A prospective multicentre study of per-oral endoscopic myotomy (POEM) for achalasia in Australia

Sunil Gupta[1,2], Mayenaaz Sidhu[1,2], Xuan Banh[3], Joseph Bradbear[3], Karen Byth[4,5], Luke F Hourigan[3,6], Spiro Raftopoulos[7], Michael J Bourke[1,2]

The known: Per-oral endoscopic myotomy (POEM) is an effective, minimally invasive treatment for people with achalasia.

The new: In the first Australian multicentre study of POEM outcomes, the mean pre-POEM Eckardt score for 142 patients was 8.0 (SD, 2.4); six months after POEM, it was 1.1 (SD 1.6), a significant reduction that was sustained two years. Clinical success was achieved in 127 patients (89%); previous treatments, including Heller myotomy, did not influence outcomes. Major adverse events were infrequent (five patients) and readily managed during the admission.

The implications: POEM is safe and efficacious as both a first line and salvage therapy for patients with achalasia.

Abstract

Objective: To describe the clinical and procedural outcomes of per-oral endoscopic myotomy (POEM) for achalasia in Australia.

Design, setting: Prospective observational study in three Australian tertiary referral centres, 5 May 2014 – 27 October 2019 (66 months).

Participants: Patients who had undergone POEM for achalasia.

Major outcome measures: Eckardt scores calculated prior to POEM and six months, one year, and two years after POEM. The primary outcome was clinical success, defined as an Eckardt score of 3 or less without a second intervention.

Results: 142 patients underwent POEM for achalasia; their mean age was 52 years (SD, 18 years), 83 were men (58%), and the median length of hospital stay two days (IQR, 1–3 days). Their mean Eckardt score before POEM was 8.0 (SD, 2.4) and 1.1 (SD, 1.6) six months after POEM; it did not change significantly between six months and two years after POEM (mean monthly increase, 0.014 points; 95% CI, −0.001 to 0.029). A total of 127 patients (89%) improved clinically after POEM. Intra-procedural capnoperitoneum was the only risk factor associated with treatment failure (adjusted hazard ratio, 2.85; 95% CI, 1.08–7.51). Previous treatments — botulinum toxin injection (25 patients, 18%), endoscopic balloon dilatation (69, 49%), and Heller myotomy (14, 10%) — did not affect POEM outcomes. Five patients (4%) experienced major adverse events, including pneumonia, oesophageal leak, empyema and melaena, that were managed during admission and without sequelae.

Conclusions: POEM is an effective treatment for achalasia. Significant reductions in Eckardt scores achieved by six months are sustained at two years. POEM can be both a first line definitive therapy and a salvage therapy for patients not helped by other treatments.

Primary oesophageal motility disorders are uncommon; in North America, the incidence of achalasia, the best described form, is 1–3 cases per 100 000 per annum and the prevalence 4–15 per 100 000 population.[1,2] Achalasia is characterised by incomplete relaxation of the lower oesophageal sphincter and failure of peristalsis. The Chicago Classification of oesophageal motility disorders defines three subtypes by their manometric features (Box 1).[3] Although the pathogenesis of achalasia is unclear, the underlying pathology is degeneration of inhibitory postganglionic nerves in the oesophagus, the integrity of which is necessary for both normal lower sphincter relaxation and peristalsis.[4] Immune-mediated destruction, genetic predisposition, and viral infections (eg, herpes zoster) have been implicated as precipitating factors.[5] Patients often experience progressive dysphagia, regurgitation of undigested food, retrosternal chest pain, and weight loss.[6] Clinical severity is assessed with the Eckardt score, whereby each symptom parameter — dysphagia, regurgitation, retrosternal pain, weight loss — is scored on a scale of 0–3 (maximum score: 12).[7] Diagnosis is confirmed by upper gastrointestinal endoscopy, barium swallow imaging, and high resolution oesophageal manometry.[8]

Treatment of achalasia is palliative and focused on disrupting the fixed tonicity of the lower oesophageal sphincter. Medical therapy is ineffective, and the benefits of endoscopic lower oesophageal sphincter botulinum toxin injections are temporary and decline over time. Symptom control can be achieved by endoscopic balloon dilatation in 70–80% of patients, but a series of procedures is often required.[9,10] Surgical treatment is by laparoscopic Heller myotomy, with or without fundoplication, with clinical success rates of 90% at three years. However, Heller myotomy is invasive and associated with complications, including perforation in as many as 7% of procedures.[11] Although most complications are recognised and treated during the index procedure, 10% of patients experience post-surgical complications.[11]

In recent years, per-oral endoscopic myotomy (POEM) has emerged as an effective, minimally invasive therapy for people with achalasia.[12,13] However, the Australian experience is limited as disease prevalence is low, and because the procedure involves specialised techniques that require endoscopic training and expertise. We report the first prospective multicentre study in Australia of the clinical and procedural outcomes of POEM for patients with achalasia.

Methods

We conducted a prospective observational study between 5 May 2014 and 27 October 2019 (66 months) in three Australian tertiary referral centres: Westmead Hospital (Sydney), Princess Alexandra Hospital (Brisbane), and Sir Charles Gairdner Hospital (Perth). All patients over 16 years of age undergoing POEM (except pregnant women) were invited to participate; participants provided written consent to providing data for the study. The results of previous evaluation (upper gastrointestinal endoscopy, barium swallow imaging, and high resolution oesophageal manometry) were obtained to confirm diagnoses according to the Chicago classification.[3] All three proceduralists (MJB, LH, SR) are highly experienced in interventional endoscopy. Eckardt scores were calculated during clinical reviews or in standardised phone interviews before POEM and at six months, one year, and two years after POEM. Technical outcomes, including procedure duration, myotomy length, hospital length of stay and adverse events,[14] were systematically recorded.

[1] Westmead Hospital, Sydney, NSW. [2] Westmead Clinical School, University of Sydney, Sydney, NSW. [3] Princess Alexandra Hospital Health Service District, Brisbane, QLD. [4] Western Sydney Local Health District Research and Education Network, Sydney, NSW. [5] NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW. [6] Gallipoli Medical Research Institute, University of Queensland, Brisbane, QLD. [7] Sir Charles Gairdner Hospital, Perth, WA. michael@citywestgastro.com.au
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1 The manometric features of achalasia, by type

Type	Key feature (all types)	Other criteria or findings
Type 1 achalasia (classic)	Elevated median integrated relaxation pressure (> 15 mmHg) and failed peristalsis	None
Type 2 achalasia (with oesophageal compression)		Pan-oesophageal pressurisation with ≥ 20% of swallows
Type 3 achalasia (spastic)		Premature (spastic) contractions with distal contractile integral exceeding 450 mmHg.s.cm with ≥ 20% of swallows

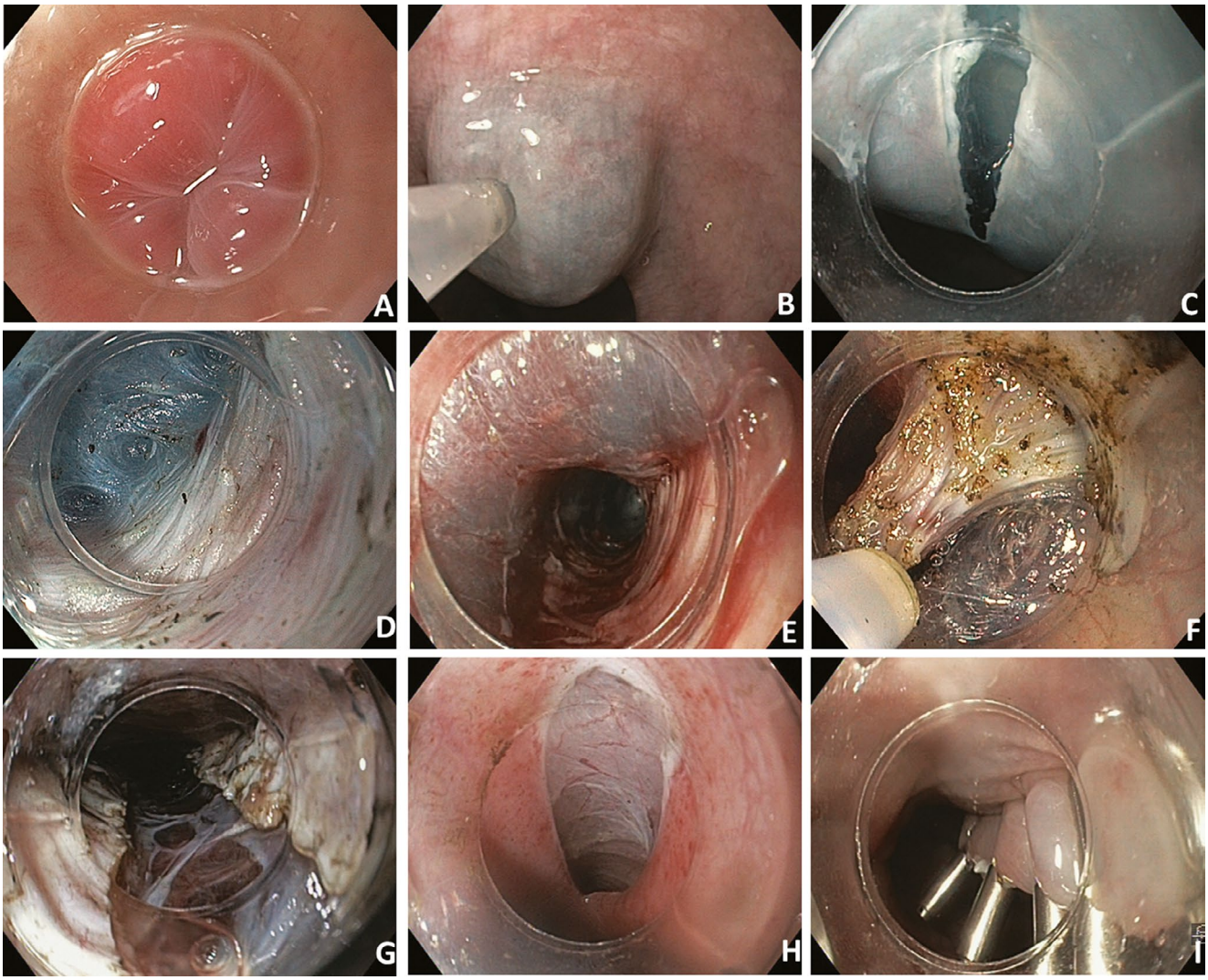
Patients and equipment

All patients underwent general anaesthesia and endotracheal intubation, and received intra-procedural antibiotics. A Triangle Tip electrosurgical knife (Olympus Medical Systems) or HybridKnife (Erbe Elektromedizin) was used with the VIO300D electrosurgical unit (Erbe Elektromedizin). All procedures were performed using a GIF-HQ190 high definition gastroscope (Olympus). A transparent distal tapered cap (ST Hood, Fujifilm) was the preferred distal attachment.

Per-oral endoscopic myotomy (POEM)

The gastro-oesophageal junction was identified, and a submucosal injection of gelofusine (500 mL) stained with indigo carmine (2 mL) administered 10 cm proximal to the junction. A 2–3 cm longitudinal mucosal incision was made either anteriorly (2 o'clock position) or posteriorly (5 o'clock position) to enter the submucosal plane and create a tunnel. Submucosal dissection within the tunnel was performed using a combination of dry cut current (effect 3, 80 W) and swift coagulation (effect 2, 50 W). A submucosal tunnel, 15–20 mm wide, was made to 2–3 cm beyond the gastro-oesophageal junction. Selective myotomy of the inner circular muscle fibres was performed using dry cut current (effect 3, 80 W). Longitudinal muscle fibres were preserved. Minor bleeding was treated with swift coagulation (effect 2, 50 W). Large vessels were coagulated prophylactically with coagulation forceps (soft coagulation; effect 4, 80 W). Capnoperitoneum was managed during the procedure with needle decompression (Box 2).

2 Per-oral endoscopic myotomy (POEM): A. Tight lower oesophageal sphincter. B. Submucosal injection of gelofusine in saline. C. Mucosal incision. D. Submucosal dissection to create submucosal tunnel. E. Completed submucosal tunnel. F. Selective myotomy of the circular muscle layer divided. G. Completed myotomy. H. Examination of mucosotomy site. I. Clip closure



Post-POEM management

Following POEM, patients fasted and were observed in hospital overnight. The following morning, patients were commenced on clear fluids. They were discharged if their condition was stable and they were afebrile, pain-free, and tolerating liquids. Instructions were provided for free fluids from day two and a soft diet from day three after POEM. All patients were prescribed proton pump inhibitors, twice daily for three months, then once daily for a further three months. The patients were clinically reviewed six weeks and six months after POEM.

Statistical analysis

Data analyses were performed in SPSS Statistics 26 (IBM) and R 3.6.0 (R Foundation for Statistical Computing). Continuous variables were summarised as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) as appropriate; categorical variables were summarised as frequencies and proportions. Within-patient effect of time on Eckardt score was assessed in linear mixed effects (LME) models, with patient identification number as the group identifier. Time was treated as a categorical (pre-POEM, and six months, one year, two years after POEM) or continuous variable (with piecewise linear parameterisation). It was included as both a random effect with a general symmetric covariance structure and as a fixed effect. The association between pre-POEM Eckardt scores and within-patient change in Eckardt score after POEM was assessed by analysing 95% confidence intervals (CIs).[15]

Outcomes

The primary outcome was clinical success, defined as an Eckardt score of 3 or less without a second intervention. Cumulative treatment failure rates are depicted in Kaplan–Meier survival curves. To assess risk factors for treatment failure, unadjusted hazard ratios (HRs) and HRs adjusted for pre-POEM Eckardt score were estimated in Cox proportional hazard models. Adverse events were analysed as a secondary outcome, and unadjusted and age-adjusted odds ratios (ORs) estimated by logistic regression. Reflux was defined as a burning sensation in the retrosternal area.[16] All tests were two-sided ($\alpha = 0.05$).

Ethics approval

The study was approved by the Human Research Ethics Committee at Westmead Hospital (reference, (4274) AURED LNR/15/WMEAD/152). Institutional review board approval was obtained at each participating site.

Results

A total of 142 consecutive patients underwent POEM at the three hospitals during the study period and consented to participation (mean age, 52 years; SD, 18 years); 83 were men (58%) (Box 3). At the time of data analysis, median follow-up time was 12 months (IQR, 12–24 months); all 142 patients were followed up at 6 months, 110 at one year (78%), and 61 at two years (43%). Seventy patients (49%) had type 2 achalasia, and 50 type 1 (35%). Previous treatments included botulinum toxin injection (25 patients, 18%), endoscopic balloon dilatation (69, 49%), and Heller myotomy (14, 10%) (Box 3).

The mucosal incision was made posteriorly in 79 patients (56%) and anteriorly in 63 (44%). Median procedure time was 85.5 minutes (IQR, 70.0–105 minutes) and median submucosal tunnelling time 40 minutes (IQR, 30.5–50.5 minutes); these times were not influenced by Chicago classification (data not shown). Median myotomy length was 10 cm (IQR, 8–10 cm); it was longest in patients with type 3 achalasia (median, 12 cm; IQR 10–16.8 cm) and shortest in those with type 1 (median, 9 cm; IQR, 8–10 cm). A median six clips (IQR, 5–7 clips) were used to close the mucosotomy site. In 30 cases (21%), intra-procedural capnoperitoneum required needle decompression. Median length of stay in hospital was two days (IQR, 1–3 days).

Eckardt scores

The mean pre-POEM Eckardt score was 8.0 (SD, 2.4); six months after POEM, the mean score was 1.1 (SD, 1.6), a statistically significant reduction of 6.9 points (95% CI, 6.5–7.3 points). The 95% CI for the linear rate of change between 6 months and 2 years after POEM included zero, indicating stability of the Eckardt

3 Baseline characteristics of 142 patients who underwent per-oral endoscopic myotomy (POEM), Australia, 5 May 2014 – 27 October 2019

Characteristic	Value	Pre-POEM Eckardt score, mean (SD)
Age (years)		
Mean (SD)	52 (18)	—
Range	16–85	—
> 60	53 (37%)	7.7 (2.2)
≤ 60	89 (63%)	8.0 (2.5)
Sex		
Men	83 (58%)	7.6 (2.4)
Women	59 (42%)	8.4 (2.3)
Indication		
Achalasia type 1	50 (35%)	7.6 (2.1)
Achalasia type 2	70 (49%)	8.4 (2.5)
Achalasia type 3	22 (16%)	7.3 (2.5)
Prior botulinum toxin injection*		
Yes	25 (18%)	8.3 (2.2)
No	116 (82%)	7.9 (2.4)
Prior Heller myotomy		
Yes	14 (10%)	8.5 (2.1)
No	128 (90%)	7.9 (2.4)
Prior endoscopic balloon dilatation*		
Yes	69 (49%)	7.8 (2.3)
No	72 (51%)	8.2 (2.4)
Manometric findings prior to POEM (lower oesophageal sphincter)		
Resting pressure (mmHg), mean(SD)	36.3 (20.7)	—
Relaxation pressure (mmHg), mean (SD)	21.4 (12.0)	—

SD = standard deviation. * Data missing for one patient.

score to two years (Box 4). Results were similar for all three achalasia types (Box 5; Supporting Information, figure 1).

Clinical success

Seventeen patients did not initially respond to treatment, but two subsequently improved spontaneously (Eckardt scores of 3 or less) without renewed intervention. A total of 127 patients (89%) had therefore improved (Box 6). A higher pre-POEM Eckardt score was associated with a greater reduction after POEM (r = 0.38; 95% CI, 0.21–0.52). We therefore adjusted hazard ratios for treatment failure risk factors for pre-POEM Eckardt score. Intra-procedural capnoperitoneum was the only potential risk factor associated with treatment failure (adjusted HR, 2.85; 95% CI, 1.08–7.51) (Box 7). In a multivariable Cox model, having a pre-POEM Eckardt score of 10 or more and/or intra-procedural capnoperitoneum did not significantly influence the treatment failure rate (Supporting Information, figure 2).

Second intervention

The Eckardt scores of the 15 patients whose condition did not improve after POEM declined from a mean of 8.5 (SD, 2.3) to 5.1 (SD, 1.0). Nine of these patients underwent further treatment at a median of 12 months (IQR, 5–12 months) after initial POEM; five again underwent POEM and four balloon dilatation. Clinical success at a median of 12 months (IQR, 6–12 months) after the second intervention was achieved in eight patients (mean Eckardt score, 1.6; SD, 1.9).

4 Estimated within-patient change in Eckardt score for 142 patients after per-oral endoscopic myotomy (POEM): linear mixed effects models

Linear mixed effects model parameter estimates	Mean change in Eckardt score (95% CI)
Time from POEM as four-level categorical variable	
From baseline to 6 months	−6.90 (−7.32 to −6.47)
From baseline to 12 months	−6.78 (−7.20 to −6.35)
From baseline to 24 months	−6.65 (−7.10 to −6.21)
Time from POEM as continuous variable	
First 6 months after POEM	−6.89 (−7.31 to −6.46)
Monthly rate of change, 6–24 months after POEM	0.014 (−0.001 to 0.029)

CI = confidence interval.

5 Follow-up and outcomes of per-oral endoscopic myotomy (POEM), by Chicago classification of achalasia type

	Achalasia type 1	Achalasia type 2	Achalasia type 3
Number of patients	50	70	22
Follow-up, six months	50 (100%)	70 (100%)	22 (100%)
Follow-up, one year	42 (84%)	56 (80%)	12 (54%)
Follow-up, two years	27 (54%)	27 (39%)	7 (32%)
Treatment failure	4 (8%)	9 (13%)	2 (9%)
Pre-POEM Eckardt score, mean (SD)	7.6 (2.1)	8.4 (2.5)	7.3 (2.5)
Post-POEM Eckardt score, mean (SD)*	0.9 (1.4)	1.1 (1.2)	1.3 (1.9)

SD = standard deviation. * At time of most recent follow-up.

Adverse events

Five patients (4%) experienced major adverse events, including an intramural oesophageal leak requiring stenting, an empyema and para-oesophageal haematoma requiring chest drain insertion, melaena managed by blood transfusion, and two cases of pneumonia treated with intravenous antibiotics. Inpatient stays were longer for these patients (mean, 9.8 days; SD, 6.9 days) than for those without major adverse events (mean, 2.6 days; SD, 1.7 days). Eleven patients (8%) experienced minor adverse events, including intra-mural oesophageal leak requiring re-clipping, atrial fibrillation, fluid overload, urinary retention, and fever without evidence of mediastinitis or peritonitis. Factors associated with adverse events were being more than 60 years old (OR, 4.40; 95% CI, 1.44–13.5) and prior botulinum toxin injection (adjusted OR, 3.90, 95% CI, 1.25–12.2) (Supporting Information, table 1). Risk of treatment failure was not significantly influenced by the occurrence of adverse events (adjusted HR, 1.64, 95% CI, 0.46–5.78) (Box 7).

Reflux

Forty-eight patients (34%) had reported symptoms compatible with reflux before undergoing POEM; such symptoms were not statistically associated with prior endoscopic balloon dilatation or Heller myotomy (data not shown). Fifteen patients reported the new onset of symptoms compatible with reflux within six months of POEM. Post-POEM reflux was more frequently reported by patients who had undergone prior treatment with balloon dilatation (21 of 69 [30%] v 12 of 72 [17%]). The POEM operational approach (anterior or posterior) did not influence the rate of post-POEM reflux (data not shown).

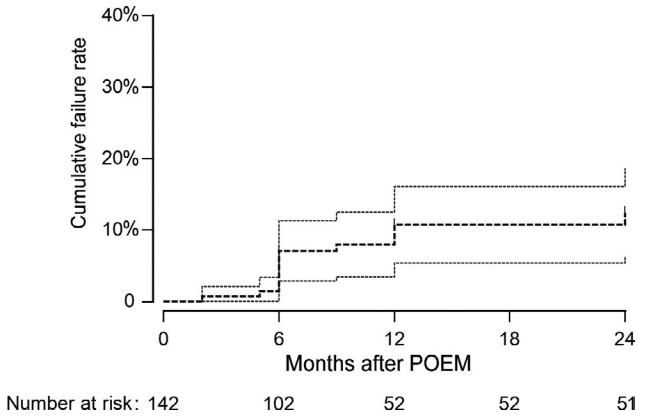
Discussion

Achalasia is uncommon, but its symptoms can be debilitating; the mean Eckardt score of the patients in our study was 8. POEM has emerged as a novel, minimally invasive treatment that is as effective as Heller myotomy.[12,13,17] We report the first multicentre assessment of POEM in Australia, and found it to be an effective and safe treatment option for patients with achalasia.

Clinical success was achieved within six months of POEM in 127 of 142 patients (89%), with a reduction in mean Eckardt scores from 8.0 (SD, 2.4) to 1.1 (SD, 1.6). As in large overseas studies,[12] this improvement was sustained at two years. Even in the 15 patients who did not improve, the mean Eckardt score declined to 5.1 (SD, 1.0), indicating that some symptoms were alleviated. Clinical success was similar for all achalasia types. As type 3 achalasia responds poorly to Heller myotomy,[18] POEM may offer an advantage to patients with this subtype, probably by enabling a longer myotomy.

We found that POEM is a safe procedure requiring a short inpatient stay (median, two days). Five patients experienced major adverse events that increased their length of stay, but the complications were readily managed during the same admission, without long term sequelae or impact on clinical success. Being over 60 years old and having previously received botulinum toxin injections were each associated with increased likelihood of adverse events; patients in both these categories are likely to be frailer and more prone to complications. A number of patients experienced new

6 Kaplan–Meier survival analysis of cumulative per-oral endoscopic myotomy (POEM) treatment failure, with 95% confidence intervals (dotted lines)



onset symptoms suggesting reflux after POEM, but a recent randomised control trial (RCT) found that the rates of reflux and Los Angeles grade C/D oesophagitis two years after POEM were similar to those following Heller myotomy.[17] Similar to a recent meta-analysis,[19] we found no difference in reflux after POEM related to which surgical approach (anterior or posterior) was undertaken.

It was unsurprising that treatment failure was associated with intra-procedural capnoperitoneum, as it may reflect technically challenging cases in which an adequate myotomy is not possible. However, one advantage of POEM is that the procedure can be repeated with the alternative approach (anterior or posterior), whereas it is extremely challenging to repeat a laparoscopic Heller myotomy. Four of the five patients who underwent POEM for a second time achieved Eckardt scores of 3 or less, similar to the success rate of 85% after repeated POEM reported by a small international study.[20] Moreover, POEM can be performed in patients who have not benefited from Heller myotomy; all 14 such patients in our study had Eckardt scores of 3 or less after POEM, indicating its value as a rescue therapy. Investigations of the impact of prior treatment on POEM outcomes have been inconclusive,[21,22] and we found that Eckardt scores and clinical success rates after POEM were similar for patients with histories of unsuccessful treatment and treatment-naïve patients. POEM is thus efficacious as both a first line and a salvage therapy.

A recent RCT indicated that POEM was superior to repeated balloon dilatation (to a maximum 40 mm), with respective clinical success rates of 92% and 76% at two years.[10] In another RCT, POEM was non-inferior to Heller myotomy with fundoplication (respective clinical success rates at two years: 83% and 82%).[17] We found a similar success rate, which, together with its safety profile and the possibility of repeat procedures, indicates that POEM is a strong candidate for adoption as the definitive first line therapy for achalasia, although further studies are required.

Limitations

At the time of our analysis, 110 (78%) and 61 patients (43%) had respectively been followed up at one and two years; loss to follow-up may have resulted in under-reporting of suboptimal outcomes. Although patients had undergone confirmatory testing before undergoing POEM a second time, the results of subsequent investigations were unavailable. Further, patients were not

7 Risk factors for treatment failure: hazard ratios, unadjusted and adjusted for Eckardt score prior to per-oral endoscopic myotomy (POEM)

Variable	Hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
Pre POEM Eckardt score (per point)	1.20 (0.97–1.50)	
Pre POEM Eckardt score ≥ 10	2.29 (0.88–5.94)	
Age (per year)	1.01 (0.98–1.04)	1.01 (0.98–1.04)
Age > 60 years	0.71 (0.25–2.02)	0.72 (0.25–2.05)
Sex (men)	0.81 (0.31–2.11)	0.90 (0.34–2.34)
Chicago classification		
Achalasia type 2 v type 1	1.91 (0.60–6.10)	1.64 (0.50–5.37)
Achalasia type 3 v type 1	1.93 (0.43–8.67)	1.92 (0.43–8.61)
Prior balloon dilatation	1.13 (0.44–2.93)	1.25 (0.48–3.25)
Prior botulinum toxin injection	1.96 (0.69–5.57)	1.81 (0.64–5.16)
Prior Heller myotomy	0.04 (0.00–39.1)	Insufficient data
Lower oesophageal sphincter resting pressure (per mmHg)	1.02 (0.99–1.04)	1.02 (0.99–1.04)
Lower oesophageal sphincter relaxation pressure (per mmHg)	0.99 (0.94–1.03)	0.99 (0.94–1.03)
Myotomy length (per cm)	0.90 (0.71–1.14)	0.91 (0.71–1.16)
POEM duration (per minute)	1.00 (0.98–1.02)	1.00 (0.98–1.02)
Tunnel duration (per minute)	1.00 (0.97–1.04)	1.01 (0.97–1.04)
Capnoperitoneum	**2.83 (1.08–7.43)**	**2.85 (1.08–7.51)**
Any adverse event	1.92 (0.55–6.67)	1.64 (0.46–5.78)

CI = confidence interval. * Adjusted for pre-POEM Eckardt score.

assessed for post-POEM reflux or oesophagitis with 24-hour pH studies or by endoscopy, unless they were indicated. However, this reflects normal clinical practice, as most symptom-free patients are unwilling to undergo uncomfortable investigations.

Conclusions

Our multicentre investigation found that POEM is a safe and effective treatment for patients with achalasia in Australia. POEM was associated with significant improvement in Eckardt score within six months, and the improvement was sustained at two-year follow-up. Adverse events were infrequent and readily managed during the inpatient admission. Although more than half the participants in our study had previously had persistent or recurrent symptoms despite a range of standard treatments, clinical response was excellent in 89% of our patients. POEM should be considered for any patient with achalasia, whether as first line or rescue therapy for people who have not experienced improvement after other treatments, including Heller myotomy.

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Supporting Information

Additional Supporting Information is included with the online version of this article.