Endoscopic management of refractory benign oesophageal strictures

Simon M. Everett

Abstract: Refractory benign oesophageal strictures are an infrequent presentation but a cause of significant morbidity and mortality. The treatment of these strictures has changed little in recent years, yet new evidence is emerging for the optimal timing and application of different therapies. In this article, we have carefully reviewed the current literature on the evaluation and management of refractory strictures and provided practical advice as to their management. A number of areas require attention in future research, including carefully designed randomised trials of endoscopic and medical therapies, and a focus on risk factors at a patient and molecular level to facilitate development of medical therapies that can reduce recurrent fibrosis in these patients.

Keywords: oesophageal, stricture, refractory

Received: 27 March 2019; revised manuscript accepted: 16 June 2019.

Introduction and aims
Benign oesophageal strictures are a common presentation to primary and secondary care with a variety of causes. Once malignancy has been excluded, strictures are usually managed by a combination of treatment of the underlying cause, attention to nutritional deficit and dilatation of the strictured segment. Endoscopic options to dilate a benign stricture have changed little in recent years. These include through the scope (TTS) balloons or bougies, both of which are usually well tolerated and effective in treating the majority of simple benign strictures. The British Society of Gastroenterology (BSG) has published guidelines in 2017 on safe dilatation of benign oesophageal strictures that have been reviewed and summarised recently.1,2

Endoscopic dilatation 1–3 times and treatment of the underlying cause will resolve oesophageal stricture in most instances. However, in some cases, the stricture is resistant to initial medical and endoscopic therapy with failure to resolve or rapid recurrence. These refractory strictures are relatively infrequent but are a cause of significant morbidity to patients and utilise a disproportionate amount of health care costs.

The aim of this article is to review the optimal management of adult patients with benign refractory strictures so as to minimise morbidity and costs. Prevention of strictureing, particularly after surgery or endoscopic therapy, is an emerging and important topic beyond the scope of this article, which focuses on treatment.

Methods
A Medline literature search for oesophageal stenosis and ‘refractory’ or ‘resistant’ or ‘recurrent’ was performed. The search was limited to studies in humans, adults and publications in English language, revealing a total of 487 citations. These were hand searched for publications relevant to the endoscopic management of refractory benign oesophageal stenosis. The reference list of all chosen publications was searched for further relevant papers.

Initial management of benign oesophageal strictures
Patients with benign oesophageal strictures typically present with dysphagia and weight loss along with symptoms related to the underlying cause. Urgent assessment and investigation is required to identify the cause and exclude malignancy. A careful history should be taken looking for underlying causes, assess the severity of symptoms and discuss future treatment objectives.
There are several clinical scores that can be used to define the degree of dysphagia, which range in complexity and application. Although dysphagia scores are most important to compare endpoints in clinical trials, incorporating a simple score such as the Ogilvie score into clinical practice can form an objective assessment before and after any intervention and provide useful data for clinical audit. A nutrition assessment should also be performed at the initial assessment to guide the timing of investigations and subsequent interventions. As a minimum, weight loss should be quantified, and when there is concern, dietetic review and additional nutritional support should be provided. It is important to correct nutritional deficit early in the treatment pathway to minimise morbidity and maximise tolerance of subsequent treatments.

Once the cause of the stricture is identified, it is important to maximise medical therapy to provide local control of any inflammation. This might involve withdrawal of potentially harmful medications such as Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or bisphosphonates and optimisation of proton pump inhibitor (PPI) therapy. In eosinophilic oesophagitis, medical therapy should be commenced ahead of or in parallel with stricture dilatation. All guidelines stress the need to biopsy strictures to exclude malignancy before dilatation and, where appropriate, the background oesophageal mucosa to rule out eosinophilic oesophagitis. The yield of targeted biopsies is high and approaches 100% if 6 biopsies are taken. When there is any doubt, biopsies should be repeated even if this adds a small delay to interventions.

When a stricture is encountered, it is important to note the endoscopic features carefully. Distance from incisors to the proximal stricture edge, length of stricture, an assessment of lumen diameter (noting the diameter of the endoscope in use), the presence of ulceration, stricture complexity (see below) and any unusual features or abnormalities in the remaining oesophagus should all be noted. Features of eosinophilic oesophagitis (termed EREFS; exudates, rings, edema, furrows and strictures) should be commented on but are not reliable and should not replace multiple oesophageal biopsies.

Dilatation can be performed with either bougies or TTS balloons. The risk of perforation is low for simple strictures, and less than the frequently quoted risk of 1%. Many versions of balloon dilator are commercially available but they typically provide graduated dilation in 1.0 or 1.5 mm increments with three sizes per balloon. Traditionally, each insufflation is for 1 min, though the optimal duration of balloon insufflation is unknown and warrants further research. Following balloon deflation there is reassessment of the mucosa; where there is minimal mucosal trauma the next size of balloon can be used, whereas if significant injury is seen it is advisable to stop and schedule a repeat examination. Fluoroscopy may be required where the stricture is refractory, long, angulated or complex. The starting and target dilatation diameter is controversial; the historic teaching of the ‘rule of 3’ was established for blind bougienage. This pragmatic guidance advised that sequential dilatation should be three measurements from the one where resistance was felt but is not applicable to dilatation where endoscopic visualisation of the mucosa is possible. There is no evidence-based target for the maximum diameter that is required; the British guidelines recommend >15 mm and symptomatic improvement. The greater priority is patient symptoms, which should be carefully evaluated before embarking on each procedure. It should be stressed that the optimum diameter will vary according to patient size, stricture aetiology (higher diameters may be preferable for postsurgical strictures) and the location in the oesophagus (narrower diameters for proximal strictures) so individualisation is paramount.

After a successful dilatation, it is recommended that further procedures should be performed weekly or two-weekly until easy passage of a ≥15 mm dilator is achieved along with symptomatic improvement. Overall, one to three dilatation sessions are sufficient to relieve dysphagia in simple strictures with a maximum of five dilations needed in >95% of patients.

**Refractory benign oesophageal strictures**

**Definition**

The definition of a refractory stricture was proposed in 2005 by Kochman and colleagues as follows:

> an anatomic restriction because of cicatricial luminal compromise or fibrosis that results in the clinical symptom of dysphagia in the absence of endoscopic evidence of inflammation. This may occur as the result of either an inability to successfully remediate...
the anatomic problem to a diameter of 14 mm over 5 sessions at 2-week intervals (refractory) or as a result of an inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent).11

This has been adopted as the standard definition by many authorities including the recent BSG guidelines. Although pragmatic, it should be understood that there is no evidence base in support of this.

In practice, what this means is that a stricture should only be considered refractory once neuromuscular causes have been excluded, the patient has had a number of sequential dilatations at short intervals and has optimised treatment for the underlying cause – this is particularly relevant for peptic and eosinophilic oesophagitis strictures. Where the ulceration or inflammation cannot be healed by medical means, further endoscopic measures to treat the stricture are less likely to succeed and alternative measures, including surgical approaches may need to be considered.

**Aetiology**

Table 1 demonstrates the common causes of benign oesophageal strictures and those that are more likely to become refractory. Increasing use of endoscopic therapy for oesophageal neoplasia is likely to increase the number of strictures requiring endoscopic therapy. There is up to 50% chance of developing a symptomatic stricture requiring endoscopic dilatation after endoscopic resections [either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)], after a resection size >75% of the oesophageal circumference and a longitudinal resection length greater than 40mm.1 Following radiofrequency ablation therapy (RFA) for oesophageal neoplasia, stricturing has been reported to occur in 9% patients, with higher frequency if there has been a prior endoscopic resection or if used for squamous neoplasia.12

Strictures can be defined as simple or complex. Simple strictures are short (<2 cm), concentric, straight, and allow the passage of a normal diameter endoscope. Complex strictures are usually longer (≥2 cm), angulated, irregular or have a severely narrowed diameter.1,10 These are more difficult to treat and have a tendency to be refractory or to recur despite dilatation.13 The currently most common aetiologies of recurrent and refractory strictures in the western world include postsurgical anastomotic, postendoscopic therapy, radiation-induced and caustic strictures.14-16 For example, in a series of 74 anastomotic strictures, 69% were considered refractory, and in a study of 63 patients with radiation-induced stricturing undergoing 303 dilatations, recurrence occurred in 33% after achieving an initial satisfactory oesophageal lumen, and 43% overall were refractory to dilatation.17,18

In the small subset of patients (approximately 10%) in whom five dilations to at least 14 mm fail to establish adequate and persistent food passage, the strictures can be very difficult to manage and the treatments may be associated with significant morbidity and mortality.19 Repici and colleagues20 reported a 15-year experience of treating refractory

| **Table 1. Causes of benign oesophageal strictures.** |
|---------------------------------------------------|
| **Intrinsic oesophageal disorders**               | **Iatrogenic or accidental**                      |
| Peptic oesophagitis                               | Postsurgical – Anastomotic*                       |
| Eosinophilic oesophagitis                         | Postradiation therapy*                           |
| Miscellaneous disorders of the squamous epithelium (e.g. scleroderma, epidermolysis bullosa dystrophica, pemphigus and pemphigoid, lichen planus) | Endoscopic therapy |
| Oncotic resection – EMR/ESD*                      | • Postendoscopic resection – EMR/ESD*             |
| Motility disorders (e.g. achalasia)               | • RFA/PDT                                       |
| Rings and webs (e.g. Schatzki ring)               | • Variceal band ligation                         |
| Long term nasogastric feeding tubes               | Caustic ingestion*                               |

EMR, Endoscopic mucosal resection; ESD, Endoscopic submucosal dissection; PDT, photodynamic therapy; RFA, Radiofrequency ablation.
*Stricture more likely to become refractory.14
strictures in two academic centres in Milan, Italy, and Philadelphia, Pennsylvania. The use of dilatation and stents was evaluated for resolution of dysphagia, adverse events and long-term outcome. In keeping with the aforementioned studies, the majority of strictures were caused by caustic (10%), postsurgical (31%), postradiotherapy (14%) or mixed aetiologies (40%). A total of 70 patients were included and a metallic or biodegradable stent (BDS) was placed in 24 patients. Using a combination of repeated dilatations, steroid injections and stent insertions, after a mean follow-up of 43.9 months, only 22 patients (31.4%) had achieved clinical stricture resolution. Success was less-frequently observed in patients treated with a stent than those treated by other means, though this is likely to be due to confounding factors. The authors found that clinical resolution tended to be lower in patients with a high or cervical stricture. Overall, eight patients (11.4%) underwent surgery and percutaneous gastrostomy (PEG) or J-tube was placed in six patients (8.6%). Serious adverse events such as perforation (3 patients) and fistula (4 patients) occurred in 10% of patients overall and 12 patients (17.1%) died during follow-up, of which 2 (2.9%) were related to stricture-related treatments. These data highlight the difficulties in treating these patients and the need to carefully counsel patients about the treatment options and related risks.

Management of refractory strictures

Broadly speaking, refractory strictures can be managed by a combination of topical drug therapy, the aim being to reduce inflammation and fibrosis, and mechanical methods to break down the fibrosis and allow tissue remodelling. As well as influencing the likelihood of refractoriness, different aetiologies also influence the location and length of strictureing. Notably, anastomotic strictures tend to be high and caustic strictures tend to be long. However, there is little evidence to support a concept of different management strategies according to the aetiology of refractory strictures, aside from the influence of length, location and complexity. Where evidence does exist for variation according to aetiology, this will be mentioned in the sections that follow.

Drug treatments

Steroid injection

Chronic inflammation leads to collagen deposition, through synthesis and activation of multiple factors, including transforming growth factor beta (TGF-β) and alpha-2-macroglobulin, which are inhibitors of collagenase activity. Steroids provide a potential mechanism to inhibit these inflammatory pathways. Therefore, steroid injection (usually 0.5 ml of 40 mg/ml triamcinolone injected into four quadrants) in the location of a stricture at the time of dilatation provides an appealing mechanism to reduce collagen deposition and fibrosis associated with chronic inflammation and therefore reduce the likelihood of stricture recurrence. This has been the subject of several small trials with varying outcomes. For example, a study from the Netherlands in 2013 failed to demonstrate a significant effect of steroid injection on dysphagia free interval or time to repeat dilatation, though with nonsignificant trends towards a benefit.

The results of individual trials will not be reviewed as these have been amalgamated in two recent meta-analyses. These studies both indicate that stricture recurrence rate is reduced after steroid injection without an increase in complications. Szapary and colleagues studied benign oesophageal strictures of all aetiologies. They identified 11 articles involving 343 patients. Their analysis demonstrated significant reduction in the interval between dilatations, a nonsignificant effect on number of repeat dilations but no change in dysphagia score between participants undergoing steroid injection with dilatation and those having dilatation alone.

However, the quality of the evidence was considered very low and there was significant heterogeneity in most data analysed. Zhang and colleagues studied benign oesophageal strictures following surgery, corrosive ingestion or peptic strictures. Although similar search strategies were employed between the two meta-analyses, Zhang and colleagues identified only 6 studies involving 176 patients. They demonstrated a significant reduction in re-stricturing rate and number of subsequent dilatations after triamcinolone injection. Dysphagia score was nonsignificantly reduced after injection. Heterogeneity was low for stricture recurrence and repeat dilatation but high for dysphagia score. Neither of these meta-analyses demonstrated an increase in complication rate after steroid injection. The studies identified in these two meta-analyses vary substantially and the quality of evidence behind them both is poor but overall these studies are supportive of steroid injection as a therapeutic modality in resistant strictures.
It is unclear if aetiology of stricture influences the effect of steroid injection. Early studies suggested benefit in peptic strictures. However, in the above meta-analyses, there was no difference in outcome between postsurgical or nonsurgical strictures, so it is likely that steroids have a role in all stricture aetiologies. A second question is whether steroid should be injected before or after the dilatation. In most studies, the injection has been performed before dilatation, including the negative Dutch study. However, a more recent randomised blinded trial of 65 patients with postsurgical anastomotic strictures evaluated triamcinolone injection (50 mg) directly into the mucosal laceration after dilatation. Those patients receiving steroid injections demonstrated significant improvement in number of dilatations to resolve strictures (2.0 versus 4.0) and more patients dysphagia free at 6 months (39% versus 16%), suggesting that injection into the disrupted mucosa may result in greater effect on collagen deposition and stricture recurrence. However, no studies have compared injection before with injection after dilatation and this should be the subject of further research.

Thus, although there remain some doubts about the magnitude of benefit of steroid injection in improving outcomes in refractory benign oesophageal strictures, and those strictures that respond best to steroid injection, current evidence favours a view that steroid injection should be used in an attempt to reduce stricture recurrence after dilatation and that this is probably relevant to strictures of all aetiologies. Although the optimal timing of steroid injection is unknown, it makes more sense to use this early in the course of the disease and dilatation programme in an attempt to diminish collagen formation, and most likely injection into the mural defect after dilatation would be more beneficial, though a trial comparing this approach to predilatation injection is required. Finally, the question of whether steroid injection should be performed at repeat dilatations is uncertain but some authors recommend that a maximum of three sessions is appropriate.

Mitomycin C

Mitomycin C is an antibiotic chemotherapeutic agent isolated from Streptomyces caespitosus that inhibits DNA synthesis through cross-linking. In doing so, it may reduce the production of fibroblasts and inhibit fibrosis. It has been evaluated for use as an antifibrotic agent in eye surgery for strabismus and glaucoma. In oesophageal strictures, it can be applied by sponge or injection. Most literature relating to use of Mitomycin C relates to caustic strictures in paediatric practice. It has been subject to a randomised controlled trial in 40 children with caustic oesophageal strictures. Application before dilatation resulted in significant reduction in the number of dilatation sessions needed to alleviate dysphagia. In adults, its use has been limited to small uncontrolled case series, the largest being 25 patients. In a study of 9 patients with true refractory strictures, following Mitomycin C application, the need for further dilatation decreased from 1.5 dilations per month to 0.39 dilations per month over a median of 10 months; however, dysphagia scores did not improve significantly from a mean of 3.2–2.6. A systematic review of Mitomycin C use in adults and children reported a complete response to therapy in 73% and a partial response in 21% though these uncontrolled data must be interpreted with considerable caution.

Other drugs

There is the potential for multiple other drug applications to inhibit fibrosis but none have been evaluated in oesophageal strictureting. The process of fibrosis is complex but increasingly well understood. Drugs that have the potential to inhibit fibrosis may work through inhibition of cellular signalling pathways, particularly growth factors such as TGF-β or cytokines such as tumour necrosis factor (TNF) or Interleukin-13 (IL-13). Intracellular enzymes and nuclear receptors such as the Janus Kinase (JAK) family and peroxisome proliferator-activated receptor gamma (PPAR-γ) are also suitable potential targets and a large literature has developed, particularly in relation to pulmonary, renal, liver and skin fibrosis with new applications of old drugs or new drugs in development. Some of these may be of benefit in the prevention of recurrent oesophageal fibrosis. The specific patient and molecular factors that are relevant to recurrent fibrosis in patients with refractory strictureting are yet to be elucidated, but if established, these may form an important basis on which to evaluate new therapies and this will form an important avenue of research in the future.

Mechanical measures

Oesophageal stents

The placement of a self-expanding stent in refractory strictures potentially allows remodelling of
the stricture around the stent with a more permanent benefit than dilatation alone. Three different types of stents have been used: self-expanding metal and plastic stents (SEMS and SEPS, respectively), and more recently BDSs have been introduced as possible treatment options. BDSs are made from polydioxanone, which is degraded by hydrolysis 8–12 weeks after placement but maintains its radial force over time, the main advantage being that it does not need to be removed. It has been proposed that the prolonged dilatory effect before stent absorption and the progressive stent degradation could represent a more favourable solution for refractory strictures compared with the use of SEMSs and SEPSs.

The option of stent usage in refractory strictures has been the subject of several small case series and three meta-analyses, the most recent conducted by the European Society of Gastrointestinal Endoscopy (ESGE) in 2015.32–35 The ESGE meta-analysis included only studies in which the definition of refractory benign oesophageal stricture was clearly stated and which included at least two sessions of endoscopic dilation before stent placement. They analysed 18 papers giving a total of 21 treatment arms and 444 patients. Of the 18 included studies, 9 used fully covered SEMS (in a total of 227 patients), 8 trials used SEPS (140 patients) and 4 studies used BDS (77 patients). Overall, the pooled clinical success rate (defined as resolution of dysphagia without needing further intervention at the end of follow-up) of stent placement in the 444 patients was 40.5%. Patients treated with plastic and metal stents did not report significantly higher success rates than patients treated with BDSs (SEPS = 46.2%; SEMS = 40.1%; BDS = 32.9%). Success rates were nonsignificantly lower in studies that used stricter definitions of refractory strictures. The overall adverse event rate was 20.6% and stent migration rate was 28.6% with no significant difference between stent type. The main reported adverse events were severe chest pain, upper gastrointestinal bleeding, perforation and aspiration pneumonia. One patient died because of massive bleeding.

Both the European and UK guidelines recommend consideration of fully covered metal stents in refractory strictures after other measures (including repeat dilatation) have failed.1,35 It is recommended that partially covered stents be avoided because of the possibility of the exposed wire mesh becoming embedded in the oesophageal mucosa due to tissue hypertrophy. Stent placement should be temporary to avoid tissue hypertrophy at the upper or lower margin of the stent, which can worsen dysphagia and cause difficulty in removal. UK guidelines recommend removal of fully covered stents after 4–8 weeks, whereas the European guidelines suggest a maximum of 3 months. Where hypertrophy has occurred and the stent cannot easily be removed, a ‘stent in stent’ technique can be used to induce pressure necrosis of the hypertrophied tissue and removal of both stents after 2 weeks.

BDS have not been compared directly with SEMS or SEPS and have in general been reserved for more resistant strictures in reported case series.36–38 Single BDS placement appears to be only temporarily effective in the majority of patients, with approximately 20% dysphagia free survival at 6 m.39 Furthermore, a small UK trial of 17 patients with refractory strictures compared use of a BDS to endoscopic dilatation and demonstrated poorer outcomes in the stent group after 6 months.40 However, as the stents do not require removal, they can reduce the need for intervention or may be suitable for repeated insertions in selected patients. In a case series of 37 stents in 20 patients, there was a significant reduction in median number of interventions in the 12 months following stent insertion compared with the preceding 12 months (2 versus 7, respectively).38 In this series, seven (35%) patients received multiple BDS (up to a maximum of nine insertions in one patient). In the largest study to date (59 stents, 28 patients), sequential placement of a first, second and then third BDS resulted in a median dysphagia free period of 90, 55 and 106 days, respectively. Nonetheless, few patients remain dysphagia free after sequential placements, suggesting that this strategy may not offer effective long-term dysphagia relief but may be suitable for selected patients in whom few other options exist.

Given the potential efficacy of stenting as a single modality treatment, the question has arisen as to whether this would be an appropriate therapy earlier in the course of treatment. A recent multicentre, randomised study enrolled patients with benign strictures with 1–5 previous dilations to receive further dilatations or insertion of a BDS. At 3 months, the BDS group (n = 32) underwent significantly fewer endoscopic dilations for recurrent stricture compared with the dilation group (n = 34). By 6 months, the number of required...
Interventions in each group were similar but the median time to recurrent dysphagia and repeat dilatation was longer and degree of activity greater in the BDS group. The number of patients experiencing adverse events was similar between the groups. Two patients in the dilatation group had nonfatal perforations whereas two patients in the BDS group died after developing tracheoesophageal fistulas at 95 and 96 days postplacement.

It should be noted that significant side effects of pain and vomiting can occur in approximately 20–50% of patients after insertion of BDSs and can persist until the stent dissolves.37,39 A further significant concern about stent placement is the development of stent-related oesophago-respiratory fistulae. These can occur in both benign and malignant strictures. In one large case series of 397 patients, a fistula developed in 4% of patients.42 The risk was highest in patients with high comorbidity scores and prior radiation therapy and occurred both in upper and mid, but not lower, oesophageal stent placements. This complication can be devastating and must be discussed with relevant patients before stent placement.

Overall, it appears reasonable to consider stent insertion for patients with true refractory strictures. However, because of safety concerns and probable lack of efficacy, they cannot be recommended for use in patients earlier in the course of treatment unless serial dilatations are not possible because of compliance or nutritional issues. Once the decision to place a stent is taken, the option of a fully covered SEMS versus a BDS can be discussed with the patient. The former requires removal after 2–3 m but has the advantage that it can be removed early if the patient suffers intolerable side effects, so may be the best choice for first stent placement. BDS cannot be removed even if pain or side effects are intolerable, but have the benefit of not requiring a second procedure so may be preferred for patients in whom repeated stent insertions may be necessary or if there are concerns about compliance with stent removal.

The introduction of ultrashort (usually 1–2 cm) lumen apposing metal stents (LAMS), that are more commonly used for transgastric drainage of pancreatic cysts or Endoscopic Ultrasound (EUS) guided biliary drainage, have provided a further stent option. These have been used successfully in small numbers of patients with refractory short oesophageal strictures. They have the advantage of having short wide flares meaning they are less likely to migrate and may be suitable for more proximal strictures. However, they have only been used in very small numbers of patients with oesophageal strictures to date.43,44

**Incisional therapy**

The mainstay of endoscopic treatment of strictures has been the application of radial or longitudinal forces to disrupt the fibrosis. However, an alternative and potentially more appealing approach is to directly incise or cauterise the fibrotic section. Thus, incisional therapy, using a needle knife or similar has gained popularity. Numerous small case series from the late 1990s have been published (Table 2), the largest number of published cases of oesophageal strictures treated with incisional therapy being 24.52 Most commonly, a needle knife has been used alone, but others have used the tip of a snare or more recently an insulated tip knife with a clear hood (cap) on the endoscope.52,53 On occasion this has been combined with argon plasma coagulation (APC), standard dilatation or stent insertion.53–55 In the main, these series report high success with low complication rates. In general, incisional therapy is reserved for very short strictures, either Schatzki rings or anastomotic strictures, and where it has been compared, short strictures <1 cm respond better to this therapy than longer strictures.52,56 Incision therapy has been compared with bougie dilatation in one randomised trial of 62 patients with previously untreated anastomotic strictures and no difference in outcomes were detected.57 Thus, overall it would appear that incisional therapy is a reasonable alternative to standard dilatation, in experienced hands, in short (commonly anastomotic) strictures or it may be tried as a rescue therapy in refractory strictures either alone or in combination with additional therapies.

**Retrograde dilatation**

Endoscopic dilatation of oesophageal stricturing requires the passage of an instrument or guidewire through the stricture. However, in rare circumstances, this proves impossible, particularly following radiation for head and neck cancers. Where this cannot be accomplished retrograde dilatation through a mature PEG tract has been reported in a limited number of small case series. For this procedure, a thin paediatric endoscope is inserted *via* the PEG into the oesophagus.
Simultaneously, a standard endoscope is inserted orally, and by means of transillumination, the stricture is punctured from below and traversed with a guidewire, which is gathered proximally allowing dilatation and stent insertion. There is little literature on this but it can be considered as a rescue treatment in highly selected patients before considering surgery.58–60

**Self-bougienage**

Home bougienage is a safe and effective alternative for resistant strictures, particularly if short, straight and proximal. Early reports were published in the 1980s and the largest series are in patients with corrosive strictures.61,62 Patients need to be motivated, well-trained and have normal pharyngeal function. However, in appropriate patients, it appears to be well tolerated, can prevent surgery and the burden of repeated hospital visits. It is generally performed with a Maloney dilator of 45–60 French. Although safe, perforation, bleeding, bacteremia, pneumonia and pneumothorax are reported complications.1,63

Table 2. Incision therapy for oesophageal strictures.

| Reference                  | Technique                                    | Number | Stricture type            | Success                           | Comments                                |
|----------------------------|----------------------------------------------|--------|---------------------------|-----------------------------------|-----------------------------------------|
| Tan and Liu45              | Electrocautery incision                      | 13     | Refractory anastomotic    | 100% immediate; 61.5% at 12 m.    | Seven needed retreatment               |
| Yano and colleagues46      | Electrocautery incision                      | 8      | Nonsurgical therapy for oesophageal cancer | 100% immediate, 37.5% at 3 m      |                                         |
| Lee and colleagues52       | Insulated tip knife, endoscopic hood/cap     | 24     | Anastomotic               | 87.5% at 2 years                  | Higher recurrence rate if stricture >1 cm long |
| Simmons and Baron47        | Electrocautery incision                      | 9      | Refractory anastomotic    | 8/9 reduction in dysphagia symptoms and reduced need for dilatations |                                         |
| Hordijk and colleagues56   | Electrocautery incision                      | 20     | Refractory anastomotic    | 60% benefit                       | All patients benefited if stricture <1 cm |
| Pross and colleagues58     | Electrocautery incision                      | 5      | Anastomotic               | Short term benefit 100%           |                                         |
| Schubert and colleagues53  | Tip of polypectomy snare with APC            | 49     | Anastomotic – oesophageal and colonic | Short term benefit 100%, four required retreatment |                                         |
| Hagiwara and colleagues54  | Electrocautery incision with balloon dilatation | 6     | Refractory anastomotic    | 5/6 benefit                       |                                         |
| Brandimante and Tursi49    | Electrocautery incision                      | 6      | Refractory anastomotic    | 100% benefit                      |                                         |
| Disario and colleagues50   | Electrocautery incision                      | 11     | Schatzki ring             | 100% immediate benefit, seven needed retreatment |                                         |
| Burdick and colleagues51   | Electrocautery incision                      | 7      | Schatzki ring             | 6/7 benefit at 6 months           |                                         |

APC, argon plasma coagulation.
with high morbidity and related mortality, due in part to the risks of treatment and the associated comorbidities of the patients. The management of such strictures is challenging and requires a systematic approach that may be best focussed in specialist hands. The options for treatment in relation to aetiology and timing are summarised in Table 3.

Once diagnosed, it is essential to confirm the nature of the stricture by careful histological evaluation and subsequently optimising medical management. The patient’s nutritional status requires careful attention to maximise their fitness for subsequent treatments and ability to survive any complications. All patients should have a rapid sequence of repeated dilatations performed by an experienced operator before being considered refractory to standard therapy. Although it may be tempting to escalate to alternative therapies such as stent insertion early in the treatment pathway, this approach may be associated with risks and lacks robust supportive evidence at the current time so should be reserved for highly selected cases.

Steroid injection now has strong evidence behind it and should be used early in the treatment algorithm and should be repeated at subsequent planned dilatations. Recent data would suggest injection should occur after dilatation but this requires confirmation. Other medical (either topical or systemic) therapies such as Mitomycin C and newer antifibrotic drugs lack evidence but should be the focus of future studies.

Incisional therapy should be considered for short strictures. For longer strictures, stent insertion has the greatest supportive evidence, but long-term success rates are relatively disappointing. If a metal stent is used, this should be fully covered and removed within 3 months to avoid tissue hypertrophy. The alternative is a BDS but as these cannot be removed, the pros and cons of using this as a first line ahead of a removable stent should be discussed with the patient. Repeated BDS insertions may be suitable for small numbers of patients. However, stents are associated with significant side effects, notably pain and vomiting, and there are concerns about fistula formation, particularly (but not exclusively) after radiotherapy, in upper/mid stent placements that must be taken into consideration.

Overall, the management of refractory strictures has changed relatively little in the last decade. There are few high-quality controlled trials, which are urgently needed. End points have varied massively and must be standardised in the future to facilitate future meta-analysis of data. Hitherto, the focus has been on examining ways to disrupt the fibrosis that is causing the stricturing. What is

| Aetiology                  | Timing and general comments                                                                 |
|----------------------------|---------------------------------------------------------------------------------------------|
| Steroid injection          | Current evidence suggests no difference in benefit according to stricture aetiology         |
|                            | Early in course of therapy Some evidence to support injection into postdilatation defect    |
| Mitomycin C injection      | Limited evidence in adults                                                                  |
| Stent insertion            | Caution required in proximal and radiation-induced strictures                               |
|                            | Rescue therapy when all other options failed. Early use may be appropriate in carefully selected patients. |
| Incisional therapy         | Short strictures, particularly rings/webs and anastomotic strictures                         |
|                            | May be used as an alternative to dilatation early in the course of therapy or as an adjunct in refractory strictures |
| Retrograde dilatation      | Use limited to patients with head and neck strictures, most commonly post radiotherapy.    |
|                            | Evidence limited to small case series. Use in cases refractory to all other therapies.       |
| Self-bougienage            | All aetiologies; literature commonly refers to postcorrosive strictures                     |
|                            | Evidence limited to case series. Use in cases refractory to all other therapies and highly motivated patients. |
very unclear from the evidence, however, is why some individuals have repeated reformation of the fibrosis after initial therapy whereas others manage with one or two dilatations. The literature advises us which strictures are more likely to become refractory but very little is known about patient-related factors that may be open to manipulation. Furthermore, detailed evaluation at the molecular level of stricture fibrosis may lead to clues as to why some strictures are more refractory than others and requires research. A paradigm shift is needed to develop agents that can reduce the fibrosis process, without impairing healing and increasing risk of perforation. This should be the focus of future study.

**Funding**
The authors received no financial support for the research, authorship, and/or publication of this article.

**Conflict of interest statement**
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**ORCID iD**
Simon M Everett https://orcid.org/0000-0002-4251-5323

**References***
1. Sami SS, Haboubi HN, Ang Y, *et al*. UK guidelines on oesophageal dilatation in clinical practice. *Gut* 2018; 67: 1000–1023.
2. Burr N and Everett SM. Management of benign oesophageal strictures. *Front Gastroenterol* 2019; 10: 177–181.
3. Patel DA, Sharda R, Hovis KL, *et al*. Patient-reported outcome measures in dysphagia: a systematic review of instrument development and validation. *Dis Esophagus* 2017; 30: 1–23.
4. Ogilvie AL, Dronfield MW, Ferguson R, *et al*. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. *Gut* 1982; 23: 1060–1067.
5. Lucendo AJ, Molina-Infante J, Arias A, *et al*. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J* 2017; 5: 335–358.
6. Lal N, Bhasin DK, Malik AK, *et al*. Optimal number of biopsy specimens in the diagnosis of carcinoma of the oesophagus. *Gut* 1992; 33: 724–726.
7. Josino IR, Madruga-Neto AC, Ribeiro IB, *et al*. Endoscopic dilation with bougies versus balloon dilation in esophageal benign strictures: systematic review and meta-analysis. *Gastroenterol Res Pract* 2018; 2018: 5874870.
8. Boyce HW Jr. Precepts of safe esophageal dilation. *Gastrointest Endosc* 1977; 23: 215.
9. van Halsema EE, Noordzij IC, vanBergeHenegouwen MI, *et al*. Endoscopic dilation of benign esophageal anastomotic strictures over 16 mm has a longer lasting effect. *Surg Endosc* 2017; 31: 1871–1881.
10. Pereira-Lima JC, Ramires RP, ZaminI Jr, *et al*. Endoscopic dilation of benign esophageal strictures: report on 1043 procedures. *Am J Gastroenterol* 1999; 94: 1497–1501.
11. Kochman ML, McClave SA and Boyce HW. The refractory and the recurrent esophageal stricture: a definition. *Gastrointest Endosc* 2005; 62: 474–475.
12. Haidry RJ, Dunn JM, Butt MA, *et al*. Radiofrequency ablation and endoscopic mucosal resection for dysplastic Barrett’s esophagus and early esophageal adenocarcinoma: outcomes of the UK National Halo RFA Registry. *Gastroenterology* 2013; 145: 87–95.
13. Rodrigues-Pinto E, Pereira P, Ribeiro A, *et al*. Risk factors with refractoriness to oesophageal dilatation for benign dysphagia. *Eur J Gastroenterol Hepatol* 2016; 28: 648–648.
14. vanBoeckel PG and Siersema PD. Refractory esophageal strictures: what to do when dilation fails. *Curr Treat Options Gastroenterol* 2015; 13: 47–58.
15. de Wijkerslooth L, Vleggaar F and Siersema P. Endoscopic management of difficult or recurrent esophageal strictures. *Am J Gastroenterol* 2011; 106: 2080–2091.
16. Lew RJ and Kochman ML. A review of endoscopic methods of esophageal dilatation. *J Clin Gastroenterol* 2002; 35: 117–126.
17. Mendelson AH, Small AJ, Agarwalla A, *et al*. Esophageal anastomotic strictures: outcomes of endoscopic dilatation, risk of recurrence and refractory stenosis, and effect of foreign body removal. *Clin Gastroenterol Hepatol* 2015; 13: 263–271.
18. Agarwalla A, Small AJ and Mendelson AH. Risk of recurrent or refractory strictures and outcome
of endoscopic dilatation for radiation-induced oesophageal strictures. Surg Endosc 2015; 29: 1903–1912.

19. Siersema P. Treatment of refractory benign esophageal strictures: it is all about being ‘patient’. Gastrointest Endosc 2016; 84: 229–231.

20. Repici A, Small A, Mendelson A, et al. Natural history and management of refractory benign esophageal strictures. Gastrointest Endosc 2016; 84: 222–228.

21. Li X, Zhu L, Wang B, et al. Drugs and targets in fibrosis. Front Pharmacol 2017; 8: 855.

22. Hirdes MMC, Van Hooft JE, Koornstra JJ, et al. Endoscopic corticosteroid injections do not reduce dysphagia after endoscopic dilation therapy in patients with esophagogastric anastomotic strictures. Clin Gas Hep 2013; 11: 795–801.

23. Szapary L, Tinusz B, Farkas N, et al. Intraluminal steroid is beneficial in refractory benign esophageal strictures: a meta-analysis. World J Gastroenterol 2018; 24: 2311–2319.

24. Zhang YW, Wei FX, Qi XP, et al. Efficacy and safety of endoscopic intraluminal triamcinolone injection for benign esophageal strictures. Gastroenterol Res Pract 2018; 2018: 7619298.

25. Ramage JI, Rumalla A, Baron TH, et al. A prospective, randomised, double-blind placebo-controlled trial of endoscopic steroid injection therapy for recalcitrant esophageal peptic strictures. Am J Gastroenterol 2005; 100: 241925.

26. Hanaoka N, Ishihara R, Motoori M, et al. Endoscopic balloon dilation followed by intraluminal steroid injection for anastomotic strictures after esophagectomy: a randomized controlled trial. Am J Gastroenterol 2018; 113: 1468–1474.

27. Anduze AL. Pterygium surgery with mitomycin-C: ten-year results. Ophthalmic Surgery and Lasers 2001; 32: 341–345.

28. El-Asmar KM, Hassan MA, Abdelkader HM, et al. Topical mitomycin C application is effective in management of localized caustic esophageal stricture: a double-blinded, randomized, placebo-controlled trial. J Pediatr Surg 2013; 48: 1621–1627.

29. Zhang Y, Wang X, Liu L, et al. Intramuscular injection of mitomycin C combined with endoscopic dilatation for benign esophageal strictures. J Digest Dis 2015; 16: 370–376.

30. Bartel MJ, Seeger K, Jeffers K, et al. Topical mitomycin C application in the treatment of refractory benign esophageal strictures in adults and comprehensive literature review. Dig Liver Dis 2016; 48: 1058–1065.

31. Rustagi T, Aslanian HR and Laine L. Treatment of refractory gastrointestinal strictures with Mitomycin C: a systematic review. J Clin Gastroenterol 2015; 49: 837–847.

32. Repici A, Hassan C, Sharma P, et al. Systematic review: the role of self-expanding plastic stents for benign esophageal strictures. Aliment Pharmacol Ther 2010; 31: 1268–1275.

33. Thomas T, Abrams KR, Subramanian V, et al. Esophageal stents for benign refractory strictures: a meta-analysis. Endoscopy 2011; 43: 386–393.

34. Fuccio L, Hassan C, Frazzoni L, et al. Clinical outcomes following stent placement in refractory benign esophageal stricture: a systematic review and meta-analysis. Endoscopy 2016; 48: 141–148.

35. Spaander M, Baron T, Siersema P, et al. Esophageal stenting for benign and malignant disease: European society of gastrointestinal endoscopy (ESGE) clinical guideline. Endoscopy 48: 939–948.

36. Repici A, Vleggaar F, Cacciatore C, et al. Efficacy and safety of biodegradable stents for refractory benign esophageal strictures: the BEST (Biodegradable Esophageal Stent) study. Gastrointest Endosc 2010; 72: 927–934.

37. Hirdes M, Siersema P, vanBoeckel PG, et al. Single and sequential biodegradable stent placement for refractory benign esophageal strictures: a prospective follow-up study. Endoscopy 2012; 44: 649–654.

38. Rabb N, Procter H, Burr N, et al. Efficacy and tolerability of biodegradable stents for recurrent benign oesophageal strictures: the Leeds experience. Poster Presentation, 25th UEG Week 2017; October 28-November 1 Poster 0280.

39. Wada T, Yoda Y, Nomura S, et al. Prospective trial of biodegradable stents for refractory benign esophageal strictures after curative treatment of esophageal cancer. Gastrointest Endosc 2017; 86: 492–499.

40. Dhar A, Close H, Viswanath YK, et al. Biodegradable stent or balloon dilatation for benign oesophageal stricture: pilot randomised controlled trial. World J Gastroenterol 2014; 20: 18199–18206.

41. Rabb N, Procter H, Burr N, et al. Efficacy and tolerability of biodegradable stents for recurrent benign oesophageal strictures: the Leeds experience. Poster Presentation, 25th UEG Week 2017; October 28-November 1 Poster 0280.

42. Bick B, Wong Kee Song L, Buttar N, et al. Stent-associated esophagorespiratory fistulas: incidence
and risk factors. *Gastrointest Endosc* 2013; 77: 181–189.

43. Irani S, Jalaj S, Ross A, et al. Use of a lumen-apposing metal stent to treat GI strictures (with videos). *Gastrointest Endosc* 2017; 85: 1285–1289.

44. Granata A, Amata M, Ligresti D, et al. Novel lumen-apposing stent to treat benign esophageal stricture. *Endoscopy* 2017; 49: E273–E274.

45. Tan Y and Liu D. Endoscopic incision for the treatment of refractory esophageal anastomotic strictures: outcomes of 13 cases with a minimum follow up of 12 months. *Rev Esp Enferm Dig* 2016; 108: 196–200.

46. Yano T, Yoda Y, Satake H, et al. Radial incision and cutting method for refractory stricture after nonsurgical treatment of esophageal cancer. *Endoscopy* 2013; 45: 316–319.

47. Simmons DT and Baron TH. Electroincision of refractory esophagogastric anastomotic strictures. *Dis Esophagus* 2006; 19: 410–414.

48. Pross M, Manger T and Lippert H. Combination of diathermia and argon plasma coagulation in treatment of cicatricial esophageal stenoses. *Zentralbl Chir* 1998; 123: 1145–1147.

49. Brandimarte G and Tursi A. Endoscopic treatment of benign anastomotic esophageal stricture with electrocautery. *Endoscopy* 2002; 34: 399–401.

50. DiSario JA, Pedersen PJ, Bichis-Canoutas C, et al. Incision of recurrent distal esophageal (Schatzki) ring after dilation. *Gastrointest Endosc* 2002; 56: 244–248.

51. Burdick JS, Venu RP and Hogan WJ. Cutting the defiant lower esophageal ring. *Gastrointest Endosc* 1993; 39: 616–619.

52. Lee TH, Lee SH, Park JY, et al. Primary incisional therapy with a modified method for patients with benign anastomotic esophageal stricture. *Gastrointest Endosc* 2009; 69: 1029–1033.

53. Schubert D, Kuhn R, Lippert H, et al. Endoscopic treatment of benign gastrointestinal anastomotic strictures using argon plasma coagulation in combination with diathermy. *Surg Endosc* 2003; 17: 1579–1582.

54. Hagiwara A, Togawa T, Yamasaki J, et al. Endoscopic incision and balloon dilatation for cicatricial anastomotic strictures. *Hepatogastroenterology* 1999; 46: 997–999.

55. Liu D, Tan Y, Wang Y, et al. Endoscopic incision with esophageal stent placement for the treatment of refractory benign oesophageal strictures. *Gastrointest Endosc* 2015; 81: 1036–1040.

56. Hordijk ML, Siersema PD, Tilanus HW, et al. Electrocautery therapy for refractory anastomotic strictures of the esophagus. *Gastrointest Endosc* 2006; 63: 157–163.

57. Hordijk ML, van Hooft JE, Hansen BE, et al. A randomized comparison of electrocautery incision with Savary bougienage for relief of anastomotic gastroesophageal strictures. *Gastrointest Endosc* 2009; 70: 849–845.

58. Dellon ES, Cullen NR, Madanick RD, et al. Outcomes of a combined antegrade and retrograde approach for dilatation of radiation-induced esophageal strictures (with video). *Gastrointest Endosc* 2010; 71: 1122–1129.

59. Kos MP, David EF and Mahieu HF. Anterograde-retrograde rendezvous approach for radiation-induced complete upper oesophageal sphincter stenosis: case report and literature review. *J Laryngol Otol* 2011; 125: 761–764.

60. Eminler AT, Uslan MI, Koksal AS, et al. Retrograde dilation of a complex radiation-induced esophageal stricture through percutaneous gastrostomy. *Acta Gastroenterol Belg* 2015; 78: 246–247.

61. Gilmore IT and Sheers R. Oesophageal self-bougienage. *Lancet* 1982; 1: 620–621.

62. Bapat RD, Bakhshi GD, Kantharia CV, et al. Self-bougienage: long-term relief of corrosive esophageal strictures. *Indian J Gastroenterol* 2001; 20: 180–182.

63. Gambardella C, Allaria A and Siciliano G. Recurrent esophageal stricture from previous caustic ingestion treated with 40-year self-dilation: case report and review of literature. *BMC Gastroenterol* 2018; 18: 68.