Ablating Barrett's metaplastic epithelium: are the techniques ready for clinical use?

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Barrett's oesophagus

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Testing of endoscopic ablation techniques for Barrett's oesophagus should follow a ''top down approach''

Barrett's oesophagus (BO) is a condition that causes many controversies. Identification and treatment of Barrett's patients gives rise to many questions such as: how great is the risk of malignant degeneration for the entire group of Barrett's patients and for individual patients? Does this risk justify the efforts, costs, and risk of endoscopic surveillance? Are we doing more harm than good in subjecting patients with non-dysplastic BO to endoscopic surveillance? Are we reducing patients' quality of life by making them (and their insurance companies) unduly worry about their condition?[1 2] The ultimate solution to these problems would be a cure for the condition, either by reverting Barrett's mucosa to normal squamous mucosa or by preventing its malignant degeneration once it has developed.

Protagonists of surgical antireflux procedures have claimed that elimination of reflux of gastric and duodenal contents into the oesophagus will prevent malignant transformation in BO but such a protective effect is not generally accepted.[3 4] Acid suppressant therapy by proton pump inhibitors (PPIs) cannot reverse Barrett's mucosa but may reduce the risk of developing dysplasia and cancer in BO, as based on ex vivo studies and two recent retrospective analyses of BO cohorts.[5–7] Data however are conflicting, and at best circumstantial evidence for a protective effect of PPIs has been provided. Several other chemoprevention agents (for example, aspirin or non-steroid anti-inflammatory drugs) are currently under investigation, but none has yet emerged as clinically relevant.

A variety of endoscopic techniques have been used to convert non-dysplastic Barrett's mucosa into normal squamous mucosa. Examples of these techniques are laser photocoagulation, multipolar electrocoagulation, argon plasma coagulation, radiofrequency ablation, cryoablation, and photodynamic therapy.[8–13] These therapies are all aimed at inducing a controlled injury to the superficial oesophageal wall layers thereby ablating the metaplastic epithelium while maintaining the integrity of the submucosa and deeper wall layers. Under aggressive acid suppressing therapy, the oesophagus is then allowed to heal in an acid free environment, promoting restoration of the normal squamous mucosa.

In this issue of *Gut*, Sharma and colleagues[14] report on a prospective randomised trial comparing multipolar electrocoagulation (MPEC) with argon plasma coagulation (APC) for ablation of Barrett's epithelium in 35 patients, almost all without dysplasia (three patients had low grade dysplasia) ***(see page 1233)***. The study was conducted at two sites and inclusion of these 35 patients took almost four years. Randomisation was stratified by Barrett's length (<3 cm *v* >3 cm). Treatment of the entire Barrett's segment (median length in this study was 3 cm) was attempted at each session using a linear paint stroke technique until a white coagulum was visualised on the entire segment of Barrett's epithelium. Endoscopic treatment sessions were continued at 4–8 week intervals until there was no endoscopically apparent Barrett's mucosa left. Endoscopic and histological reversal of Barrett's oesophagus was achieved in 12 of 16 (75%) patients treated with MPEC compared with 12 of 19 (63%) treated with APC. No specific patient characteristic, including age, Barrett's length, hiatus hernia size, acid control during high dose PPI therapy, or type of ablation therapy was associated with incomplete reversal of Barrett's mucosa.

Although there were no severe complications in this study, the majority of patients had complaints of a sore throat, odynophagia, epigastric pain, or low grade fever, and one patient needed dilatation of a stricture.

At least three other randomised ablation studies have been published addressing the removal of non-dysplastic Barrett's mucosa. Dulai *et al* randomised 52 patients with Barrett's oesophagus 2–7 cm in length to treatment with APC or MPEC.[9] Unfortunately, randomisation was ineffective in that patients in the MPEC arm had a significantly shorter mean length of BO (0.9 cm). The mean number of treatment sessions required for endoscopic ablation was 2.9 for MPEC versus 3.8 for APC ($p = 0.04$). Yet this difference was not found after adjusting for the baseline difference in BO length between the groups. The proportion of patients with complete endoscopic and histological ablation was 81% for MPEC versus 65% for APC ($p = 0.21$). Ackroyd *et al* randomised 40 non-dysplastic Barrett's patients who had undergone prior fundoplication to either APC or endoscopic surveillance.[10] Overall, complete ablation was achieved in 12 of 19 (63%) patients in the APC group and in three of 20 (15%) in the surveillance group ($p<0.01$). Finally, Hage *et al* randomised 40 patients (32 with no dysplasia and eight with low grade dysplasia) to either APC (two sessions) or two treatment protocols using 5-ALA induced photodynamic therapy (ALA-PDT).[13] Additional treatment with APC was allowed in the PDT groups. Histological examination at 12 months revealed complete ablation in 82% and 90% of PDT patients and in 67% of patients in the APC group (NS). Side effects were more common after PDT than APC therapy and one patient died three days after treatment with PDT, presumably from cardiac arrhythmia due to 5-ALA administration or its photodynamic effect.

Summarising these findings we can conclude that complete ablation of non-dysplastic Barrett's oesophagus is feasible, that severe complications are rare but do occur, and that complete endoscopic and histological eradication of Barrett's mucosa is achieved in approximately 70% of cases, with follow up generally being limited to 1–2 years.

The concept of ablating non-dysplastic Barrett's oesophagus is that reduction in surface area of Barrett's epithelium will reduce or even ameliorate the rate of progression to oesophageal cancer but there is no proof that this concept is valid. Given the small chance of malignant degeneration in these patients, all of these studies on ablation techniques for patients with non-dysplastic Barrett's oesophagus have been underpowered to demonstrate such an effect.

What are the criteria of an ideal ablation technique in Barrett's oesophagus? Firstly, it should remove all dysplasia and intestinal metaplasia. Secondly, the neosquamous mucosa that develops after ablation should be free of oncogenetic abnormalities such

as those present in the pretreatment metaplastic mucosa, and no residual areas of metaplastic columnar mucosa should remain hidden underneath it (''buried Barrett's''). Thirdly, it should be very precisely targeted at the mucosa without damaging the deeper layers, thereby minimising complications and preserving the normal functional characteristics of the oesophagus. Finally, it should be quick and easy, removing all Barrett's mucosa, preferentially in one procedure. Neither MPEC nor APC meets these criteria at the current time. In the study of Sharma and colleagues,[14] MPEC and APC required a mean number of 3.8 and 3.4 treatment sessions, respectively, which is in accordance with the other studies mentioned above. A success rate of approximately 70%, with the need for endoscopic surveillance irrespective of whether or not Barrett's mucosa is successfully eradicated, is another negative point for APC and MPEC, as Sharma *et al* rightfully admit in their well balanced discussion. Furthermore, with many ablation techniques, including APC and MPEC, it is difficult to target the depth of ablation and there seems a trade off between effective eradication and complications, both depending on the depth of injury induced. Finally, APC and MPEC may be associated with buried Barrett's and anecdotal reports on subsquamous cancers after APC in Barrett's have been reported.[15 16]

Is there a future for endoscopic ablation of non-dysplastic Barrett's mucosa? Hopes are set for risk stratification, using either patient characteristics (for example, sex, age, length of Barrett's segment, severity of the underlying reflux disease) and/or a combination of biomarkers.[17 18] Thus far, however, developing such a stratification index has been illusive. Given all of this, we fully agree with Sharma and colleagues[14] that endoscopic ablation techniques should not be routinely applied in patients with non-dysplastic Barrett's oesophagus.

We even question if it is justifiable to use them within the context of clinical trials. In our opinion, novel ablation techniques should first be tested in patients with Barrett's oesophagus and high grade dysplasia. A second group could be patients with a consensus diagnosis of low grade dysplasia.[19] In these patient groups, prospective testing and comparing of ablation techniques seems much more justified given the alternative management options (for example, oesophagectomy for high grade dysplasia or intensive follow up for low grade dysplasia). Before applying ablation techniques in non-dysplastic Barrett's patients, studies in dysplastic patients should have demonstrated that some of the aforementioned criteria for the ideal ablation techniques are met. In our opinion, the development of new endoscopic ablation techniques for Barrett's oesophagus should be performed through a ''top down approach'': first showing efficacy and safety in dysplastic patients before applying them in patients that clearly have less to gain and more to lose.

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