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Horizon Scanning Technology Prioritising Summary

Circumferential, endoscopic radiofrequency ablation of Barrett's oesophagus

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ASERNIP-S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

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PRIORITISING SUMMARY

REGISTER ID **S000089**

NAME OF TECHNOLOGY **HALO^{360} CIRCUMFERENTIAL RADIOFREQUENCY ABLATION SYSTEM**

PURPOSE AND TARGET GROUP **TO ABLATE PRE-MALIGNANT EPITHELIUM IN PATIENTS WITH BARRETT'S OESOPHAGUS**

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- ☐ Yet to emerge
- ☑ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☑ Yes — ARTG number **140684**
- ☐ No
- ☐ Not applicable

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	**Limited Use**	**Widely Diffused**
Brussels	✓		
The Netherlands	✓		
Germany	✓		
United States	✓		

IMPACT SUMMARY

Circumferential endoscopic radiofrequency ablation is a potential alternative to thermal, photochemical or mechanical methods for removing the pre-malignant epithelium in patients with Barrett's oesophagus. This technology is currently in the experimental stage in Australia.

BACKGROUND

Barrett's oesophagus is a condition where the normal oesophageal cells are replaced with intestinal columnar epithelium, and is commonly diagnosed in patients suffering from

chronic gastroesophageal reflux disease (GERD) (Schuchert and Luketich 2007). A normal oesophagus is lined with flat, thin squamous cells and when the oesophagus is exposed to gastric juices these cells become irritated. When untreated, a constant exposure to reflux conditions can cause metaplasia in the oesophagus resulting in the development of intestinal columnar epithelium. Suggestive endoscopic results (visible columnar epithelium above the oesophagogastric junction) may be confirmed as Barrett's oesophagus when an endoscopic biopsy reveals the presence of intestinal column metaplasia (British Society of Gastroenterology 2005; Smith et al 2006).
This metaplasia can continue, increasing through low-grade to high-grade dysplasia and culminating in invasive cancer (British Society of Gastroenterology 2005). Patients with high-grade dysplasia have a 2% to 10% per year risk of developing adenocarcinoma (Ganz et al 2008). Barrett's oesophagus is regarded as a premalignant condition (Schuchert and Luketich 2007) and the objective of treatment is to prevent the development of adenocarcinoma.

Intestinal metaplasia is treated by preventing further oesophageal injury (through managing GERD symptoms) and with continual endoscopic monitoring to detect development of dysplasia (Smith et al 2006). Once low- or high-grade dysplasia is present there is an increased likelihood of developing malignancy. Although management has historically included intensive surveillance endoscopy every 3 months, therapeutic strategies are currently preferred for most patients. When the Barrett's epithelium is injured or removed and GERD is controlled the oesophagus may re-establish the normal squamous epithelium (Roorda et al 2007).
The current endoscopic therapies for removal of the Barrett's epithelium include:

- argon-plasma coagulation
- electro-coagulation
- laser ablation
- radiofrequency ablation
- photodynamic therapy
- endoscopic mucosal resection
- minimally invasive oesophagectomy (Smith et al 2006)

Each of these treatments has accompanying limitations such as technical difficulty and stricture formation, photosensitivity, operative morbidity and mortality (Ganz et al 2008). Thus another technique for complete removal of the epithelium with fewer risks would significantly benefit patients (Smith et al 2006).

A new option for removal of Barrett's epithelium is the HALO^{360} circumferential radiofrequency ablation system (Barrx^{TM} Medical, Sunnyvale California USA). This system allows the inner diameter of the oesophagus to be ablated quickly during an outpatient procedure, with uniform removal of epithelium to a controlled ablation depth. The patient is placed under conscious sedation and a sizing balloon is used to measure the inner diameter of the oesophagus. An appropriately sized radiofrequency ablation catheter is selected and introduced over a guidewire in a side-by-side manner with an endoscope. The catheter's balloon is then inflated and energy applied (300W and either 10 J/cm^2 or 12 J/cm^2), circumferentially ablating the epithelium to a depth of less than 1 mm. The catheter is then removed and cleaned, and reintroduced if necessary. The

clinician removes the ablated epithelium using irrigation and suction using the endoscope (Barrx Medical Inc).

CLINICAL NEED AND BURDEN OF DISEASE

Barrett's oesophagus is a pre-cancerous condition which left untreated can progress to oesophageal cancer. Between 1993 and 2003 the incidence of oesophageal cancer in Australia increased by 26% (AIHW 2007). Oesophageal cancer is still relatively rare in Australia, but importantly is becoming more common. Annually approximately 1000 Australians are diagnosed with cancer of the oesophagus (Australian cancer study and study of digestive health) and between 1993 and 2003 the average number of new annual cases of oesophageal cancer was 1098 (AIHW 2007). The combined number of deaths caused by GORD and other diseases of the oesophagus was 172 in 2006 (ABS 2008). Barrett's oesophagus affects approximately 1% of the population in the USA, while GORD affects approximately 10–20% of the Western world (Dent et al 2005; Hebbard and Nandurkar 2004).

DIFFUSION

The Barrx^{TM} Medical Halo^{360} system has been approved by both the US Food and Drug Administration (FDA) (K051168) and the Australian Therapeutic Goods Administration (ATGA) (140684). The FDA approved the device in 2005 for the purpose of the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to the oesophagus (FDA).

Trials of circumferential radiofrequency ablation are currently being conducted in Brussels, The Netherlands, Germany and the United States. Australia appears to be in the experimental stage with this technology, with the Royal Melbourne and St Vincent's Hospitals to begin using the Halo^{360} and Halo^{90} for dysplastic Barrett's oesophagus in 2008-2009 (Victorian Government Health Information 2008).

COMPARATORS

Due to the high rate of progression to oesophageal adenocarcinoma the standard of care for high grade dysplasia is oesophagectomy (Smith et al 2006). Oesophagectomy allows the complete removal of all Barrett's epithelium and oesophageal adenocarcinoma, yet has significant morbidity and mortality risks for the patient. When performed to treat oesophageal adenocarcinoma, oesophagectomy may have a mortality rate of 4-6% and this rate may be lower when performed to treat high grade dysplasia (Smith et al 2006).

SAFETY AND EFFECTIVENESS ISSUES

Two level II studies and one level IV study were eligible for inclusion in this summary. Each study assessed the effectiveness of the HALO^{360} circumferential radiofrequency ablation system for the treatment of patients with Barrett's oesophagus of varying severity. The identified RCTs were dosage studies and did not compare circumferential radiofrequency ablation to another type of Barrett's epithelium removal, including oesophagectomy.

In the randomised controlled trial (RCT) conducted by Dunkin et al (2006) 13 male patients aged 49-85 years with adenocarcinoma at or near the gastroesophageal junction were enrolled. The patients all underwent ablation prior to oesophagectomy, and were randomised to one of three energy density groups: 8, 10 or 12 J/cm^2. There were no details as to how patients were randomised. After using the 8 J/cm^2 setting in one patient, the authors determined that the ablation effect at that setting was negligible and all remaining patients were randomised to either 10 or 12 J/cm^2. Patients who had received any previous ablative or resective oesophageal procedure, or who had an oesophageal stricture preventing passage of the endoscope or catheter were excluded.
All ablations were performed under general anaesthesia. Two separate circumferential ablation zones were planned for each patient, each 3 cm in length. Zone one received one radiofrequency application (1x), whereas zone 2 received two radiofrequency applications (2x) with 1 or 2 minutes between applications. Following ablation, visual assessments of the ablation areas were made and oesophagectomy was performed. Each oesophagectomy specimen was opened longitudinally and photographed and fixed in formalin. One pathologist reviewed all histopathology, and was blinded to treatment group and zone of treatment. The outcomes measured were complete epithelial ablation; the maximum depth of ablation; and the thickness of residual ablation effect.

In the RCT conducted by Smith et al (2006) eight men aged 45-71 years with histopathologically diagnosed high-grade dysplasia were enrolled. The patients all underwent ablation prior to oesophagectomy and were randomised to receive 10, 12 or 14 J/cm^2 of energy density and 2, 3 or 4 applications. There were no details as to how the patients were randomised. Patients who had oesophageal stricture preventing passage of an endoscope or catheter or previous ablative therapy to the oesophagus were excluded. All ablations were performed under general anaesthesia before the planned oesophagectomy procedure. In patients with adequate endoscopic length of Barrett's oesophagus, a second separate ablation zone was also created. A total of ten ablation zones were created in the eight patients. Following ablation oesophagectomy was performed. At removal each specimen was opened longitudinally and photographed and fixed in formalin. A single blinded pathologist reviewed all histopathology slides. The outcomes measured were maximum ablation depth and complete ablation of all intestinal metaplasia and high grade dysplasia.

In the study conducted by Ganz et al (2008) 142 consecutive patients (median age 67 years) with high grade dysplasia Barrett's oesophagus were enrolled at 16 academic and community centres. The patients underwent a median of 1 ablation session. Ablations were performed as an outpatient procedure and most patients received conscious sedation. Some patients received propofol or general anaesthesia due to issues with upper endoscopies, physician preference, or comorbidity. All patients received ablation at the 12 J/cm2 density. Following ablation patients received endoscopies at approximately 3 month intervals and if persistent Barrett's oesophagus was evident another ablation was performed. All treated patients were included in the safety analysis, whereas only those with post ablation endoscopy with biopsies were included in the effectiveness analysis. Curiously, if specimens obtained within 3 months of ablation revealed adenocarcinoma, the case was deemed a prevalent cancer and the patient was included in the safety

analysis and excluded from the effectiveness analysis, thus introducing experimental bias. Effectiveness outcomes included 1) all biopsy specimen fragments were negative for high grade dysplasia; 2) all biopsy specimens were negative for any dysplasia; 3) all biopsy specimens were negative for intestinal metaplasia.

SAFETY

In the RCT by Dunkin et al (2006) one patient had a superficial, 1-cm long mucosal injury that occurred during sizing and may have been due to previous radiotherapy. There were no device malfunctions and no other complications relating to the ablation procedure were reported. After oesophagectomy there were no cases of pleural effusion, perforation, or transmural thermal injury, although there was a small amount of perioesophageal oedema in two patients, including the patient who had received previous radiotherapy.

In the RCT by Smith et al (2006) there were no device-related adverse events. The authors reported that ablation using the highest treatment setting of 14 J/cm^2 was accompanied by mild oedema in the superficial layer of the submucosa. Upon oesophagectomy the authors reported that there was no transmural thermal or mechanical injury, perioesophageal fluid, or other adverse events in the mediastinum or abdomen at the gastroesophageal junction.

In the study by Ganz et al (2008) there were no serious adverse events reported. There was one stricture noted at follow-up endoscopy (0.4%) and the patient was asymptomatic and required no dilation.

EFFECTIVENESS

In the RCT by Dunkin et al (2006) 12 of the original 13 patients received circumferential radiofrequency ablation. One patient was excluded from analysis as the endoscope and catheter could not be simultaneously introduced into the oesophagus. The histological sections from a patient who received ablations at 8 J/cm^2 showed that the ablation depth was mid epithelium even at 2x. As the epithelium was either unchanged or ablated to mid epithelium depth with viable cells near the basement membrane, all subsequent ablations were performed at either 10 or 12 J/cm^2. Complete epithelial ablation was consistently achieved at 10 J/cm^2 (2x) and 12 J/cm^2 (1x or 2x). Visual assessments were made of the immediate post ablation endoscopy images. The zones treated with 10 J/cm^2 (2x) and 12 J/cm^2 (1x or 2x) had uniform, circumferential ablations while the zones treated with 8 J/cm^2 (1x or 2x) and 10 J/cm^2 (1x) had less visible ablative effects and/or less uniformity of ablation. The maximum ablation depth was directly related to energy density and, for the 10 J/cm^2 sections, to the number of ablative treatments (1x vs 2x). The maximum ablation depth for all zones treated at 10 J/cm^2 (2x) and 12 J/cm^2 (1x or 2x) was lamina propria or muscularis propria. The maximum ablative depth for zones treated with 8 J/cm^2 (1x or 2x) was mid epithelium, and for zones treated with 10 J/cm^2 (1x) was either mid epithelium or lamina propria.

In the RCT by Smith et al (2006) the maximum ablation depth increased as the energy density and number of applications increased. No specimen showed histologic evidence of ablation to the submucosa, and the deepest ablation level was achieved at 14 J/cm2 (4x) with evidence of mild oedema in the superficial layer of the submucosa. In all 2x ablation zones, ablation was limited to the lamina propria whereas in all 4x zones the ablation reached to, but not through, the muscularis mucosae. Complete removal of all intestinal metaplasia and high grade dysplasia was achieved in 9 of the 10 ablation zones. At 12 J/cm2 (2x) 99.9% of intestinal metaplasia and high grade dysplasia was completely ablated, although a single focus of high grade dysplasia within the lamina propria was detected at the ablation margin. The authors suggested that this may have been due to incomplete overlap of the second application. In the 9 remaining ablation zones the histologic sections showed either complete removal of all intestinal metaplasia and high grade dysplasia, or residual intestinal metaplasia or high grade dysplasia with irreversible ablative changes. The residual intestinal metaplasia or high grade dysplasia were likely not viable because of the significant thermal injury.[1]

In the study by Ganz et al (2008) only 92 of the 142 patients had at least one follow-up biopsy session, making them eligible for the efficacy cohort. The efficacy cohort was not significantly different from the safety cohort as a whole in terms of baseline demographics and Barrett's oesophagus length. The median follow-up from primary ablation to the last available endoscopic biopsy was 12 months. Biopsy specimen fragments were negative for high-grade dysplasia in 90.2% of patients and negative for dysplasia in 80.4% of patients (9 patients without high grade dysplasia had persistent low grade dysplasia at last follow up). Biopsy specimen fragments were negative for intestinal metaplasia in 54.3% of patients, which appears to be quite low for an outcome that is the primary purpose of this device. At follow up no patients from the effectiveness cohort had been referred for an oesophagectomy. A subgroup analysis was conducted to assess the histologic response rates between patients who had a baseline oesophageal mucosal resection (EMR) (n=24) versus those with no baseline EMR (n=68). All biopsy specimen fragments were negative for high grade dysplasia in 87.5% (EMR) versus 90.8 (no EMR); negative for dysplasia in 81.3% (EMR) versus 80.3% (no EMR); and negative for intestinal metaplasia in 62.5% (EMR) versus 52.6% (no EMR). All 5 patients with baseline mucosal adenocarcinoma resected with an EMR before ablation showed a negative result for intestinal metaplasia after the last biopsy.

COST IMPACT

No information regarding cost effectiveness was identified from the retrieved material. One RCT reported that the successful removal of low-grade dysplasia would reduce the need for endoscopy from every 6 months to every 2 or 3 years, and in patients with nondysplastic Barrett's oesophagus successful ablation would eliminate the need for surveillance, thus reducing attendant health care costs (Dunkin et al 2005). The risk of progression to adenocarcinoma could also be reduced.

[1] These "ghost cells" were cells with severe loss of cytoarchitectural features, loss of nuclei, and/or presence of coagulative changes.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

No issues were identified from the retrieved material.

SUMMARY OF FINDINGS

From the included studies it is unclear whether circumferential radiofrequency ablation is a suitable alternative to more invasive surgical interventions as none of the studies compared treatment to the current gold standard of oesophagectomy. The patient numbers were very low for all studies. The two RCTs lacked compelling evidence of effectiveness. One RCT (Dunkin et al 2006) did not report if all dysplasia and metaplasia were eliminated and the other RCT (Smith et al 2006) had only ten sites for assessment. Both RCTs were basically dose-response experiments and did not compare circumferential radiofrequency ablation to other types of ablation.

Overall, the two RCTs reported that effective ablation was achieved in 27 of 32 ablation zones. The maximum ablation depth was the muscularis mucosae. One level IV study found that ablation removed high-grade dysplasia in 90.2% of patients, dysplasia in 80.4% of patients and intestinal metaplasia in 54.3% of patients. The best energy density to use appeared to be either 10 or 12 J/cm2 with either one or two applications, as 8 J/cm2 appeared to be too low and ineffective, while 14 J/cm2 appeared to be too high and was accompanied by mucosal oedema.

There were few adverse events reported including superficial mucosal injury during sizing, mild oedema in the superficial layer of the submucosa and one stricture. Future studies should assess circumferential radiofrequency ablation compared to other types of ablation or oesophagectomy, and should ascertain the maximum energy densities that are safe and effective to use, as 14 J/cm2 causes mild oedema.

HEALTHPACT ACTION

Based on the lack of RCTs which compared circumferential radiofrequency ablation to other therapies for Barrett's oesophagus, the potential of this technology as an alternative remains unclear. As studies with longer follow up are required, it is recommended that this technique is monitored for 12 months for future developments.

NUMBER OF STUDIES INCLUDED

Total number of studies	3
Level II evidence	2
Level IV evidence	1

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SEARCH CRITERIA TO BE USED

Halo 360
circumferential ablation
Barrett's esophagus