalisability		population/s studied in the body of evidence are similar to the target population		
Applicability			probably applicable to Australian healthcare context with some caveats	

Adapted from (NHMRC 2008)

Conclusions

Literature findings

Lack of comparative data has prevented the comparison of the safety and effectiveness of RFA to existing interventions including surveillance, APC, EMR and oesophagectomy. In addition, results were conflicted by the reporting of safety and effectiveness results of mixed patient populations in some studies, many of which included patients of disease severity classified as beyond the scope of this assessment. Further difficultly was encountered as there was duplication between some studies, and this was not always clear. One RCT was available for inclusion (Shaheen et al 2009) comparing RFA to a sham procedure. All other studies included were case series with low patient numbers (10 to 142 patients) and short-term follow-up.

Safety

A total of five studies (one RCT) were included for the safety analysis. A total of 23 complications occurred in 411 patients included in this assessment, following multiple treatment sessions with RFA. Most adverse events were minor and resolved without additional intervention.

Effectiveness

A total of six studies were included in the effectiveness analysis. The complete histological eradication of IM across all included studies ranged from 54 per cent (Ganz et al 2008) to 91 per cent (Pouw et al 2008). Notably, in the RCT (Shaheen et al 2009) the CR-IM and CR-D rates were lower in the control group (57% and 59% respectively), than those of the RFA group (98% and 99%) ($P<0.001$).

Evidence of subsquamous IM was found in five patients (Pouw et al 2008, Shaheen et al 2009) treated with RFA.

Cost-effectiveness

The objective of this section was to conduct an economic evaluation of the therapeutic use of RFA in BO with dysplasia. Following advice from the Advisory Panel, it was decided that the treatment of HGD and LGD would be considered separately.

Given there was sufficient evidence of superior effectiveness of RFA in treating LGD compared to surveillance, a full cost-utility analysis of RFA for the treatment of LGD was undertaken. A decision analytic model was developed to estimate the incremental cost per quality adjusted life year (QALY) of using RFA over surveillance.

Based on a number of estimates and assumptions:

- For LGD, replacing surveillance with RFA would yield an additional benefit of 0.129 QALYs at an additional cost of $10,175. This gives an incremental ICER for RFA compared to surveillance of $78,975 per QALY.

- The main drivers of the cost-effectiveness result are the probability of eradication of LGD after treatment with RFA, the probability of progressing to cancer from LGD and the cost of RFA.

- In the sensitivity analysis, if the frequency of surveillance is reduced after eradication of low grade or HGD, the resulting ICER is $71,075.

There was insufficient comparative evidence to undertake a full cost-effectiveness analysis of RFA for the treatment of HGD. A cost analysis was conducted to compare the annual cost of treating HGD with RFA, oesophagectomy, EMR or APC.

- Based on an estimated prevalence of 100 cases of HGD, if direct replacement of RFA occurred for oesophagectomy the overall cost savings would be $1,214,588. If RFA was used to treat 100 patients instead of EMR or APC, there would be a total additional cost of $778,156 or $606,155, respectively.

- The cost analysis assumes that RFA, EMR, APC and oesophagectomy are identical in terms of effectiveness and does not take into account, for example, any reduction in quality of life that may occur post-surgery with oesophagectomy. Individual patient characteristics may mean that all four treatment options are not interchangeable.

Appendix A: MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine, general practice, clinical epidemiology, clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or affiliation**
Professor Robyn Ward (Chair)	Medical oncology
Associate Professor Frederick Khafagi (Deputy Chair)	Nuclear medicine
Professor Jim Butler (Economics Sub-committee Chair)	Health economics
Associate Professor John Atherton	Cardiology
Professor Justin Beilby	General practice/research
Associate Professor Michael Bilous	Anatomical pathology
Professor Jim Bishop AO	Chief Medical Officer (*ex officio member*)
Professor Peter Cameron	Trauma and emergency medicine
Associate Professor Kirsty Douglas	General practice/research
Dr Kwun Fong	Thoracic medicine
Professor Richard Fox	Medical oncology
Professor John Horvath	Renal medicine/health workforce
Ms Elizabeth Koff	Health administration
Professor Helen Lapsley	Health economics
Professor Peter McCluskey	Ophthalmology
Mr Russell McGowan	Consumer health representative
Dr Allan McKenzie	Radiology
Dr Graeme Suthers	Genetics/pathology
Mr David Swan	AHMAC representative
Professor Ken Thomson	Radiology
Dr Christine Tippett	Obstetrics/gynaecology
Associate Professor David Winlaw	Paediatric cardiothoracic surgery
Dr Caroline Wright	Colorectal cancer/surgery

Appendix B: Advisory Panel and Evaluators

Advisory Panel - Radiofrequency ablation for Barrett's oesophagus with dysplasia Application no. 1143

Member	Nomination / expertise or affiliation
Dr Caroline Wright (Chair)	Member of MSAC Colorectal cancer
A/Professor Michael Bilous (Deputy Chair)	Member of MSAC Anatomical pathology
Dr Philip Craig	Gastroenterologist
Professor Reginald Vincent Norrie Lord	Upper gastro-intestinal surgeon
Dr Peter Tagkalidis	Gastroenterologist
Dr David Carlisle Whiteman	Medical epidemiologist
Mrs Juli Ferguson	Consumer health representative

Evaluation Sub-committee input

Name	Affiliation
Professor Andrew Wilson	ESC member

Evaluators

Name	Organisation
Ms Stefanie Gurgacz	ASERNIP-S
Dr Alun Cameron	ASERNIP-S
Ms Jody Church	CHERE
Dr Stephen Goodall	CHERE

Appendix C: Current reimbursement arrangements

Table 35 MBS item numbers associated with Barrett's oesophagus with dysplasia

MBS item number	Descriptor	Number of services 2009-10
30473	Oesophagoscopy (not being a service to which item 41816 or 41822 applies), gastroscopy, duodenoscopy or panendoscopy (1 or more such procedures), with or without biopsy, not being a service associated with a service to which item 30476 or 30478 applies Fee: $167.40 Benefit: 75%=$125.55, 85%=$142.30	296,814
30478	Oesophagoscopy (not being a service to which item 41816, 41822 or 41825 applies), gastroscopy, duodenoscopy or panendoscopy (1 or more such procedures), with 1 or more of the following endoscopic procedures - polypectomy, removal of foreign body, diathermy, heater probe or laser coagulation, or sclerosing injection of bleeding upper gastrointestinal lesions, not being a service associated with a service to which item 30473 or 30476 applies Fee: $232.05 Benefit: 75%=$174.05, 85%=$197.25	10,725
30479	Endoscopic laser therapy for neoplasia and benign vascular lesions or strictures of the gastrointestinal tract Fee: $449.95 Benefit: 75%=$337.50, 85%=$382.50	1,134
30535[a]	Oesophagectomy with gastric reconstruction by abdominal mobilisation and thoracotomy Fee: $1,603.50 Benefit: 75%=$1,202.65	57
41816	Oesophagoscopy (with rigid oesophagoscope) Fee: $175.45 Benefit: 75% = $131.60 85% = $149.15	1,059
41822	Oesophagoscopy (with rigid oesophagoscope), with biopsy Fee: $225.70 Benefit: 75%=$169.30	260

a This procedure was noted as the most relevant comparator by the applicant.

Table 36 AIHW data on the number of relevant public hospital procedures

Procedure item number	Descriptor	Number of services 07-08
858	Oesophagectomy by abdominal and thoracic mobilisation	52
859	Oesophagectomy by abdominal and cervical mobilisation	57
860	Oesophagectomy by abdominal and transthoracic mobilisation	320
Total oesophagectomies		429
30473-04	Oesophagoscopy with biopsy	697
30478-13	Oesophagoscopy with excision of lesion	74
30559-00	Local excision of the oesophagus	29
41822-00	Rigid oesophagoscopy with biopsy	216
30479-00	Endoscopic laser therapy to the oesophagus	135

MBS Item number 30535 shown in Table 35 was identified by the applicant as being of most relevance to this assessment. However, there are a total of 17 item numbers listed on the MBS for oesophagectomy. In the financial year 2008-09 the services provided for these individual 17 item numbers ranged between one and 81. A total of 267 services were provided for all 17 items in this financial year.

Notably, neither the MBS nor AIHW data regarding the number of procedures separates the data according to indication. Therefore it is unclear from this data how many oesophagectomies are undertaken specifically for BO.

Table 37 Current MBS indications for radiofrequency ablation

MBS item number	Descriptor
32500 - 32517	Varicose veins.
35616	Endometrium, endoscopic examination and ablation of, by microwave or thermal balloon or radiofrequency electrosurgery, for chronic refractory menorrhagia including any hysteroscopy performed on the same day, with or without uterine curettage Fee: $424.90 Benefit: 75%=$318.70
50950	Nonresectable hepatocellular carcinoma, destruction of, by percutaneous radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50952 applies Fee: $772.25 Benefit: 75%=$579.20, 85%=$703.15
50952	Nonresectable hepatocellular carcinoma, destruction of, by open or laparoscopic radiofrequency ablation, where a multi-disciplinary team has assessed that percutaneous radiofrequency ablation cannot be performed or is not practical because of one or more of the following clinical circumstances: - percutaneous access cannot be achieved - vital organs/tissues are at risk of damage from the percutaneous RFA procedure, or - resection of one part of the liver is possible; however, there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50950 applies. Fee: $772.25 Benefit: 75%=$579.20, 85%=$703.15

Appendix D: Ongoing trials

Title: Micro-layer ablation of Barrett's Metaplasia- a two-phase, multi-center trial - Extension of follow-up to five years

Institution: Multi-centre study, USA and Puerto Rico

Contact: David E Fleischer, Mayo Clinic Minnesota USA

Start date: November 2003

Expected completion date: October 2009

Identifier: US NIH clinicaltrials.gov NCT00489268

Title: HALO Patient registry: ablation of Barrett's esophagus

Institution: Gastrointestinal Associates and sites across the USA [recruiting]

Contact: Shirin R Hasan, David S Utley (Barrx Medical)

Start date: July 2007

Expected completion date: December 2019

Identifier: US NIH clinicaltrials.gov NCT00848237

Title: Ablation of intestinal metaplasia containing dysplasia

Institution: Multi-institutional study within the USA

Contact: David S Utley (Barrx Medical)

Start date: February 2006

Expected completion date: October 2013

Identifier: US NIH clinicaltrials.gov NCT00282672

Appendix E: Studies included in the review

Ganz RA, Overholt BF, Sharma VK, Fleischer DE, Shaheen NJ, Lightdale CJ, Freeman SR, Pruitt RE, Urayama SM, Gress F, Pavey DA, Branch MS, Savides TJ, Chang KJ, Muthusamy VR, Bohorfoush AG, Pace SC, DeMeester SR, Eysselein VE, Panjehpour M, Triadafilopoulos G, 2008. 'Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. Multicenter Registry', *Gastrointest Endosc*, 68(1), 35-40.

Pouw RE, Gondrie JJ, Sondermeijer CM, ten Kate FJ, van Gulik TM, Krishnadath KK, Fockens P, Weusten BL, Bergman JJ, 2008. 'Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection', *J Gastrointest Surg*, 12(10), 1627-1636.

Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ, 2009. 'Radiofrequency ablation in Barrett's esophagus with dysplasia', *N Engl J Med*, 360(22), 2277-2288.

Sharma VK, Jae KH, Das A, Wells CD, Nguyen CC, Fleischer DE, 2009. 'Circumferential and focal ablation of Barrett's esophagus containing dysplasia', *Am J Gastroenterol*, 104(2), 310-317.

Sharma VK, Kim HJ, Das A, Dean P, DePetris G, Fleischer DE, 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(5), 380-387.

Vassiliou MC, von Renteln D, Wiener DC, Gordon SR, Rothstein RI, 2010. 'Treatment of ultralong-segment Barrett's using focal and balloon-based radiofrequency ablation', *Surg Endosc,* 24(1), 786-791 .

Systematic reviews, HTA reviews and guidelines

Bennett C, Green S, Barr H, Bhandari P, DeCaestecker J, Ragunath K, Singh R, Tawil A and Jankowski J, 2010. 'Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus', *Cochrane Database of Systematic Reviews*, Issue 11.

California Technology Assessment Forum 2010. Radiofrequency ablation as a treatment of dysplastic Barrett's esophagus, Californian Technology Assessment Forum 2010.

Fernando HC, Murthy SC, Hoffstetter W, Shrager J, Bridges C, Mitchell J, Landreneau R, Clough E, Watson T, 2009. 'The Society of Thoracic Surgeons practice guideline series: Guidelines for the management of Barrett's esophagus with high-grade dysplasia', *Annals of Thoracic Surgery*, 87, 1193-2002.

Li Y, Li L, Yu C, Liu Y, Xu C, 2008, 'A systematic review and meta-analysis of the treatment for Barrett's esophagus, Digestive Diseases and Sciences, 53(2), 2837-2846

National Institute for Health and Clinical Excellence, 2010a. *Ablative therapy for the treatment of Barrett's oesophagus (CG106)*, <http://www.evidence.nhs.uk/search.aspx?t=CG106> [Accessed 20 September 2010].

National Institute for Health and Clinical Excellence, 2010b, *Thorascopically assisted oesophagectomy (IPG189)*, <http://www.nice.org.uk/nicemedia/live/11260/31578/31578.pdf> [Accessed 20 September 2010].

National Institute for Health and Clinical Excellence 2010c, Epithelial radiofrequency ablation for Barrett's oesophagus, <http://www.nice.org.uk/nicemedia/live/11359/48933/48933.pdf> [Accessed 20 September 2010].

Rees JR, Lao-Sirieix P, Wong A, Fitzgerald RC, 2010. 'Treatment for Barrett's oesophagus', *Cochrane Systematic Review Database*, Jan 20, no. 1.

Wang K, Sampliner R and the Practice Parameters Committee of the American College of Gastroenterology 2008, 'Updated guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus', American Journal of Gastroenterology, 103(3), 788-797

Stefanidis D, Hope W, Kohn G, Reardon P, Richardson W, Fanelli R and the SAGES Guidelines Committee 2010, 'Guidelines for surgical treatment of gastroesophageal reflux disease', SAGES, February 2010.

Technology Assessment Unit of McGill University 2009, 'Radiofrequency ablation for treatment of Barrett's esophagus: A systematic review and cost analysis', report number 46, 12 November 2009

Wani S, Puli S, Shaheen N, Wethoff B, Slehria S, Bansal A, Rastogi A, Sayana H, Sharma P, 2009, 'Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: A meta-analysis and systematic review, *American Journal of Gastroenterology*, 104(1), 502-513.

Appendix F: Electronic databases searched

Centre for Reviews and Dissemination (CRD) / International Network of Agencies for Health Technology Assessment (INAHTA) databases – including: NHS Economic Evaluation Database (NHS EED) / Database of Abstracts of Reviews of Effect (DARE) / Heath Technology Assessment (HTA) Database
http://www.york.ac.uk/inst/crd/

Trip database
http://www.tripdatabase.com

Adelaide Health Technology Assessment (AHTA)
www.health.adelaide.edu.au/publichealth/consult/health_techn_assess.html

Centre for Clinical Effectiveness, Monash University
www.mihsr.monash.org/cce/

Health Economics Unit, Monash University
chpe.buseco.monash.edu.au

Medical Services Advisory Committee (MSAC)
www.msac.gov.au

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)
www.aetmis.gouv.qc.ca/site/index.php?home

Alberta Heritage Foundation for Medical Research (AHFMR)
www.ahfmr.ab.ca/publications/

Canadian Agency for Drugs and Technologies in Health (CADTH)
www.cadth.ca/index.php/en/home

Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database
www.mycabot.ca

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University
www.chepa.org

Centre for Health Services and Policy Research (CHSPR), University of British Columbia
www.chspr.ubc.ca

Health Utilities Index (HUI)
www.fhs.mcmaster.ca/hug/index.htm

Institute for Clinical and Evaluative Studies (ICES)
www.ices.on.ca

Institute of Health Economics (IHE)
www.ihe.ca/

Ministry of Health and Long-Term Care – Medical Advisory Secretariat
http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html

New Zealand Health Technology Assessment (NZHTA)
http://nzhta.chmeds.ac.nz/

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/clinic/techix.htm

Harvard School of Public Health – Cost-Utility Analysis Registry
http://www.tufts-nemc.org/cearegistry/

U.S. Blue Cross/ Blue Shield Association Technology Evaluation Centre (TEC)
www.bcbs.com/betterknowledge/tec/

Veterans' Affairs Technology Assessment Program (VATAP)
www.va.gov/vatap/publications.htm

Appendix G: Additional Tables

Safety

Table 38 Previous EMR vs adverse events

Study ID	n	EMR n (%)[a]	AE n	Incidence (%)
RCT				
Shaheen et al 2009	127	11 (9)	4	3
Case Series				
Pouw et al 2008	44	31 (70)	10	23
Sharma et al 2009	63	2 (3)	3	5
Sharma et al 2008	10	NR	1	10
Ganz et al 2008	92	24 (26)	-	-
Vassiliou et al 2010	25	3[a] (12)	5	20

a % of total study population

Effectiveness

Table 39 Previous EMR vs effectiveness outcomes

Study ID	n	EMR	Primary outcome Histological eradication	Secondary outcome Disease progression
RCT				
Shaheen et al 2009	127	11 (9)		
Intervention			CR-IM 97.5% LGD; 98.5% HGD [b]	Total 3/84 (3.6%); 1/42 (2.4%) HGD [c]
Control			CR-IM 56.9% LGD; 58.6% HGD	Total 7/43 (16.3%), 4/21 (19%) HGD [d]
Case Series				
Pouw et al 2008	44	31(70)	CR-IM 40/44 (91%)	1/1475 biopsies showed buried glands
Sharma et al 2009	63	2 (3)	CR-IM LGD 33//39 (87%) CR-IM HGD 16/24 (67%); CR-D 19/24 (79%)	No buried glands reported
Sharma et al 2008	10	NR	CR-IM 9/10 (90%); CR-D 10/10 (100%)	No buried glands reported
Ganz et al 2008	92	24 (26)	CR-HGD 85/92 (90.2%); CR-D 77/92 (80.4%), CR-IM 50/92 (54.3%)	No buried glands reported
Vassiliou et al 2010	25	3[a](12)	CR-IM 11/14 (78.5%), CR-D 2/14 (14.3%)	No buried glands reported

a IMC patients; [b] $P<0.001$; [c] $P=0.03$; [d] $P=0.04$

Economic evaluation

Table 40 Calculation of average costs for complications with oesophagectomy

	Unit cost	Units	Total
Stricture			
Dilation of stricture (MBS 41819)	$330	1	$330
MBS 41819 copayment	$241	1	$241
Initiation of anaesthesia (MBS 20320)	$81	1	$81
MBS 20320 copayment	$50	1	$50
Total stricture			$701
Anastomic leak			
CT Scan for anastomic leak (MBS 56101)	$173	2	$345
MBS 56101 copayment	$92	2	$185
Radiological drainage procedures	$0	1	$0
MBS copayment	$0	1	$0
Parenteral feeding (MBS 34538)	$197	1	$197
MBS 34538 copayment	$132	1	$132
Hospitalisation (1 week)	$518	7	$3,625
Antibiotics	$199	1	$199
ICU extension	$1,832	2	$3,664
ICU attendance first day (MBS 13870)	$261	1	$261
MBS 13870 copayment	$149	1	$149
ICU attendance subsequent days (MBS 13873)	$194	1	$194
MBS 13873 copayment	$104	1	$104
Thoracoscopy (MBS 38436)	$180	1	$180
MBS 38436 copayment	$74	1	$74
Initiation of anaesthesia (MBS 20740)	$81	1	$81
MBS 20740 copayment	$50	1	$50
Thoractomy (MBS 38418)	$692	1	$692
MBS 38418 copayment	$510	1	$510
Initiation of anaesthesia (MBS 20500)	$214	1	$214
MBS 20500 copayment	$1,150	1	$1,150
Assistance (MBS 51303)	$138	1	$138
MBS 51303 copayment	$329	1	$329
Total radiological			$4,682
Total clinical			
With surgery			$9,055
Without surgery			$12,472
Other complications			
Blood transfusion (MBS 13309)	$206	1	$206
Co-payment (MBS 13309)	$93	1	$93
Total blood transfusion			$299

MBS., medicare benefits schedule; ICU, intensive care unit; CT scan, computed tomography scan.

Appendix H: Excluded studies

Table 41 Patient overlap identified between studies

Study	n
Pouw (Gondrie) et al 2008	44[a] (12+12+11+ 9)
Pouw et al 2009	33[b] (11+12+10)
Gondrie et al 2008	12
Beaumont et al 2009	12

[a] case series comprised of 4 sequential prospective trials
b case series comprised of 3 sequential prospective trials

Outcomes not relevant to this assessment

Adler DC, Zhou C, Tsai TH, Lee HC, Becker L, Schmitt JM, Huang Q, Fujimoto JG, Mashimo H, 2009. 'Three-dimensional optical coherence tomography of Barrett's esophagus and buried glands beneath neosquamous epithelium following radiofrequency ablation', *Endoscopy*, 41(9), 773-776.

Janssens F, Rougemont AL, Deviere J, Fockens P, Dumonceau JM, 2009. 'Symptomatic esophageal stricture and buried metaplasia after radiofrequency ablation of Barrett's esophagus', *Endoscopy*, 41 Suppl 2, E214-E215.

Incorrect indication

Dunkin BJ, Martinez J, Bejarano PA, Smith CD, Chang K, Livingstone AS, Melvin WS, 2006. 'Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device', *Surgical Endoscopy*, 20(1), 125-130 [Epub].

Ganz RA, Utley DS, Stern RA, Jackson J, Batts KP, Termin P, 2004. 'Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus', *Gastrointest Endosc*, 60(6), 1002-1010.

Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Kate FJ, Fockens P, Deviere J, Neuhaus H, Bergman JJ, 2009. 'Efficacy of Radiofrequency Ablation Combined With Endoscopic Resection for Barrett's Esophagus With Early Neoplasia', *Clin Gastroenterol Hepatology*; 8(1), 23-29.

Pouw RE, Gondrie JJ, Curvers WL, Sondermeijer CM, ten Kate FJ, Bergman JJ, 2008. 'Successful balloon-based radiofrequency ablation of a widespread early squamous cell carcinoma and high-grade dysplasia of the esophagus: a case report', *Gastrointest Endosc*, 68(3), 537-541.

Sampliner RE, Camargo E, Prasad AR, 2006. 'Association of ablation of Barrett's esophagus with high-grade dysplasia and adenocarcinoma of the gastric cardia', *Dis Esophagus*, 19(4), 277-279.

Smith CD, Bejarano PA, Melvin WS, Patti MG, Muthusamy R, Dunkin BJ, 2007. 'Endoscopic ablation of intestinal metaplasia containing high-grade dysplasia in esophagectomy patients using a balloon-based ablation system' *Surg Endosc*, 21(4), 560-569.

Did not meet inclusion criteria regarding population

Dos Santos RS, Bizekis C, Ebright M, Desimone M, Daly BD, Fernando HC, 2010. 'Radiofrequency ablation for Barrett's esophagus and low-grade dysplasia in combination with an antireflux procedure: A new paradigm', *J Thorac Cardiovasc Surg*; 139, 713-716

Eldaif SM, Lin E, Singh KA, Force SD, Miller DL, 2009. 'Radiofrequency ablation of Barrett's esophagus: short-term results', *Ann Thorac Surg*; 87(2): 405-410.

Fleischer DE, Sharma VK, 2010. 'Endoscopic ablation of Barrett's esophagus using the HALO system', *Interventional and Therapeutic Gastrointestinal Endoscopy, Frontiers of Gastrointestinal Research*, 27(4), 140-146.

Fleischer DE, Overholt BF, Sharma VK, Reymunde A, Kimmey MB, Chuttani R, Chang KJ, Lightdale CJ, Santiago N, Pleskow DK, Dean PJ, Wang KK, 2008. 'Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up', *Gastrointest Endosc*, 68(5), 867-876.

Hernandez JC, Reicher S, Chung D, Pham BV, Tsai F, Disibio G, French S, Eysselein VE, 2008. 'Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia', *Endoscopy*, 40(5), 388-392.

Hubbard N and Velanovich V, 2007. 'Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus in patients with fundoplications', *Surg Endosc*, 21(4), 625-628.

Sharma VK, Wang KK, Overholt BF, Lightdale CJ, Fennerty MB, Dean PJ, Pleskow DK, Chuttani R, Reymunde A, Santiago N, Chang KJ, Kimmey MB, Fleischer DE, 2007. 'Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients', *Gastrointest Endosc*, 65(2), 185-195.

Lyday WD, Corbett FS, Kuperman DA, Kalvaria I, Mavrelis PG, Shughoury AB, Pruitt RE, 2010. 'Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry', *Endoscopy*, 42(2), 272-278.

Roorda AK, Marcus SN, Triadafilopoulos G, 2007. 'Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia', *Dis Esophagus*; 20(6), 516-522.

Velanovich V, 2009. 'Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: initial results and lessons learned', *Surg Endosc,* 23(10), 2175-2180.

No clinical data

Choueiri NE and Prather CM, 2009. 'Barrett's esophagus: a pre-cancerous condition approach to diagnosis and management', *Mo.Med*, 106(5), 339-342.

Yachimski P, Nishioka NS, Richards E, Hur C, 2008. 'Treatment of Barrett's esophagus with high-grade dysplasia or cancer: predictors of surgical versus endoscopic therapy', *Clin Gastroenterol Hepatol*, 6(11), 1206-1211.

Cited patient overlap

Beaumont H, Gondrie JJ, McMahon BP, Pouw RE, Gregersen H, Bergman JJ, Boeckxstaens GE, 2009. 'Stepwise radiofrequency ablation of Barrett's esophagus preserves esophageal inner diameter, compliance, and motility', *Endoscopy*, 41(1), 2-8.

Gondrie JJ, Pouw RE, Sondermeijer CM, Peters FP, Curvers WL, Rosmolen WD, Ten Kate F, Fockens P, Bergman JJ, 2008. 'Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system', *Endoscopy*, 40(5), 370-379.

Gondrie JJ, Pouw RE, Sondermeijer CM, Peters FP, Curvers WL, Rosmolen WD, Krishnadath KK, Ten Kate F, Fockens P, Bergman JJ, 2008. 'Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients', *Endoscopy*, 40(5), 359-369.

Pouw RE, Gondrie JJ, Rygiel AM, Sondermeijer CM, ten Kate FJ, Odze RD, Vieth M, Krishnadath KK, Bergman JJ, 2009. 'Properties of the neosquamous epithelium after radiofrequency ablation of Barrett's esophagus containing neoplasia', *Am J Gastroenterol*, 104(6), 1366-1373.

Abbreviations

AE	adverse event
AIHW	Australian Institute of Health and Welfare
APC	argon plasma coagulation
AR-DRG	Australian Refined Diagnostic Related Group
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical
BO	Barrett's oesophagus
CR-IM	complete histological eradication of intestinal metaplasia
CR-D	complete histological eradication of dysplasia
CT	computed tomography
EMSN	Extended Medicare Safety Net
EMR	endoscopic mucosal resection
EUS	endoscopic ultrasound
FDA	Food and Drug Administration
GA	general anaesthesia
GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
HGD	high-grade dysplasia
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IM	intestinal metaplasia
IMC	intramucosal cancer
LGD	low-grade dysplasia
MBS	Medicare Benefits Schedule
MPEC	multipolar electrocoagulation
MSAC	Medical Services Advisory Committee

NICE	National Institute for Health and Clinical Excellence
PDT	photodynamic therapy
PICO	population, intervention, comparator, outcome
PPI	proton pump inhibitors
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RFA	radiofrequency ablation
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
TGA	Therapeutic Goods Administration
UK	United Kingdom

References

Ackroyd R, Brown NJ, Dvis MF, Stephenson TJ, Macrus SL, Stoddard CJ, Johnson AG, Reed MW, 2000. 'Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial', *Gut,* 47(5), 612-617.

Ackroyd R, Tam W, Schoeman M, Devitt PG, Watson DI, 2004. 'Prospective randomised controlled trial of argon plasma coagulation ablation vs endoscopic surveillance of patients with Barrett's esophagus after anti-reflux surgery', *Gastrointestinal Endoscopy*, 59(1), 1-7.

Australian Institute of Health and Welfare
http://www.aihw.gov.au/hospitals/datacubes/index.cfm [Accessed 14/01/2010].

Ajumobi A, Bahjri K, Jackson C, Griffin R, 2009. 'Surveillance of Barrett's oesophagus: An audit of practice', *Digestive Diseases and Sciences*, 55(6), 1615-1621 [Epub].

Attwood SE, Lewis CJ, Caplin S, Hemming K, and Armstrong G, 2003. 'Argon beam plasma coagulation as therapy for high-grade dysplasia in Barrett's esophagus', *Clinical Gastroenterology & Hepatology,* 1(4), 258-263.

Boger CP, Turner D, Poderick P, Pater P, 2010. 'A UK-based cost-utility analysis of radiofrequency ablation or oesophagectomy for the management of high-grade dysplasia in Barrett's Oesophagus', *Alimentary Pharmacology and Therapeutics,* 32(11-12), 1365-2036.

Conio M, Ponchon T, Blanchi S, Filiberti, R, 2006, 'Endoscopic Mucosal Resection', *American Journal of Gastroeneterology*, 101(3), 653-663.

Food and Drug Administration USA
http://www.fda.gov/MedicalDevices/default.htm [Accessed 14/01/2010].

Franchimont D, Van Laethem JL, Deviere J, 2003. 'Argon plasma coagulation in Barrett's oesophagus', *Gastrointestinal Endoscopy Clinics of North America*, 13(3), 457-466.

Hage, M, Siersema, PD, Van Dekken, H, Steyerberg, EW, Haringsma, J, Van, DV, Grool, TE, Van Veen, RLP, Sterenborg, HJCM, Kuipers, EJ, 2004, '5-Aminolevulinic acid photodynamic therapy versus argon plasma coagulation for ablation of Barrett's oesophagus: A randomised trial', *Gut*, 53(6), 785-90.

Hage M, Siersema PD, Vissers KJ, Steyerberg EW, Haringsma J, Kuipers EJ, Van Dekken H, 2005. 'Molecular evaluation of ablative therapy of Barrett's oesophagus', *Journal of Pathology,* 205(1), 57-64.

Inadomi JM, Somsouk M, Madanick RD, Thomas JP, Shaheen NJ, 2009. 'A cost-utility analysis of ablative therapy for Barrett's Esophagus', *Gastroenterology,* 136, 2101-2114 e2101-2106.

Kelty, CJ, Ackroyd, R, Brown, NJ, Stephenson, TJ, Stoddard, CJ, Reed, MWR, 2004. 'Endoscopic ablation of Barrett's oesophagus: A randomized-controlled trial of photodynamic therapy vs. argon plasma coagulation', *Alimentary Pharmacology & Therapeutics*, 20(11-12), 1289-96.

Kendall BJ, Whiteman DC, 2006. 'Temporal changes in the endoscopic frequency of new cases of Barrett's esophagus in an Australian health region', *American Journal of Gastroenterology*, 101(6), 1178-1182.

Khan K, Riet G, Glanville J, Sowden A, Kleijnen, 2001, Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews, CRD Report no. 4 edn 2, March 2001.

Kind P, Hardman G, Macran S, 1999. 'UK population norms for EQ-5D', *Centre for Health Economics Discussion Paper 172*.

Kumar V, Abbas AK, Fausto N, 2005. *Robbins and Cotran Pathologic Basis of Disease*, 7th edn, Elsevier Sauders, Philadelphia USA.

Lalwani AK, 2008. 'Malignant disorders of the esophagus', McGraw Hill, New York, USA.

MSAC, Cameron A, Russin A, Hoggan B, 2008, Endoscopic plasma coagulation of gastrointestinal bleeding and oesophageal stents, MSAC Application 1106, Assessment Report. Commonwealth of Australia, Canberra ACT.

Medicare Benefits Schedule, 2009. http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1 [Accessed 14/01/2010].

Moss A, Bourke M, Hourigan L, Gupta S, Williams S, Tran K, Swan M, Hopper A, Kwan V, Bailey A, 2009, 'Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: An essential staging procedure with long-term therapeutic benefit', *American Journal of Gastroenterology*, epub February 2010.

NHMRC, 1999. 'A guide to the development, implementation and evaluation of clinical practice guidelines', National Health and Medical Research Council, Canberra.

NHMRC 2000. How to use the evidence: assessment and application of scientific evidence. Canberra: National Health and Medical Research Council.

NHMRC 2008, 'NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Pilot program 2005-2007, Canberra: NHMRC 2005.

Overholt BF, Lightdale CJ, Wang KK, Canto MI, Burdick S, Haggit RC, Bronner MP, Taylor SL, Grace MG, Depot M, 2005. 'Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial', *Gastrointestinal Endoscopy*, 62(4), 488-498.

Overholt BF, Wang KK, Burdick JS, Lightdale CJ, Kimmey M, Nava HR, Sivak MV Jr, Nishioka N, Barr H, Marcon N, Pedrosa M, Bronner MP, Grace M, Depot M, 2007. 'Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia', *Gastrointestinal Endoscopy*, 66(3), 460-468.

Ragunath, K, Krasner, N, Raman, VS, Haqqani, MT, Phillips, CJ, Cheung, I, 2005. 'Endoscopic ablation of dysplastic Barrett's oesophagus comparing argon plasma coagulation and photodynamic therapy: a randomized prospective trial assessing efficacy and cost-effectiveness', *Scandinavian Journal of Gastroenterology*, 40(7), 750-8.

Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P, 2008. 'Incidence of esophageal adenocarcinoma in patients with Barrett's Esophagus and high-grade dysplasia: A meta-analysis', *Gastrointest Endosc*, 67, 394-398.

Rees JRE, Lao-Sirieix P, Wong A, Fitzgerald RC. Treatment of Barrett's oesophagus, 2010. *Cochrane Database of Systematic Reviews*, Issue 1.

Schulz H, Miehlke S, Antos D, Schentke KU, Vieth M, Stolte M, Bayerdörffer E, 2000. 'Ablation of barrett's epithelium by endoscopic argon plasma coagulation in combination with high-dose omeprazole', *Gastrointest Endosc*, 51, 659-663.

Sgourakis, Gockel I, Radtke A, Musholt T, Timm S, Rink A, Tsiamis A, Constantine K, Lang H, 2010. 'Minimally invasive versus open esophagectomy: Meta-analysis of outcomes', *Digestive Diseases and Sciences*, Feb 2010.

Sharma P, 2009. 'Barrett's Oesophagus', *The New England Journal of Medicine*, 361(26)2548-2556.

Shaheen NJ, Sharma P, Overholt B, Wolfsen H, Sampliner R, Wang K, Galanko J, Bronner M, Goldblum J, Bennett A, Jobe B, Eisen G, Fennerty M, Hunter J, Fleischer D, Sharma V, Hawes R, Hoffman B, Rothstein R, Gordon S, Mashimo H, Chang K, Muthusamy R, Edmundowicz S, Spechler S, Siddiqui A, Souza R, Infantolino A, Falk G, Kimmey M, Madanick R, Chak A, Lightdale C, 2009. 'Radiofrequency ablation in Barrett's oesophagus with dysplasia', *The New England Journal of Medicine*, 360(22)2277-2288.

Somerville M, Garside R, Pitt M, Stein K, 2008. 'Surveillance of Barrett's Oesophagus: Is it worthwhile?', *European Journal of Cancer*,44: 588-599.

State Government of Victoria Department of Human Services, 2009. 'Health Technology News' [Internet], Department of Human Services, Australia. Available from: http://www.health.vic.gov.au/newtech/ [Accessed 21 Jan 2010].

Terano A, Morita K, Nakamura T, Ohkura Y, Ono Y, Fujimori T, 2002. Barrett's esophagus. *Journal of Gastroenterology,* 37(9), 685-690.

Therapeutics Goods Administration Australia, https://www.ebs.tga.gov.au/ebs/ANZTPAR/PublicWeb.nsf/cuMedicines?OpenView [Accessed 14/01/2010].

Van Laethem JL, Jagodzinski R, Peny MO, Cremer M, Deviere J, 2001. 'Argon plasma coagulation in the treatment of Barrett's high-grade dysplasia and in situ adenocarcinoma', *Endoscopy*, 33(3), 257-261.

Wang KK, Sampliner RE, 2001. 'Mucosal ablation therapy of barrett esophagus', *Mayo Clinic Proceedings,* 76(4), 433-437.

Waxman I, Konda VJA, 2009, 'Mucosal ablation of Barrett esophagus', *Nature Reviews Gastroenterology & Hepatology*, 6(7), 393-401.