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ABLATION OF BARRETT'S OESOPHAGUS – TOWARDS IMPROVED OUTCOMES FOR OESOPHAGEAL CANCER?

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ABSTRACT

Barrett's oesophagus is the major risk factor for oesophageal adenocarcinoma. The management of Barrett's oesophagus entails treating reflux symptoms with acid-suppressing medication or surgery (fundoplication). However neither form of anti-reflux therapy produces predictable regression, or prevents cancer development. Patients with Barrett's oesophagus usually undergo endoscopic surveillance which aims to identify dysplastic changes or cancer at its earliest stage, when treatment outcomes should be better. Alternative endoscopic interventions are now available and are suggested for the treatment of early cancer, and prevention of progression of Barrett's oesophagus to cancer. Such treatments could minimize the risks associated with oesophagectomy. The current status of these interventions is reviewed.

Various endoscopic interventions have been described, but with long term outcomes uncertain, they remain somewhat controversial. Radiofrequency ablation (RFA) of dysplastic Barrett's oesophagus might reduce the risk of cancer progression, although cancer development has been reported after this treatment. Endoscopic mucosal resection (EMR) allows a 1.5 to 2 cm diameter piece of oesophageal mucosa to be removed. This provides better pathology for diagnosis and staging, and if the lesion is confined to the mucosa and fully excised, EMR can be curative. The combination of EMR and RFA has been used for multifocal lesions, but long term outcomes are unknown. The new endoscopic interventions for Barrett's oesophagus and early oesophageal cancer have potential to improve clinical outcomes, although evidence which confirms superiority over oesphagectomy is limited. Longer term outcome data and data from larger cohorts is required to confirm the appropriateness of these procedures.

KEY WORDS

Barrett's oesophagus, oesophageal adenocarcinoma, endoscopic therapy, ablation, mucosal resection

Introduction

Barrett's oesophagus is an adaptive response to repeated episodes of reflux of gastric contents into the oesophageal lumen, following which the mucosa in the distal oesophagus undergoes metaplastic change from squamous to a columnar mucosa. A recent study estimates that this condition probably affects 5.6% of the population in the USA [1]. In the Western World the incidence appears to be increasing [2], and this is important because Barrett's oesophagus is the major risk factor for the development of oesophageal adenocarcinoma. Patients with Barrett's oesophagus carry a risk of oesophageal adenocarcinoma that is 30-125 times higher than that of an age-matched population [3], and the annual risk of this cancer developing in Barrett's oesophagus is reported to be from 0.2% to 2.1% [4]. In addition, the incidence of oesophageal adenocarcinoma in Europe [5], North America [6], and Australia [7] is increasing at a rate exceeding that of any other cancer, with a near 6 fold increase over the last 3 to 4 decades, predominantly in men. The prognosis for this cancer is poor and approximately 90% of sufferers will die from this disease. This is because potentially curative treatment, usually oesophagectomy, is only feasible in approximately 25-30% of individuals, and surgical treatment is associated with significant morbidity and mortality.

At present, the management of Barrett's oesophagus entails treating reflux with acid-suppressing medication (usually a proton pump inhibitor (PPI)) or surgery (fundoplication), followed by regular endoscopic surveillance. Whilst there have been isolated reports of Barrett's oesophagus regressing following medical therapy [8] and fundoplication [9,10], neither produces predictable regression, or prevents cancer development [11]. Oesophagectomy for Barrett's oesophagus in the absence of adenocarcinoma is not recommended, except in "fit" patients who progress to high grade dysplasia (HGD), the stage before invasive cancer, although even this is controversial as there is only a limited understanding of the natural history of HGD [12]. Hence, alternative endoscopic interventions for early stage disease could minimize the morbidity and mortality associated with oesophagectomy, and might improve outcomes. Over the last 2 decades various endoscopic interventions have been described, although their place in the treatment spectrum still remains somewhat controversial. In this paper, the current status of endoscopic interventions for HGD and early cancer arising in Barrett's oesophagus is reviewed.

Endoscopic Ablation of Barrett's oesophagus

Various endoscopic techniques have been investigated for eradicating Barrett's oesophagus epithelium, in particular dysplastic epithelium. Both focal ablation techniques (argon plasma

coagulation (APC), multipolar electrocoagulation, laser heater probe, and endoscopic mucosal resection (EMR)) and field ablation techniques (photodynamic therapy (PDT) and radiofrequency ablation (RFA)) [13] have been used to ablate dysplastic and non-dysplastic Barrett's oesophagus mucosa. The destruction of metaplastic columnar mucosa in an acid free environment is usually followed by regeneration with a squamous mucosa, irrespective of the method used. If applied to treatment of cancer or HGD, the goal of therapy should be to remove any target lesion, and to ablate all intestinal metaplasia (both dysplastic and non-dysplastic) to eliminate the risk of recurrence in the remaining Barrett's oesophagus segment [14, 15].

In most patients, new squamous mucosa formed after ablation (neosquamous mucosa) has a histopathological structure which is similar to that of normal oesophageal mucosa[16]. Whilst it is hoped that the neosquamous mucosa has a reduced cancer risk, the evidence supporting this is currently limited. Even if the risk is reduced, there remains the potential for malignancy to arise in islands of retained columnar mucosa or in buried areas of columnar mucosa lying underneath neosquamous mucosa. Cancer may also arise from within regenerated neosquamous mucosa, as this mucosa has not yet been shown to be stable. There has been a case report of cancer arising in neosquamous mucosa [17], and there have been reports of HGD and oesophageal adenocarcinoma developing following an endoscopically assessed 100% complete eradication response to ablation [18, 19]. The questions that should be asked therefore are; does ablation reduce or eliminate the risk of cancer, and which technique is most effective and/or cost effective?

Photodynamic therapy

Photodynamic therapy (PDT) entails administering a photosensitizing drug which sensitizes tissue to specific wavelengths of light. Non-thermal light of the appropriate wavelength delivered via an endoscope activates the photosensitizer, and this results in mucosal injury. It is thus a field ablation technique which can achieve circumferential ablation over a 3-7cm segment length. PDT ablation achieves complete reversion of columnar to squamous epithelium in 50-90% of treated patients [20, 21], although it is associated with morbidity including chest pain and odynophagia [22], photosensitivity, and up 36% of treated patients will develop a post-treatment oesophageal stricture [23].

In 2005 Overholt et al reported a trial of PDT ablation vs. surveillance in patients with HGD [24]. Although this trial showed less progression to cancer at 5 yrs following PDT (21/136 vs. 20/70), the progression rate after PDT was still 15% [23], indicating that the risk of cancer was only halved.

Follow-up in this study was incomplete, and in 1/3 of patients PDT was followed by an oesophageal stricture which required endoscopic dilatation. Nevertheless, this trial provided evidence that the risk of malignancy arising in dysplastic Barrett's oesophagus might be reduced by endoscopic ablation. It remains, however, the only randomized trial to evaluate PDT for the prevention of cancer, and one of the few randomized trials in this area. PDT has largely been replaced by other cheaper and more widely available ablation methods, and it is no longer available in Australia or New Zealand.

Argon Plasma Coagulation (APC)

Argon Plasma Coagulation (APC) ablation uses monopolar electrocautery, via a stream of argon gas plasma which carries an electrical charge through to the closest mucosal surface, allowing ablation without direct contact. APC ablation is associated with a low incidence of post-procedural problems, and it is relatively inexpensive. At short term follow-up, APC has been shown to be reasonably effective for ablation of non-dysplastic Barrett's oesophagus. Van Laethem et al [25] reported that 25 of 31 patients (81%) taking 40mg of omeprazole daily had complete endoscopic regression of their Barrett's oesophagus one month after APC treatment, although this decreased to 61% when buried Barrett's glands discovered on endoscopic biopsy were added to the data analysis. The significance of buried glands is uncertain but does sound a note of caution as to the need for ongoing surveillance. Similarly, when using both histopathological and endoscopic assessment criteria, Kahaleh et al [26] reported only 22 of 39 (56%) patients, using 20-40mg omeprazole per day, had complete eradication of Barrett's oesophagus with APC at 1 month . Basu et al [27] found in a study of 50 patients with medically controlled reflux and a mean 5.9 cm length of Barrett's oesophagus, greater than 90% of Barrett's oesophageal mucosa was eradicated in only 68% of patients. With very high dose PPI therapy (120mg omeprazole daily) at the time of ablation, and high power APC (90W), Madisch et al [28] reported 70 patients with initial 100% complete Barrett's oesophagus ablation, but a subsequent histopathological relapse rate of 3% per year.

Trials of Barrett's oesophagus ablation in patients who had undergone previous antireflux surgery to control reflux are few and involve small patient numbers. Pinotti et al [29] enrolled 19 patients at least 2 months following laparoscopic Nissen fundoplication and reported 100% success for the elimination of Barrett's oesophagus with APC treatment. Similarly Ferraris et al [30] completely eradicated the Barrett's oesophagus mucosa in 46 post-fundoplication patients. Morino et al [31] observed histopathologically complete squamous re-epithelialisation in 20 of 23 patients treated with APC after laparoscopic fundoplication.

We enrolled 126 patients with non-dysplastic Barrett's oesophagus or low grade dysplasia (LGD) into 2 randomised controlled trials evaluating APC ablation vs. endoscopy surveillance [10, 32, 33]. In these trials 95-100% macroscopic (endoscopic) ablation was achieved after 2-6 treatment sessions, and outcome data suggested a more durable response in patients who had undergone antireflux surgery compared with patients whose acid reflux was managed with proton pump inhibitor medication [32, 33]. In patients who underwent ablation after fundoplication, a stable neosquamous epithelium was confirmed 5 years post-ablation by both endoscopic and histopathological criteria, with no progression to cancer or high grade dysplasia [10]. In addition, during 5 year follow-up, 3 control (surveillance only) patients within the post-fundoplication trial progressed to dysplasia, suggesting the possibility of a better outcome following APC ablation [10]. However, whether APC ablation of intestinal metaplasia reduces the longer term risk of dysplasia and malignancy is still uncertain, with no evidence yet reported to support this. In clinical practice APC ablation is falling out of favour and is being replaced by RFA in many parts of the world

Radiofrequency ablation (RFA)

RFA is a newer technique which employs a bipolar array technology to create an electrical field, and this generates frictional heating of cellular water. There are currently two devices available, a circumferential (HALO360) ablation catheter balloon-based device and an endoscope-mounted (HALO90) device. This is a relatively expensive treatment, with the cost of RFA ablation consumables varying between A$5,000 and A$8,000 for a full course of treatment, and this has limited uptake in Australia and New Zealand. Ablation depth in ex vivo studies has been shown to be 0.5 to 1 mm. This correlates with the depth of the muscularis mucosae, and therefore "theoretically" might avoid post-ablation stricture formation. As RFA diffusely treats the entire epithelium it achieves uniform ablation, and it has been suggested that it minimises the risk of buried residual columnar mucosa – "buried glands". Reported results have generally been good, and might be superior to other ablation methods, but follow-up remains short. Fleischer et al reported 2.5 year follow-up in a multicentre trial involving RFA treatment of Barrett's oesophagus without dysplasia. Complete endoscopic and histopathologic ablation was achieved in 60 of 61 patients (complete remission - 98.4%), with no strictures or buried "subsquamous" glands [34]. Ganz et al reported a multicentre US study that included 142 patients with HGD with a median Barrett's oesophagus segment length of 6 cm. Of 92 patients who had at least one follow-up biopsy, at a median of 12 months complete remission of HGD was observed in 90%. However, intestinal metaplasia was identified at 46% of follow-up endoscopies [35], suggesting that complete eradication

following RFA cannot be reliably predicted. Vaccaro et al reported that the cumulative incidence of newly detected intestinal metaplasia at one year after RFA in patients who had complete eradication of intestinal metaplasia was 25.9% [36]. Vaccaro et al also reported that dysplasia was detected in 8.5% of the group that had been deemed to have had complete eradication of Barrett's oesophagus at one year follow-up, highlighting the need for continued surveillance after RFA [36]. A case of squamous cell dysplasia arising in the neosquamous epithelium after RFA for HGD has also been reported [17].

Shaheen et al reported a multicentre randomized trial of RFA ablation vs. surveillance for dysplastic Barrett's oesophagus and observed 77% complete regression of intestinal metaplasia following RFA vs. 0% for controls at 12 months, as well as complete remission of HGD in 80% of the treated group [37]. Sub-squamous Barrett's oesophagus epithelium was found via rigorous biopsy sampling in 5.1% of RFA-treated patients at 12 months follow up, versus 25.2% at baseline, and 40% in the control group at 12 months. RFA decreased the rate of progression to cancer, although the number of cancers in the trial was small (1/84 vs. 4/43; p=0.04) and cancer prevention was not the primary end point. More recently Shaheen et al reported 3 year follow-up from the same trial in which 25% of patients who initially had dysplasia and had complete eradication of intestinal metaplasia were found to have newly detected IM [19]. They also reported disease progression in 4.2% of the ablation group, and thus concluded that the RFA treated population is still at high-risk, and suggested that RFA-treated patients still require ongoing endoscopic monitoring. This study remains the only randomized trial evaluating RFA for HGD. It is limited by its relatively short term follow-up, and it was funded by the device manufacturer. Other independently funded trials with longer term follow-up are needed to confirm these results, as well as equivalent cancer control to oesophagectomy.

Endoscopic Mucosal resection

Endoscopic mucosal resection (EMR) was developed in Japan by Inoue et al for treatment of superficial squamous cell carcinomas of the oesophagus [38]. This technique is now widely used for excisional biopsy of small (less than 2 cm) mucosal irregularities or nodules in patients with Barrett's oesophagus, HGD and intramucosal adenocarcinoma., although several studies on focal EMR alone have demonstrated a high rate of synchronous and recurrent lesion development, ranging from 14% to 47% [14]. EMR also provides a larger and deeper biopsy specimen, allowing more precise determination of the depth of tumor penetration than other methods [39]. Current data support EMR for diagnosis, as a treatment for focal mucosal oesophageal adenocarcinoma, and as an adjunct to RFA in the treatment of dysplastic Barrett's oesophagus epithelium [40].

Complete eradication of Barrett's oesophagus mucosa using EMR has been advocated and performed in some centres. However, the risk of complications makes this use more controversial. Complete responses have ranged from 76% to 100%, although the complication profile of more extensive, circumferential EMR includes stricture formation, with an incidence rate that approaches 50%, as well as bleeding and oesophageal perforation. In a series of 73 patients, symptomatic oesophageal stricture formation was noted in 24.7% of patients undergoing EMR. In multivariate analysis stricture formation was associated strongly with resection of >50% of the circumference of the oesophagus [41]. However, it appears that large non-circumferential EMRs of up to 12 cm^2 can be performed safely [42].

Gondrie et al combined EMR with RFA to treat patients with HGD or intramucosal cancer. An endoscopic and histopathological complete response for intramucosal cancer, dysplasia, and intestinal metaplasia was reported for all 12 (100%) patients [43]. Furthermore, stricture rates for RFA post-EMR appear to be comparable to RFA alone [44].This suggests that EMR might be performed with curative intent for tumors at low risk for metastatic spread, and then can be combined with mucosal ablation for complete removal of metaplastic or dysplastic oesophageal epithelium to prevent further lesion development, although more evidence is needed to support this proposal. Again, there is little longer term outcome data to support this approach, and it remains for the proponents to demonstrate long term safety and efficacy. This will require larger series from other centres, with good longer term follow-up. If good outcomes can be demonstrated, then this approach may represent a significant advance for the treatment on HGD and intramucosal cancer.

Ablation outcome vs. method of treatment of gastro-oesophageal reflux

Treatment of gastro-oesophageal reflux might influence the neoplastic potential of neosquamous tissue, and anti-reflux surgery might provide a more stable environment for the maintenance of neosquamous epithelium than in patients with reflux managed with PPI's. The rationale for this suggestion is that effective anti-reflux surgery controls both acid and bile reflux, and bile reflux appears to be an important factor in the etiology of Barrett's oesophagus [45]. Although PPI therapy reduces gastric acid secretion it does not eliminate all acid reflux, nor does it directly control bile reflux. In randomised trials of APC ablation reported previously from our Department, at 12 months 19 of 20 (95%) patients who had undergone ablation following a fundoplication maintained greater than 95% Barrett's oesophagus ablation, whereas in patients managed by PPIs who underwent APC ablation, only 14 of 23 (61%) patients maintained this degree of ablation ($p = 0.01$) [47,48]. These

findings are consistent with other reports of relatively durable outcomes in post-fundoplication patients [29-31, 46] vs. less durable ablation outcomes following APC in patients managed with PPIs [25-27, 47]. How this apparent difference in the stability of neosquamous epithelium affects neoplastic potential in the oesophageal mucosa, however, is unknown.

Cost effectiveness of surveillance and endoscopic therapy

With the outcome for patients presenting with advanced stage oesophageal adenocarcinoma poor, regular surveillance endoscopy to detect early neoplasia has been recommended by most of the international gastroenterological societies [48]. Neoplasias discovered during endoscopic surveillance are often curable, and some of these early lesions appear to be suitable for treatment with endoscopic therapy. However, surveillance is costly in terms of quality adjusted life years gained[18] and there are difficulties in disease detection as biopsies are generally taken in the absence of a visible target lesion within the Barrett's oesophagus tissue. The rate of progression from Barrett's oesophagus to adenocarcinoma has been reported to range from 0.2 to 2.1% per year, but it is probably less than 1% each year [49].

There have been several evaluations of the cost effectiveness of Barrett's oesophagus surveillance, and some have suggested that surveillance might do more harm than good, or is unlikely to be cost-effective at usual levels of willingness to pay [50-52]. However, these studies have been based on economic modeling, and the outcomes are specific to both the health care funding model in their countries of origin – USA and the UK, and the level of patient and endoscopist compliance. Further, these studies have had to rely on a limited evidence base that necessarily contains a large degree of uncertainty. Currently, there is evidence that surveillance-detected adenocarcinomas of the oesophagus are more likely to be diagnosed at the earlier T1 stage, and therefore have a better prognosis than cancers which present with symptoms [53-55]. However, there is a lack of evidence that surveillance actually improves long term survival in patients undergoing regular endoscopy surveillance [56]. This is because most patients in a Barrett's oesophagus surveillance program will die of diseases other than oesophageal cancer [57].

If endoscopic ablation reduces cancer incidence, this might be a more cost-effective approach than surveillance endoscopy. Modeling studies indicate that ablation might be a good option in patients with low grade dysplasia or no dysplasia, but cost effectiveness depends on the long-term effectiveness of ablation (prevention of cancer) and whether surveillance endoscopy can be discontinued after successful ablation[58, 59]. This modeling suggests that if ablation can permanently

eradicate non-dysplastic metaplasia in at least 40% of patients, and avoid the need for ongoing endoscopy, ablation would be preferred to surveillance [59]. In a threshold analysis, the critical determinants of the cost-effectiveness of ablation were the response to ablation, total cost of ablation, and risk of progression to dysplasia [58]. Cost and response are relatively straightforward to assess. However, the risk of progression is inherently difficult to ascertain due to the low rate of progression from Barrett's oesophagus. For the end point of cancer prevention to be investigated in randomized trials, these would need to be multi-centre to recruit a sufficient number of patients, and would require a long period of follow-up. Such studies might be facilitated with the addition of biomarkers. For now health economic modeling is the most efficient way to address these questions, although the reliability of any model is only as good as the data which underpins it. Larger patterns of care studies are needed to inform such work.

Biomarker use in Endoscopic Surveillance

Surveillance outcomes and cost-effectiveness might be improved through the identification and use of appropriate biomarkers to identify risk of progression to cancer, and thereby direct surveillance efforts specifically at high risk individuals. Inadomi et al identified that the use of a biomarker or a panel of biomarkers, whose sensitivity and specificity to predict cancer development exceeded 80%, could be a more viable strategy than dysplasia-based surveillance, and overcome the inherent inter- and intra-observer variations in dysplasia diagnosis that currently limit the effectiveness of surveillance programs [51]. Furthermore, with the potentially improved cost-effectiveness of bio-marker based surveillance combined with endoscopic therapy for early cancer, targeted population screening may also become cost-effective.

However, biomarker development has proved challenging as oesophageal adenocarcinoma is a heterogeneous disease [60, 61]. Phenotypic and genotypic heterogeneity have also been observed in Barrett's oesophagus epithelium [62, 63]. This is highlighted by the observation that genetic clonal diversity in Barrett's epithelium is associated with progression to adenocarcinoma [61]. It has therefore not yet been possible to develop a panel of biomarkers to meet the requirements indicated by the study of Inadomi et al [51]. For example, the combination of 17p LOH, 9pLOH, and aneuploidy/tetraploidy has been shown to have a sensitivity for predicting cancer development of 59% at 10 years follow-up in a high risk population [64]. In a blinded multi centre study, a panel of 8 DNA methylation based biomarkers had a sensitivity for cancer prediction of 60% at 4 years when modeled against an 80% specificity [65].

The problem of genotypic heterogeneity has clearly limited the use of biomarkers in this disease, but it may be feasible to utilize biomarkers with sensitivity and specificity lower than 80% if endoscopic ablation techniques become sufficiently effective at preventing disease progression to allow lengthening of surveillance intervals, or to allow replacement of endoscopic surveillance with non-endoscopic forms of surveillance [59].

Molecular biology studies assessing the normality of neo-squamous mucosa

Although ablation of Barrett's oesophagus produces a neosquamous epithelium, there have been reports of oesophageal adenocarcinoma developing after ablation [66, 67]. Incomplete ablation and/or residual metaplastic glands under an apparently normal looking neosquamous epithelium may be responsible for post ablation neoplasia. Consistent with this are reports that recurrent and/or persistent Barrett's oesophagus after ablation therapy contains genetic alterations associated with malignancy [68]. In some patients the neosquamous epithelium that regenerates following ablation may harbor genetic abnormalities. Paulson et al reported a patient (1 of 20) that had a p16 deletion in an island of neosquamous epithelium after ablation that was identical to that seen in the Barrett's epithelium [69]. Lopes et al found that those patients who expressed p53 in their metaplastic mucosa were subsequently found to express p53 in their neosquamous epithelium after APC ablation [70]. These reports suggest that neosquamous mucosa is abnormal in some patients after ablation.

Two recent studies have investigated the genetic normality of the neosquamous mucosa after RFA. Pouw et al reported normalization of Ki-67 and p53 protein expression measured by immunohistochemistry, and of chromosomal abnormalities involving chromosomes 1 and 9 and the loci for the tumour suppressor genes p16 and p53 for 22 patients with Barrett's oesophagus containing early cancer and/or high-grade intraepithelial neoplasia [71]. The results of this study suggest that RFA may produce a more normalized neosquamous epithelium than PDT or APC ablation. However, the molecular heterogeneity of this disease does not allow us to draw firm conclusions. Pouw et al acknowledged this by stating that they did not evaluate other molecular changes which might be important in this disease such as the specific mutational status of other genes such as p53 or p16, loss of heterozygosity (LOH), or alterations in protein expression. Galipeau et al reported that 80% of patients with aneuploidy, p53 LOH, and p16 LOH developed cancer at 6 years [64], so these biomarkers may also need to be evaluated in patients treated with RFA. However, 12% of patients that did not have any of these specific markers also developed cancer within 10 years, suggesting that the approach of using specific biomarkers might be limited by molecular heterogeneity and the broad range of potential lesions.

Post-ablation abnormalities may occur if some pre-malignant lesions are resistant to ablation. For example, p16 allelic loss has been reported to be associated with a decreased response to ablation [72]. This type of lesion may reside in stem cells and/or occult columnar tissue (islands or buried), and its presence could potentially be detected in neo-squamous mucosa either directly, or as a field effect. In support of this, we have previously reported that the Barrett's oesophagus associated microRNA, miR-143, is expressed at higher levels in post-APC ablation neo-squamous mucosa in some patients, and in pre-ablation proximal squamous tissue above Barrett's oesophagus, compared to the squamous oesophageal mucosa of healthy patients [73]. Whether this is due to the presence of ablation resistant stem cells and/or residual occult columnar tissue, or from a field effect, is unknown. The possibility that neo-squamous tissue may not be normal in some patients suggests the need for surveillance following ablation, and for further studies which compare the molecular profile of neosquamous epithelium with normal squamous epithelium. Although neosquamous epithelium has been shown to occasionally retain some markers associated with Barrett's oesophagus epithelium, it may also differ from normal squamous epithelium in the expression of unsuspected but important genes.

Conclusions

Endoscopic ablation has been introduced into clinical practice largely without formal evaluation, and it is not certain that this has improved any clinical outcomes. Due to the use of endoscopy facilities and consumables, ablation is associated with significant cost, and this has limited the uptake of RFA in particular in some parts of the world, including Australia and New Zealand. Hence, determining whether ablation reduces the risk of cancer sufficiently in Barrett's oesophagus and whether ablation can be cost-effective, is important.

To date there have been no randomized trials comparing endoscopic therapies with surgery for early stage oesophageal cancers [74], although studies to date suggest that endoscopic therapies produce increased survival at 4 years for oesophageal cancers compared to no therapy [75] and population based data suggests that patients with early oesophageal cancer managed with endoscopic therapy have equivalent long-term survival compared to those treated with surgical resection [76]. However, despite these encouraging observations, intensive surveillance is still required after endoscopic therapy, and this brings into question the cost-effectiveness of all of the new endoscopy based strategies. Studies are required to better determine the effectiveness of ablation strategies for Barrett's oesophagus at both the clinical and the cellular level, and such studies should also

investigate whether the method of reflux control impacts on outcomes. Good efficacy at long term follow-up, in large patient cohorts should be demonstrated. Until such studies are reported, patients should remain on close endoscopic follow-up, and outcomes should be carefully audited. Nevertheless, if in the future, high quality evidence confirms that ablation is an effective alternative to surgical oesophagectomy in patients with HGD or intramucosal cancer, endoscopic treatment might replace oesophagectomy for early stage disease. For now, it is likely we are in transition to a new clinical paradigm. Oesophageal surgeons need to be actively engaged in the development, assessment and implementation of these new techniques.

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