CLINICAL IMPLICATION OF THE CHICAGO CLASSIFICATION FOR ACHALASIA

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To

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Table of Contents

Table of Figures

Table of Tables

Thesis abstract

1.1 Introduction

Knowledge and treatment of achalasia has evolved significantly. The Chicago classification system has seen widespread introduction, claiming clinical relevance. We aim to:

1) Provide a review of the literature relevant to surgeons,
2) Define the incidence of achalasia in South Australia,
3) Assess the utility of the Chicago classification in predicting outcome after treatment
4) Describe the clinical presentation of type III achalasia

1.2 Methods

1) Literature review focusing on areas of relevance to surgeons
2) Achalasia diagnoses in South Australia were identified from motility laboratory databases. Incidence and age-standardised incidences were calculated using population data from the Australian Bureau of Statistics.
3) Patients were identified from a database of patients treated with cardiomyotomy. Manometry tracings were re-reported to determine subtypes. Outcomes were assessed by annual questionnaires and analysed using a mixed effects logistics regression model.
   Patients undergoing pneumatic dilatation for achalasia were identified retrospectively. Outcome was assessed by review of records and questionnaire, analysis with a multivariate logistic GEE model.
4) Patients with type III achalasia, type II achalasia and distal oesophageal spasm were identified from endoscopy suite records and surgical database. Clinical information was retrieved from case notes and database records. Groups were compared regarding clinical presentation.

1.3 Results

The incidence of achalasia in South Australia was 2.3 to 2.8 per 100,000 pa. Mean age at diagnosis was 62.1 ± 18.1 (SD) years. Incidence increased with age (Spearman rho = 0.95, $P < 0.01$). Age-standardised incidence was 2.1 (CI 1.8 – 2.3) to 2.5 (CI 2.2 – 2.7).

195 cardiomyotomy patients were subtyped (type I n=60; type II n= 111, type III n=24); 176 returned questionnaires. Type III was less likely to have a successful outcome (type II vs. type III Odds ratio (OR) 0.38, 95% confidence interval (CI) 0.15-0.94, p 0.035). There was no difference in outcome between types I and II.

Pneumatic dilatation cohort was 42 patients (62 dilatations). Chicago subtype was not predictive of outcome.

Type III achalasia has a similar clinical presentation to type II. It presents in an older age group (63yo vs 52yo type III v type II, mean, p= 0.006). Patients had symptoms for a mean of 4.5 years prior to diagnosis compared with 2.5 years (type II achalasia).

1.4 Conclusions

Treatment of achalasia with laparoscopic cardiomyotomy is the gold standard. Type III achalasia may not response as well to standard treatment. POEM shows promise, especially for treating type III achalasia but has high rates of post-procedure reflux.

In the South Australian population, the incidence of achalasia is approximately double that previously described.

Type III achalasia is a predictor of treatment failure after cardiomyotomy. Chicago classification did not predict difference in outcome between types I and II achalasia.

In a small cohort of patients undergoing pneumatic dilatation the Chicago classification is not predictive of outcome.

Type III achalasia presents similarly to type II achalasia, suggesting symptoms are predominantly caused by lower oesophageal sphincter obstruction rather than oesophageal spasm. An older age of presentation raises the possibility of a different underlying pathophysiology.

Thesis declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Chapter 2 Introduction and literature review

2.1 The normal swallow

2.1.1 Anatomy

2.1.1.1 Oesophagus

To understand oesophageal motility disorders it is important to first consider the relevant anatomy of the oesophagus, and physiology of the normal swallow. The oesophagus is a muscular tube approximately 25cm in length, which begins in the neck extending from the pharynx through the thoracic cavity and the muscular portion of the diaphragm, into the abdominal compartment where it has a short course prior to reaching the stomach (figure 1). It consists of a mucosa lined by stratified squamous epithelium, a submucosa and muscular layer consisting of an inner circular muscle layer and an outer longitudinal layer of muscle. Unlike the rest of the gastrointestinal tract there is no serosa, rather a thin adventitia. The muscular layer in the upper third of the oesophagus is skeletal muscle which becomes visceral or smooth muscle fibres in the lower two thirds of the oesophagus(1).

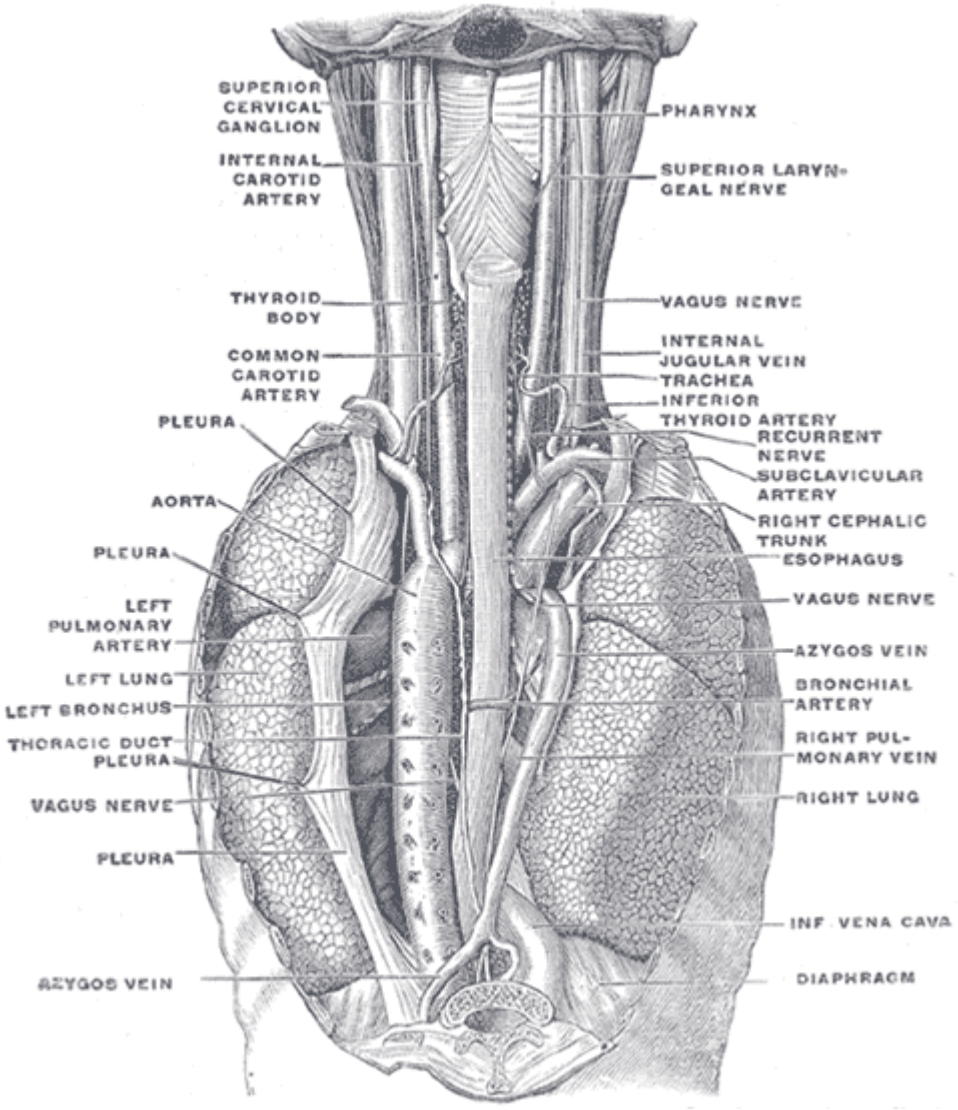

Figure 2-1 The position and relation of the oesophagus in the cervical region and in the posterior mediastinum as seen from behind.(2)

2.1.1.2 Lower oesophageal sphincter

The contents of the stomach are highly acidic, and the lower end of the oesophagus functions as a sphincter preventing pathological reflux of gastric contents back into the oesophagus. The circular muscle in the distal (approximately) three centimetres of the oesophagus functions as this sphincter - remaining contracted as a baseline state (3). Other factors are also important in preventing reflux of gastric contents. Fibres from the right crus of the diaphragm pass around the oesophagus to the left to help maintain an acute angle – the 'angle of His' – between the oesophagus and stomach (4). The pressure within the oesophagus is a slightly negative pressure as it takes on the negative pressure of the surrounding thoracic cavity. The distal couple of centimetres of the oesophagus is however in the abdominal cavity which has a slight positive pressure. This positive pressure acting on the lower portion of the oesophagus and occluding it is thought to add to the antireflux function of the lower oesophageal sphincter. Lastly as the oesophagus passes through a muscular portion of the diaphragm, the effect of the muscular contraction of the diaphragm during inspiration is also to cause an extrinsic pressure on the oesophagus - aiding the antireflux function of the lower oesophagus.

2.1.1.3 Nerve supply and physiology of a swallow

The oesophagus, as does the rest of the gastrointestinal tract, contains a myenteric plexus, a network of nerves between the circular and longitudinal muscular layers, and a submucosal plexus. The striated muscle in the upper third of the oesophagus is supplied by the recurrent laryngeal nerve and sympathetic fibres, which reach the oesophagus via the inferior thyroid arteries. Autonomic ganglia in the myenteric plexus receive preganglionic fibres from the dorsal motor nucleus of the vagus, and supply the smooth muscle of the distal two thirds of the oesophagus including the lower oesophageal sphincter. The neurones in the myenteric plexus are of two types - excitatory (cholinergic) and inhibitory (nitric oxide and vasoactive intestinal polypeptide) (5, 6) with a different distribution throughout the lower two thirds of the oesophagus. The excitatory neurons predominate proximally and the inhibitory neurons predominate distally(7). The longitudinal layer of muscle is supplied by excitatory neurons only. The vagus in addition innervates the inhibitory post ganglionic neurons (8, 9).

A swallow begins the voluntary and pharyngeal phases which move the food bolus toward the back of the mouth and into the upper oesophagus whilst protecting the trachea from aspiration. This process takes less than two seconds and the rapid peristaltic pressure wave created continues as the primary peristaltic wave in the oesophageal phase of swallowing. The primary peristaltic wave is a high pressure wave caused by coordinated contractions of the circular muscle layer moving down the oesophagus to propel a food bolus. There are three segments to a peristaltic wave, the first in the proximal oesophagus, the second with the distal oesophagus and a third distinct segment in the distal oesophagus as the wave approaches the lower oesophageal sphincter (figure 2) . Secondary peristaltic waves are initiated when distention of the oesophagus is caused by residual food which was not cleared by the primary wave. Peristaltic waves are mediated by the myenteric plexus in conjunction with the vagus nerve. As a peristaltic waves progress, the lower oesophageal sphincter relaxes to allow the bolus to pass (3) (figure 3). This is known as deglutitive relaxation, and is mediated by the vagus nerve synapsing with the myenteric plexus inhibitory neurons, probably with nitric oxide as the main neurotransmitter (9). Neural control of both a peristaltic wave and its associated deglutitive relaxation is complex and not fully understood, but both are under control of the myenteric plexus in conjunction with vagal input.

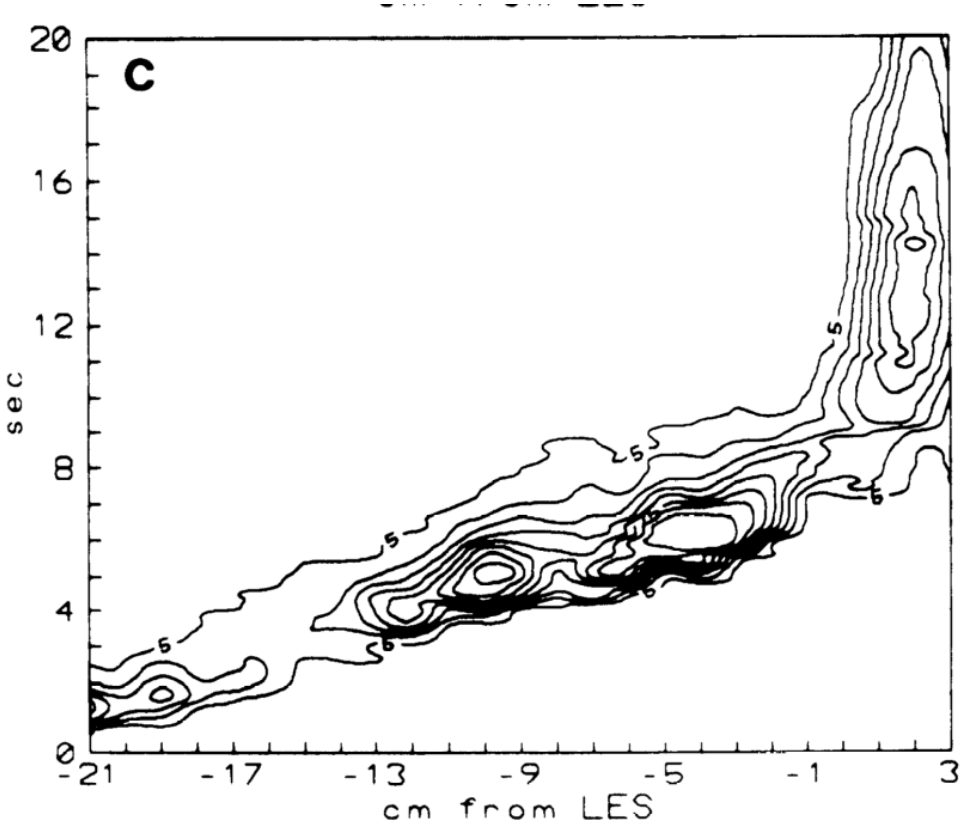

Figure 2-2 *Contractile segments of an oesophageal peristaltic wave, Clouse (1993) (10)*

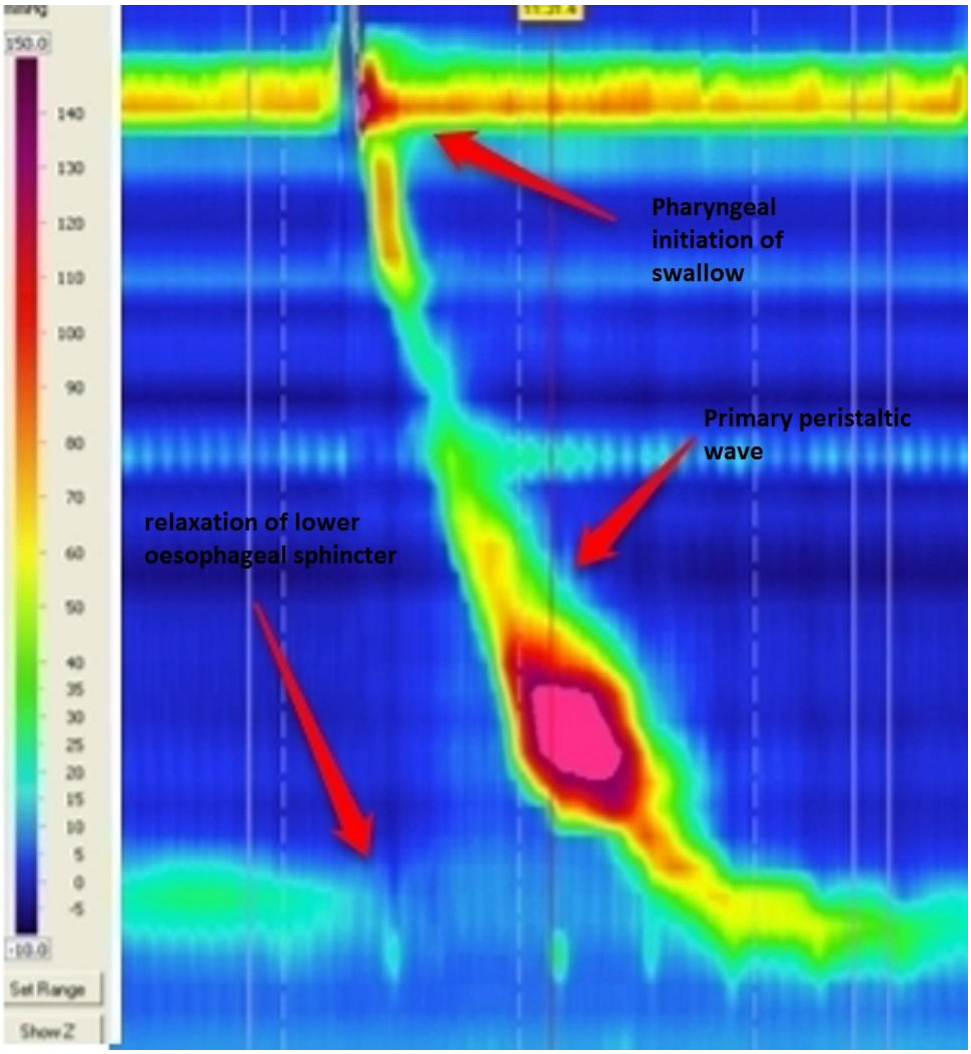

Figure 2-3 A normal swallow. High resolution manometry demonstrates normal physiology and innervation demonstrating the pressure wave in the upper third of the oesophagus, lower two thirds with the differing distribution of excitatory and inhibitory neurons as well as deglutitive relaxation of the lower oesophageal sphincter (9, 10).

The function of the longitudinal muscle of the oesophagus is less well understood, but it contracts in a synchronised fashion with the peristaltic wave of the circular muscle. It contracts during peristalsis in a cranial-caudal direction, resulting in oesophageal wall thickening, luminal obstruction behind the bolus, with the muscle immediately distal to this contraction relaxes allowing a lower pressure and distension of the wall to accommodate the bolus. (11, 12).

2.2 Achalasia

2.2.1 Definition

Oesophageal achalasia is a failure of normal relaxation of the lower oesophageal sphincter associated with uncoordinated contractions of the thoracic oesophagus resulting in functional obstruction and difficulty swallowing (Stedmans Medical Dictionary, 27th Ed). Also known as achalasia of the cardia or most commonly referred to simply as achalasia it is distinct from cricopharyngeal achalasia (failure of relaxation of the *upper* oesophageal sphincter), or achalasia of any other sphincter in the body.

Achalasia is considered a primary motility disorder of the oesophagus as it is 1) not a consequence of another medical condition (hence primary) and 2) the pathology lies predominantly in the innervation of the oesophagus (hence motility) rather than in a demonstrable mechanical abnormality (e.g. stricture or malignancy).

There are different phenotypes of achalasia recognised. All patients with achalasia have a failure of relaxation of the lower oesophageal sphincter but the abnormalities of peristalsis in the oesophagus above can be varied.

In the first widely used phenotypic subdivision of achalasia Vantrappen et al described different manometric presentations of swallowing disorders. They described achalasia as absence of relaxation of the LOS and absent peristalsis with or without vigorous contractions, also describing diffuse oesophageal spasm as vigorous contractions with some peristalsis and relaxations of the sphincter, but also conditions where overlap was seen to occur (13).

In 2008 (14) based on work done with high resolution manometry, Pandolfino et al described 3 types of achalasia. Type I achalasia is where the aperistaltic oesophageal abnormality is of low pressure. Type II is where the oesophagus develops pan-oesophageal pressurisations. Type III achalasia is where there are spastic contractions in the oesophagus. A fourth group called as EGJ (oesophago-gastric junction) obstruction has a failure of relaxation of the lower oesophageal sphincter but preserved peristalsis. When this is identified on manometry it is more likely to be due to an intrinsic or extrinsic obstruction, but if this is excluded may represent a further subgroup of achalasia although not formally diagnosed as such (figure 4). This description of subtypes is now used routinely in clinical practice.

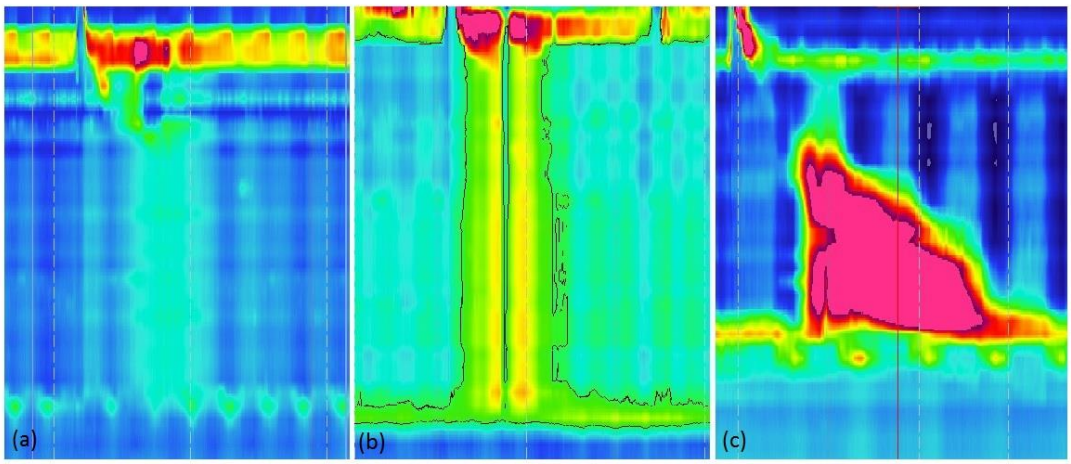

Figure 2-4. Chicago subtypes on high resolution manometry. Type I (a) with minimal pan-oesophageal pressurisations, type II (b) with pan-oesophageal pressurisations reaching above 30mg – demonstrated by the black line, type III (c) achalasia with spasm.

2.2.2 Aetiology, associations and pathophysiology

Achalasia is a disease with an unknown aetiology(15). What is known is that the pathophysiology includes inflammation at the level of the myenteric plexus and in most cases neuronal loss, thought to be progressive. Examination of specimens from patients with earlier stage achalasia shows an inflammatory response and beginnings of neuronal loss (16, 17) with examination of specimens from late stage achalasia showing near to complete neuronal loss and associated fibrosis (18) From this, and from the nature of the inflammatory infiltrate, it is hypothesised that achalasia may be an autoimmune disease, probably with an initiating viral insult such as HSV-1(19). An important caveat to this is that patients with vigorous achalasia, which presumably correspond to what is now known as type III achalasia, have not been shown to have neuronal loss and have a lesser degree of inflammatory infiltrate in the myenteric plexus (16).

Loss of function of the myenteric plexus, and its supply to the circular muscle of the oesophagus, leads to the failure of peristalsis seen in achalasia as well as the failure of relaxation of the LOS. The longitudinal muscle still may contract despite the loss of circular muscle function and may be one of the reasons that three manometric phenotypes are seen. In type I achalasia, the longitudinal muscle is least likely to contract. In type II achalasia the longitudinal muscle does contract strongly and is the cause behind the pan oesophageal pressurisation wave that is seen. The contraction will cause a decrease in the lumen of the oesophagus as the muscle contracts, and thickening causing decreased compliance both results in an increase in pressure. With neither the circular or longitudinal muscle contracting in a segmental manner and the LOS remaining closed, this pressure wave is transmitted throughout the oesophagus, resulting in the high pressure zone being pan-oesophageal. Type III achalasia again, is different to types I and II with *both* the circular and longitudinal muscle contracting, but in this phenotype the contraction is a disordered contraction, rather than the sequential and synchronous contractions of regular peristalsis (11). Also supporting a differing pathophysiological process in type III achalasia is the observation of an older age of presentation (20).

Autoimmune diseases have been associated with achalasia with patients having a 3-4x increased risk of a concurrent diagnosis of an autoimmune condition such as type I diabetes, hypothyroidism, systemic lupus erythematosus or uveitis (21).

2.2.3 Incidence

Achalasia is a rare disease with annual incidence usually quoted at 1/100000 and reported incidence in the literature between 0.3 – 1.34/100,000 (22-24). Estimates vary and are dependent on the method used for identifying cases. Estimates based on manometric diagnosis may underestimate incidence depending on accessibility to manometry and local referral pattern whereas incidence estimates from code searches are prone to significant error rates.

2.2.4 Natural history

Achalasia is a progressive disease and with no clearly identifiable or treatable cause. Treatments are directed at mitigating its effects rather than achieving a cure. Patients with early stage achalasia show no obviously demonstrable macroscopic abnormalities, but as obstruction persists, begin to get dilation of the oesophagus and thickening of the musculature in the oesophageal wall (18, 25). An oesophageal sump can develop with stasis of food persisting in this sump, even after relief of gastro-oesophageal junction obstruction has been obtained with treatment. With progressive disease the oesophagus

can become so damaged that oesophagectomy is the only option (26). Even with treatment, achalasia can progress, with 10-20% of patients developing a mega-oesophagus over a twenty year period.

Dilation of the oesophagus can be classified into four stages. Stage I has a normal oesophageal and stages progress through to stage IV where a significant sump exists, and contrast can be demonstrated to persist on a contrast study (27).

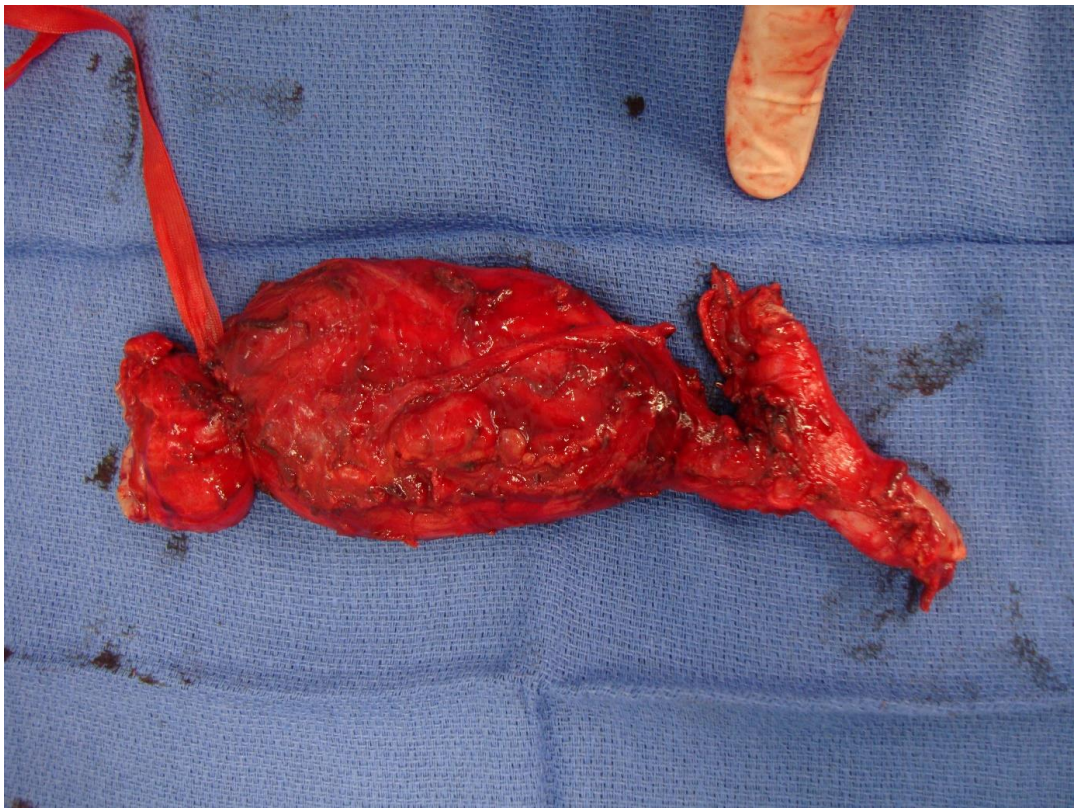

Figure 2-5 Oesophagectomy specimen for end stage achalasia. Tie is on the proximal oesophagus (left of picture) and gloved finger is at the level of the cardia. In between is the abnormal dilated and thickened oesophagus.

Lower oesophageal and some mid-oesophageal diverticulae are also sequelae of motility disorders, most commonly achalasia. The hypothesised pathogenesis is that repeated high pressures in the oesophagus, result in outpouchings in the oesophageal wall. A similar pathological progress occurs in crico-pharyngeal pouches above the crico-pharyngeus(28, 29).

Achalasia is also a risk factor for oesophageal cancer – both for squamous cell carcinoma and adenocarcinoma - increasing the risk by up to 33 times the population based risk (30, 31). It is unclear whether or not this risk can be mitigated by surveillance endoscopy and identification of tumours at an early stage (32). It is likely that squamous cell carcinoma develops as a result of stasis in the oesophagus, the subsequent inflammation being an irritant to the squamous mucosa leading to dysplasia. Adenocarcinoma in an achalasia patient may not be due to the underlying disease process, but is conceivably due to gastro-oesophageal reflux which can occur after achalasia treatment. Achalasia is not believed to have an effect on life expectancy.(33)

2.2.5 Differential diagnosis

The differential diagnosis for dysphagia is broad and includes neurological diseases such as cerebrovascular accidents and degenerative disorders, intrinsic obstructing lesions such as tumours or schatzki rings, extrinsic obstruction from mediastinal pathology or vascular compression, motility disorders, eosinophilic oesophagitis, peptic stricture, medical intervention (e.g. fundoplication or gastric banding) or scleroderma. The differential for a manometric picture of achalasia, especially in cases where there is preservation of a degree of peristalsis is pseudo-achalasia. Pseudo-achalasia is a descriptive term where a mass or infiltrate, usually malignant, causes either mechanical obstruction of the GOJ or effects the myenteric plexus to cause an achalasic picture. Occasionally an aperistaltic oesophagus can look manometrically similar to an achalasic patient.

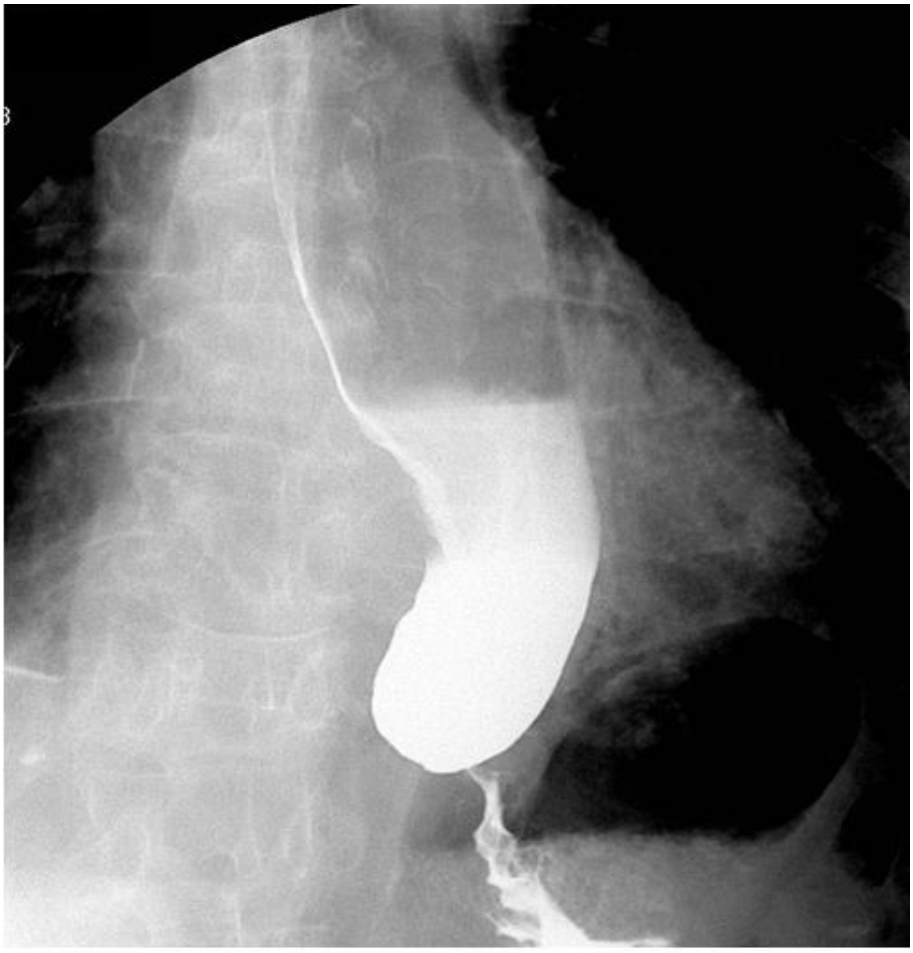

Figure 2-6 Barium of pseudo-achalasia. This patient was confirmed to have a gastro-oesophageal junction malignancy on endoscopy and biopsy.

2.2.6 Diagnosis

2.2.6.1 History and examination

The main symptoms of achalasia include dysphagia, regurgitation, chest pain and weight loss (23, 28, 34, 35). Dysphagia begins with liquids and progresses to solids. Patients need to spend longer chewing their food, and describe needing to wash each

mouthful down with large volumes of water. Regurgitation can predispose to aspiration and associated respiratory conditions (36, 37). Physical examination aids little to achieving a diagnosis, other than to confirm a history of weight loss. This constellation of symptoms and signs is however very similar to any other cause of obstruction of the gastro-oesophageal junction, such as the more commonly occurring malignant tumours or benign strictures. Gastro-oesophageal reflux disease symptoms can also be easily confused with achalasia symptoms, with the regurgitation of food failing to pass the gastro-oesophageal junction being mistaken for reflux of gastric contents. Patients also frequently complain of heartburn, and other non-specific upper gastrointestinal symptoms often attributed to reflux disease (23). Achalasia can be mimicked by consequences of surgical procedures such as fundoplication or laparoscopic adjustable gastric banding. Due to the overlap of symptoms and manometry findings between conditions the term 'pseudo-achalasia' is commonly used to describe a mechanical cause presenting with the clinical or manometric impression of achalasia (38). Hence the diagnosis of achalasia rests both on the positive findings of failure of relaxation of the lower oesophageal sphincter with associated aperistalasis *and* exclusion of a malignant infiltration or mechanical obstruction.

2.2.6.2 Investigations

2.2.6.2.1 Barium swallow

Barium swallow is the traditional investigation of choice for dysphagia and involves the patient swallowing barium or another contrast agent while XRay films are taken of the oesophagus and stomach. It is now used as an adjunct to endoscopy and manometry. A barium oeosophagram enables the mucosal outline of the oesophagus to be seen, demonstrating obstructive abnormalities such as tumours or strictures. It also assesses the degree of oesophageal dilation and can give information regarding peristalsis or spasm (manifested as a corkscrew appearance), that may be present. The classical appearance of a barium swallow in achalasia is of a birds-beak appearance at the lower oesophageal sphincter, with a dilated oesophagus above this, but these features are not universally present (36, 39, 40). In later disease the oesophageal dilation forms a sigmoid shape. Timed barium oesophogram is a technique used to interpret a barium swallow which looks to quantify oesophageal emptying of the ingested barium, making use of the fact that oesophageal clearance is markedly delayed in achalasia compared to a normal population. It has been used both in the diagnosis, but also the follow up and post-treatment assessment of achalasia patients (39, 41).

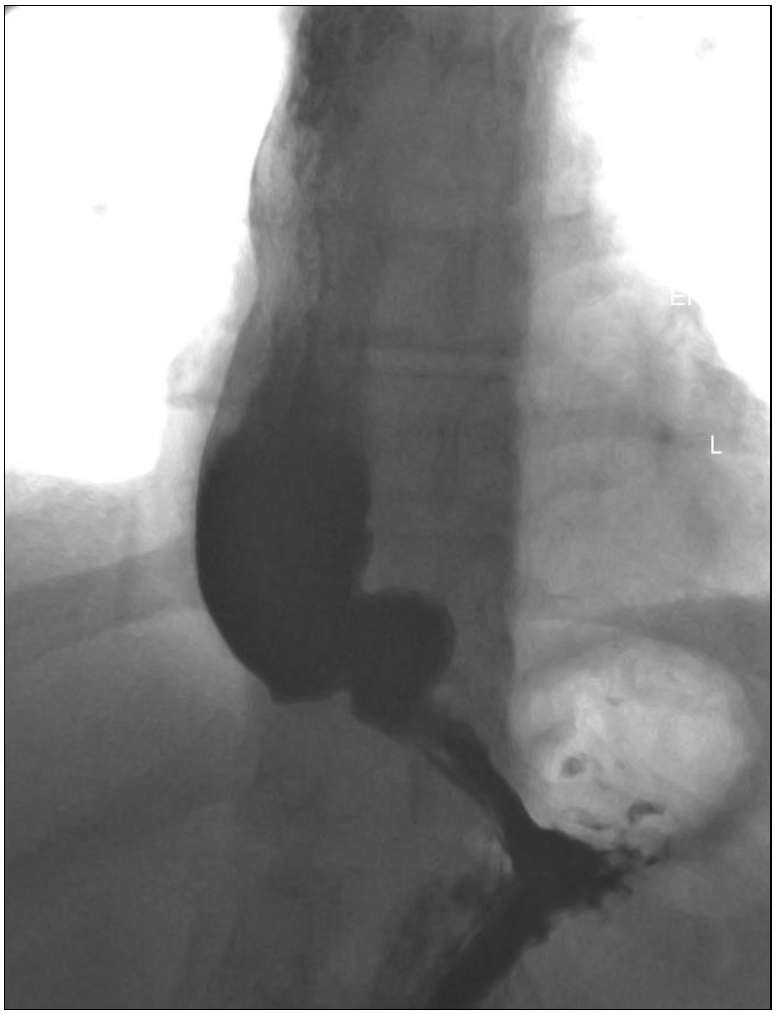

Figure 2-7 barium oesophogram demonstrating oesophageal dilation and early sump formation

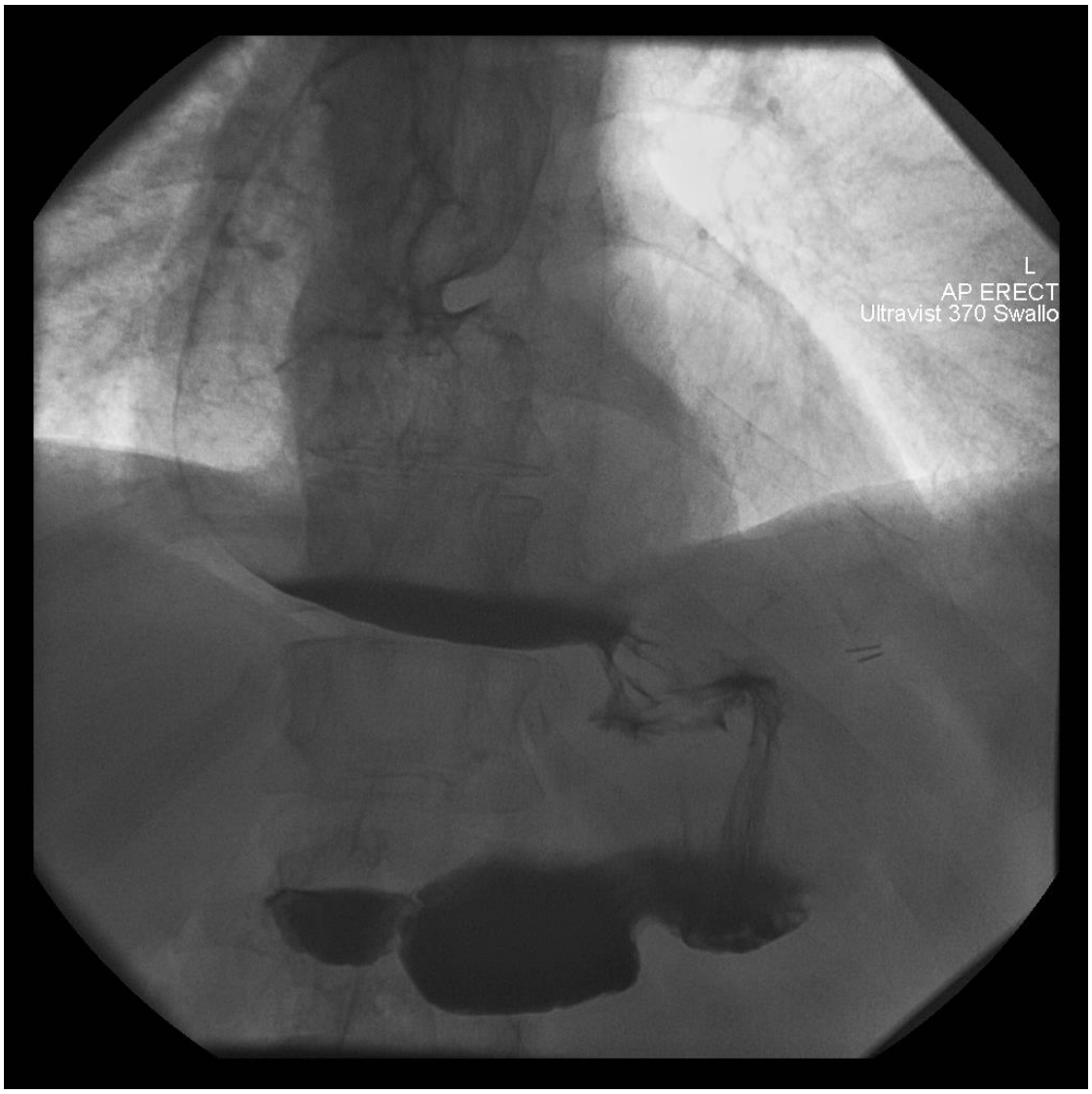

Figure 2-8 Barium study demonstrating sump formation with retention of barium retained in sump on a delayed image.

2.2.6.2.2 Oesophageal scintigraphy

Oesophageal scintigraphy is a less widely used technique for evaluating oesophageal function. It is a nuclear medicine test involving the swallowing of a radionuclide labelled bolus. Images are taken sequentially at intervals (usually the 1, 2 and 5 minute mark) with clearance of the bolus occurring in a normal population, usually within 1-2minutes and always by the 5 minute mark. In achalasia there is a high sensitivity for detecting the delayed oesophageal transit time that occurs, defined as failure of clearance of the bolus by the 5 minute mark, so although manometry and barium studies are often the investigations of choice for diagnosis of achalasia scintigraphy is a useful adjunct for monitoring response to treatment (42).

2.2.6.2.3 Endoscopy

Flexible fibre-optic endoscopy of the oesophagus and stomach is routinely performed in the workup of all achalasia patients. Endoscopic examination of the oesophagus usually reveals a macroscopically normal appearance (23, 28). As disease progresses

endoscopic findings can include a dilated oesophagus, retention of food in the oesophagus, a whitish appearance to the mucosa, functional stenosis of the GOJ, abnormal contractions of the oesophageal body and a pinstripe appearance if indigo-carmine is applied to the mucosa (43). However the main role of endoscopy is primarily to *exclude* a malignant infiltration of the GOJ (36, 44).

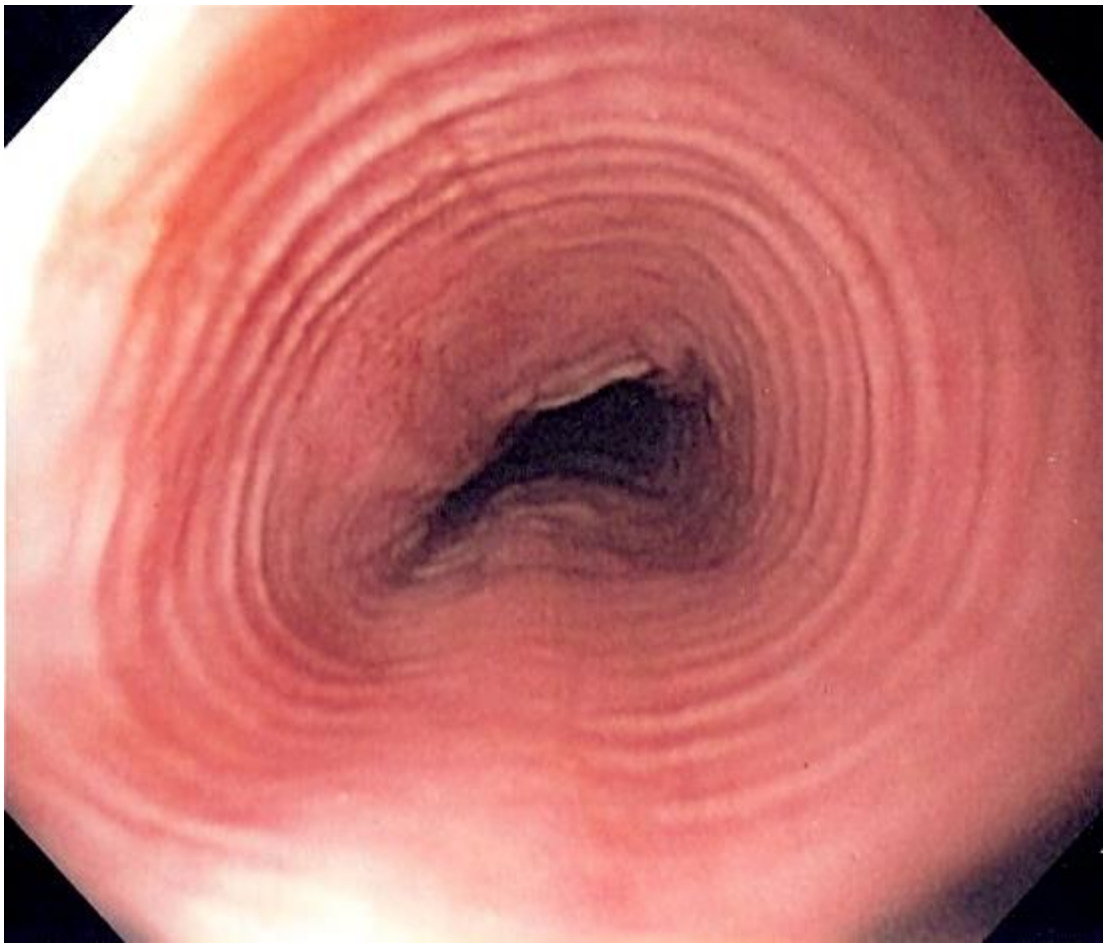

Figure 2-9 Endoscopic image of oesosinophilic oesophagitis, one of the differential diagnoses of dysphagia

2.2.6.2.4 Endoscopic ultrasound

Endoscopic ultrasound is a useful adjunct to endoscopy in the diagnosis or exclusion of pseudo-achalasia. It can provide higher resolution images of the GOJ than external imaging such as CT, as well as facilitating biopsy of any mass lesion identified. Although not routinely required it is useful in cases with a high suspicion of pseudo-achalasia and a normal CT scan. (45)

2.2.6.2.5 Computerised Tomography (CT scan)

Computerised Tomography can be used to differentiate between achalasia and pseudo-achalasia. CT scan findings in achalasia can include oesophageal dilation, a smooth narrowing at the GOJ and symmetrical wall thickening. Findings suggestive of malignancy include nodular narrowing, asymmetrical wall thickening or symmetrical wall thickening >10mm or presence of a mass (46, 47). The need for a CT scan as part of work-up for an achalasia patient is a clinical decision, although recommended

strongly for patients with the variant of achalasia known as OGJ or EGJ obstruction, these patients being at higher risk for being a case of pseudo-achalasia rather than true achalasia (see discussion under Manometry, Chicago classification, subtypes).

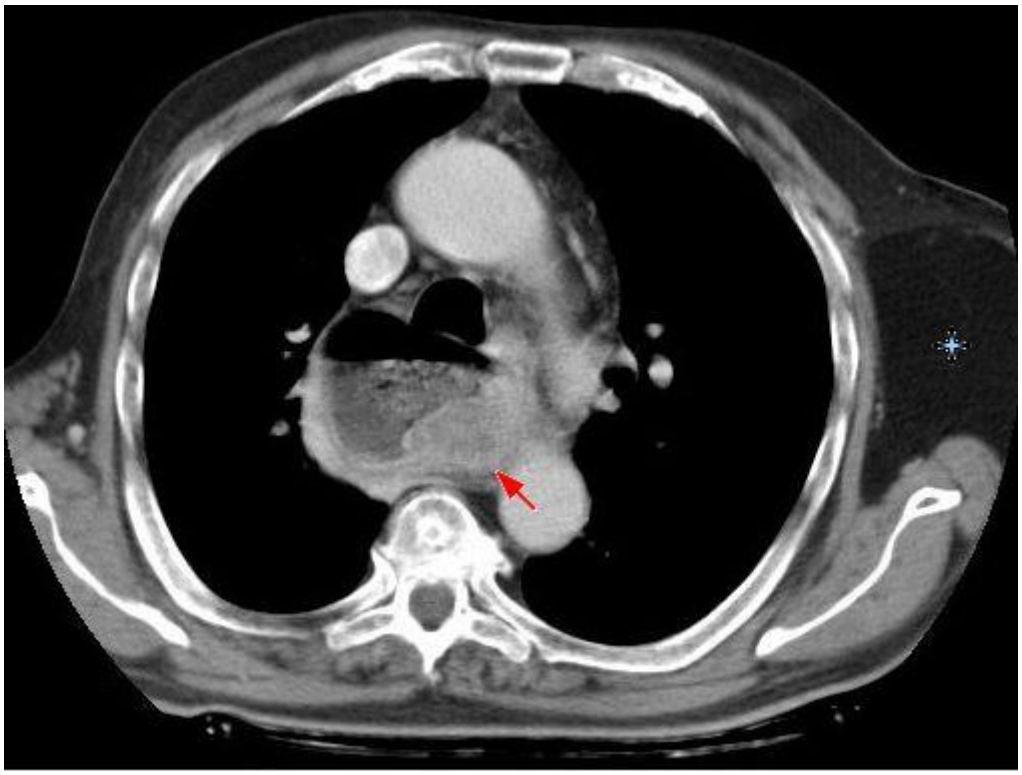

Figure 2-10 Computed tomography image demonstrating dilated oesophagus with malignant lesion demonstrated by red arrow.

2.2.6.2.6 Manometry

Manometry is the gold standard for achieving a diagnosis of achalasia. A catheter with pressure sensors is inserted via the nose and the patient is asked to perform a series of swallows. Continuous pressure measurements are obtained and in achalasia demonstrate both failure of LOS relaxation after pharyngeal initiation of a swallow and oesophageal aperistalsis. There are two types of manometry: conventional water perfused manometry, and solid state manometry. Data obtained can be analysed on a paper trace or electronically using computer software. The data can be displayed using line plots or converted to topographical (Clouse) plots. This is all discussed in more detail below (see discussion under Manometry).

2.2.7 Treatments

2.2.7.1 Medical

Medical treatments are not recommended routinely for the treatment of achalasia. Some drugs have properties that can improve symptomology but none are in common usage.

Calcium channel blockers and nitrates are the most commonly discussed medical treatments for achalasia. They can be used to decrease the LOS resting pressure. Problems with their usage include that only partial relaxation of the LOS is achieved, and this effect wears off over time as tolerance develops. They also have significant side effects and in a frail patient alternatives such as Botox injection (see below) into the LOS are much better tolerated (48, 49).

Sildenafil interferes with nitric oxide metabolism thereby inducing smooth muscle relaxation. In the oesophagus this causes decrease peristaltic amplitude as well as a decrease in LOS tone. Relaxation is however short lived (up to 8hours) and side effects preclude regular usage. (50) Sildenafil is not in regular clinical use for achalasia treatment.

2.2.7.2 Endoscopic

2.2.7.2.1 Botox

Botulinum toxin is an inhibitor of acetylcholine release from nerve endings. It can be injected endoscopically into the lower oesophageal sphincter to cause relaxation. It is a safe treatment with good initial results, but unfortunately recurrence of symptoms and lower oesophageal sphincter tone occurs over the following 6-12months in the majority of cases (51, 52). It is commonly reserved for elderly patients who are unfit for the risks of LHM or PD.

2.2.7.2.2 Pneumatic Dilatation

Pneumatic dilatation (PD) is a treatment directed at disrupting the lower oesophageal sphincter by the insufflation of a balloon across the GOJ to tear or stretch the muscles of the lower oesophageal sphincter.

The balloon is placed across the GOJ endoscopically and position is confirmed either visually or using XRay. It is insufflated using a pump under manual control which also contains a pressure sensor for a reading of the internal pressure of the balloon. In an achalasia patient as insufflation begins a 'waist' can be seen in the balloon corresponding to the tight GOJ, and insufflation is normally continued until this waist disappears. Protocols for performing pneumatic dilation vary and there is no accepted standard world-wide for how many PD are performed, when they are performed, the size of the balloon or to what pressure it is insufflated. Also the number of repeat dilations that are performed before considering that the treatment has failed varies from centre to centre. Even in a large multi-centre RCT, performed within the last 5 years (53), the protocol for PD had to be changed mid trial due to unacceptable rates of oesophageal perforation.

Although a good response is initially seen dysphagia often recurs particularly after only one dilation and is not a durable as after a LHM. Oesophageal perforation is the major risk factor. Although PD seems attractive in the elderly where trying to avoid a Heller myotomy and general anaesthetic, if a perforation does occur it can require a thoracotomy to repair, carrying with it much greater morbidity.

2.2.7.2.3 Per-Oral Endoscopic Myotomy (POEM)

Per-oral endoscopic myotomy (POEM) is an emerging treatment for achalasia that is rapidly gaining international acceptance. It is performed by endoscopically creating a submucosal tunnel, and then dividing the circular muscle of the distal oesophagus, LOS and cardia. Its perceived advantages are that not only is it is an endoscopic rather than operative procedure, but also that a longer myotomy can be performed. Disadvantages include the requirement of advanced endoscopic technical skills, the substantial learning curve in a relatively uncommon disease, the lack of long-term follow up and potential for high rates of gastro-oesophageal reflux (54). High volume centres are reporting good five-year outcomes in prospective cohort studies for POEM but no randomised controlled trial has yet to compare it to conventional therapies (cardiomyotomy or pneumatic dilatation) (55, 56).

2.2.7.3 Surgical

2.2.7.3.1 Heller cardiomyotomy

In 1914 Heller described an extra-mucosal myotomy for spasm of the gastric cardia with oesophageal dilation. Pneumatic dilation became more common when it was shown to obtain reasonable results and had negligible recovery compared to a thoracotomy or laparotomy. A return to surgical myotomy occurred with the introduction of thorascopic and laparoscopic surgery after a description by Pellegrini and colleagues (57).

2.2.7.3.1.1 Laparoscopic myotomy

A laparoscopic Heller cardiomyotomy (LHM) has become the surgical gold standard for treatment of achalasia. It involves division of the phreno-oesophageal ligament to obtain access to the oesophagus, dividing the serosa and muscular layers at the gastric cardia then extending this myotomy up the anterior oesophagus while leaving the mucosa intact. The anterior fat pat needs to be elevated to allow a myotomy on the gastric side of at least 2-3 cm(58). It is often performed with a fundoplication – see discussion below. Patients can usually be discharged after a two day hospital stay (59).

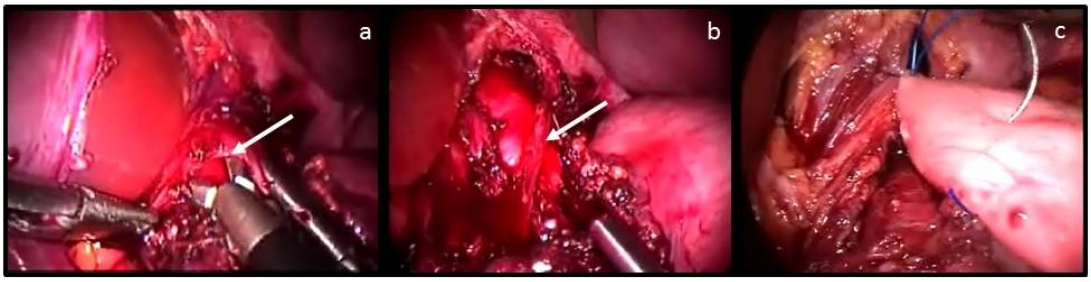

Figure 2-11 Laparoscopic Heller cardiomyotomy. Muscular fibres as indicated by the arrow in (a) are lifted off the underlying mucosa and divided. In (b) mucosa can be seen through the completed myotomy with the overlying anterior vagus indicated by the arrow. The procedure is completed by the formation of an anterior, 'Dor' fundoplication (c).

2.2.7.3.1.2 Thorascopic myotomy

A surgical myotomy of lower oesophageal sphincter can also be performed via a transthoracic route. Although technically feasible a laparoscopic rather than thorascopic approach provides both a shorter operative time as well as a shorter hospital stay and recovery. There is probably no difference in morbidity with either approach but there is a trend towards superior long term outcomes with LHM (60). Also of concern is the inability to perform a concurrent reflux procedure with a thorascopic approach, which raises concern about long term reflux control with disruption of the LOS. This disruption is not as extensive as in a LHM as the phreno-oesophageal ligament is not divided. For these reasons the myotomy is performed in the vast majority cases laparoscopically, particularly as LHM has excellent long term outcomes (61)

2.2.7.3.1.3 Myotomy and Fundoplication

Disruption of the lower oesophageal sphincter and hiatal dissection during LHM impairs the anti-reflux mechanisms at the lower end of the sphincter. This can lead to increased reflux and acid exposure to the distal oesophagus. Addition of a fundoplication can modify this decreasing the rate of post operative reflux from has

high as 50% down to 10% (62, 63). Current recommendations (SAGES) based on a systematic review, are that a fundoplication should be routinely performed (64, 65). Although no difference in outcomes between the commonly used partial fundoplication's - anterior (DOR) and a posterior 270 degree (toupet) are evident, performing a full wrap (Nissan) does increase the risk of developing dysphagia (66)

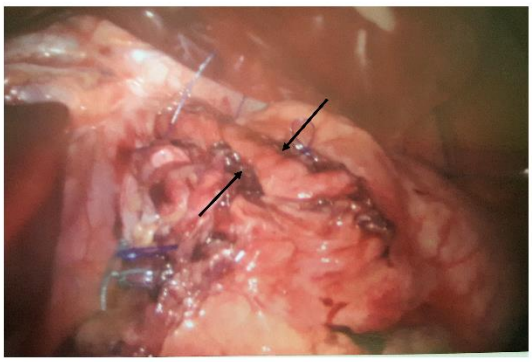

Figure 2-12 Heller myotomy with posterior 'toupet' fundoplication. Black arrows demonstrate edge of myotomy sutured to fundus. Image courtesy of Mr Steven Kelly

2.2.7.3.2 Oesophagectomy

The majority of endoscopic and surgical treatments for achalasia involved disrupting a tight lower oesophageal sphincter. However in more advanced cases the oesophagus above the sphincter has become grossly distended, fibrotic and unable to facilitate passage of boluses to the stomach even with an open GOJ(67). In these cases – where essentially the oesophagus is not worth preserving - an oesophagectomy may be performed. This is obviously an approach with significant morbidity so is generally reserved for only the latest stage disease when all other options have been exhausted (68, 69).

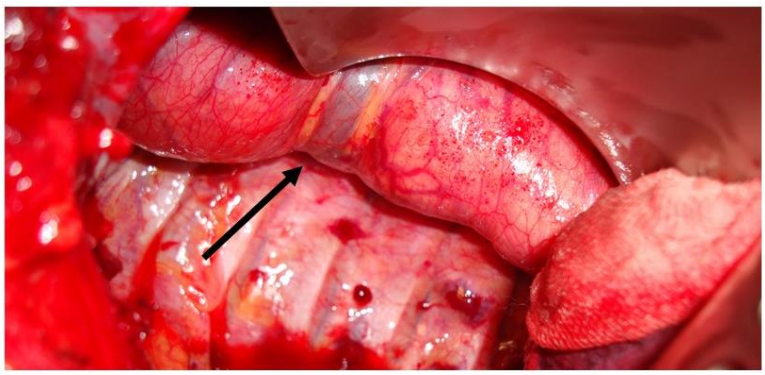

Figure 2-13 Dilated oesophagus from end-stage achalasia at thoracotomy. Retractor top right. Arrow indicating azygos vein tented over oesophagus.

2.2.7.3.3 Cardioplasty

In attempts to avoid the morbidity of an oesophagectomy, cardioplasty can be performed. The lower oesophagus and cardia of the stomach are incised longitudinally,

and closed transversely to create a wide stoma either with a sutured or stapled technique (67). As this has the same problem as cardiomyotomy and dilation, inasmuch as the oesophageal body dysmotility and problems from sump formation are not addressed, *and* the procedure creates ideal conditions for volume reflux, it has not been widely adopted (69). Success has been had in South American populations with mega-oesophagus from Chagas disease where it is performed in combination with an antireflux procedure – either a posterior partial fundoplication (70) or a distal gastrectomy (71).

2.2.7.4 Which treatment is best?

There is no international consensus on which treatment should be performed preferentially for achalasia treatment. Pneumatic dilation, laparoscopic cardiomyotomy and POEM are all used as primary treatment in varying centres according to local preference and expertise.

2.2.7.4.1 Comparisons between treatments

2.2.7.4.1.1 Hellers cardiomyotomy vs pneumatic dilation

The difficulty in directly comparing pneumatic dilation (PD) to laparoscopic Hellers myotomy (LHM) is the problem of deciding what to compare, particularly in defining what constitutes a treatment failure. LHM is a single procedure where the degree of success is readily assessed with any of a variety of dysphagia scores, quality of life scores or necessity of reintervention. PD on the other hand is more difficult to assess due to the considerable variability of protocols used by different centres and clinicians. Initial dilation can be anywhere from 30mmHg to 40mmHg, consist of a single dilatation or a series of 3 dilatations, be empiric or be graded to symptom response. A subsequent recurrence in dysphagia is often not considered a treatment failure but merely an indication for a repeat dilation as part of an ongoing treatment regime. If this interpretation is applied it makes any deterioration in a dysphagia score moot. If a treatment failure is defined as a LHM after PD or visa versa, this is also difficult to translate across centres as it is significantly influenced by individual patient and clinician preferences.

The most significant complication of PD is oesophageal perforation which occurs at a rate of approximately 5% (72)). This is a significant complication and can require a thoracotomy to repair the defect. Oesophageal perforation can also occur in LHM. Perforation occurs during the myotomy due to mucosal injury but is usually recognised at the time of surgery, and the mucosotomy is repaired primarily, with the only added morbidity being the additional surgical time taken for suturing. Thus this same complication although often seemingly directly compared (61), carries very different implications and should not be held in direct comparison.

The European Achalasia Trial group published the largest RCT comparing LHM and PD with just under 100 patients in each arm. Patients undergoing PD underwent 2 dilations (30mm then 35mm balloon) with a 3rd dilation (40mm balloon) if dysphagia persisted. They were then allowed a further 2 series of dilations prior to be counted as a treatment failure. LHM was performed with at least a 6cm myotomy on the oesophageal body and 1-1.5cm myotomy on the gastric side and a DOR fundoplication. Similar outcomes were seen in both arms with follow up averaging 43months. In a setting where most patients are treated with LHM and overall PD numbers are low (or visa versa) it is not clear whether these results are directly applicable, as PD was performed by experienced gastroenterologists with relatively high volume practice.

Follow up is also relatively short and there is concern that results after PD may not be as durable as after LHM (61).

Recently the long term results of a randomised control trial (73) have been reported which although having less patients than the European Achalasia trial (53), did present five year follow up data. It suggests that pneumatic dilation is associated with significantly more treatment failures than LHM. The outcome differences between these two groups is likely explained by the length of follow up, with LHM representing a more durable approach long term (61), and also the different definition of treatment failure used by both studies.

Meta-analyses in the last few years addressing the issue of PD vs LHM have both suggested an advantage to LHM in both short and long term follow up. A meta-analysis of 3 RCTs looking PD vs LHM which including the European Achalasia Trial data suggests greater response to LHM than PD in short term (up to 1year) follow up. The occurrence of significant complications (perforation requiring intervention) was also less in the LHM group (72). Another meta-analysis looking at non randomised studies but including 36 series with long term (>5year) follow up also suggests greater durability of LHM (61)

Cost analysis of the two treatment options is reported, with PD being more cost effective than LHM and Botox injections (53, 74). This is obviously an important consideration in some health care environments but in Australia where neither treatments carry a prohibitive cost, clinical decisions are generally made according to which treatment will serve the patient best.

Subgroups of patients who are at risk of requiring repeated dilations include patients less than the age of 40, particularly if male. These patients are recommended LHM over PD (48, 53).

Ultimately deciding whether PD or LHM is the best treatment for achalasia is a decision between a cheaper treatment which needs to be repeated (PD), or a slightly more expensive treatment (LHM) which will have a more durable outcome.

2.2.7.4.1.2 POEM vs LHM or PD

Although we are still waiting for a randomised control trial to compare POEM against either of the standard treatments, non randomised comparisons (75) and case series (55) suggest that relief of dysphagia will be similar but raise concerns about long term gastro-oesophageal reflux rates (54).

2.2.7.4.2 Reflux after treatment

Will reflux be the ultimate discriminator between treatments? In opening up the GOJ to improve swallowing the ability to prevent acid reflux is also impaired. The antireflux mechanisms of the gastro-oesophageal junction are complex and multifactorial (76) The weight to which each known mechanisms contributes to the overall effect is uncertain, but what is clear is that achalasia treatment does impair each anti-reflux mechanism to a varying extent. All treatments disrupt the lower oesophageal sphincter muscles impairing its ability to maintain tone preventing gastric content reflux. In addition surgical myotomy disrupts the phreno-oesophageal ligament leading potentially to an alteration in the physiological effects of the crural diaphragam, and theoretically at least the possibility of a small hiatus hernia and an acid pouch. Disrupting the angle of insertion of the oesophagus to the stomach, the named ‘angle of

His' which occurs during surgical myotomy, also may predispose to post operative reflux. Reflux can be more significant in an achalasia patient, as not only do gastric contents reflux, but the normal oesophageal response of tertiary peristaltic events to clear the refluxate may be impaired due to the oesophageal body dysfunction (77).

Acid reflux is a concern for multiple reasons. Firstly heartburn symptoms can effect quality of life. Secondly oesophagitis is readily recognised after achalasia treatments (55, 65). This can lead to development of peptic strictures and recurrence of dysphagia. Literature on peptic strictures in achalasia is sparse due to multiple reasons. When dysphagia recurs, the treatment is usually pneumatic dilatation whether the cause is stricture, fibrosis, progressive disease or complication of a fundoplication. Distinguishing between peptic stricture, fibrosis or progressive disease is difficult clinically, and the number of cases to potentially investigate are low, due to both the low incidence of achalasia and the fact that strictures occur during long term follow-up.

The third concern with long term reflux is the theoretical risk of malignancy. The increased risk of oesophageal SCC is presumably due to stagnation of food, due to an amotile oesophagus, with subsequent inflammation leading to dysplasia. The increased rate of adenocarcinoma seen in achalasia cannot be explained by this mechanism, and is potentially due to a mechanism of reflux leading to metaplasia and dysplasia at the lower end of the oesophagus. The established precursor lesion to adenocarcinoma, Barretts oesophagus, has been identified in 7% of achalasia patients treated with LHM despite a DOR fundoplication also being used in this cohort (32). This risk of adenocarcinoma is too small to be evident in most study populations, but has been demonstrated in population cohorts (78).

Rates of reflux after treatment for achalasia is poorly reported in the literature. Most publications report reflux symptoms, rather than objective measures such as pH studies. This is problematic as reflux symptoms both in achalasic and non achalasic patient populations do not correlate with objective measures (79, 80). Reflux as measured by pH study is probably as high as 55% after POEM (54) and around 15% after LHM with fundoplication (65)

Table 2.1 Reflux after treatments for achalasia as measured by pH study or diagnosis of Barretts oesophagus

Study author	Treatment	Time after treatment	Reflux on pH	Rate of Barretts
Gossage et al(32)	LHM +DOR	5years		5/68 (7%)
Teitelbaum et al(81)	POEM	1year	4/13	
Boeckstaens et al* (53)	LHM+DOR	1yr	15% (n ~66)	
Boeckstaens et al (53)	PD	1yr	23% (n ~66)	
Rawlings et al*(82)	LHM +DOR	6-12months	41.7% (n 24)	
Rawlings et al(82)	LHM + Toupet	6-12months	21% (19)	
Novais et al* (83)	PD	1-3 months	31% (n 42)	
Novais et al (83)	LHM + DOR	1-3 months	4.7% (n 43)	
Richards et al (62)	LHM +DOR	6 months	9.1% (n 22)	
Richards et al (62)	LHM	6 months	47.6% (n 21)	
Khashab et al(84)	POEM		(88%) 22/25 tested (unclear which group tested (whole cohort was 60)	
Familiari et al (54)	POEM	6-12months	53.4% (39/73)	
Jones et al(85)	POEM	6 months	58% (15/26)	
Swanstrom et al(86)	POEM		6/13 (46%)	
Campos (meta-analysis)(65)	LHM without fundoplication		41.5%	
Campos (meta-analysis)(65)	LHM with fundoplication		14.5%	

*indicates randomised controlled trial with comparison between the 2 groups in the table

2.3 Manometry

2.3.1 Definition

Manometry is the gold standard for diagnosis of achalasia. It provides a reading of the pressures in the oesophagus, across the lower oesophageal sphincter and in the upper stomach. A manometry catheter is placed via the nose into the oesophagus and with the lower end in the upper part of the stomach. It is calibrated and the patient is asked to perform a series of swallows which are recorded. A normal study demonstrates the propagation of the normal peristaltic wave with deglutitive relaxation of the lower oesophageal sphincter. Abnormal patterns of oesophageal contraction and lower oesophageal sphincter function are readily demonstrated (87).

2.3.2 History and evolution

Manometry equipment has evolved since the first balloon tipped catheters used in the nineteenth century with innovation and application of new technology. Manometry found its place in clinical practice with water-perfused manometry catheters, a system where water is perfused through the catheter, and out of a side hole at the intracorporeal end of the catheter. This measures the increased resistance transmitted back through the column of water when pressure in the oesophageal body rises and impedes the outflow

of water. Sensitivity and resolution of measuring oesophageal contractions depends on both the spacing and number of sensors in the oesophageal body. Measuring the pressure across the lower oesophageal sphincter, vital in the diagnosis of achalasia, is more difficult as during a study the lower oesophageal sphincter moves in relation to the fixed point of the catheter at the nose. This movement occurs during respiration or if spasm of the oesophagus occurs. A 'pull through' technique was initially used to assess the lower oesophageal sphincter tone and position. In this technique a sensor was placed in the stomach and as it was withdrawn or 'pulled through' the sphincter, the rise and then subsequent fall in pressure as it entered the oesophagus was observed (88) This technique is unable to allow for the LOS baseline and reflexual relaxation to be easily analysed concurrently with oesophageal peristalsis. Evolution of this technique led to the 'Dent sleeve' being added to the lower end of catheters. This technique utilises a 5-6cm long silicone strip over a perfused sensor measuring the greatest pressure over the strip length. This allows continuous measurement of the highest pressure across the sphincter, even accounting for some vertical movement of the sphincter during a study. Importantly it also allowed for consistent measurement of the LOS pressure during a swallow, and assessment then not only of its basal pressure, but also of its deglutitive relaxation (89). More recently catheters utilising solid state technology have been introduced from a research setting into clinical practice and allow greater standardisation and sensitivity (see discussion below under technical, solid state technology).

2.3.3 Technical

2.3.3.1.1.1 Water perfused manometry

Water perfused manometry relies on water perfusing through a silicone tube with one end connected to a pressure transducer and the other end placed in the oesophagus or stomach. Pressure on the lower end occludes a side hole through which water drips thereby increasing the pressure in the tubing which in turn is transmitted to the pressure transducer. This system although robust and useful has limitations – every pressure sensor requires a separate silicone tube within the catheter which limits the number of sensors, and gravity and vertical position of the transducer relative to the sensor will affect the pressure readings. The first water perfused systems used had catheters with only 1 or 2 pressure sensors, these evolved to the addition of more sensors and a Dent sleeve, and now can have sensors at 1cm increments in the distal catheter.

Figure 2-14 Water perfused catheter

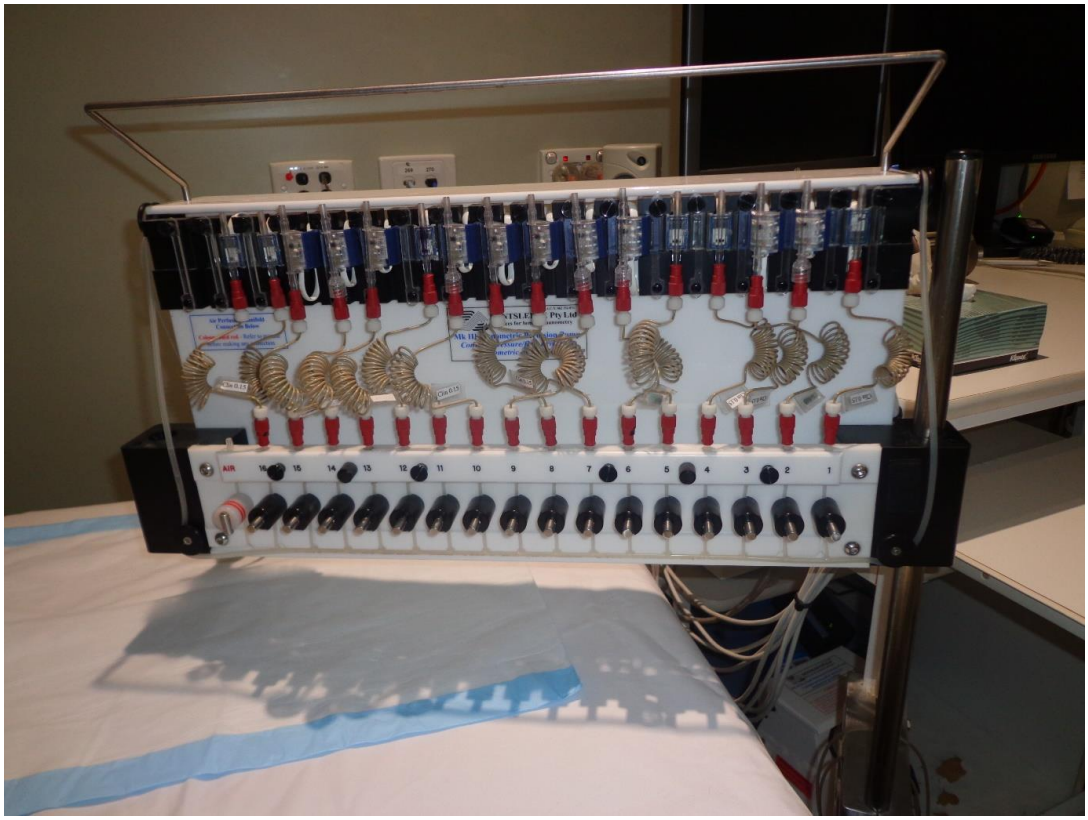

Figure 2-15 Water-perfused system

2.3.3.1.1.2 Solid state technology

Solid state catheters give a high resolution manometry tracing. The electronic pressure sensors have advantages over water-perfused sensors as they require calibration only to

temperature which is done electronically, rather than being subjected to the variations of a water perfused system. They are designed to work with specialised software which calculate metrics from each swallow electronically. The High Resolution Manometry working party is continuing to develop the metrics used to analyse data using these systems, and the new versions of the Chicago classification system are incorporated into the software updates. This all leads to a more standardised analysis.

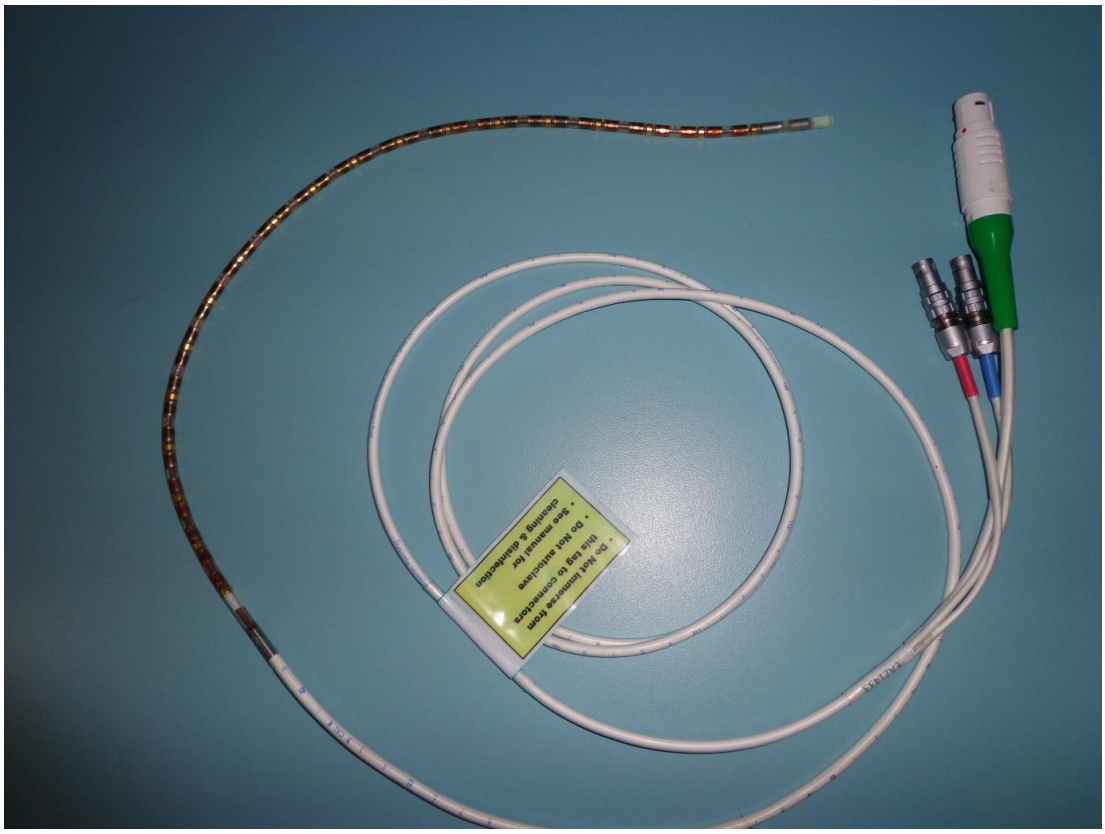

Figure 2-16 Solid state catheter

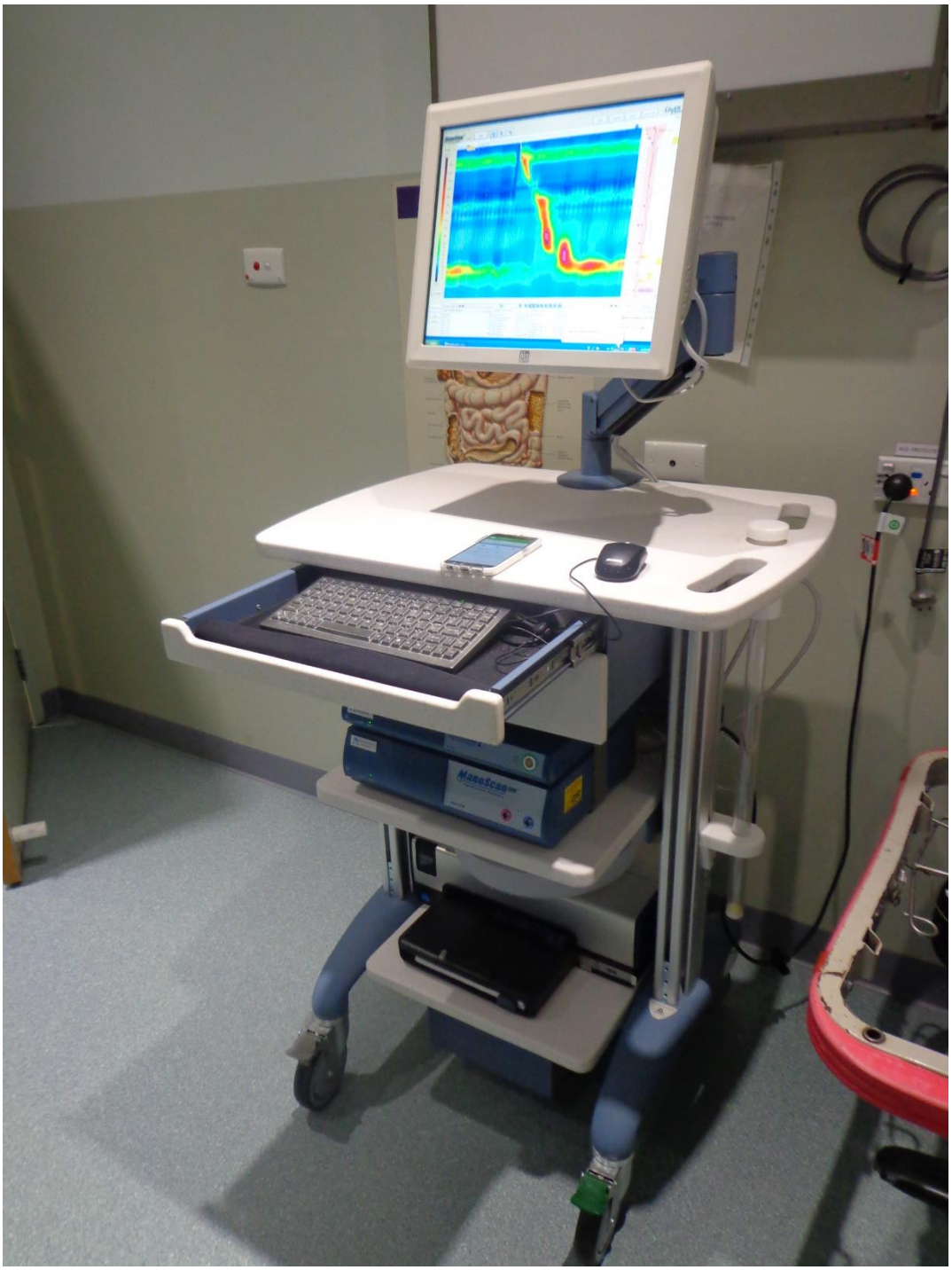

Figure 2-17 Hardware and software for recording and analysis from a solid state catheter.

2.3.3.1.1.3 Line and topographical plots

Manometry data are a continuous measurement of pressure in the oesophagus or stomach at the level at which the sensor is placed. As well as variations in the catheters used to measure the pressure, there are different ways these data can be displayed. Data are most easily displayed as a line plots with the x-axis representing time and the y-axis representing pressure. Data from the more proximal sensors are displayed at the top of the page and from the more distal sensors at the bottom. Early manometry systems, particularly those utilising hard copy tracings use this method of display. Limitations of include the unwieldiness of displaying data, with each sensor requiring a line trace that need to be displayed in parallel. Also although most features of a swallow such as

peristalsis can readily been seen, subtleties such as the progressive pressurisation of the oesophagus that occurs over the course of an achalasic trace can easily be missed.

In 1993 Ray Clouse described displaying pressure in the form of a topographic plot (10). In this method the x-axis stays as time but the y-axis becomes the distance from the incisors. Pressure is displayed by colour variation with convention being that blues and green colours represent lower pressures with reds and purples representing higher pressures. Before computers were in regular use this was not a feasible method of routinely reporting manometry, but as technology and software have developed, data is now routinely displayed topographically. Modern software allows both line plots and topographical plots to be used simultaneously to report a study.

2.3.3.1.1.4 High resolution

The terminology 'High resolution' is used in oesophageal manometry to describe sensors placed at 1cm increments. Modern water-perfused catheters can often incorporate 16 sensors allowing for a high resolution trace to be obtained across the lower oesophageal sphincter, which is usually the most critical area in diagnosing oesophageal dysmotility. These systems usually have 'low resolution' eg 3cm spacings in the oesophageal body where it can be argued that there is little clinical advantage to 1cm over 3cm increments. Solid state catheters used in clinical practice have 36 sensors all at 1cm increments, which allow for a high resolution trace across the lower oesophageal sphincter, but also in the oesophageal body and across the upper oesophageal sphincter.

2.3.3.1.1.5 Protocol

The study protocol commences with the catheter being passed trans-nasally through the oesophagus until the tip lies in the stomach. A five minute period of rest is taken to give the patient time to adjust to the catheter and secondary contractions to subside. A series of ten, five mL water swallows is undertaken with the patient in the supine position. Variations of this protocol include addition of alternate positions such as further swallows in an upright position, tests such as swallowing a cup of water, or performing a series of rapid swallows or ingestion of solid or semi-solid foods. These can be performed to aid assessment of non-specific motility disorders in the elderly, where a description of their functional swallow may be beneficial (upright, semi-solid, solid swallows), or to further assess lower oesophageal sphincter relaxation (cup of water) or peristalsis (multiple rapid swallows looking for augmentation).

2.3.3.1.1.6 Interpretation

Manometry is reported by a clinician taking into account patient history and symptoms, often provided with the referral or obtained during a short pre-test consultation. The interpretation of a water-perfused study differs from that of study performed with a solid state catheter due to the calculations performed and reported.

2.3.3.1.1.6.1 Interpretation of a water-perfused catheter study

In a water-perfused study baseline pressure of the lower oesophageal sphincter is measured during a quiescent period of the baseline tracing. Nadir pressure is calculated during the water swallows. Low oesophageal sphincter pressure is always measured relative to intra-gastric pressure. Peristalsis is assessed during the water swallows with normal peristalsis being progression of a pressure wave down the oesophagus with deglutitive relaxation of the lower oesophageal sphincter being observed. The strength of the pressure wave is measured at its peak relative to oesophageal baseline pressure.

Although some of the Chicago classification metrics can be applied to a water-perfused study they are not strictly transferrable.

2.3.3.1.1.6.2 Interpretation of a solid-state catheter study

Interpretation of a study using a solid state catheter is usually performed in conjunction with software configured to report according to the Chicago classification (see below under History, Chicago classification). After calibrating for temperature much of the analysis is automated. The reporting physician checks for a period of relative quiescence in the baseline period and confirms that the landmarks including upper and lower oesophageal sphincters and respiratory inversion point are accurately identified. Each swallow is checked individually for these landmarks, and that the software has accurately identified the commencement of peristalsis, the contractile deceleration point and the peristaltic wave. After this has been checked and adjusted as necessary, the software calculates the metrics required to report according to the Chicago classification. The main metrics are summarised in table 2. The study is then analysed according to the Chicago classification algorithm which priorities assessment of the lower oesophageal sphincter and then assessment of the oesophageal body (table 3).

Table 2.2 Terminology used by Chicago classification

Term	Description	Interpretation*
Integrated relaxation pressure (IRP)	Measures the relaxation of the lower oesophageal sphincter during peristalsis calculated by measuring the lowest pressure over a four second, non sequential period during sphincter nadir.	<15mmHg is normal >15mmHg is failure to relax
Distal Contractile Integer (DCI)	Measures peristaltic strength by calculating the area under the distal oesophageal pressure wave at the 20mmHg contour (amplitude x duration x length)	<100mmHg.s.cm is failed <450mmHg.s.cm is weak >8000mmHg.s.cm is hypercontractile
Distal latency (DL)	Measures the speed of the peristaltic wave by calculating the distance in seconds from onset of peristalsis to the contractile deceleration point (the point marking transition from the second to third segments).	<4.5seconds is considered premature and a sign of a spastic contraction

Table 2.3 Oesophageal motility disorders defined by Chicago classification version 3(90)

Table 4 The Chicago Classification of esophageal motility v3.0

Achalasia and EGJ outflow obstruction	Criteria
Type I achalasia (classic achalasia)	Elevated median IRP (>15 mmHg*), 100% failed peristalsis (DCI <100 mmHg·s·cm) *Premature contractions with DCI values less than* 450 mmHg·s·cm *satisfy criteria for failed peristalsis*
Type II achalasia (with esophageal compression)	Elevated median IRP (>15 mmHg*), 100% failed peristalsis, panesophageal pressurization with ≥20% of swallows *Contractions may be masked by esophageal pressurization and DCI should not be calculated*
Type III achalasia (spastic achalasia)	Elevated median IRP (>15 mmHg*), no normal peristalsis, premature (spastic) contractions with DCI >450 mmHg·s·cm with ≥20% of swallows *May be mixed with panesophageal pressurization*
EGJ outflow obstruction	Elevated median IRP (>15 mmHg*), sufficient evidence of peristalsis such that criteria for types I-III achalasia are not met†
Major disorders of peristalsis	(Not encountered in normal subjects)
Absent contractility	Normal median IRP, 100% failed peristalsis *Achalasia should be considered when IRP values are borderline and when there is evidence of esophageal pressurization* *Premature contractions with DCI values less than* 450 mmHg·s·cm *meet criteria for failed peristalsis*
Distal esophageal spasm	Normal median IRP, ≥20% premature contractions with DCI >450 mmHg·s·cm*. Some normal peristalsis may be present.
Hypercontractile esophagus (jackhammer)	At least two swallows with DCI >8000 mmHg·s·cm*,‡ *Hypercontractility may involve, or even be localized to, the LES*
Minor disorders of peristalsis	(Characterized by contractile vigor and contraction pattern)
Ineffective esophageal motility (IEM)	≥50% ineffective swallows *Ineffective swallows can be failed or weak (DCI<450 mmHg·s·cm)* *Multiple repetitive swallow assessment may be helpful in determining peristaltic reserve*
Fragmented peristalsis	≥50% fragmented contractions with DCI > 450 mmHg·s·cm
Normal esophageal motility	Not fulfilling any of the above classifications

*Cutoff value dependent on the manometric hardware; this is the cutoff for the Sierra device. †Potential etiologies: early achalasia, mechanical obstruction, esophageal wall stiffness, or manifestation of hiatal hernia. ‡Hypercontractile esophagus can be a manifestation of outflow obstruction as evident by instances in which it occurs in association with an IRP greater than the upper limit of normal.

2.3.4 Manometric classification systems

Classification systems have been described to attempt to better understand achalasia and related swallowing disorders. Vantrappen et al (1979) categorised all swallowing disorders according to three observed parameters on manometry. The lower oesophageal sphincter was considered to relax appropriately or not to have, the oesophageal body was considered to have peristalsis or not to and swallows were considered to be vigorous or non-vigorous. A vigorous contraction was considered to be one where a spastic contraction (6cm duration, >70mmHg) occurred, or 3 or more (repetitive) pressure waves occurred in response to a swallow (91). This gave rise to the terminology of vigorous or non-vigorous achalasia. As high resolution manometry was introduced into clinical practice Pandolfino et al (2008) described three subtypes of achalasia and a fourth group – obstruction of the lower oesophageal junction with some peristalsis. Type I is described as achalasia with minimal oesophageal pressurisation, Type II as achalasia with pan-oesophageal pressurisation and Type III as achalasia with spasm.

With the introduction of high resolution manometry, in conjunction with pressure topographic plots (92) providing a more intuitive method of analysing data produced, a systematic method of classifying swallowing disorders of the oesophagus was introduced in 2007 (93). This approach seeks to apply a systematic approach to manometric measurements to diagnose swallowing disorders in a standardised manner and is known as the Chicago classification. The development of the Chicago classification system is overseen by the High Resolution Manometry Working Party which meets to further develop and revise the system which is now in its third edition (90). Version 1 uses Pandolfinos description of achalasia subtypes, but the criteria for

type III achalasia has evolved, with the HRM metric ‘distal latency’ being the important measurement to define a spasm, replacing pressurisation front velocity, a metric now no longer used. The Chicago classification describes all primary motor disorders of the oesophagus with the exception of upper oesophageal sphincter disorders and post-surgical studies.

2.3.5 Application of the Chicago classification to a water-perfused catheter study.

In seeking to apply the Chicago Classification (CC) achalasia subtypes to water-perfused manometry certain factors must be addressed. Firstly the failure of relaxation of the lower oesophageal sphincter essential to the diagnosis of achalasia needs to be confirmed. The Integrated Relaxation Pressure (IRP) is used with HRM to confirm this and can also be calculated using specialised software used with water-perfused systems.

Secondly the classification of achalasia according to CC depends on the pattern of dysfunction in the distal oesophagus. This is calculated using the manometry metrics unique to HRM and not directly transferrable to conventional manometry.

To distinguish between type I and II achalasia the magnitude of the panoesophageal pressurisation needs to be calculated. Solid state catheters determine a pressure measurement in the oesophageal body in mmHg relative to atmospheric pressure after calibration for temperature. Water-perfused manometers require calibration for resistance of the catheter tubing, and for the impact of gravity (manifested in the position of patient relative to recording sensor). As such there is no direct corollary for measuring oesophageal body pressure in mmHg against atmospheric – on which the Chicago classification separates type I from type II achalasia. The most logical measure of oesophageal pressurisation to use is the traditional measure of wave amplitude (in mmHg) against end expiratory oesophageal pressure. Oesophageal pressure correlates to intra-pleural pressure as the oesophagus lies within the mediastinum. Intra-pleural pressure is slightly (approximately 2.5cm H20/ <2mmHg) negative at end expiration, but the negative pressure increases with inspiration and towards the apex of the lung. The variation between the base and apex of the lung is approximately 8cmH20 or 6mmHg(3). This has the effect that the pressure recorded at each manometry sensor, in a cranial direction, contains a greater component of negative pleural pressure. This means the pan-oesophageal pressurisation tends towards lower absolute measurements. This effect is therefore not a function of the degree of contraction of the oesophagus but rather artefact from pleural pressure variation. In high resolution manometry as the sensor is calibrated to atmospheric pressure this is not accounted for. In conventional manometry as the pressure wave is calculated from the end expiratory oesophageal pressure immediately before the swallow on each sensor (which also includes this pleural pressure variation artefact), it provides a measurement independent of this and more reflective of the strength of the oesophageal contraction. Again the effect is small and probably inconsequential.

Another difficulty that is encountered during analysis of conventional manometry to a HRM classification scheme, particularly if seeking to apply the classification retrospectively is the swallow protocol. The protocol for CC is based on the patient undergoing a five minute rest period to assess basal sphincter pressure, followed by ten consecutive five mL water swallows in a supine position (94). This is a standardised approach but has not always either been the routine approach in many manometry laboratories and is not always able to be obtained. Swallow protocols can include

varying numbers of swallows, either deliberately or by an inability of the patient to tolerate the full number of swallows planned, varying patient positions such as a lateral position or an upright position, or adding swallows of solid material for example bread in addition to water swallows. Swallows of 200mLs water or a series of multiple rapid swallows can also be used to potentiate the swallow to aid in delineation of an underlying disorder. Incomplete protocols can still be usefully interpreted particularly in the appropriate clinical context (95)

The rationale for calculating pressure against end expiration is that the pressure of the pleural space and hence oesophagus is closest to zero, and also most constant during this phase of respiration. It does lead to a discrepancy in the direct application of this measure to mmHg as calculated against atmospheric as used by Chicago classification/ solid state catheters, although this discrepancy is small (in the order of 2-3mmHg). It also creates more room for human error with clinical judgement having to be applied to determine the end expiration point on the tracing, rather than reading a computer generated number. A third confounding factor is that over the course of a manometry study, if the LOS fails to relax, as is pathognomic of achalasia, the oesophagus often slowly pressurises. This is not taken into account when using solid state catheters, when calculating the degree of pressurisation, but when measuring manually the end expiratory value will slowly rise as this occurs leading to a relative decrease in the measurement of oesophageal pressure (calculated as pressure above end-expiratory pressure). This may lead a borderline pan-oesophageal pressurisation to be undercalled as <30mmHg, rather than >30mmHg towards the end of a tracing, due to this effect of oesophageal pressurisation.

Overall these potential errors are of a low magnitude and the concept of reclassifying a water-perfused trace according to the Chicago classification is considered to be a reasonable approach.

2.3.6 Assessment tools

Assessment of swallowing can be done either objectively by observing a patient eat a meal or subjectively by patient self-report e.g. by questionnaire. The latter has the advantage of being practical for large cohort follow up while the former is not. There is little point however in performing questionnaires if they bear no correlation to what the patient can objectively eat, which is why validated scores are used preferentially.

2.3.6.1 Eckardt score

A score for grading severity of symptoms based on the frequency of the most commonly reported symptoms was described by Eckardt in 1992 (96) and assigns a numerical value to each of the four most common symptoms, addition of these to each other allows a score to be calculated on a scale of 0 to 12 with 0 representing an asymptomatic patient and 12 the most severely affected. (See table) If you remove weight loss from the score it also allows for assessment of clinical response to treatments such as myotomy and pneumatic dilation for achalasia (53, 96, 97) .

Table 2.4 Eckhardt score for Achalasia

Score	Weight Loss (kg)	Dysphagia	Chest Pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5-10	Daily	Daily	Daily
3	>10	Each meal	Several times a day	Each meal

2.3.6.2 Dakkak swallowing score

Dakkak et al looked at a series of patient with oesophageal strictures and validated a nine-point questionnaire assessing swallowing of various foods from water through to steak. A score out of 45 was obtained with 0 being a patient who cannot eat or drink anything and 45 a patient who has no difficulty. They found a strong correlation between the patient reported and researcher observed consumption of the 9 food items validating their score for assessing dysphagia for research purposes.(98)

2.3.6.3 Visick score

Originally described in 1948 looking at outcomes after elective gastrectomy for peptic ulcer disease the Visick score and its modifications has been widely used to assess outcomes after upper gastrointestinal surgery (99). It assigns patients a category according to symptom resolution and whether or not it is controlled with simple measures or interferes with daily life. The Visick score when reported by patients probably correlates better with resolution of symptoms such as heartburn rather than dysphagia and regurgitation, at least after antireflux surgery (100).

2.4 Aims of thesis

2.4.1 To assess the incidence of achalasia in the local South Australian population

2.4.2 To provide an update of current literature for a surgical audience

2.4.3 To report clinical outcomes of patients after laparoscopic Hellers cardiomyotomy according to Chicago subtypes

2.4.4 To report clinical outcomes of patients after pneumatic dilation by Chicago subtypes

2.4.5 To clinically describe type III achalasia

Chapter 3 Incidence of Achalasia in South Australia Based on Oesophageal Manometry Findings

Running Head: **Incidence of achalasia in South Australia**

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3.2 Statement of Authorship

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Contribution to the Paper	Data collection and analysis Drafting of paper Critical review and appraisal of draft prior to submission
Overall percentage (%)	30%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the secondary author of this paper.
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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3.3 Abstract

3.3.1 Background and Aims:

Achalasia is a disorder of esophageal motility with a reported incidence of 0.5–1.6 per 100,000 persons per year in Europe, Asia, Canada, and America. However, estimates of incidence values have been derived predominantly from retrospective searches of databases of hospital discharge codes and personal communications with gastroenterologists, and are likely to be incorrect. We performed a cohort study based on esophageal manometry findings to determine the incidence of achalasia in South Australia.

3.3.2 Methods:

We collected data from the Australian Bureau of Statistics on the South Australian population. Cases of achalasia diagnosed by esophageal manometry were identified from the 3 adult manometry laboratory databases in South Australia. Endoscopy reports and case notes were reviewed for correlations with diagnoses. The annual incidence of achalasia in the South Australian population was calculated for the decade 2004 to 2013. Findings were standardized to those of the European Standard Population based on age.

3.3.3 Results:

The annual incidence of achalasia in South Australia ranged from 2.3 to 2.8 per 100,000 persons. The mean age at diagnosis was 62.1 ± 18.1 years. The incidence of achalasia increased with age (Spearman rho = 0.95, $P < 0.01$). The age-standardized incidence ranged from 2.1 (95% confidence interval, 1.8 – 2.3) to 2.5 (95% confidence interval, 2.2 – 2.7).

3.3.4 Conclusion:

Based on a cohort study of esophageal manometry, we determined the incidence of achalasia in South Australia to be 2.3 – 2.8 per 100,000 persons and to increase with age. South Australia's relative geographic isolation and the population's access to manometry allowed for more accurate identification of cases than hospital code analyses, with a low probability of missed cases.

3.4 Introduction

Achalasia is a disorder of esophageal motility defined by absent peristalsis and impaired relaxation of the lower esophageal sphincter in the absence of lower esophageal sphincter obstruction. The pathophysiology involves degeneration of the inhibitory neurons of the myenteric plexus, however the etiology remains unknown. Achalasia becomes more common with age, and has no sex predilection (22, 23, 101-105). Historically, reported annual incidence rates have been 0.5 – 1.2 per 100,000 population (Table 1), and achalasia accounts for 5% of presentations with dysphagia (106). These studies of incidence are derived predominantly from retrospective searches of databases of hospital discharge codes and personal communications with gastroenterologists and are likely to be inaccurate. While some studies quote suspected case detection error rates of 5-10% (105), when case notes have been directly cross-checked with database search results, the error rate is 50- 66% (107, 108).

More recently, where significant measures have been taken to reduce the case identification error rate, the reported incidence of achalasia has been as high as 1.6 per

100,000 population in both Canadian and Italian populations (104, 108). Of interest, these reports coincided with the introduction of high-resolution manometry and pressure topography plotting in 2000(109). This has become the gold standard for diagnosing and classifying achalasia(110) raising the possibility that, with the introduction of this new technology, there is an improved diagnostic capacity for the identification of patients with achalasia.

In South Australia, during the past decade, the adult South Australian population has had routine esophageal manometry performed at one of three manometry laboratories for investigation of dysphagia not associated with structural abnormalities. Each laboratory has maintained prospective databases of patient demographics and manometry results. Therefore, in South Australia, it seems possible to identify and validate all diagnosed cases of achalasia by a search of these three prospective adult manometry databases. The incidence of achalasia in the Australian population has not been reported previously and will provide information regarding local burden of disease.

3.5 Methods

This study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital in Adelaide, South Australia (HREC/14/RAH/326, Protocol no. 140803).

3.5.1 Cohort

Data for the South Australian adult population for the decade 2004 to 2013 were obtained from the Australian Bureau of Statistics. Adults were defined as 18 years and older. Geographical population data were available in 2008 and 2013. Residence was defined as Capital City if living in Greater Capital City Statistical Area (GCCSA), Greater Adelaide (4GADE), and Regional/Remote if living in GCCSA Rest of SA (4RSAU) as per the Australian Statistical Geography Standard 2011.

3.5.2 Esophageal Manometry

During 2004 – 2013, esophageal manometry was performed at one of three adult laboratories and the patient details and corresponding manometry report recorded in a prospective database. One additional motility laboratory exists in Adelaide, which services the paediatric population, but access to this data proved too difficult for inclusion in our study. To the authors' knowledge, no one in Adelaide offers manometry in the private sector, as the Medicare Benefits Schedule fee fails to cover the costs of the procedure. Esophageal pressures were measured using low and high-resolution manometry (HRM) with motility displayed as a continuum of pressure and time using a color display.

Manometric data from the Gut Function Laboratory, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital were acquired between 2004 and 2012 using a Dentsleeve 10 channel water perfused system. Pharyngeal and esophageal channels were spaced 3cm apart and the remaining 2 channels (7-8) incorporated a 6 cm Dent-sleeve and proximal gastric side-hole (Dentsleeve International, Toronto, Canada). All lumina were perfused with degassed distilled water at a rate of 0.15ml/min using a low compliance perfusion pump. Data were recorded at 25Hz and analyzed using specialized software (*POLYGRAM* NET™ Functional Diagnostics, Skovlunde Denmark and Trace Version v1.2, Hebbard, Melbourne, Australia©). From 2013, data were acquired using either a 16 channel water-perfused system or a 36 channel solid state

catheter, with the solid state system used preferentially for dysphagia referrals. In the water-perfused system, pharyngeal and esophageal channels were spaced 3cm apart and the remaining 7 channels (10-16) incorporated a 6 cm e-sleeve with 1cm recording intervals across the LOS, and a proximal gastric side-hole (Dentsleeve International, Ontario, Canada). Data were obtained at 25 Hz and analyzed using the Solar GI HRM System with Quickview Analysis Program (Medical Measurement Systems, Michigan, USA). The solid-state catheter is a ManoScan 36-channel assembly with 1 cm pressure sensor spacings. Data were obtained at 50Hz and analyzed with ManoView (Sierra Scientific/Covidien, a Medtronic company, Los Angeles, CA, USA).

Data from the Oesophageal Function Laboratory, Department of Surgery, Royal Adelaide Hospital were acquired between 2004 and 2010 using a Dentsleeve 8 channel water perfused system, as described above. Data were obtained at 40Hz and analysed using Acquidata Gastromac (Neomedix Systems, Belrose, NSW, Australia). From 2010, data were acquired at 50Hz using a ManoScan catheter as described above and analysed with ManoView (Sierra Scientific/Covidien, a Medtronic company, Los Angeles, CA, USA).

Data from the Oesophageal Function Laboratory, Investigation and Procedures Unit Repatriation Hospital were obtained using the Dentsleeve 16 channel water perfused system, as described above. Data were recorded at 25Hz and analyzed using specialized software (Trace Version v1.2, Hebbard, Melbourne, Australia).

3.5.3 Case Identification

New manometric diagnoses of achalasia were identified by a search of the three prospective South Australian adult manometry databases (Figure 1). Two databases had the capacity for identification of manometry reports using search functions that extracted reports from the database within a restricted time frame and that contained the word “achalasia” or “non-specific motility disorder”. The remaining database had no in-built search function and every manometry report generated between 2004 and 2013 was reviewed. All reports were reviewed and excluded if:

- The report stated “not achalasia”, “achalasia excluded”, “EGJ (esophago-gastric junction) outflow obstruction”, or provided no further description of features of achalasia when reporting “Non-specific motility disorder (NSMD)” or “LES relaxation present”.
- Patients were not residents of South Australia
- Patients had previously been diagnosed with achalasia outside of the specified time frame, and were undergoing post-treatment manometry
- They were duplicate reports (i.e. patients who underwent manometry at more than one laboratory or on more than one occasion). After a diagnosis of achalasia, any subsequent manometry study was excluded to avoid inclusion of prevalence cases

A final review was performed to identify patients with pseudo-achalasia (i.e. esophageal or junctional cancer). This was achieved by reviewing all endoscopy results (where possible) and those with pseudo-achalasia were excluded.

3.5.4 Data Collection and Statistical Analysis

Data recorded included the date of manometry, patient age, sex, suburb of residence, and the diagnosis details. A diagnosis of achalasia was defined as “definite” where

either the manometry report was conclusive or the report was ambiguous but the patient was clinically treated as achalasia, and "likely" where the manometry report was ambiguous or endoscopy records were unavailable to rule out pseudo-achalasia in a patient aged 50 years and older. An ambiguous report described features of achalasia together with an alternative diagnosis such as diffuse esophageal spasm (DES) or non-specific motility disorder (NSMD), or made statements such as "suggestive of achalasia" or "partial expression achalasia".

The annual incidence of achalasia was calculated as new diagnoses per 100,000 population during the period 2004 to 2013. Adult incidence data are given as a mean in a range: "Definite" to "All (definite and likely)" cases. Further analysis was performed using "All" rates. Spearman's rank correlation was performed to identify any change in incidence across time or with age. Poisson regression analysis was performed to determine the crude and age-adjusted Incidence Rate Ratios (IRR) of the male and female, and separately the Capital City and Regional/Remote subpopulations, with age-adjustment performed using the mean age of identified cases. Independent samples t-test was performed to determine difference in age at diagnosis between subpopulations. Statistical significance was accepted at $P < 0.05$. Analyses were performed using the SPSS Statistics Package v17.0 (Chicago, IL, USA), except Poisson regression, which was performed using STATA v14 (StataCorp LP, 2014, College Station, TX, USA).

Age-standardised rates for adults 18 years and older were determined using the European Standard Population of 1976 (111) as follows:

Age-standardised rate =

$$\frac{\sum(P_k m_k)}{\sum P_k}$$

Where P_k = Standard population in age group.

m_k = Observed incidence rate (cases per 100,000 persons in age group 20-24, 25-30,..., 80-84, 85+ yrs)

3.6 Results

350 cases of achalasia were identified during the ten-year period, of which 288 (82%) were classified as “definite” and 62 (18%) as “likely”. On average, the annual incidence of achalasia in South Australia was 2.3 – 2.8 per 100,000 population (Table 2). The incidence of achalasia was similar in females (2.55 – 3.12 per 100,000) compared to that in males (2.05 – 2.47 per 100,000, Definite Cases P =0.06; All Cases P=0.03, IRR = 0.8). The incidence did not change across time during the study period.

The mean age at diagnosis was 62.1 ± 18.1 (SD) yrs (Median = 65.8 yrs; Range 17.6 – 99.3 yrs) and was not different between males and females. Patients that received a definite diagnosis were significantly younger (59.9 ± 1.11) than those who received a likely diagnosis (72.1 ± 1.9, $P < 0.001$).

The incidence of achalasia increased with age (Spearman rho = 0.95, $P < 0.01$) (Figure 2). The overall age-standardized all-cases incidence (European Standard Population) range was 2.1 (CI 1.8 – 2.3) to 2.5 (CI 2.2 – 2.7), and 2.3 (CI 1.9 – 2.7) for males, and 2.6 (CI 2.2 – 2.9) for females. The age-standardized incidence of achalasia was not different between the Capital City (2.5 per 100,000 CI 2.2 – 2.8) and Regional/Remote South Australian (2.0 per 100,000 CI 1.6 – 2.5) populations.

3.7 Discussion

This work is the first of its kind in Australia and reports the highest incidence of achalasia to date at 2.3 to 2.8 cases per 100,000 population. This is almost 50% higher than the current highest reported incidence of 1.6 per 100,000 in both Italian and Canadian populations published since 2000.

The population of South Australia is ideally suited for an estimation of the incidence of achalasia. There is ready access to and high uptake of manometry services, as all laboratories have acceptable waiting times, and provide services at no out-of-pocket cost to patients. The access for regional and remote patients is also favourable with government-subsidized travel to Adelaide for manometry services. In our study we identified and validated new cases of achalasia by a search of all three prospectively maintained South Australian adult manometry laboratories. This will not have captured patients who have declined further investigation of a swallowing disorder, or patients from South Australia who underwent manometry interstate or overseas. We considered the frequency of travel elsewhere for motility studies to be negligible, as the nearest neighbouring manometry laboratory is 700km away.

In recent times there has been an increased recognition of the importance of manometry in investigating benign esophageal disease(112) and an improvement in diagnostic pathways for esophageal diseases. In past studies of incidence, diagnoses of achalasia have often been made using clinical history, barium study, and endoscopy. The gold standard to diagnose achalasia is esophageal manometry, and this is aspired to in South Australian practice with liberal referral for manometry for both investigation of reflux disease and motility disorders. Consistently, manometry has been identified as providing new information in 87% of patients(113), and altering the diagnosis in 30-44% and management plan in 44-66% of patients(113, 114). Therefore, earlier estimates of the incidence of achalasia performed in the absence of routine esophageal manometry as an adjunct to diagnosis, would likely have incorrectly estimated the burden of disease.

During the study period of 2004 – 2013, the manometric definition of achalasia has evolved from the absence of peristalsis, presence of pan-esophageal pressurization, and

impaired lower esophageal sphincter (LES) relaxation to the current Chicago Classification v3.0 definition, which describes cases of achalasia as a median integrated LES relaxation pressure above the limit of normal and 100% absence of peristalsis for types 1 and 2, and fragments only of retained peristalsis or evidence of esophageal spasm for type 3 (90). However, it is important to state that it is not high-resolution manometry (HRM) in of itself, which is responsible for the increased incidence of achalasia demonstrated in our study. Many of the cases in our study were before the introduction of HRM. It is likely the combination of temporo-spatial plots (Clouse plots), together with appropriate recording power across the gastro-esophageal junction, which has contributed to the observed increase.

An ambiguous interpretation of manometry output is not unique to South Australia. Diffuse esophageal spasm (DES) evolving into a diagnosis of achalasia on repeat manometry is a well documented phenomena (13, 23, 115), and was observed in the current cohort. Of interest, in this study, patients with ambiguous manometry reports, or likely diagnoses, were significantly older than those who received a definite diagnosis. This may reflect an age-related deterioration in esophageal motility and function. The prevalence of achalasia, DES, and non-specific motility disorder (NSMD) all increase with age(116-119). We deliberately reported the incidence as a range to ensure we had not over-estimated by including ambiguous reports.

The incidence of achalasia increases with age(23, 101). South Australia has a high proportion (17%) of people aged 65 years and over, and an average age at diagnosis of 62 years, compared with 50 years in Hong Kong(120) or Korea(101), and 45 years in Iceland(107). It follows that an ageing population provides a potential explanation for the reported higher incidence. We therefore performed an age-standardization using the European Standard Population, unchanged since 1976. The age-standardized rate remained high at 2.1 to 2.5 cases per 100,000 population, therefore the higher reported incidence in this study cannot be explained by an aging population.

It is also unlikely that the higher incidence represents genetic variation between countries. There is little evidence that the incidence of achalasia differs between ethnic populations. A familial pattern in presentation of the disease has never been identified(103, 107, 121). In South Leicester, there was no difference in incidence between the British and South Asian populations and, in Israel there was no difference between people with different ethnic or residential backgrounds. Only in Singapore has a difference been demonstrated between the Malay, South Asian and Chinese population(24), however the data set was small, no age-standardization between ethnic populations was made(24), and there were significant ethnic differences in health care utilization thus introducing bias into the case identification process (122, 123). Furthermore, both Australia and Canada have a broadly genetically diverse population.

It is currently accepted that achalasia has no sex predilection (22, 23, 101-105, 116), supported by our results. As well, there was no difference in incidence between the Capital City and Regional/Remote populations and therefore no potential environmental causes for the disease were identified.

Our study is not perfect. First, it is widely accepted that not all cases of achalasia require manometry for diagnosis, and in some cases, manometry is not possible due to technical reasons (i.e. inability for the catheter to traverse the lower esophageal sphincter). However, omission of these few cases will only underestimate the incidence

of achalasia. Second, case note review of all 350 cases was not logistically possible as case notes were spread out over numerous private and public hospitals, as well as private gastroenterologists/surgeons' consulting rooms. To avoid false elevation of the incidence rate, we retrieved almost all endoscopy reports to exclude patients with pseudo-achalasia. It is possible that some cases were missed.

This study reports the highest and what we believe to be the most accurate incidence of achalasia to date: 2.3 – 2.8 per 100,000 population. This is likely to be the consequence of improved diagnostic pathways for esophageal motility and reflux disorders, specifically the use of manometry, and data storage in prospectively maintained databases. The unique situation in South Australia of relative geographic isolation and ready access to manometry has allowed accurate identification of cases, with a low probability of missed cases, from all adult manometry laboratories rather than hospital coding. We suspect that the incidence of achalasia worldwide is higher than previously recognized and that future epidemiological studies using similar methodologies will confirm this.

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3.10 Figures and tables

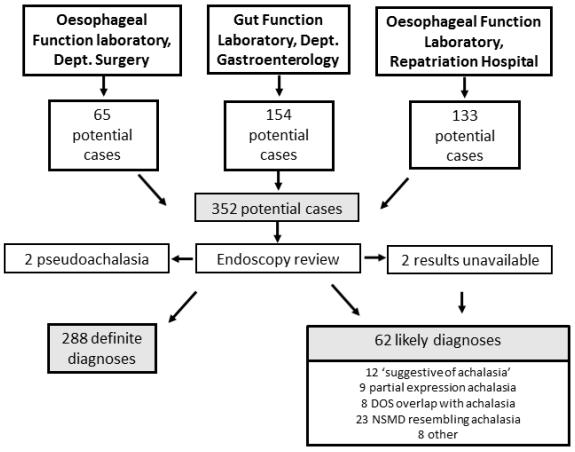

Figure 3-1 New manometric diagnoses of achalasia identified from three prospective South Australian adult manometry databases.

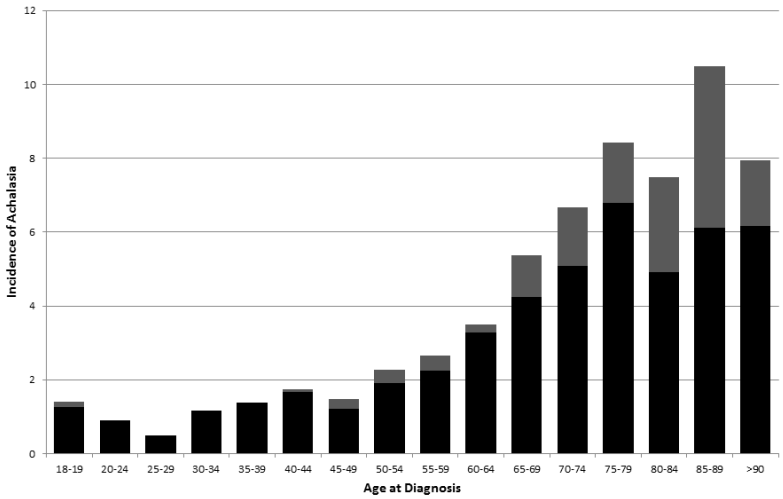

Figure 3-2 The incidence of achalasia increases with age (Black = "definite" cases, Grey = "likely" cases, Spearman rho = 0.95, $P < 0.01$).

Table 3.1 All publications reporting an incidence of achalasia.

Study	Cohort Location	Years	Method of Case Identification	Number of diagnoses	Incidence M/F (per 100,000)
Earlam(124)	Rochester, USA	1925 - 1964	Gastroenterologist estimations of disease frequency. ICD code	11	**0.6**
Mayberry(125)	Cardiff	1926 - 1977	Not identified	48	**0.4**
Galen(126)	Virginia	1975 - 1980	Not identified	31	**0.6**
Mayberry(127)	Nottingham	1966 - 1983	ICD code, case notes	53	**0.51**
Arber (103)	Israel	1973 - 1978	Direct communication with gastroenterologists, ICD Code, case notes.	Overall 162	**0.8**
		1979 - 1983		Overall 162	**1.1**
Mayberry(22)	Scotland	1972 -1983	Direct communication with specialists. ICD Code	583	**1.12**
	Wales	1970 - 1973		197	**0.71**
	Northern Ireland	1970 - 1973		153	**0.98**
	Eire	1976 - 1982		453	**1.34**
	England	1972 - 1983		4920	**1.08**
Stein(128)	Zimbabwean natives	1974 - 1988	Not identified	25	**0.03**
Mayberry(105)	New Zealand	1980 – 1984	ICD code	152	**0.95**
Howard(23)	Edinburgh, Lothian Region	1986 - 1991	Registry Search – confirmed by endoscopy and manometry	38	**0.80/0.83**
Ho (24)	Singapore	1989 - 1996	Manometry, case notes	49	**0.3/0.27**
Birgisson(107)	Iceland	1952 – 2002	ICD code, case notes	62	**0.55**
Farrukh(102)	South Asians in Leicester	1986 - 2005	ICD code, Endoscopy, manometry, and botulinum toxin stock transaction registries, case notes	13	**0.89**
Gennaro (104)	Veneto Region, Italy	2001 - 2005	ICD code, case notes	365	**1.59/1.58**
Sadowski(108)	Alberta, Canada	2007	ICD or procedure code (balloon dilation or esophagomyotomy).	463	**1.85/1.43**
Kim (101)	Republic of Korea	2011	ICD code	191	**0.33/0.44**

Table 3.2 The absolute number of patients with new manometric diagnoses of achalasia, and annual incidence of achalasia during 2004 to 2013.

	Number of Diagnoses			**Incidence** (per 100,000)	
	Definite	All	SA Population	Definite	All
2004	23	36	1,181,426	1.95	3.05
2005	24	30	1,192,921	2.01	2.51
2006	30	31	1,206,272	2.49	2.57
2007	26	28	1,222,299	2.13	2.29
2008	26	32	1,238,801	2.10	2.58
2009	33	38	1,257,427	2.62	3.02
2010	30	33	1,274,474	2.35	2.59
2011	39	52	1,286,613	3.03	4.04
2012	23	26	1,300,612	1.77	2.00
2013	34	44	1,313,936	2.59	3.35
Total	**288**	**350**		**2.30**	**2.80**

Chapter 4 Update in Achalasia – What the Surgeon needs to know

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Overall percentage (%)	65%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
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4.2 Abstract

Achalasia is a motility disorder encountered by surgeons during the investigation and treatment of dysphagia. Recent advances in manometry technology, a widely accepted new classification system and a new treatment rapidly gaining international acceptance have changed the working knowledge required to successfully manage patients with achalasia. We review the Chicago classification subtypes of achalasia with type II achalasia being a predictor of success and type III achalasia a predictor of treatment failure. We review per-oral endoscopic myotomy as an emerging treatment option and its potential for improving the treatment of type III achalasia.

4.3 Introduction

Achalasia remains the most distinctive albeit relatively rare of the motility disorders of the oesophagus. Significant changes to understanding and treatment of the disease have occurred over the last decade. The Chicago classification system, now widely accepted into clinical practice, has identified subtypes of achalasia that have been shown to predict response to myotomy or dilation. Type III achalasia is the strongest predictor of failure with type II achalasia a predictor of success. A new treatment for achalasia, per-oral endoscopic myotomy (POEM), a natural orifice transluminal endoscopic surgery (NOTES) procedure, is developing acceptance but consensus has not been reached on appropriate indications. We review POEM and discuss its potential place in the treatment of achalasia.

4.4 Manometry

The diagnosis of achalasia is based on the finding of failure of relaxation of the lower oesophageal sphincter, aperistalsis of the oesophageal body, and the exclusion of malignancy or obstruction – so called ‘pseudoachalasia’. Classical symptoms of dysphagia, regurgitation, chest pain, and weight loss are not always present and if present, are often misinterpreted by patients and clinicians as reflux.

Whilst endoscopy and barium swallow are mandatory in the assessment and diagnosis of achalasia, manometry is the diagnostic gold standard. The hallmarks are both incomplete lower oesophageal sphincter (LOS) relaxation after pharyngeal initiation of a swallow and oesophageal aperistalsis. Recently, high resolution solid state catheters using electronic pressure sensors at 1cm spacings have been introduced into clinical practice and are beginning to replace water-perfused systems. Although many water-perfused systems give a similar resolution across the LOS, the solid-state catheters give high resolution over the entire length of the oesophagus. The transducers require zeroing for temperature only, compared to water-perfused systems where the reading can be influenced by the pump and pressure in the catheter tubing, as well as gravity and position of the catheter relative to the transducer. Solid-state catheters and their corresponding software analyse the tracing using metrics described by a high resolution manometry working party (the Chicago classification, described in more detail in the next section), and the terminology differs from that used with traditional water-perfused systems (Table 1). These metrics are clearly defined and calculated automatically by computer software then checked by the reporting clinician. Along with more accurate measurements, this allows for greater standardisation and less inter-observer variability.

4.5 The Chicago Classification

The Chicago classification classifies achalasia patients into 3 subtypes based on the pattern of the oesophageal body dysfunction, which occurs concurrently with the failure of the lower oesophageal sphincter (LOS) to relax. A fourth group, oesophago-gastric junction obstruction, is also described where oesophageal peristalsis is preserved. This group may in some cases represent an evolving achalasia but can also be due to mechanical obstruction, more likely than in the achalasia group subtypes (90, 129).

4.5.1 Type I achalasia

Type I achalasia is characterised by minimal oesophageal body function, peristaltic or otherwise, with only low level oesophageal pressurisations of <30mmHg (9, 14) (Figure 1a). It is thought to represent a later presentation of type II achalasia with more extensive neural loss, leading to minimal oesophageal body function, peristaltic or otherwise. It represents 25-40% of patients. Fitting with the hypothesis of a later presentation, these patients often have dilation of the oesophageal body as shown on barium swallow (Figure 2a).

4.5.2 Type II achalasia

Type II achalasia is the most frequently encountered type of achalasia with 50-65% of patients falling into this category. It is characterised by more substantial pan-oesophageal pressurisations (>30mmHg) indicative of a degree of preserved albeit pathological oesophageal muscle function (Figure 1b). This residual oesophageal muscle function is thought to correlate with less myenteric neuronal loss than in type I achalasia, probably due to an earlier presentation of the disease. The pressurisations that are seen are due to residual longitudinal and circular muscle contractions(11) . These patients often have the typical bird's beak appearance on barium study but generally have not yet progressed to oesophageal dilation (Figure 2b).

4.5.3 Type III achalasia

The group of patients with type III achalasia represent overlap with what was known as vigorous or spastic achalasia. They are a group of patients where the body of the oesophagus exhibits spastic activity in addition to failure of the lower oesophageal sphincter to relax. This spasm is different from the pan oesophageal pressurisation found in types I and II as it is in the distal two thirds of the oesophagus, it is premature (defined by distal latency), and it generally has a higher pressure (90) (Figure 1c). Patients with type III achalasia have preservation of myenteric neurons but impaired inhibitory post-ganglionic neural function (9). The circular muscle still functions but exhibits unco-ordinated rather than absent contractions (9, 11). On barium swallow, the spasm is sometimes shown as a corkscrew appearance similar to that seen in diffuse oesophageal spasm (Figure 2c). In these patients, the lower oesophageal sphincter may also be slightly longer (4-5cm vs. 3-4cm in types I and II (130)) than seen in the other subtypes. Type III achalasia is the least common of the 3 subtypes making up only about 10% of achalasia patients.

4.6 Impact of manometric subtype on treatment outcome

Type II achalasia has the best response to either cardiomyotomy or pneumatic dilatation with a greater than 95% success rate (130, 131). A presentation at an early stage of the disease correlates with residual oesophageal muscle function that aids oesophageal emptying after disruption of the LOS (9).

Type I achalasia patients have an almost complete loss of oesophageal muscle function and greater oesophageal dilation. Success rates with laparoscopic myotomy or pneumatic dilation in this group are slightly lower, in the order of 80-85% (130, 131).

The clinical significance of type III achalasia is that the response to cardiomyotomy or pneumatic dilatation are only around 50% (14, 130, 131). Perhaps the reason that disruption of the LOS in type III patients does not always work is that the treatment addresses only half of the disease, namely the sphincter, and not the oesophageal body. The spasm in a type III patient remains untreated and may be the cause of residual symptoms such as pain, regurgitation, and dysphagia. Another potential reason for a suboptimal response in type III achalasia could be an inadequate myotomy with failure to provide a myotomy of sufficient length to cover the longer sphincter length that may occur. This issue has led to the adoption of the term 'long myotomy' by some gastroenterologists. The term means a slightly longer myotomy across the GOJ (to cover this extra length), rather than a traditional long myotomy (to the level of the azygos vein).

4.7 Where does POEM fit in?

Whilst laparoscopic cardiomyotomy with partial fundoplication remains the gold standard for treatment of achalasia (61, 72), there is debate on whether per-oral endoscopic myotomy has equivalent results in type I and type II achalasia or even superiority in type III achalasia patients who have a poorer response to traditional treatment.

4.7.1 What is POEM?

Per-oral endoscopic myotomy (POEM) involves the creation of an endoscopic submucosal tunnel, followed by division of the circular muscle layer of the distal oesophagus, LOS, and cardia (Figure 3). Advantages of POEM include its relative non-invasive nature (i.e. endoscopic rather than operative procedure), and the longer length of myotomy. Disadvantages include the requirement of advanced endoscopic technical skills, the substantial learning curve in a relatively uncommon disease, and the lack of long-term follow up.

4.7.2 Efficacy of POEM

Short term outcomes for POEM are promising. High volume centres are reporting success rates in the order of 91.3% (n = 423) which persist at three year follow-up 88.5% (n = 61)(55) and smaller western series show similar results (81, 86). It must be noted that these are prospective cohort studies and as yet there has been no randomised controlled trial to compare POEM to conventional therapies (cardiomyotomy or pneumatic dilatation)(55, 56). It would however, seem intuitive that we can predict long-term outcomes by applying first principles. A POEM, like a laparoscopic cardiomyotomy, divides the lower oesophageal sphincter muscles under direct vision rather than tearing them in a less controlled manner as occurs with pneumatic dilatation. This clean division underlies the lower re-intervention rate seen after cardiomyotomy compared to pneumatic dilatation, which usually requires at least two or three repeat

interventions. One would expect a similar long-term outcome in POEM patients with effective relief of dysphagia with five-year success rates at least 76% (61) and perhaps as high as 87% (132).

4.7.3 Is reflux a concern?

POEM, unlike a laparoscopic cardiomyotomy, does not include an anti-reflux procedure. Whether or not this is detrimental is unclear. In laparoscopic cardiomyotomy, reflux occurs postoperatively in 41.5% of patients if a fundoplication is omitted, and is often asymptomatic (64, 65). However, the high rate of pathological reflux has led to the adoption of Heller's cardiomyotomy *with* partial fundoplication as the gold standard (Society of American Gastrointestinal and Endoscopic Surgeons – strong recommendation), and this lowers the reflux rate to 14.5% (64). After pneumatic dilation, rates are in the order of 23-31% (53, 83). Achalasia patients have a long life expectancy and leaving them with potentially decades of pathological reflux is a concern. Not only does opening the gastro-oesophageal junction lead to reflux but also oesophageal clearance of reflux is impaired due to the underlying oesophageal body dysmotility. Over time, uncontrolled reflux leads to peptic strictures resulting in dysphagia, the very problem that led to treatment in the first place. Also of concern is the reflux – metaplasia – dysplasia – adenocarcinoma sequence established in the Barrett's literature (32, 78). Our institution's recent endoscopic review of 68 achalasia patients at least 5 years post-cardiomyotomy, uncovered 7% with unsuspected Barrett's oesophagus (32).

All treatments for achalasia disrupt the anti-reflux mechanisms of the gastro-oesophageal junction (GOJ). Surgical cardiomyotomy, in addition to dividing the lower oesophageal sphincter, also includes division of the phreno-oesophageal ligament, which theoretically impairs crural augmentation, as well as loss of the angle of His. These impairments are compensated for by the addition of a partial fundoplication.

POEM divides the lower oesophageal sphincter muscles, theoretically leaving the other mechanisms intact, but does not provide any compensatory anti-reflux procedure. Given the complex multi-factorial nature of acid reflux, and the unknown importance of these anti-reflux mechanisms relative to each other(76), it is difficult to accurately predict how much reflux will occur after a POEM or in which patients reflux will occur.

Two significant points have emerged from recent publications with regards to reflux after POEM. First, rates of pathological reflux as determined by *objective* pH studies post-POEM are between 31 and 88%, with the largest series (n=73) estimating 53% (54, 81, 84, 85). Second, as with laparoscopic cardiomyotomy, there is no correlation between reflux symptoms and objective measures of reflux, as patients with pathological reflux in this cohort are often asymptomatic (54, 85). Given the high rate of asymptomatic pathological reflux after POEM, patients should be prepared to undergo objective testing post-POEM, or alternatively, begin empiric treatment with anti-secretory medication.

4.7.4 POEM in type III achalasia

The above arguments relate mostly to type I or type II achalasia. In type III achalasia, POEM has a clearer potential advantage. In type III achalasia, a degree of chest pain, regurgitation, and dysphagia experienced may be due in greater part to oesophageal

body spasm, distinct from type I and II achalasia where symptoms are due primarily to GOJ obstruction. The myotomy in POEM can be extended more proximally on the oesophageal side than with a laparoscopic cardiomyotomy, potentially treating oesophageal spasm as well as dividing the lower oesophageal sphincter. The myotomy also be adjusted to the degree and length of the spasm as demonstrated by high resolution manometry.

The concept of treatment type III achalasia with POEM has been supported by a multi-centre retrospective review demonstrating a 96.3% (n = 46) success in type III achalasia (133). As type III achalasia patients respond poorly to traditional treatments (50% success compared to 80-90% with types I and II), there is certainly an argument developing for considering POEM as primary therapy for type III achalasia. Given the low incidence of type III achalasia (10% of all achalasia) it is unlikely that we will ever get a randomised control trial to confirm this. Data suggesting response rates above 90% to POEM in diffuse oesophageal spasm, a condition similar to type III achalasia but without the raised lower oesophageal sphincter pressures, also supports POEM as the preferred treatment for type III achalasia (133).

4.8 Conclusion

Advances in manometry technology and a new classification system are driving our understanding of achalasia. Although the treatment of achalasia with a laparoscopic cardiomyotomy is the gold standard for relief of dysphagia, it is important to recognise that type III achalasia may not response as well to standard treatment. POEM is an emerging technology that shows promise, especially for treatment of type III achalasia. Rates of asymptomatic reflux are high post-POEM, so patients undergoing POEM need to be counselled and be willing to take long-term anti-secretory medication if necessary.

4.9 Figures

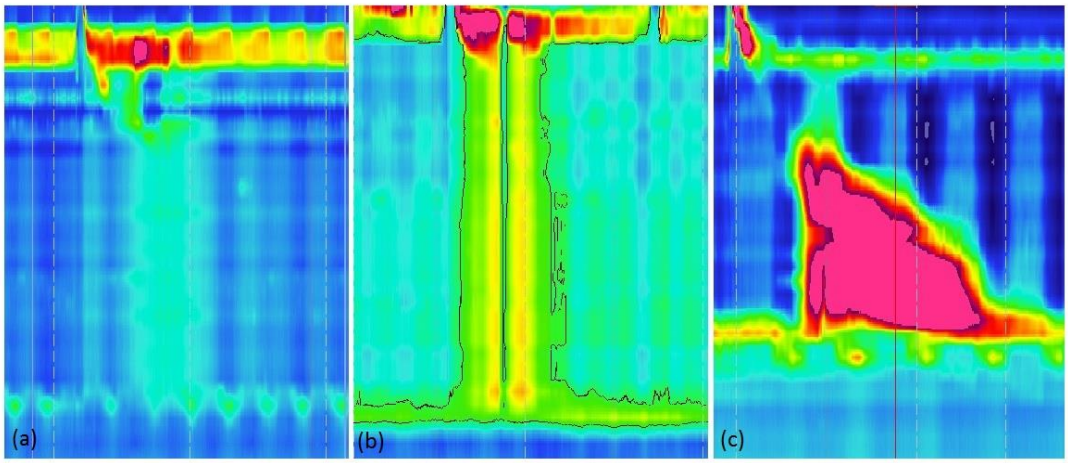

Figure 4-1 High resolution manometry demonstrating achalasia subtypes. Type I (a) characterised by minimal oesophageal pressurisations, type II (b) with pan-oesophageal pressurisation wave (black line demarcates 30mmHg contour) and type III (c) with premature spastic contractions.

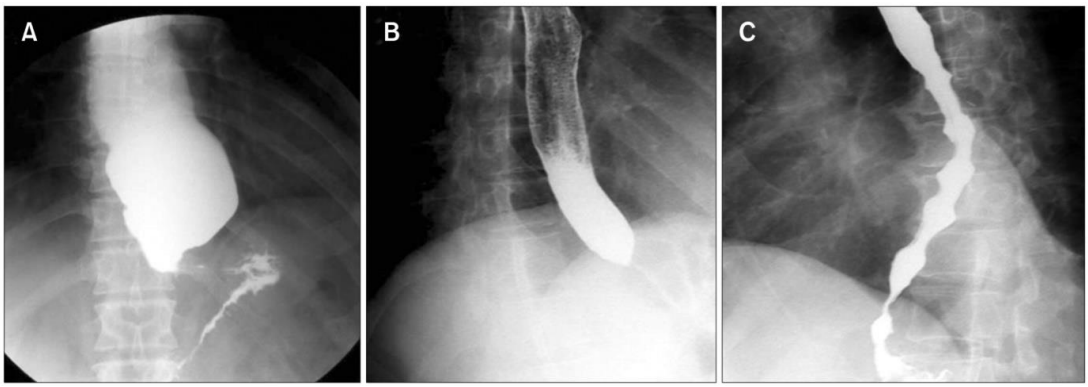

Figure 4-2 Barium oesophagograms demonstrating type I achalasia (A) with dilated oesophagus and bird's beak appearance at LOS, type II achalasia (B) with non-dilated oesophagus but narrowing at LOS, type III achalasia (C) with corkscrew appearance from spasm in the oesophageal body. (Reproduced with permission of Journal of Neurogastroenterology and Motility(34))

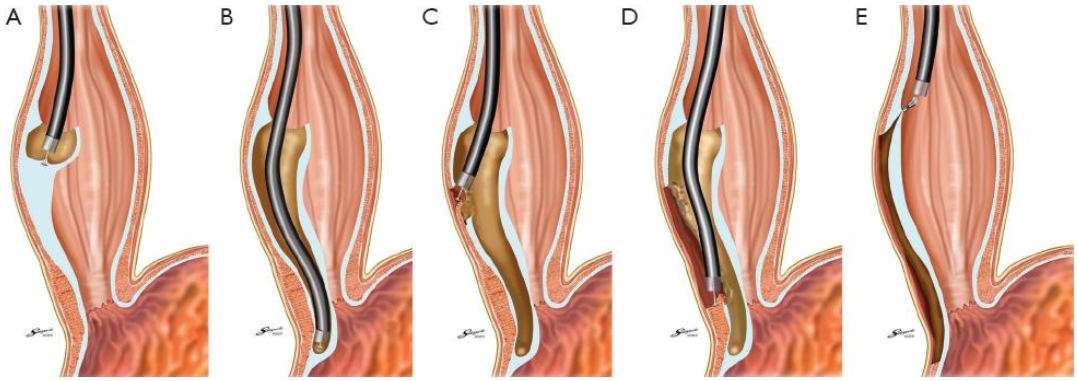

Figure 4-3 Schematic representation of a POEM procedure, showing the oesophageal mucosa is breached about half way down the oesophagus and the dissection continued in the submucosal plane until the cardia is reached. At that stage the myotomy can be performed to the length determined by the surgeon-endoscopist. (Reproduced with permission of Georg Thieme Verlag KG(134))

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Chapter 5 Evaluation of outcome after cardiomyotomy for achalasia using the Chicago classification

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5.1 Statement of Authorship

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5.2 Abstract

5.2.1 Background

Achalasia can be subdivided into manometric subtypes according to the Chicago classification. These subtypes are proposed to predict outcome after treatment. This hypothesis was tested using a database of patients who underwent laparoscopic Heller's cardiomyotomy with anterior fundoplication.

5.2.2 Methods

All patients who underwent Heller's cardiomyotomy for achalasia between June 1993 and March 2015 were identified from an institutional database. Manometry tracings were retrieved and re-reported according the Chicago classification. Outcome was assessed by a postal questionnaire, and designated a success if the modified Eckardt score was 3 or less, and the patient had not undergone subsequent surgery or pneumatic dilatation. Difference in outcome after cardiomyotomy was analysed with a mixed-effects logistic regression model.

5.2.3 Results

Sixty, 111 and 24 patients had type I, II and II achalasia respectively. Patients with type III achalasia were more likely to be older than those with type I or II (mean age 63 *versus* 50 and 49 years respectively; $P = 0.001$). Some 176 of 195 patients returned questionnaires after surgery. Type III achalasia was less likely to have a successful outcome than type II (odds ratio (OR) 0.38, 95 per cent c.i. 0.15 to 0.94; $P = 0.035$). There was no significant difference in outcome between types I and II achalasia (II *versus* I: OR 0.87, 0.47 to 1.60; P 0.663). The success rate at 3-year follow-up was 69 per cent (22 of 32) for type I, 66 per cent (33 of 50) for type II and 31 per cent (4 of 13) for type III.

5.2.4 Conclusion

Type III achalasia is a predictor of poor outcome after cardiomyotomy. There was no difference in outcome between types I and II achalasia.

5.3 Introduction

Achalasia is a rare but debilitating condition characterized by dysfunction of both the lower oesophageal sphincter (LOS) and muscle of the oesophageal body. This leads to progressive dysphagia, regurgitation, chest pain and weight loss[1]. Treatment is palliative, directed at disrupting the LOS to enable passage of food and aid oesophageal emptying. There is no effective treatment for the oesophageal body dysfunction, although on occasion a degree of peristalsis can return after a successful cardiomyotomy or pneumatic dilatation[2].

In 1993, Clouse and Staiano[3] first described the presentation of oesophageal peristalsis as a topographical plot to supplement conventional line tracings. This, in combination with the introduction of solid-state technology into manometry catheters, has led to what is commonly referred to as high-resolution manometry (HRM) gradually replacing water-perfused systems in clinical practice. A HRM working party has produced the Chicago classification of motility disorders, which describes three subtypes of achalasia based on oesophageal body dysfunction[4,5]. These subtypes are hypothesized to correlate with distinct pathophysiological groups as well as influence treatment outcomes[6].

Type I achalasia is proposed to correspond to a later presentation of achalasia, with an atonic oesophagus, increased oesophageal diameter and a lesser response to treatment owing to reliance on gravity alone to empty the oesophagus. It is characterized manometrically by a lack of oesophageal pressurization. Type II achalasia is represented by pan-oesophageal pressurizations greater than 30 mmHg, presumably from residual muscle activity at an earlier stage of the disease[6,7]. This residual oesophageal activity may result in better oesophageal emptying after treatment relative to that in a patient with type I achalasia. Type III achalasia is rarer but distinctive, with oesophageal spasm being the defining feature[6]. As spasm may be a significant contributor to symptoms, and is not directly treated with a cardiomyotomy, type III achalasia may be a negative predictor of outcome[8].

The standard treatment for achalasia includes laparoscopic Heller's cardiomyotomy with fundoplication[9,10] or pneumatic dilatation[11,12]. Peroral endoscopic myotomy (POEM) is an emerging treatment that is gaining acceptance[13,14]. These three treatments aim to relieve the obstruction at the gastro-oesophageal junction, with the exception that in POEM the option exists to extend a myotomy proximally, in order to treat spasm.

The subtypes of achalasia described by the Chicago classification can be identified not only by HRM but also in conventional manometric recordings[15,16]. Published data suggest that the outcomes of achalasia treated by laparoscopic Heller's cardiomyotomy are predicted by Chicago classification subtypes[15]. The aim of the present study was to test this by analysis of a surgical database maintained for patients who underwent cardiomyotomy, with review and re-reporting of original manometry tracings.

5.4 Methods

The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee (HREC/15/RAH/13).

5.4.1 Patient selection

Patients were identified from a database of laparoscopic Heller's cardiomyotomy maintained at the Department of Surgery, Adelaide University and Flinders Medical Centre, South Australia. In South Australia, oesophageal manometry is performed routinely in adults at three centres and the database was cross-checked against patient records at all three centres. Patients were included for this study if both the manometric recording and report were available for review, and the recording was dated before myotomy or pneumatic dilatation. If a patient had multiple manometry recordings available, the tracing closest to the date of surgery was used. Exclusion criteria were: diagnosis of oesophagogastric obstruction or other non-achalasia condition, previous oesophageal surgery, or a manometric recording with insufficient data to subtype (for example, if only 3 of 10 swallows were performed owing to patient discomfort).

5.4.2 Manometry

For HRM studies, acquisition was performed with a ManoScan 36 channel catheter and analysed with Manoview program (Sierra Scientific/Covidien, a Medtronic company, Los Angeles, CA, USA)). Various water-perfused systems were used across the study interval. Water-perfused systems all had pressure sensors at 3-cm intervals in the oesophageal body and used either a sleeve sensor or sensors at 1-cm increments across the LOS. Protocols among the laboratories varied, but included recording of ten water swallows as a minimum. Three computer systems were used across the study interval, all allowing display of line plots and on-screen measurements (Trace Version v1.2, Hebbard, Melbourne, Australia©; Solar GI ® Quickview Analysis Program (Medical Measurement Systems, Michigan, USA) ; *POLYGRAM* NET™ Functional Diagnostics, Skovlunde Denmark). One laboratory also had hard copy tracings available for analysis (Acquidata Gastromac, Neomedix Systems, Belrose, NSW, Australia).

Reports were reviewed for all patients. Patients who had achalasia diagnosed, but did not have a Chicago subtype reported, also had their manometry tracing reviewed by the primary author under the supervision of a senior gastroenterologist whose regular clinical practice involves weekly reporting of manometry. The first 40 tracings were reviewed concurrently with a gastroenterologist and thereafter by the primary author alone, unless the tracing was not straightforward in which case it was also reviewed by a second reviewer.

The Chicago classification (version 3.0) was used to subtype HRM studies[4]. Achalasia that was diagnosed using water-perfused systems was classified as types I-III based on criteria described and validated by Salvador and colleagues[15,16]. Ten water swallows were assessed for each patient. Line tracings at 8 and 13 cm above the LOS were assessed, and each swallow was classified as having either no pressurizations, or pressurizations below 30 mmHg, a pan-oesophageal pressurization exceeding 30 mmHg, or a spasm defined as pressures over 70 mmHg for at least 6 s[15,16]. Studies were classified as indicating type I achalasia if none or one of ten swallows had a pressurization exceeding 30 mmHg, type II if two or more of ten swallows had pan-oesophageal pressurizations greater than 30 mmHg, and type III achalasia if two or more swallows were associated with a spasm. If peristalsis was present in the swallows, patients were excluded as this represented oesophagogastric outlet obstruction. These patients also had a distal latency estimated to ensure that they did not have type III achalasia. No patients with peristalsis had an estimated distal latency below 4.5 s. LOS relaxation was not reassessed.

5.4.3 Surgery

Primary surgery for achalasia was standardized for all upper gastrointestinal surgeons who contribute to the database. The approach was laparoscopic and involved mobilization of the phreno-oesophageal ligament, the anterior oesophagus and fat pad. The anterior vagus was preserved and an anterior myotomy was performed by dividing the muscle layers of the oesophagus with hook diathermy. A 6-cm myotomy was created on the oesophageal side, and a minimum 2-cm myotomy was created on the gastric side. Measurement of the myotomy was by surgeon estimate using the length of instrument jaws. The adequacy of myotomy was checked endoscopically (to ensure the junction was open when the endoscope was positioned in the distal oesophagus) and then an anterior 180° fundoplication was performed. The technique used for the first seven patients in this series was a Dor patch with an anterior wrap secured to both sides of the myotomy, but not to the hiatal ring. This technique then changed to a standard anterior 180° fundoplication in 1994–1996. A routine contrast study was undertaken on the day after surgery before starting oral intake. All operations were performed by one of ten upper gastrointestinal surgeons, or a fellow under their direct supervision.

5.4.4 Follow-up

Demographic information, preoperative investigations including endoscopy and manometry, previous surgery and operative details were all recorded on a standard pro forma by the surgeon. Routine clinical follow-up involved a clinic visit at 4–6 weeks, followed by a final visit at 3–4 months to ensure that the patient was tolerating a normal diet. Symptoms, both preoperative and postoperative, were assessed by questionnaire with follow-up intervals at 3 and 12 months, then annually until the patient had died or declined further follow up. A modified Eckardt score was calculated at each follow-up visit (*Table 1*). The main outcome measure was success, defined as a modified Eckardt score of 3 or less, and no subsequent surgery or pneumatic dilatation. Conversely, if the patient had a modified Eckardt score greater than 3 or had required a subsequent operation or pneumatic dilatation, follow-up at that time point was designated a failure. Other information collected included: Dakkak swallowing score[17], Visick score[18], patient-reported outcome, patient satisfaction on a visual analogue scale, and whether or not the patient would undergo surgery again. The patient-reported outcome measure was obtained by asking patients whether they considered the outcome of their cardiomyotomy to be excellent with no residual symptoms, to have led to a major improvement with minor residual symptoms only, major improvement but still with some significant symptoms, or poor with no improvement or worse than before the procedure. Reflux symptoms and use of antireflux medication were recorded, and a composite reflux score was calculated based on patient-reported frequency of heartburn and acid reflux. It was considered positive if the patient had heartburn or acid reflux a few times a week or was taking a proton pump inhibitor.

5.4.5 Statistical analysis

Differences in sex distribution among subtypes were analysed with Pearson's χ^2 test. Differences in age and in duration of symptoms before surgery were assessed by one-way ANOVA. The success of myotomy was analysed using a mixed-effects logistic regression. Data were adjusted for age as it was the only significant variable among subgroups, and type II was selected as the main comparison group because it was the largest group, but also because differences between type II *versus* type I and type II *versus* type III were judged to be the most clinically relevant. Integration with mean-variance adaptive Gauss–Hermite quadrature was used to demonstrate the validity of

this method, with differences among groups being maintained over time. The difference across all groups was significant ($P = 0.009$), thereby allowing analysis among groups. This analysis was repeated to assess for differences between types I and III. Patient-reported outcome was also analysed using this method by comparing patients who reported excellent and complete recovery or a good outcome (major improvement and only minor problems) to those who reported either fair outcomes (major improvement but still with significant problems) or poor outcome (minor improvement or symptoms the same as, or worse than before surgery). Logistic regression at each time point was used to assess outcome measures. The measures assessed were: would the patient repeat surgery again, use of proton pump inhibitor and reflux composite score. Visick scores were assessed with an ordered logistic regression. Satisfaction scores on a visual analogue scale and Dakkak scores were analysed by means of quantile regression. A graphical representation of success of the procedure was also created using a logistic generalized estimating equation.

5.5 Results

Since 1993, a total of 338 patients were enrolled in the database. A proportion of these had manometry reports but no tracings to review owing to routine disposal of hard copy tracings at two of the three laboratories, or corruption of digital files in the mid-2000s. After exclusions, 195 patients could be subtyped (*Fig. 1*). The types of manometric catheter and recording are summarized in *Fig. 1* (supporting information).

Cardiomyotomy was completed laparoscopically in 97.9 per cent of patients, with a mean (s.d.) myotomy length of 6.2 (1.2) cm and a median (range) operating time of 80 (30–240) min. Fourteen patients (7.2 per cent) had undergone pneumatic dilatation before myotomy (but had manometry before dilatation). The operative mortality rate was zero. Operative complications and further interventions are summarized in *Table 1* (supporting information).

5.5.1 Achalasia subtypes

Achalasia subtyping was possible in 195 patients; patient characteristics and outcome are summarized in *Table 2*. There was no difference among the groups with regards to sex or time of onset of symptoms before surgery, but patients with type III achalasia were older (mean age 63 years *versus* 50 and 49 years for types I and II respectively; $P = 0.001$).

5.5.2 Outcomes

In total 176 patients returned 846 questionnaires between 3 months and 22 years after surgery, with a mean follow-up of 4 years. Nineteen patients declined to fill out postoperative questionnaires. One patient developed oesophageal squamous cell carcinoma 8 years after surgery and was removed from analysis at this point.

Success across all time points differed significantly among subtypes on mixed-effects logistic regression (*Table 3*). Patients with type III achalasia had a poorer outcome than those with type II. However, outcomes for patients with type II were similar to those in patients with type I achalasia. There was a trend towards worse outcome for type III compared with type I, but this was not statistically significant. A graph created using a logistic generalized estimating equation returned the same results as the mixed-effects logistic regression, but allowed better visual representation (*Fig. 2*).

The patient-reported outcome measure was also analysed with a mixed-effects logistic regression across all time points (*Table 3*). It showed a significant difference between

types II and III achalasia. This was the only measure to also show a statistical difference between types II and I.

Dakkak swallowing scores were similar among the subgroups at all time points (*Fig. 3*). Patient satisfaction showed no difference among subtypes in the first 5 years, but at 5- and 10-year follow-up, patients with type III achalasia were significantly less satisfied than those with type II ($p = 0.009$; $p = 0.000$). As regards whether the patients would undergo surgery again if faced with the same choice, differences among subtypes across the whole follow-up period could not be analysed because the responses were skewed (over 90 per cent of patients answered yes). However, patients with type III achalasia were less likely to answer yes at some time points (2 and 5 years), but no difference among groups was found at the other time points (*Table 3*). The median Visick category across all groups was 2 (mild symptoms, easily controlled); no significant differences were found among groups at any time point, although this was expected given the power of the hypothesis tests. There were no significant differences among subtypes in percentage of patients on proton pump inhibitors, with overall rates of 12.6, 15.3 and 34.8 per cent at 3-, 5- and 10-year follow-up respectively. Composite reflux scores were also not significantly different among subgroups, with overall rates of 35.8, 43.5 and 54.4 per cent at 3, 5 and 10 years.

5.6 Discussion

In this study, patients with type III achalasia did worse than those with types I and II after laparoscopic cardiomyotomy. Using a mixed-effects logistic regression model, it was possible to use all of the follow-up data, despite variance in length of follow-up between patients. This model also compensated for missed data points, which occurred over the study period.

The observation that type III achalasia is predictor of poor prognosis is likely to be of clinical significance and is supported by some other outcome measures. This difference is consistent with the findings of the other large cohorts reporting on the difference in treatment outcome between achalasia subtypes[15,16]. Of interest, dysphagia scores did not differ between subtypes, suggesting that the worse outcome observed in patients with type III achalasia was due to persistent chest pain and/or regurgitation. Patients with type III achalasia were significantly older than the other patients, in accordance with previous reports[19] and compatible with the hypothesis of a different underlying pathophysiological process[6]. This also raises the question of whether laparoscopic Heller's cardiomyotomy and anterior fundoplication should still be the standard treatment for type III achalasia. The argument to treat type III achalasia primarily with a longer myotomy, either laparoscopically or with POEM, is worth considering given the present results and recent, albeit early, outcomes after POEM for type III achalasia[20,21]. However, emerging evidence supports an antireflux component to any long myotomy, as POEM has a pathological reflux rate in the order of 53 per cent[22,23].

With the exception of patient-reported outcomes, there was no significant difference in comparisons of type II with type I achalasia, although the overall trend was in favour of a better outcome after treatment of type II than type I. This is consistent with findings in other large series. Although it seems possible that type I achalasia responds less well than type II, the difference is small and probably not clinically relevant. Patients with types I and II achalasia both do very well with laparoscopic Heller's myotomy and anterior fundoplication, with a sustained improvement across all parameters assessed, including proportion with a good result at over 15-year follow-up.

An objective definition of successful treatment of achalasia is difficult, with published series defining success differently[14–16]. The questionnaires used in the present study assess the same parameters as a standard Eckardt score, but use a different frequency for symptoms. Defining success by this method will underestimate success compared with a standard Eckardt score at a similar level, and certainly seemed to underestimate success compared with other parameters assessed in this study. Nonetheless, it is important to assess differences between subtypes using this modification of the Eckardt score, rather than any other parameters, as this score includes not only dysphagia and regurgitation but also chest pain. This is important as type III achalasia (with spasm) may have pain as the more prominent feature.

Classifying water-perfused manometry into Chicago subtypes has been validated by previous authors[15], although there are technical limitations that need to be considered. The differentiation between type I and II achalasia is based on determining a pan-oesophageal pressurization reaching 30 mmHg, which is readily seen in both water-perfused and solid-state manometry. The measurement in a solid-state catheter is relative to atmospheric pressure, but in a water-perfused system it is calculated against oesophageal baseline pressure at end expiration. As this pressure is equivalent to an intrapleural pressure of only –2 to 3 mmHg, this is a close approximation, but does rely on accurate identification of oesophageal pressurization. This can be problematic in a patient with achalasia, where in some instances the oesophagus pressurizes over the duration of the study. Nonetheless, in all but one tracing, which only had three swallows available for analysis and was subsequently excluded, tracings fell easily into either a type I or type II category. Type III achalasia depended on identifying premature or spastic contractions, for which the Chicago criteria are less readily applied to line tracings. The criteria for spasm, validated by Salvador and colleagues[15] for the same purpose of reclassifying line tracings according to the Chicago classification, were used. Changes to the Chicago classification with regard to type III achalasia have occurred since then, with the definition of a spastic contraction now depending on measurement of distal latency rather than the strength and duration of contraction. This raised the possibility that some patients with a weaker but still premature contraction were not diagnosed with type III achalasia but with gastro-oesophageal obstruction. To ensure this was not the case, estimated distal latencies for patients with peristalsis, who were considered to have gastro-oesophageal obstruction, were calculated and confirmed that none had type III achalasia.

The present study has strengths and weaknesses. Classification of achalasia subtypes using conventional tracings is subject to error, and it is possible that the wrong subtype was assigned in a few patients. Nonetheless, this study involved supervision by two experienced gastroenterologists with a vast amount of experience and expertise in oesophageal motility. Furthermore, all three laboratories have had longstanding continuity with technical staff, providing consistency with manometric studies performed over the past three decades. Second, although the pro forma completed by participating surgeons at the time of surgery included a question regarding preoperative barium swallow, and presence of dilatation and/or sigmoid oesophagus, some patients with a sigmoid oesophagus may have been missed in the type I group. This would have increased this group's Eckhardt score, thereby decreasing the success of surgery.

5.7 Acknowledgements

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Disclosure: The authors declare no conflict of interest.

5.8 Figures and tables

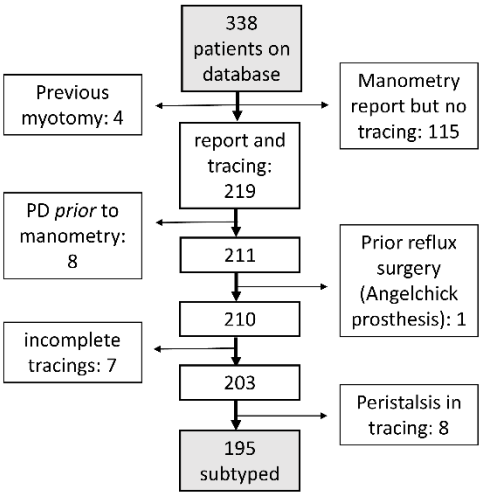

Figure 5-1 Patient flow chart. PD, pneumatic dilatation

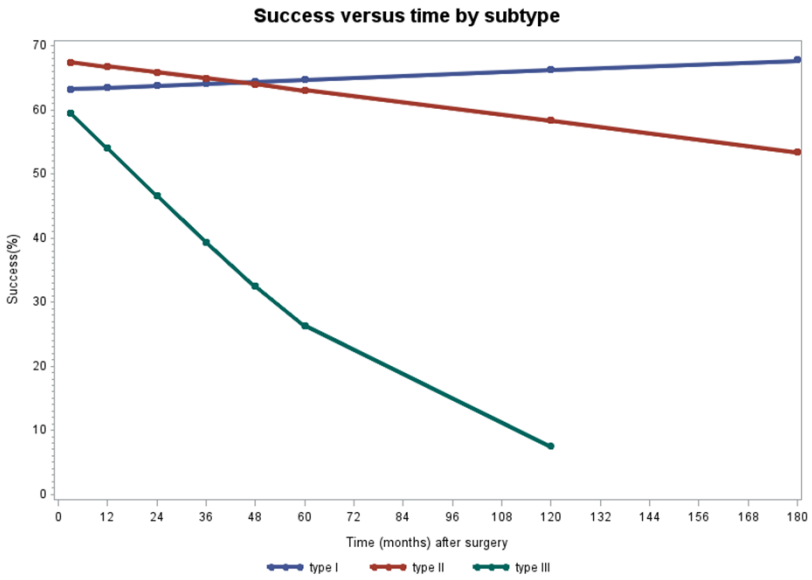

Figure 5-2 Success over time by subtype of achalasia. The graph was created using a logistic generalized estimating equation. Type III was a predictor of poor outcome compared with the other types, but there was no difference between types I and II

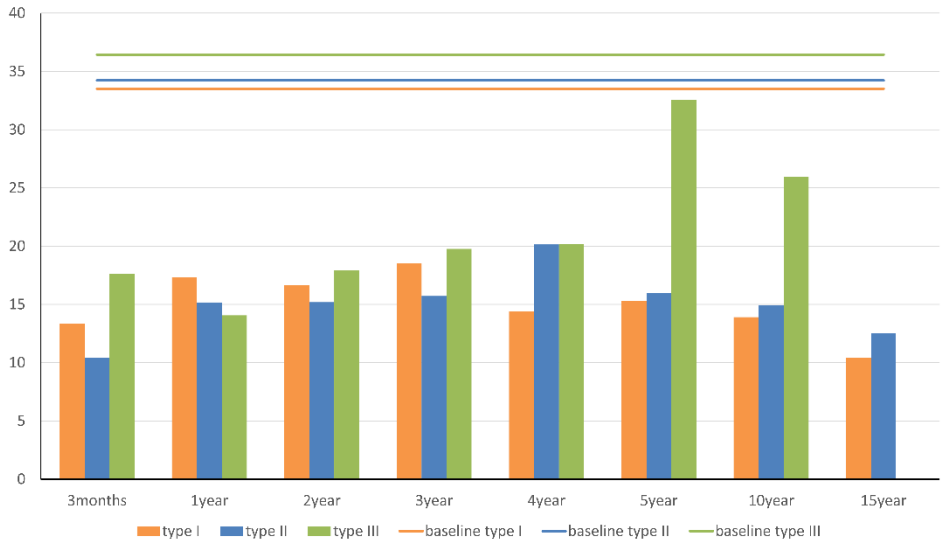

Figure 5-3 Dakkak composite swallowing scores in relation to subtypes of achalasia. A score of 45 represents complete dysphagia and 0 indicates no impairment

Table 1 Modified Eckardt score

	Never	Once per month	Few times per week	Daily
Dysphagia	0	1	2	3
Chest pain	0	1	2	3
Regurgitation	0	1	2	3

Table 5.1 Success defined by a total score of 3 or less.

	Type I (n = 60)	Type II (n = 111)	Type III (n = 24)
Age (years)*	50(18)	49(19)	63(13)
Sex ratio (M : F)	28 : 32	54 : 57	14 : 10
Duration of symptoms (months, mean)	36	26	31
Success†			
3 months	30 of 45 (67)	73 of 88 (83)	13 of 19 (68)
1 year	21 of 39 (54)	37 of 65 (57)	10 of 18 (56)
3 years	22 of 32 (69)	33 of 50 (66)	4 of 13 (31)
5 years	21 of 34 (62)	21 of 40 (53)	1 of 8 (13)
10 years	15 of 20 (75)	16 of 25 (64)	1 of 2 (50)
15 years	4 of 7 (57)	6 of 8 (75)	–
Patient-reported outcome‡			
3 months	36 of 45 (80)	74 of 82 (90)	10 of 16 (63)
1 year	27 of 39 (69)	55 of 66 (83)	11 of 18 (61)
3 years	21 of 32 (66)	42 of 51 (82)	8 of 13 (62)
5 years	26 of 34 (76)	29 of 41 (71)	4 of 9 (44)
10 years	14 of 20 (70)	21 of 25 (84)	1 of 2 (50)
15 years	7 of 7 (100)	8 of 8 (100)	–
Would repeat surgery again			
3 months	44 of 47 (94)	82 of 83 (99)	14 of 16 (88)
1 year	37 of 40 (93)	61 of 64 (95)	14 of 16 (88)
3 years	30 of 32 (94)	48 of 48 (100)	11 of 12 (92)
5 years	32 of 34 (94)	38 of 40 (95)	6 of 9 (67)
10 years	20 of 20 (100)	24 of 25 (96)	1 of 2 (50)
15 years	7 of 7 (100)	8 of 8 (100)	–
Median satisfaction score§			
3 months	9 (n = 50)	9 (n = 91)	9 (n = 20)
1 year	8 (n = 40)	9 (n = 67)	8.5 (n = 18)
3 years	9.5 (n = 32)	9 (n = 52)	8 (n = 13)
5 years	8 (n = 34)	8 (n = 43)	5 (n = 9)
10 years	9.5 (n = 20)	9 (n = 26)	4 (n = 2)
15 years	9 (n = 7)	9 (n = 8)	–

Table 5.2 Demographic data and outcomes by subtype of achalasia

*Values in parentheses are percentages unless indicated otherwise; *values are mean (s.d.). †Defined as modified Eckardt score 3 or less and no endoscopic or surgical reintervention. ‡Excellent or major improvement with minor problems only. §Measured on a visual analogue scale ranging from 1 to 10.*

	Odds ratio	*P*
Success*		0.009
Type II *versus* III	0.38 (0.15, 0.94)	0.035
Type II *versus* I	0.87 (0.47, 1.60)	0.663
Type III *versus* I	2.29 (0.88, 5.92)	0.089
Patient-reported outcome†		0.023
Type II *versus* I	0.28 (0.08, 0.96)	0.043
Type II *versus* III	0.06 (0.01, 0.40)	0.003
Would repeat surgery again (type II *versus* III)		
1 year	0.34 (0.05, 2.26)	0.267
2 years	0.10 (0.01, 0.59)	0.012
4 years	0.01 (0.01, 1.54)	0.104
5 years	0.11 (0.01, 0.77)	0.026
10 years	0.01 (0.01, 1.54)	0.068

Table 5.3 Likelihood of success, patient-reported outcome measure and the patient opting for repeat surgery.

*Values in parentheses are 95 per cent confidence intervals. *Defined as modified Eckardt score 3 or less and no endoscopic or surgical reintervention. †Excellent or major improvement with minor problems only. Likelihood of success and patient-reported outcome measure were analysed by mixed-effects logistic regression using all follow-up time points. Would repeat surgery again was analysed with logistic regression at individual time points.*

5.9 Supplementary figures and tables

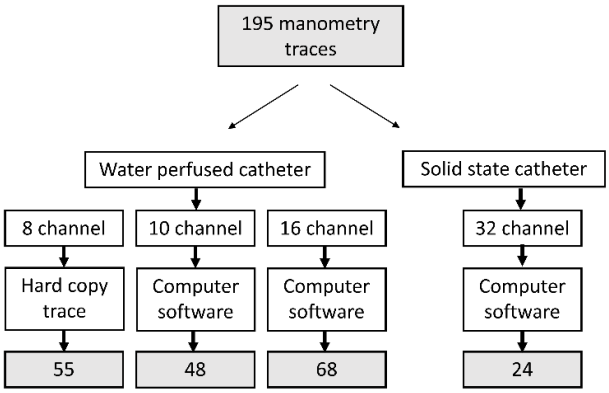

Figure 5-4 (supplementary figure 1) Types of manometry assemblies and recordings. All computer software allowed analysis of both line plots and colour topographic plots

	No. of patients (n = 195)
Operative complications	
Operative mortality	0
Mucosal perforation identified during surgery	16
Conversion to open surgery (all for repair of oesophageal perforations)	4
Return to theatre, suture of oesophageal perforation	2
Return to theatre, fundoplication revision <1week after surgery	2
Return to theatre, diagnostic laparoscopy (for ?leak)	1
Oesophageal perforation, managed conservatively	3
Postoperative bleed, managed conservatively	1
Long-term reinterventions	
Redo cardiomyotomy	4
Pneumatic dilatation	13
Cardioplasty*	2
Long myotomy	1
Oesophagectomy	2
Oesophageal diverticulectomy	1

Table 5.4 (Supplementary table 1) Operative complications and long-term reinterventions

**Laparoscopic stapled cardioplasty is a novel procedure that widens the gastro-oesophageal junction in end-stage achalasia by firing a linear stapler between the fundus and oesophageal sump (69)*

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Chapter 6 Pneumatic dilation for achalasia, does Chicago subtype make a difference?

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6.1 Statement of Authorship

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Peter Hamer
Contribution to the Paper	Study design and approvals Manometry reporting Data collection and analysis Drafting of paper
Overall percentage (%)	65%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 30/6/2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	8/8/16

6.2 Abstract

6.2.1 Goals and Background

Pneumatic dilatation is an accepted treatment for achalasia. Chicago classification subtypes can predict treatment outcome. In our institution surgical cardiomyotomy is the preferred first-line treatment, with some patients electing for pneumatic dilatation. We determine if the Chicago classification subtypes predict success in this population.

6.2.2 Study

Patients were identified by retrospective review of endoscopy suite records. Subtype was recorded, or determined from review of original manometry trace. Outcome was assessed by case-note review and postal questionnaire. Logistic regression assessed difference in outcome among subtypes. Difference in outcome for pneumatic dilatation and patients undergoing surgical cardiomyotomy was assessed with multivariate logistic GEE model.

6.2.3 Results

42 patients had pneumatic dilatation for achalasia (type I: 6 patients; type II:19, type III: 5, untyped: 12). Success, (major improvement in symptoms without subsequent cardiomyotomy or dilatation) was determined in 35 patients (type I: 4, type II : 16, type III :4 , untyped : 11). Success was 74% at short term follow up. Chicago subtype was not predictive of outcome. Questionnaire response showed improvement in the majority of parameters assessed. Comparison with cardiomyotomy patients showed odds of follow-up success of cardiomyotomy 6.8 times that of PD (OR=6.8, 95% CI: 3.1, 14.9).

6.2.4 Conclusions

Chicago subtype classification does not predict outcome in a series of this size. Although overall results were good, patients did not do as well as cardiomyotomy patients, perhaps due to an institutional preference for cardiomyotomy resulting in a self-selected cohort of patients more likely to elect to live with residual symptoms than seek repeat dilatation.

6.3 Introduction

Achalasia is a relatively rare condition with an incidence of approximately 2.5/100000 (135). Treatments are directed at relieving the obstruction at the lower oesophageal sphincter, although the pathological process also includes oesophageal body dysfunction. Pneumatic dilation is an endoscopic treatment whereby a balloon is inflated across the gastro-oesophageal junction to stretch the fibres of the sphincter (136, 137). Results in the short to medium term are excellent (53, 138) although long term results may not be as durable as a surgical myotomy (61). Established predictors of a poor outcome and need for repeated interventions include younger patients less than forty years of age, particularly if male (48, 53). More recently, subtypes I to III of achalasia have been described that are based on patterns of oesophageal body activity identified using high resolution manometry. It is hypothesised that type III achalasia and to a lesser extent type I achalasia are also predictors of poor outcome due the oesophageal spasm and lack of residual oesophageal muscle activity that characterises each respectively. (14, 90) This spasm and neural denervation is not addressed by pneumatic dilation and may contribute to ongoing symptoms. This hypothesis has been

supported by re- analysis of the European achalasia trial database (131) and other smaller series (139) as well as analysis of patients treated by cardiomyotomy (130).

In our institution Heller cardiomyotomy with anterior fundoplication is the preferred primary treatment for achalasia because of the more durable relief it provides. Nonetheless a significant proportion of patients elect to be treated primarily with balloon dilatation, usually due to the desire to avoid a surgical procedure and its perceived higher risks. We reviewed retrospectively the outcomes of this cohort treated with primary pneumatic dilation for achalasia, including analysis of outcome by Chicago subtype and compared their outcome to those who underwent primary cardiomyotomy.

6.4 Methods

The study was approved by the Royal Adelaide Hospital Human Research Ethics committee study number: HREC/15/RAH/13.

Patients were identified by a search of the endoscopy suite database used for reporting of all procedures between 2000 and 2013 (Endoscribe Mediboss PTY LTD Bedford Park, South Australia) and between 2013 and 2015 (Provation ® MD Gastroenterology, Minneapolis, Minnesota, United States of America). Search of the endoscopy suite booking system was also performed in order to ensure no cases were missed. Endoscopy reports were reviewed to confirm that a pneumatic dilation was performed for achalasia.

Case notes and endoscopy reports were reviewed and data collected in an excel spreadsheet including patient age, gender, information on the pneumatic dilation including number of dilations, size of balloon, length of inflation and any complications. Follow up information was recorded including time of follow up interval, requirement for further interventions, complications and outcomes. Due to the retrospective nature of the project insufficient information was available to calculate Eckardt scores so patient outcome was grouped into excellent outcome with no problems, good outcome with major improvement and minor residual problems easily treated, fair outcome with major improvement but still some significant difficulties or poor outcome with minimal improvement or symptoms worse than before. Short term follow-up was defined as follow-up within 1 year of dilatation and late or last known follow-up any time after this.

Patients who had progressed to laparoscopic Heller cardiomyotomy had additional information retrieved from the prospective database maintained by the Department of Surgery including information from questionnaires sent annually to all post-operative patients. Patients who had not come to surgery were contacted and asked to complete a questionnaire assessing their outcomes including dysphagia, chest pain, regurgitation, Dakkak (98), visual analogue dysphagia scores, Visick category(100) satisfaction with procedure and overall outcome.

Manometry reports were reviewed for all patients with subtype according to the Chicago classification recorded. Where classification had not been reported due to the study having been performed prior to widespread adoption of the Chicago classification the original tracing was reviewed and re-reported. As these studies were performed

using water-perfused manometry rather than solid state technology, criteria as described and validated by Salvador et al were used to reclassify tracings (130).

In our institution pneumatic dilation is repeated with increasing size of balloon up to three times, if an adequate clinical response has not been obtained. For analysis of outcome any repeat dilation performed within 12 months was considered part of a series of dilations and any dilation performed after this a separate intervention. Success was defined as patients with major improvement in symptoms as identified by case-note review or questionnaire response. Failure was defined as poor outcome with minor or no improvement or a requirement for further intervention. The only exceptions to this were three patients who elected for a surgical myotomy after a single pneumatic dilation with a 30mm balloon. These were not considered as a failure and were removed from the analysis

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Logistic regression was used to examine any association between subtype and short or long term outcome. Bivariate logistic regressions were used to examine for any association between outcome and covariates. Comparison to a cohort of cardiomyotomy patients from the surgical database was performed using a linear regression to assess differences in age between the two groups. Logistic GEE model was used to look for differences in outcome according to gender, age and subtype. Multivariate logistic GEE model was then used to assess for outcome according to intervention type controlling for subtype as it was found to be significant.

Analysis of the questionnaire data was performed using SPSS Statistics version23 (Armonk, NY: IBM Corp). Pre- and post dilatation symptom scales were analysed with a Wilcoxon Signed rank test. Comparison between symptom scales of those who had had primary PD alone and those who had required LHM were performed with a Mann Whitney U test.

6.5 Results

Between 2000 and 2014, 54 patients had pneumatic dilatation of whom 42 were primary pneumatic dilatation for achalasia, on whom 62 dilatations were performed. Nine patients had dilatation performed to salvage Heller cardiomyotomy, 2 had dilatation after surgery for non-achalasic conditions e.g. vertical banded gastroplasty and 1 had dilatation for OGJ obstruction (figure 1). Of the patients who had primary pneumatic dilatation for achalasia there was a 74% overall success rate. Last known follow-up was available for 36/42 patients, (mean 17 months, median 5.5 months, SD 36months). Exclusions and subtypes are seen in Figure 1, and the patient characteristics and results are summarised in Table 1. All cases notes were reviewed and in addition questionnaires were obtained for 18 patients.

Pneumatic dilation details are seen in Table 2. Three patients (6%) had perforations**,** two required thoracotomy and one was managed conservatively. No deaths occurred. Late sequelae such as reflux and reflux complications were unable to be assessed due insufficient information recorded in the case notes.

Seven of the 42 patients had manometry with a solid state catheter, ManoScan system (Sierra Scientific/ Given Imaging). Thirty-five patients had water-perfused manometry

and the original trace was reviewed using either Trace Version v1.2, Hebbard, Melbourne, Australia, or Quickview Analysis Program (Medical Measurement Systems

Gender, age, or the number of dilations were not found to have any association with outcome. Size of last dilation was more likely to correlate with a successful last known follow-up (Odds Ratio=0.54, 95% CI: 0.32, 0.89. p=0.02) with a lower sized balloon more predictive of success.

Subtype as defined by the Chicago classification was not predictive of success either for short or last known follow-up (p 0.82, p 0.37). Patient characteristics and outcomes are seen in table 1.

6.5.1 Questionnaire analysis.

Questionnaires were returned for 18 patients. Of these 10 (55%) of this cohort had progressed to surgery compared to 26% of the overall cohort and so the cohort was not considered representative. The 8 patients who had not come to surgery had an average age of 62 and mean follow up time of 4.6 years. The 10 patients who had subsequently come to surgery had an average age of 51 and mean follow up time of 4.6years since their dilation and 3.4 years since surgery. Results of patients who had not come to surgery were excellent with statistically significant improvement across all parameters with the exception of chest pain and odynophagia where only a trend was seen (see figure 2). Post surgical results of patients who had their pneumatic dilation followed by surgery were the same as those who had had a successful pneumatic dilation across all parameters, except on a liquid dysphagia visual analogue scale where the group that had progressed to surgery did worse (p=0.027, table 3). Forty-six percent of patients across both groups had returned to a normal diet and 91% thought they had made the correct decision to undergo primary pneumatic dilation. With respect to the Visick category, 4% were in category 1 (asymptomatic), 50% in category 2 (mild symptoms, easily controlled), 21% in category 3 (moderate symptoms, not controlled by simple methods), and 25% in category 4 (moderate symptoms which interfere with life). No patients had been adversely affected by dilation (category 5, symptoms worse than before procedure).

6.5.2 Comparison to laparoscopic cardiomyotomy

To determine success rates compared to cardiomyotomy, the cohort of patients treated with primary pneumatic dilatation for achalasia were compared against a separate cohort of 195 patients who had undergone laparoscopic cardiomyotomy with Dor fundoplication. These patients are from a prospective database maintained by the department of surgery (data awaiting publication elsewhere) and included 60 type I achalasia, 111 type II achalasia and 24 type III achalasia patients. They had follow-up ranging between 3 months and 22 years post operatively, a mean length of follow up of 4 years, and had been followed up on average 4.3 times each. The PD cohort were significantly older than the surgical cohort (62yo vs 52yo). When both cohorts were combined there was no association between gender or age and outcome (P value=0.8237, P value=0.6682), but there was between subtype and outcome (P =0.0083). Due to the variability in follow-up due the retrospective nature of this study a direct comparison of success was able to be calculated at the 1 year follow up (74% success for PD, 92% for LHM). To assess outcome using all follow-up data available, a multivariate logistic GEE model was used. This accounts for the variation in length of follow up between patients. There was a statistically significant difference between

outcomes of PD and LHM with LHM having odds of follow-up success 6.8 times that of PD (OR=6.8, 95% CI: 3.1, 14.9), when controlled for subtype.

6.6 Discussion

In this study we have looked at a cohort of patients with achalasia whom have elected for pneumatic dilation despite an institutional preference for laparoscopic cardiomyotomy. A good initial success rate was obtained with an early follow-up (1 year) success of 76% with minimal morbidity (6% perforation rate) and no mortality. 35% of patients required a further intervention with 3 receiving further dilations and 12 progressing to surgery. Those who progressed to surgery had very similar outcomes to those who did not require further intervention suggesting that although patients had to undergo two procedures they were not adversely affected by choosing to have a primary dilation.

Chicago subtypes as described for high resolution manometry are readily recognisable on water-perfused systems. In our series of 42 patients we have not shown a statistically significant difference between subtypes, although this is not unexpected given the low absolute numbers. Any difference between type III achalasia and the other subtypes is difficult to demonstrate as type III is a rare subset of achalasia making up only 17% of our cohort. The difference in outcome between type I and type II is probably less marked with a larger study after cardiomyotomy showing only a 10% difference in success and is unlikely to be seen in cohorts of our size. We did see a trend towards an older age of type IIIs and a worse outcome which is consistent with previously reported studies.

The finding that the size of the last balloon dilation used is predictive of outcome is not unexpected as if a patient has a good response to a 30 or 35mm balloon they do not go on to have a dilation with a larger balloon. Patients who have dilation with a large balloon are more likely to fail their series of dilations and be referred for surgery.

Pneumatic dilation outcomes in our institution are not as favourable as after cardiomyotomy. There are likely to be multiple factors for this given our institutional preference for laparoscopic Hellers cardiomyotomy. Patients are likely to be older with more comorbidities and this can decrease the aggressiveness of the dilation series. Older patients are also more likely to elect to live with residual symptoms, rather than seeking further dilations than a younger patient would. Our impression is also that this self-selected cohort of pneumatic dilatation patients is a group who are less likely to represent requesting repeat dilatations, electing to live with symptoms as long as they consider them manageable.

Limitations of our study include the retrospective nature of the review with success and failure determined in a majority of cases by case-note review. Grouping of patients into Chicago subtypes by review of water-perfused manometry is conceptually sound but not a perfect correlation. Traces in the vast majority of cases fall easily into a category, but the cut-off of 30mmHg is referenced to oesophageal baseline rather than atmosphere (a difference usually of 2-3mmHg). The questionnaires sent were robust but the cohort where questionnaires were available for analysis were not representative of the entire cohort. The comparison between the pneumatic dilation and surgical cohorts must be interpreted with caution as there is both selection bias across the cohorts as well as a difference in how the follow up data was collected as the surgical database is a prospective database.

Pneumatic dilation is a safe and effective treatment for achalasia. Chicago subtypes are not demonstrated to have an impact on treatment outcome in this cohort.

6.7 Acknowledgements

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6.9 Figure and tables

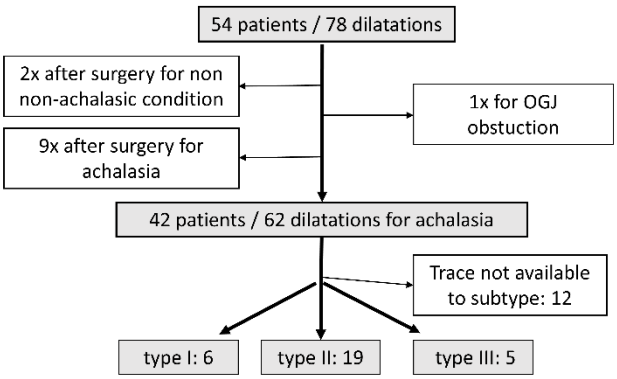

Figure 6-1 Exclusions and subtypes.

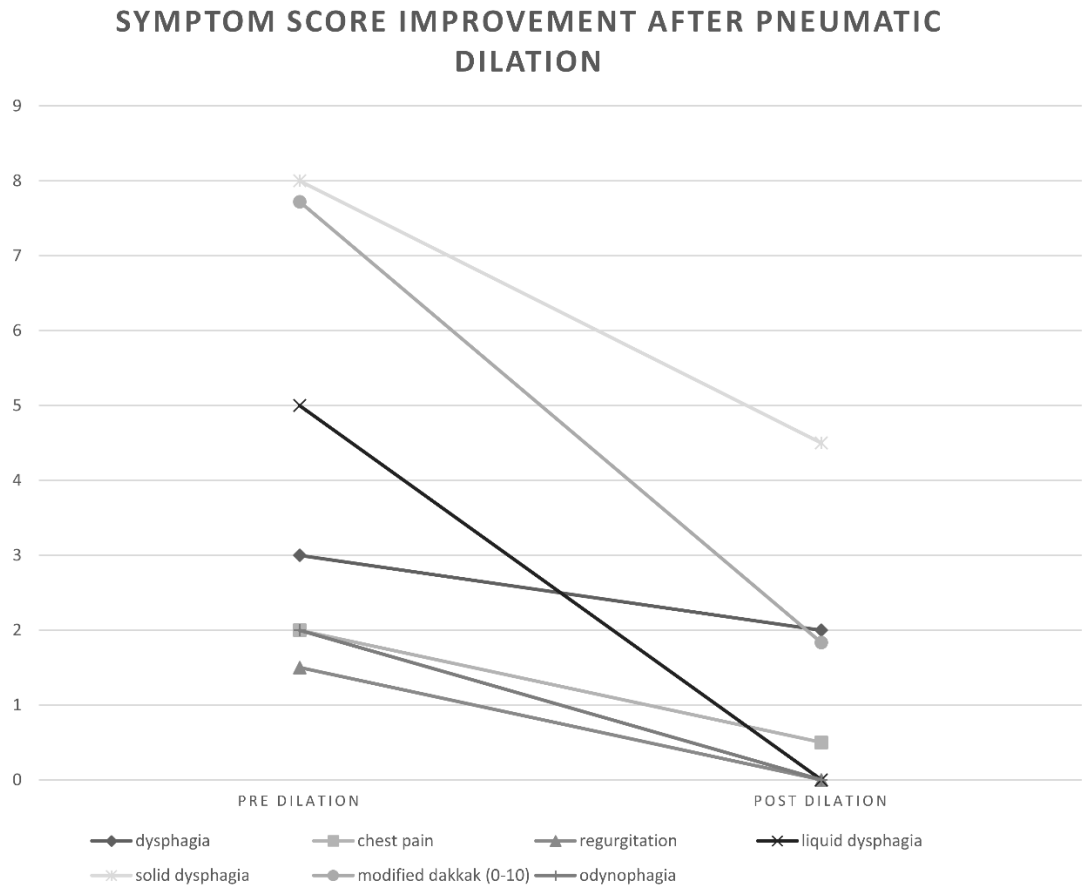

Figure 6-2 Symptom improvement for pneumatic dilation cohort who did not progress to cardiomyotomy. Dysphagia, chest pain, regurgitation and odynophagia are scored 0-3 with 0 being a frequency of never, 1 few times per month, 2 few times per week, 3 daily. Liquid dysphagia, solid dysphagia and Dakkak scores are represented on a scale of 0-10.

	Type I	Type II	Type III	Trace not available to subtype	All patients
Number of patients	6	19	5	12	42
Age (mean)	66	65	72	56	62
Gender m/f	1/5	10/9	4/1	4/8	19/23
Short term success (%)	4/4 (100)	14/16 (87.5)	3/4 (75)	5/11 (45)	74% (n=35)
Last known follow-up success (%)	3/4 (75)	9/16 (56)	1/4 (25)	4/11 (45)	17/34 49% (n=35)

Table 6.1 Patient characteristics and outcome. Overall and as per subtype.

Number of dilations in series		Size of last balloon(mmHg)	
1	64%	30	40%
2	26%	35	43%
3	7%	40	10%
4	3%	not recorded	7%

Table 6.2 Pneumatic dilations per patient.

	PD alone (n=8)	PD followed by surgery (n=10)
Dysphagia frequency *	2	2
Chest pain frequency	0.5	0.5
Regurgitation frequency	0	1
Odynophagia frequency	0	2
Heartburn frequency	0	1
Liquid dysphagia score (0-10), median	0	6
Solid dysphagia score, median (0-10), median	4.5	4
Dakkak swallowing score (0-45), median	8	17

*Table 6.3 Post dilation and post-operative symptom analysis for patients who had pneumatic dilation compared to those who had pneumatic dilation followed by surgery. *Frequency is graded 0 = never, 1 = few times per month, 2 = few times per week, 3 = daily.*

Chapter 7 Type III achalasia – a clinical description

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7.2 Abstract

7.2.1 Background

Achalasia is a disease characterised by dysphagia, regurgitation, chest pain and weight loss. It is now routinely classified into 3 subtypes according to the Chicago classification. Type III achalasia is characterised by lower esophageal sphincter obstruction but also spastic activity in the esophageal body. This spastic activity could lead to a different symptom profile to other achalasia patients.

7.2.2 Methods

We reviewed the notes of 36 patients with type III achalasia to determine their clinical presentation. We compared them with 137 patients with type II achalasia and 21 with distal esophageal spasm.

7.2.3 Key Results

Type III patients had a mean age of 63 years, 15 (42%) were female and 21 (58%) male, they had symptoms for 4 ½ years prior to diagnosis. 97% presented with dysphagia, 79% with regurgitation, 61% with chest pain and 22% with weight loss. This pattern was similar to that of type II patients with the exception of age (63yo vs 52yo) and length of symptoms prior to diagnosis (4.5years vs 2.5years). Type III patients had a similar age (63yo and 64yo) to distal esophageal spasm patients but had other symptoms less frequently.

7.2.4 Conclusions and Inferences

Type III patients have a similar symptom profile to type II patients, and more symptoms than distal esophageal spasm patients, suggesting that most symptoms in achalasia are due to lower esophageal sphincter obstruction rather than esophageal spasm. Type III achalasia patients arise in a distinctly older population than type II achalasia, suggesting these two groups might be distinct regarding their underlying pathophysiological process.

7.3 Key points summary

1) Type III achalasia is distinct from other achalasia groups with spastic esophageal activity. This may lead to a different symptom profile.
2) Type III achalasia presents in older patients but with similar symptoms to other achalasia patients
3) Achalasia symptoms are caused predominantly by lower esophageal sphincter obstruction rather than spastic esophageal activity. Type III achalasia arises in a different patient population to type II achalasia.

7.4 Introduction

The first recorded description of achalasia is attributed to Thomas Willis who described a male patient with a condition marked by 'an almost perpetual vomiting', who maintained his nutrition by use of a whale probang for at least 16 years (140). Today, patients usually present for treatment at an earlier stage of disease and such disabling regurgitation is rarely seen. Recent descriptions of the clinical presentation of achalasia emphasise the almost universal presentation of dysphagia, alongside other typical symptoms of regurgitation, chest pain, and weight loss which occur in 60-80% of patients (28).

Achalasia is now routinely divided into three subgroups according to the Chicago classification v3.0 (90). Type III achalasia is characterised by manometric evidence of esophageal spasm (figure 1), and may be due to a different underlying pathophysiological process from that in than types I and II achalasia. Evidence for this includes pathological evidence of preservation of myenteric neurons, rather than progressive neuronal loss seen in types I and II achalasia (9), as well as a different manometric picture, and an older patient cohort (20, 131). Treatment outcomes after relieving the obstruction at the lower esophageal sphincter are also inferior in type III achalasia, potentially due to residual symptoms from untreated esophageal spasm (141).

Distal esophageal spasm is also defined by the Chicago classification v3.0 using the same criteria for spasm as for type III achalasia (Distal contractile Integral of >450Hg.s.cm and Distal latency <4.5seconds) except without obstruction at the lower esophageal sphincter (as defined by integrated relaxation pressure). It also presents with symptoms of dysphagia, regurgitation, and chest pain.

As type III achalasia represents only about 10% of all presentations of achalasia, and patients have esophageal spasm in addition to obstruction at the lower esophageal sphincter, we hypothesised that they may present with a different symptom profile to that which has been previously described for achalasia. The aim of this study was to describe the clinical presentation of patients with type III achalasia, to describe the symptom profile of these patients, and to compare its presentation to that of type II achalasia and distal esophageal spasm.

7.5 Methods

The study was approved by Royal Adelaide Hospital Human Research Ethics Committee (HREC/15/RAH/262).

Patients with type II and III achalasia were identified from the databases maintained by the Gut Function Laboratory, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital and Oesophageal Function Laboratory, Investigation and Procedures Unit Repatriation Hospital, and the Department of Surgery database for Heller cardiomyotomy (University of Adelaide) which includes type III achalasia patients subtyped by conventional manometry from a previous project (data in press). Patients with distal esophageal spasm were identified from the Gut Function Laboratory database.

Patient files and endoscopy records were reviewed for all patients. All manometry reports were reviewed and only patients with unequivocal manometric diagnoses were

included. In cases where the referral came from outside of the hospital, the private referring specialist was contacted and notes and endoscopy reports requested. The initial case-note entry or letter from the treating specialist was sought specifically and this clinical information was used preferentially. Information on preoperative symptoms from the surgical database was also used. Patients were excluded if an endoscopy report was not available, in order to ensure patients with pseudo-achalasia were not included in the cohort. Information on the presenting complaint was recorded separately when available. All comorbidities were recorded and psychiatric, autoimmune and cardiovascular complaints grouped to look for variations between the 2 achalasia groups and distal spasm group**.**

Two hundred and three patients were identified from the databases with unequivocal diagnoses (37 type III, 138 type II and 29 distal spasm). One patient was excluded because on review of the report and trace they had been incorrectly labelled type III achalasia. Sufficient information was available on the data bases for analysis on 129 patients. Clinical records were requested on 73 patients from the treating specialist or public hospital and these patients were included if a letter or case note entry from the treating specialist detailing the patients clinical presentation prior to diagnosis of their motility disorder was available. These patients also had information on weight loss, cervical dysphagia, epigastric discomfort and episodes of food bolus obstruction recorded, which were not available from the database records. Clinical records were not available for 9 cases (1 type II and 8 distal spasm) and these patients were excluded. Patients with distal spasm were disproportionately represented at this stage of exclusion as they were more likely to have been seen privately (i.e. not in the public system) and these records were more difficult to access. Information on degree of weight loss was initially sought but was not complete so patients were grouped into either weight loss or no weight loss. There was not enough information available in the case notes to analyse differences in contrast swallow appearance.

Statistical analysis was done using SPSS Statistics version 23 (Armonk, NY: IBM Corp). Differences among disease types were assessed with a one-way ANOVA for age, Kruskal-wallis for length of symptoms prior to presentation, and Pearson-chi and Fishers exact for differences between gender and frequencies of symptoms among subtypes.

7.6 Results

The cohort for analysis included 36 type III achalasia, 137 type II achalasia and 21 distal spasm patients. Manometry was performed with solid state high resolution manometry for 41 patients, a 16-channel water-perfused system for 54 patients, and a lower resolution water-perfused system in a further 99 patients.

7.6.1 Type III achalasia

Type III patients had a mean age of 63 years, 15 (42%) were female and 21 (58%) male, they had experienced symptoms for 4 ½ years prior to diagnosis. Almost all (97%) presented with dysphagia, 79% with regurgitation, 61% with chest pain and 22% with weight loss (figure 2). Dysphagia with solids occurred in 97% and dysphagia with liquids in 80%. Autoimmune comorbidities were noted in 3%, psychiatric comorbidities in 6% and a cardiovascular history in 33%.

7.6.2 Type III achalasia vs Type II achalasia

Patients with type III achalasia were older than those with type II achalasia (63 years vs. 52 years p= 0.006), and had experienced symptoms for a longer time prior to diagnosis (4.5 years vs. 2.5 years p=0.014) (Table 1). Type III achalasia patients had symptoms of dysphagia to liquids, regurgitation, and retrosternal chest pain with similar frequency to those in type II achalasia patients. Symptoms of dysphagia, dysphagia to solids, as well as less frequent symptoms of cervical dysphagia, odynophagia, epigastric discomfort, and food bolus obstruction were similar between achalasia groups.

7.6.3 Type III achalasia vs distal esophageal spasm

Type III patients had a similar age of presentation to distal spasm patients (63 years, 64 years) as well as length of symptoms prior to onset (mean 4.5years, 4.5years). Both diseases also had trend towards a greater frequency of male patients compared to female patients. Type III achalasia patients had symptoms of dysphagia to liquids, regurgitation and retrosternal chest pain more frequently than distal spasm patients.

7.7 Discussion

Patients with type III achalasia present with dysphagia, regurgitation, chest pain, and weight loss in order of descending frequency (figure 2). Almost all patients with type III achalasia have dysphagia and this is their predominant symptom. One fifth (22%) of patients report a degree of weight loss at presentation. This symptom profile is very similar to Eckhart's description of the clinical presentation of all patients with achalasia which predates the Chicago classification (28).

The clinical symptoms with the greatest effect on the patient's quality of life, namely dysphagia to solids and liquids, regurgitation and chest pain, are more closely correlated between types II and III achalasia than with distal spasm, suggesting that these symptoms are caused predominantly by the failure of the lower esophageal sphincter deglutitive relaxation mechanism, rather than by esophageal body spasm. As lower esophageal sphincter obstruction is the major determinant of achalasia symptomology, this lends support, at least by first principles, to treat type III achalasia by opening up the sphincter– i.e. cardiomyotomy, pneumatic dilatation and shorter-length per oral endoscopic myotomy, rather than attempting long myotomy, either surgical or by POEM, aiming to address the spasm.

A different age of onset between type III and type II achalasia is suggestive that these two achalasia subtypes may actually represent two separate disease processes occurring in two different patient populations. Limited pathological studies exist which support this hypothesis, suggesting that type III achalasia may occur due to a dysfunction of, rather than the progressive loss of, myenteric neurons (18, 142). Why type II achalasia should present more frequently with weight loss than type III achalasia is also unclear – although perhaps the fact that patients take longer to reach diagnosis hints at a slower onset of disease with perhaps milder symptoms. Differences among subtypes with regards to co-morbidities were not found, except with respect to an increase in cardiovascular problems in type lll achalasia. This difference is probably related to the older mean age in this group.

Type III achalasia shares manometric similarities between achalasia as well as distal esophageal spasm. Since traces with distal esophageal spasm can look strikingly similar to a type III achalasia (see figure 1), it is not surprising that there is an overlap of symptomatology. However, symptoms that might intuitively seem more likely to be

associated with spastic activity – pain symptoms, cervical dysphagia, and dysphagia to liquids were *not* seen more frequently in the spastic disorders, occurring in less or similar frequency when compared with type II achalasia. The mechanism behind chest pain in achalasia is not well understood, in fact the actual mechanism for any chest pain of esophageal origin has not been clearly delineated (143). Potential hypotheses include stimulation of chemoreceptors or mechanoreceptors by acid or bile reflux, or by spasm or distension of the esophagus (35, 144, 145). In our cohort the patient groups (types II and III achalasia) which had LOS dysfunction were the groups with the most significant chest pain symptoms. Spasm did not seem to add to chest pain severity (comparing types II and III achalasia) and patients with spasm alone, although some did have chest pain, overall had less chest pain than achalasics. What mechanism is primarily responsible for chest pain in achalasia is unclear, but it would seem from our results that it has more to do with LOS obstruction than spasm.

The most obvious similarity between type III achalasia and distal spasm in this study was the demographic distribution. Type III achalasia patients present with a mean age of 63, 11 years older than type II patients and similar in age of presentation to distal spasm (64 years). Although not statistically significant when compared amongst disease types, a male preponderance in both spastic disorders was seen, which was not present in type II achalasia or has ever been described in a cohort of achalasia patients (135). Perhaps type III achalasia should be considered more often as a spastic disorder alongside distal spasm rather than being grouped with types I and II achalasia?

Evolution of spasm patients to achalasia has been described, and hypotheses of type III achalasia being a precursor to the other achalasia subtypes have been suggested (18). The relatively short lag time between disease onset and diagnosis across all three diseases in this study argues against this being a common pathway. It suggests instead that type III achalasia presents primarily in its own right as primary motor disorders of the esophagus, rather than, for example, a type II achalasia being a late presentation of type III achalasia.

Limitations to our study include its retrospective nature although considerable effort was made to find clinical information dating from prior to the initial diagnosis. We had insufficient numbers to look at associated co-morbidities or to detect any association between auto-immune diseases or psychiatric co-morbidities. It would also have been interesting to examine differences in contrast swallow imaging but due to the nature of the study we were unable to do this. Our other limitation lies in the manometry equipment with not all patients being diagnosed with a high resolution system. Although the method we used to subtype achalasia using water-perfused systems has been validated (130) it still relies on recognition of spastic activity by amplitude and duration rather than distal latency.

7.8 Conclusions

Type III achalasia patients universally present with dysphagia, as well as symptoms of regurgitation, chest pain, and weight loss. Its clinical presentation is very similar to type II achalasia as symptoms are to be predominantly caused by obstruction at the lower esophageal sphincter, rather than spasm. Type III achalasia patients however arise in a distinctly older population than type II achalasia, suggesting these two groups may be distinct regarding their underlying pathophysiological process.

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7.10 Figures and tables

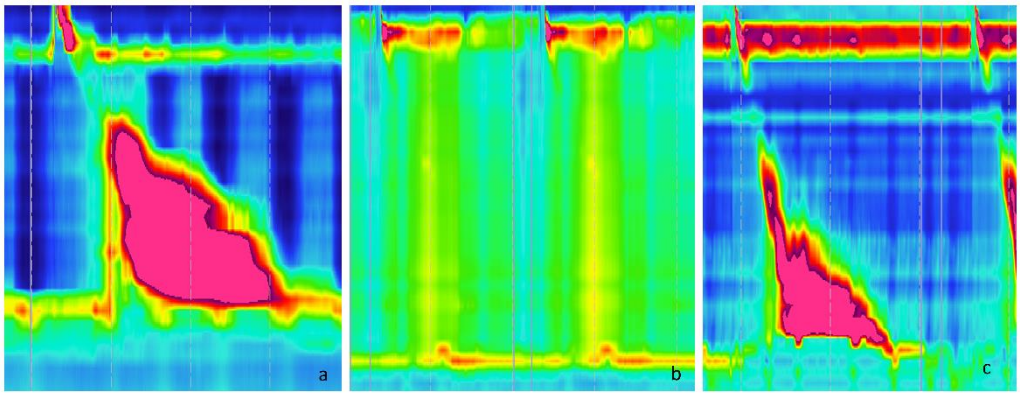

Figure 7-1 High resolution manometry plots of type III achalasia (a), type II achalasia (b) and distal esophageal spasm (c).

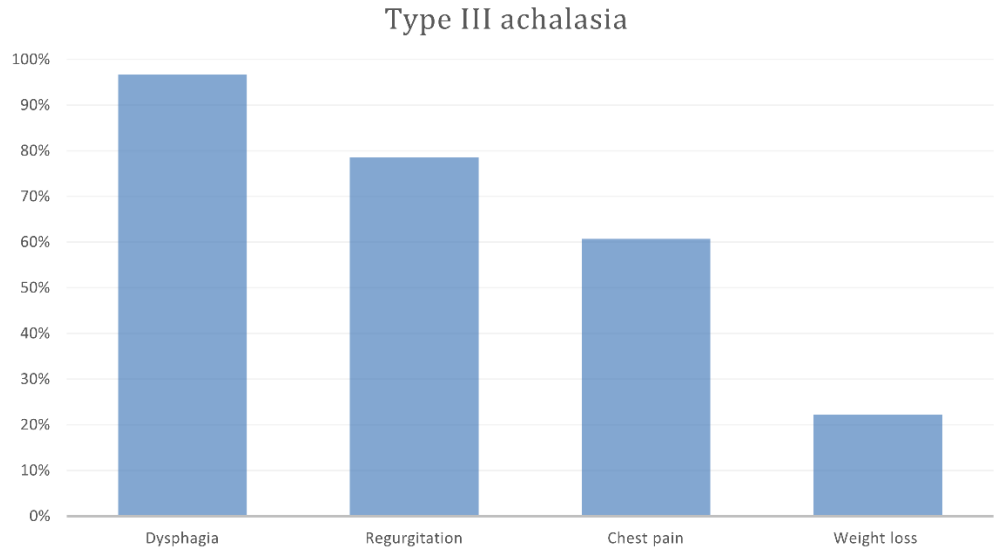

Figure 7-2 Common symptoms in type III achalasia.

	Type III (%)	Type II (%)	Distal spasm (%)	p value
gender (m/f)	21/15	69/68	12/9	ns
age of patient at diagnosis (mean, years)	63	52	64	0.00
length of symptoms prior to diagnosis (mean, years)	4.5	2.5	4.5	0.02
Dysphagia	30/31 (97)	105/114 (92)	19/20 (95)	ns
dysphagia to liquids	24/30 (80)	75/111 (68)	7/15 (27)	0.001
dysphagia to solids	29/30 (97)	101/112 (90)	14/16 (88)	ns
Regurgitation	22/28 (79)	88/111 (79)	5/16 (31)	0.00
retrosternal chest pain	17/28 (61)	66/109 (61)	5/17 (29)	0.043
Heartburn	8/21 (38)	16/29 (55)	5/16 (31)	0.003
weight loss	4/18 (22)	14/23 (61)	2/15 (13)	0.024
cervical dysphagia	2/21 (10)	3/27 (11)	4/15 (27)	ns
Odynophagia	5/23 (22)	6/28 (21)	0/15 (0)	ns
epigastric discomfort	6/21 (29)	8/29 (28)	4/15 (27)	ns
food bolus obstruction	0/18 (0)	1/24 (4)	2/15 (13)	ns
autoimmune comorbidity	1/33 (3)	6/129 (5)	1/17 (6)	ns
psychiatric comorbidity	2/33 (6)	10/131 (8)	2/17 (12)	ns
cardiovascular comorbidity	11/33 (33)	11/124 (9)	7/17 (41)	0.001

Table 7.1 Differences in presentation among type III achalasia, distal esophageal spasm and type II achalasia.

Chapter 8 Conclusions

8.1.1 To assess the incidence of achalasia in the local South Australian population

We have determined the annual incidence of achalasia in the South Australian population to be 2.3-2.8/100000. This finding is significant as it is represents a two-fold increase in incidence to what has been previously reported. Our study differs from previous reports of incidence as we have been able to access data from all motility services providing manometry to the adult population in a relatively geographically isolated State. This gives us confidence in both accuracy of diagnosis as well as size of the population cohort.

Incidence of a particular disease is important in making decisions about allocation of resources, both financial and in the development of expertise. Per-oral endoscopic myotomy (POEM) is gaining traction as a treatment option for achalasia patients, but long-term data is currently unavailable, and it requires an advanced endoscopic skill set, with a learning curve of at least 30-40 to achieve competency, and 60 cases to achieve expert status. From the work included in this thesis, it is clear that for types II and III achalasia, laparoscopic cardiomyotomy remains the gold standard. POEM may have a place in the treatment of type III achalasia, but the number of patients presenting with this in South Australia is very small, and may not be sufficient to justify the introduction of POEM. The data acquired during this project will be instrumental in guiding decisions re. treatment options in South Australia.

8.1.2 To provide an update of current literature for a surgical audience

Important developments in the pathophysiology, diagnosis, and treatment of achalasia have been described, focusing on areas of most interest to a upper gastrointestinal surgeon. Areas of recent change include advances in the technology used for motility studies, which have been the catalyst for the development of the Chicago classification system. The other area of particular interest for a surgical audience is the development of per-oral endoscopic myotomy (POEM) for the treatment of achalasia. We have performed a comprehensive review of these two topics, particularly focusing on the rates of post-procedural reflux. As this is higher than has been previously suggested, it may turn out to be the Achilles heel of the procedure, particularly when compared to Heller's cardiomyotomy.

8.1.3 To report clinical outcomes of patients after laparoscopic Heller's cardiomyotomy according to Chicago subtypes

Using a prospective surgical database of patients treated for achalasia, we identified 195 patients who met our inclusion criteria. Namely, having a diagnosis of achalasia, undergoing a laparoscopic Heller's cardiomyotomy, and having an accessible preoperative manometry tracing. We identified 60 patients with type I achalasia, 111 with type II achalasia, and 24 with type III achalasia. We defined clinical success by 1) no further intervention and 2) a modification of the Eckardt score. To maximise follow-up data, which consisted of questionnaire-based follow-up, in some cases up to twenty years post-operatively, we analysed success among subtypes using a mixed effects logistic regression model. Success differed among subtypes (p 0.0017, table 4.3). Type III achalasia had a poorer prognosis when compared with type I achalasia (III vs. I Odds ratio 0.38, p 0.035) but there was no difference between types I and II achalasia.

We conclude that Type III achalasia is a predictor of poor prognosis to traditional Heller's cardiomyotomy. The difference in outcome between types I and II achalasia which was hypothesised in the original description (and shown in the only other two cohorts of similar size) was not demonstrated. This difference, if real, is small and not likely to be of any real clinical significance.

8.1.4 To report clinical outcomes of patients after pneumatic dilation by Chicago subtypes

We performed a retrospective review of patients treated by primary pneumatic dilation for achalasia at a single institution across a fifteen-year period. Outcomes of patients were good with a 76% initial success rate, although 35% required further intervention over the long term (either repeat dilation or Heller's cardiomyotomy). Forty-two patients had primary pneumatic dilation for achalasia over this time period: 6 with type I achalasia, 19 type II achalasia and 5 type III achalasia with 12 not having their original tracing still available for subtyping. No difference in outcome among subgroups was found in this study although the power of this cohort was probably too small.

Further analysis of these patients using questionnaire-based follow-up allowed comparison between a subgroup who had primary pneumatic dilation and required no further intervention, and patients who subsequently required Heller's cardiomyotomy. No difference in outcome amongst these two groups was found suggesting that patients who elected for pneumatic dilation were successfully salvaged with a Heller's cardiomyotomy, and still had a good overall outcome.

The cohort of primary pneumatic dilation (PD) patients was compared to the primary Heller's cardiomyotomy cohort described in the previous chapter. The primary Heller's cardiomyotomy cohort had a statistically significant increased odds of follow-up success 6.8 times that of PD (OR=6.8, 95% CI: 3.1, 14.9). This difference must be interpreted with caution for two reasons. First, the Heller's cardiomyotomy cohort had prospective follow-up whereas the pneumatic dilation cohort had retrospective follow-up. Second, the local preference for treating patients with achalasia is Heller's cardiomyotomy, which may impart significant selection bias when considering a direct comparison between these two groups.

8.1.5 To clinically describe type III achalasia

Type III achalasia patients present with dysphagia (96%), regurgitation (82%), retrosternal chest pain (55%), and weight loss (22%). The cohort of patients used for this analysis was compared to patients who had been diagnosed with type II achalasia and distal oesophageal spasm. The clinical presentation of patients in these 3 groups was very similar with few differences. Of note, weight loss was more likely to occur in type II achalasia than either of the spastic disorders, and achalasia patients (type II and III) were more likely to suffer regurgitation than the distal oesophageal spasm group. Type III achalasia patients were more likely to present with dysphagia to liquids than patients with distal oesophageal spasm.

Type III achalasia patients presented on average 10 years later than patients with type II achalasia, raising the possibility that it may have a different underlying pathophysiological pathway.

8.1.6 Future directions

8.1.6.1 Changes in achalasia treatment

Per-oral endoscopic myotomy (POEM) is an emerging treatment option for achalasia. Due to its perceived benefits of being a more minimally invasive option, as well as its potential place in the treatment armamentarium of spastic motility disorders, it is gaining traction as a legitimate treatment option for the primary treatment of achalasia. Randomised controlled trials should be conducted before it can be recommended over the current gold standard of laparoscopic Heller's cardiomyotomy with Dor 180-degree fundoplication. We have demonstrated by a review of the literature that silent acid reflux can occur in about 50% of patients after POEM. We have also demonstrated that type III achalasia is a predictor of poor outcome. When these trials are conducted it will be important to document post-procedural reflux using objective measures (pH studies) rather than relying on clinical symptoms. Subtype of achalasia should be documented prior to treatment and type III achalasia should not be compared directly with types I and II achalasia but treated as a separate cohort.

8.1.6.2 Confirmation of results by solid state high resolution manometric studies

Our assessment of outcome after Heller's cardiomyotomy according to subtype, was based on the assumption that the Chicago subtypes can be seen in retrospect on water-perfused tracings. Although there are many reasons for believing this is a valid assumption, the Chicago classification is based on tracings performed using solid state high resolution catheters and the metrics generated by accompanying software. Due to the relatively recent introduction of these catheters into clinical practice in South Australia, only a minority of our cohort had had their diagnosis made with these catheters. Over time, as a cohort of patients accumulates who have been diagnosed prospectively using this technology, this study can be repeated to confirm our results. Due to the low incidence of achalasia (although higher than previously thought), and the need for sufficient numbers to demonstrate a difference, it may well be some years before this is possible.

8.1.6.3 Defining success after achalasia

One of the areas of controversy we encountered during this thesis was the definition of successful treatment after achalasia. As no treatment can reverse the disease, treatment is aimed at removing the obstruction at the gastro-oesophageal junction to allow an aperistaltic oesophagus to drain. In other words, the <u>improvement</u> of symptoms. Different research groups have defined success differently. Some use an improvement in dysphagia alone, and some a combination of improvement in dysphagia, regurgitation, chest pain and weight loss (Eckhardt score). All use slightly different thresholds to define success. Also, not all research groups consider the need for further intervention as treatment failure of the initial intervention.

In the absence of a cure for achalasia, treatment success should be defined as a treatment which:

1) Allows the patient to eat a healthy, well balanced diet, which maintains weight, and allows them to eat without embarrassment in social situations
2) Eliminates regurgitation
3) Residual symptoms are easily treated by simple measures
4) Prevents or limits progression of, oesophageal dilatation and sump formation
5) Does not require further intervention after first treatment or course of treatments

6) Has acceptable rates of post-procedural gastro-oesophageal reflux disease.

No scale for treatment success, which fulfils the above criteria currently exists. Work is needed to define and validate a questionnaire/scale of success against these minimum criteria. When per-oral endoscopic myotomy (POEM) is ready to undergo a randomised-controlled trial, it will be important to use to a validated useful measure of successful treatment.

8.1.6.4 Differences in oesophageal emptying between types I and II achalasia.

Types I and II achalasia have been described in the Chicago classification as two difference subtypes based on a somewhat arbitrary value of pan-oesophageal pressurisation above or below the value of 30mmHg. The clinical significance of dividing these two groups is based on the hypothesis that those demonstrating more oesophageal activity (type II achalasia) should clear their oesophagus more readily after treatment than those with less oesophageal activity (type I achalasia, pressurisation <30mmHg). As we have not demonstrated a difference in clinical outcome between types I and II achalasia, this hypothesis is called into question. We plan to use the laparoscopic Heller's cardiomyotomy database and additional data collected for subtyping these patients to test this hypothesis. The cardiomyotomy database collects information on dysphagia to liquids and solids, which can be used as a surrogate marker for oesophageal clearance. We will examine whether or not there is a correlation between improvement of dysphagia in types I and II achalasia as described, and whether or not there is another threshold that more closes predicts outcome, and whether or not the correlation is linear.

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