Thesis

Therapy of Achalasia - A Retrospective Data Analysis at an Esophagus Specialty Outpatient Clinic

submitted by

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Graz, date 19.09.2024

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Zusammenfassung

Hintergrund: Die Achalasie ist eine seltene,primäre Motilitätsstörung der Speiseröhre, welche durch eine gestörte Entspannung des unteren Ösophagussphinkters und fehlende Peristaltik der glatten Muskulatur gekennzeichnet ist. Die vermutliche Hauptursache ist der Verlust inhibitorischer Nervenzellen, allerdings ist der genaue pathophysiologische Mechanismus unbekannt. Das Hauptziel dieser Studie war es, die Behandlungsergebnisse von Patient:innen zu bewerten, die sich zwischen Januar 2012 und Februar 2023 in der Ösophagus-Spezialambulanz des Universitätsklinikums Graz vorgestellt haben, und diese mit den neuesten Behandlungsempfehlungen zu vergleichen. **Methoden:** Mit Hilfe einer Schlagwörterabfrage wurden Patient:innen im genannten Zeitraum ermittelt, die zwecks Achalasieabklärung im LKH-Graz vorstellig waren. Zur Diagnosestellung einer Achalasie wurde zunächst eine Endoskopie durchgeführt um Differenzialdiagnosen auszuschließen. Anschließend wurde wird die hochauflösende Manometrie (HRM) als Goldstandard zur Diagnosestellung verwendet. Dabei wird die Erkrankung gemäß dem Chicago-Protokoll 4.0 in die Subtypen 1, 2 und 3 eingeteilt, basierend auf dem beobachteten Relaxationsmuster. Nur Patient:innen mit bestätigter Achalasie wurden in die Studie eingeschlossen. Die Therapien wurden nach Therapieerfolg, Remissionsdauer und Komplikationen beurteilt. **Ergebnisse:** Im Beobachtungszeitraum wurden insgesamt 125 Patient:innen erfasst. Es wurden 123 Botoxinjektionen (88% Erfolg) durchgeführt, mit 78% der Patient:innen nach 6 Monaten und 56% nach 12 Monaten in Remission. Zudem gab es 94 pneumatische Dilatationen (PD)(89% Erfolg), mit 84% der Patient:innen nach einem Jahr und 66% nach 5 Jahren in Remission. Weiterhin wurden 21 Heller-Myotomien (LHM) (100% Erfolg) durchgeführt, wobei nach einem Jahr alle und nach 5 Jahren 89% der Patient:innen in Remission waren. Schließlich wurden 15 perorale endoskopische Myotomien (POEM) (93% Erfolg) durchgeführt, wobei nach 2 Jahren follow-up derzeit alle Patient:innen in Remission sind. Bei PD und POEM war der Beobachtungszeitraum zu früh gewählt um Langzeitergebnisse endgültig bewerten zu können. Es wurde ein Plattenepithelkarzinom (ESCC) beobachtet. Nach PD, LHM und POEM entwickelte jeweils 1 Patient:in, der als therapiebezogene Komplikation eine PPI- bedürftige gastroösophageale Refluxkrankheit (GERD) entwickelt hat, eine Barrettmukosa**. Fazit:** Mit 125 betreuten Patient:innen innerhalb von 10 Jahren stellt Achalasie eine seltene, aber ernstzunehmende Erkrankung auch an der Medizinischen Universität Graz dar. Alle vier Therapieoptionen erzielten

Remissionsraten ähnlich der publizierten Literatur. Das Auftreten von Vorstufen und manifesten Karzinomen war während des Beobachtunsgzeitraum selten. Bei vorhandener Expertise im Zentrum, sollte jüngeren Patient:innen eine LHM oder POEM wegen längerer Remissionzeit angeboten werden. PD hat sich als gute Alternative bestätigt. Botox-Injektionen sollte Patient:innen in schlechten Allgemeinzustand vorbehalten werden.

Abstract

Background: Achalasia is a rare primary motility disorder of the esophagus, characterized by impaired relaxation of the lower esophageal sphincter and the absence of peristalsis in the smooth muscle. The likely main cause is the loss of inhibitory nerve cells. However, the exact pathophysiological mechanism remains unknown. The main objective of this study was to evaluate the treatment outcomes of patients who presented at the Esophagus Specialty Outpatient Clinic of the University Hospital Graz between January 2012 and February 2023, and to compare these with the latest treatment recommendations. **Methods:** Using a keyword search, patients who presented at Univercity Hospital Graz for achalasia evaluation during the specified period were identified. Endoscopy was initially performed to rule out differential diagnoses for achalasia diagnosis. High-resolution manometry (HRM), considered the gold standard for diagnosis, was then used. The disease was classified into subtypes 1, 2, and 3 based on the observed relaxation patterns, according to the Chicago Protocol 4.0. Only patients with confirmed achalasia were included in the study. The therapies were evaluated based on therapeutic success, remission duration, and complications. **Results:** During the observation period, a total of 125 patients were identified. A total of 123 botulinum injections achieved an 88% success rate, with 78% in remission after six months and 56% after 12 months. Of 94 pneumatic dilations (PD), 89% were successful, with 84% in remission after one year and 66% after five years. All 21 Heller myotomies (LHM) had a 100% success rate, with all patients in remission after one year and 89% in remission after five years. Lastly, 15 peroral endoscopic myotomies (POEM) procedures had a 93% success rate, with all patients currently in remission after 2 years of follow up. For PD and POEM, the observation period was too short to conclusively assess long-term results. One squamous cell carcinoma (ESCC) was observed. Following PD, LHM, and POEM, one patient developed Barrett's mucosa as a therapy-related complication, requiring proton pump inhibitors (PPI) for gastroesophageal reflux disease (GERD). **Conclusion:** With 125 treated patients over 10 years, achalasia remains a rare but serious condition, even at the Medical University of Graz. All four treatment options achieved remission rates similar to those reported in the literature. The occurrence of precancerous lesions and manifested carcinomas was rare during the observation period. For younger patients, LHM or POEM should be offered due to the longer remission time, when provided

expertise is available at the center. PD has proven to be a good alternative. Botulinum toxin injections should be reserved for patients in poor general condition.

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Glossary and Abbreviations

EA	Esophageal Adenocarcinoma
EGD	Esophagogastroduodenoscopy
EGJ	Gastroesophageal junction
EGJOO	Esophagogastric junction outflow obstruction
EMD	Esophageal motility disorder
EoE	Eosinophilic esophagitis
ESCC	Esophageal squamous cell carcinoma
ESS	Eckardt-Symptom-Score
FLIP	Endoluminal functional lumen imaging probe
GERD	Gastroesophageal reflux disease
HRM	High resolution manometry
IRP	Integrated relaxation pressure
LES	Lower esophageal sphincter
LHM	Laproscopic Heller myotomy
PD	Pneumatic dilation
POEM	Peroral endoscopic myotomy
TBE	Timed Barium Esophagogram
UES	Upper esophageal sphincter

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1 Introduction

1.1 Anatomy of the esophagus

The esophagus (oesophagus) serves as the connecting passage between the pharynx and the stomach. It is a muscular hollow organ about 25-30 cm long, responsible for transporting food. The esophagus is divided into three sections: the cervical part (pars cervicalis), the thoracic part (pars thoracica), and the abdominal part (pars abdominalis). The pars cervicalis measures approximately 5-8 cm in length. It's located in the upper mediastinum within the thorax. Here it lies directly behind the trachea. From there, the esophagus continues as the pars thoracica, running to the right of the aorta into the posterior mediastinum, which is also the longest segment, measuring about 16 cm. In this section, it lies adjacent to the left atrium. Finally, at the esophageal hiatus, the esophagus passes through the diaphragm and transitions into the stomach as its pars abdominalis. It is intraperitoneal. (1) There are three natural constrictions in the esophagus. (Figure 1) The narrowest is at the beginning, known as the cricoid narrowing (angustia cricoidea). It's located approximately at the level of the cricoid cartilage with a diameter of just 1.5 cm. This is a true sphincter formed by the interaction of the esophagus's circular muscle and the cricopharyngeus muscle. The upper esophageal sphincter (UES) is further sealed by a venous plexus in the submucosa. At rest the UES remains closed.

The second narrowing is called aortic narrowing (angustia aortica), which is primarily caused by the compression of the esophagus as it passes under the aortic arch. Finally, there is the diaphragmatic narrowing (angustia diaphragmatica), which occurs when the esophagus passes through the diaphragmatic slit. The esophagus is anchored in place by the phrenicoesophageal ligament and the diaphragm's musculature. Just before this narrowing, the esophagus is physiologically more capable of expansion, allowing food to remain there briefly. The closure between the terminal esophagus and the stomach is managed by the lower esophageal sphincter (LES), which is not a "true" sphincter. The resting closure is maintained by various mechanisms, such as the angiomuscular flap valve.(2)

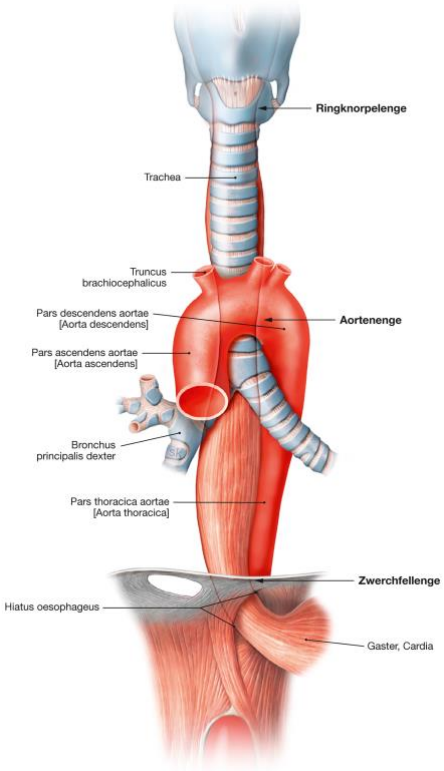


Figure 1:**Narrowings of the esophagus** *S 5.120 Speiseröhre; S. Klebe aus Paulsen/Waschke. Sobotta Atlas der Anatomie. 25. A. 2022 © Elsevier GmbH(3)*

1.2 Histology

The wall structure of the esophagus is divided into the tunica mucosa, tela submucosa, tunica muscularis, and tunica adventitia. (Figure 2) The tunica mucosa consists of non-keratinized, stratified squamous epithelium. Within the subsequent thin lamina propria, we find lymph follicles as well as venous plexuses. The lower ones contribute to the closure of the LES. There is a lamina muscularis mucosa consisting predominantly of smooth muscle. The mucous membranes of the stomach and esophagus are clearly distinguishable. (2) The boundary of particular importance in clinical practice is called the Z-line. (1) It is not uncommon to find clusters of gastric mucosae in the lower third of the esophagus. The tela submucosa serves as a kind of sliding layer between the lamina muscularis mucosae and the tunica muscularis. Here we find mucous glands (glandulae oesophageae) that facilitate the movement of the food bolus. This layer also contains part of the visceral innervation through

the Meissner's submucosal plexus. (Figure 3) Depending on the height of the esophagus, the tunica muscularis consists of striated muscle in the upper third, a mix of striated and smooth muscle in the middle third, and exclusively smooth muscle in the lower third. The tunica muscularis contains a continuous system between an outer longitudinal muscle layer and an inner circular muscle layer. These are not strictly separated, but rather resemble the winding of a screw because of their interwoven course. Between the two layers, we find another visceral nerve plexus: the myenteric Auerbach's plexus. The tunica adventitia consists of loose connective tissue. It’s covered by the peritoneum only in the pars abdominalis. Blood vessels and nerve strands run through this layer. Here we also find the esophageal plexus, which is supplied by the vagus nerve (N.Vagus).(2)

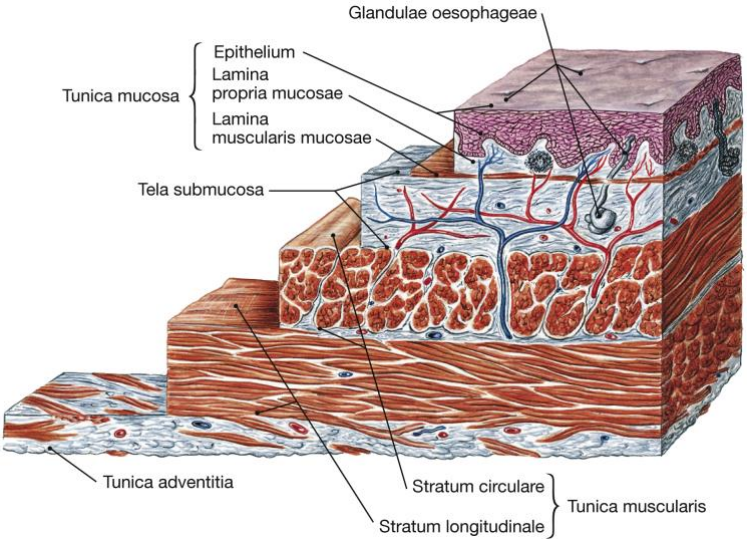


Figure 2: **Layered structure of the esophagus** *5.119 Speiseröhre Wand, Sobotta-Archiv aus Paulsen/Waschke. Sobotta Atlas der Anatomie. 25. A. 2022 © Elsevier GmbH*

The innervation of the esophagus involves a complex interaction between the enteric nervous system and the autonomic nervous system, which includes both sympathetic and parasympathetic influences. Although the enteric nervous system operates within the autonomic nervous system hierarchy and can be modulated by it, it is also capable of functioning independently. This includes the submucosal and myenteric plexus, specifically in the context of the gastrointestinal tract (GIT) and the esophagus.

The submucosal plexus primarily regulates secretion and transepithelial transport, while the myenteric plexus is responsible for controlling muscle contraction and tone. These plexuses

are influenced by a variety of neurotransmitters, including acetylcholine, nitric oxide (NO), and noradrenaline. A balance between cholinergic and nicotinic stimulation is crucial for the proper coordination of the swallowing process.(4)

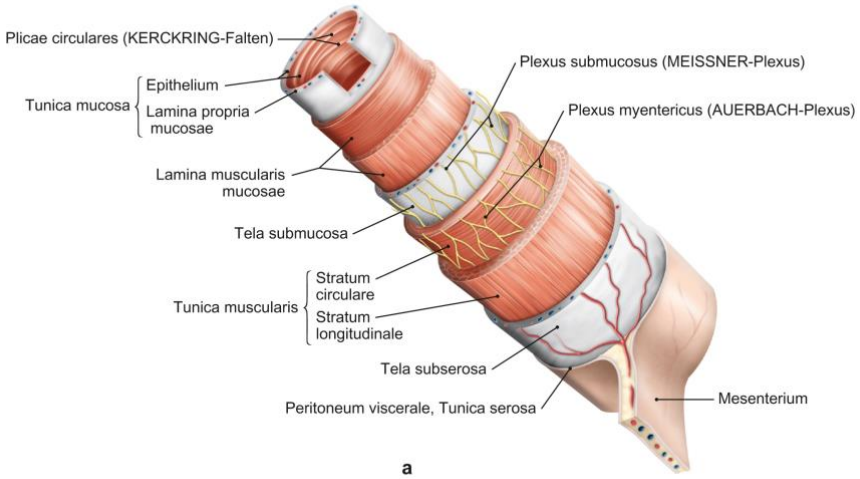
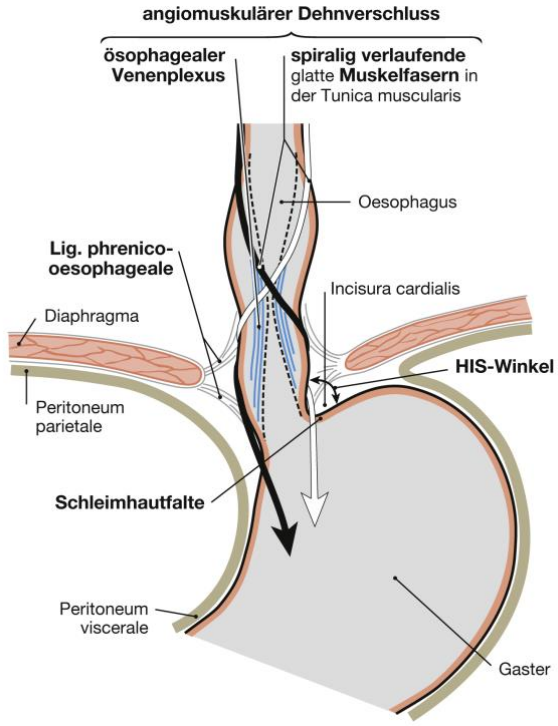


Figure 3: **Plexus myentericus und Auerbach** *6.58a Plexus, M. Hoffmann aus Hombach-Klonisch/Klonisch/Peeler. Sobotta Clinical Atlas of Human Anatomy. 1st ed. 2019 © Elsevier GmbH*

The esophagus is controlled by two sphincters: the UES and the LES. The UES is composed of the cricopharyngeus muscle, esophageal muscle, and a dense venous plexus. It remains closed due to the influence of cholinergic and nicotinic neurotransmitters. The resting tone in the esophageal lumen is primarily determined by the pressure within the mediastinum. On the other hand, the LES is not a true sphincter. Its closure is achieved through a variety of mechanisms. The angiomuscular flap valve (Figure 4) is formed by the tunica muscularis arrangement, which, resembling the threads of a screw, seals the cervical and abdominal parts of the esophagus at rest, leaving only the thoracic part partially open.(2)

During swallowing, the peristaltic wave induces contraction of the longitudinal muscles, which sequentially opens the lumen. Additionally, similar to the UES, a venous plexus in the submucosa ensures a tight seal. A mucosal fold at the angle between the gastric fundus and the esophageal entry (HIS angle) also prevents the stomach contents from rising back up. The phrenicoesophageal ligament anchors the esophagus at the diaphragmatic slit, and both this attachment and the tone of the diaphragm muscles contribute to a tighter closure. Finally,

there is a pressure difference of 15-25 mmHg compared to the gastric fundus. This pressure gradient further aids in closing the LES and prevents stomach contents from refluxing into the esophagus.(2)



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1.3 Deglutition

Swallowing is a complex and coordinated process that integrates both voluntary and involuntary actions, engaging various muscle groups and five cranial nerves (V, VII, IX, X, XII). At the outset, the soft palate rises to block food or liquid from entering the nasal cavity. Simultaneously, the vocal cords close, and the epiglottis folds over the laryngeal opening to protect the airway.(5)

Swallowing is categorized into three phases: the oral phase, the pharyngeal phase, and the esophageal phase. In the oral phase, the tongue propels food or liquid from the mouth into the pharynx. This action stimulates mechanoreceptors, initiating the involuntary swallowing reflex via the glossopharyngeal and vagus nerves, which are linked to the swallowing center. The soft palate then elevates to block the nasopharynx, while the peristaltic contraction of the pharynx propels the bolus through the UES. The UES momentarily relaxes, reducing

muscle tone for 1-2 seconds, allowing the bolus to pass. The typical closure pressure of the UES ranges from 50 to 100 mmHg.(6)

In addition to preventing food from returning to the esophagus, this increased pressure also prevents air from being swallowed continuously. The epiglottis closes off the trachea during swallowing, preventing aspiration of food particles. If this fails, "swallowing the wrong way" can occur, triggering the cough reflex. During the pharyngeal phase, the trachea is blocked, temporarily halting breathing (known as swallowing apnea). Once the peristaltic wave reaches the esophagus, the UES closes again. The final phase occurs within the esophagus itself, where the movement initiated during the pharyngeal phase continues as primary peristalsis. If food is not adequately transported to the stomach, a secondary peristaltic wave is triggered by the stretching of the esophageal wall. The enteric nervous system then takes over coordination. Mucous glands in the submucosa secrete mucus, facilitating the bolus's passage. However, the speed of passage and pressure depend on the bolus's size and consistency, as well as the body's position. In an upright position, liquids take about 1 second to pass, while solid particles may take 10 seconds or more. Under increasing pressure, ranging from 30 to 120 mmHg depending on the bolus, the LES opens for 6-9 seconds. Relaxation is achieved by actively inhibiting the muscle tone through VIP (vasoactive intestinal peptide) and NO-containing neurons, along with reduced cholinergic innervation. This allows the bolus to reach the stomach in approximately 7-10 seconds. The LES then closes again, maintaining an elevated resting tone briefly (7)

During the closure of the LES, a brief reflux of stomach contents is considered physiological. However, pathological reflux occurs when this backflow happens too frequently or persists for an extended period. This can be objectively measured, for example, via pH monitoring. The primary anti-reflux mechanism is maintained by the LES, which adjusts its pressure according to abdominal pressure. This adaptation is critical during times of strain or the passage of a food bolus. Additional anti-reflux mechanisms are important, especially those that involve esophageal clearance through secondary peristalsis and salivation.(5)

Understanding these mechanisms is crucial for correctly applying the gold standard in diagnostics, high-resolution manometry (HRM).

1.4 Prevalence and etiology

Achalasia is a rare motility disorder, with an annual incidence of 1.63 per 100,000 and a prevalence of 10.82 per 100,000. However, these figures may be significantly underestimated. Estimates suggest that symptoms like heartburn and chest pain, commonly attributed to other conditions, initially misdiagnose 27–42% of achalasia patients.(5) A recent American epidemiological study conducted in regions with HRM usage revealed an annual incidence of 10.5 per 100,000 and a prevalence of 18 per 100,000, suggesting that these rates are at least two to three times higher than previously reported. Consequently, given the lack of global standardization in diagnostic criteria and technology, the true prevalence of achalasia remains uncertain.(8)

The period between the first appearance of symptoms and the diagnosis of achalasia can last several years, largely due to its nonspecific nature and rarity.(9) Despite this, a significant rise in the incidence of achalasia has been noted with the implementation of HRM. However, this change in epidemiology is not solely attributable to HRM; it is also believed that there has been an increase in the incidence of the disease, coupled with enhanced awareness due to advancements in diagnostic methods.(10) A recent large cohort study in the USA indicated that the median age of achalasia patients is 52.7 years, with women comprising 56% of the patient population.

A large-scale multicenter study conducted in Japan in 2016 identified male gender and a family history of achalasia as significant risk factors for the condition, while education and occupation did not present a significantly higher risk.(11) In contrast, another study linked socioeconomic status and lifestyle factors to the development of Achalasia, with those in lower occupational roles being at the highest risk. This latter study also suggested that international travel and pet ownership could increase the likelihood of developing the condition.(12)

1.5 Pathogenesis

The esophagus is critical in the digestive system because it facilitates the transport of nutrients. Disorders affecting the esophagus are generally classified into structural changes, such as stenoses, or motility disorders, which can cause dysphagia. These motility disorders

may result from neurological issues or develop directly within the digestive tract. One such motility disorder is esophageal achalasia, which is characterized by the LES inability to relax sufficiently, causing a blockage in esophageal outflow. This condition occurs despite the gastroesophageal junction (EGJ) being free from any structural obstruction and is typically associated with the loss of esophageal peristalsis or the presence of abnormal, spasmodic contractions. Achalasia is commonly divided into primary and secondary forms, with primary achalasia thought to result from the degeneration of ganglion cells in the distal esophagus and LES.(12)

Pseudoachalasia, also known as secondary achalasia, has similar symptoms but is usually caused by structural problems like malignant tumors at the EGJ.(13) Other secondary forms of achalasia include Chagas disease, which results from Trypanosoma cruzi infection of the lower esophagus. The underlying cause of the more common primary achalasia remains unknown.(5) However, it is widely hypothesized that the degeneration of the esophageal nerve cells leads to significant histological alterations in the esophageal mucosa, playing a crucial role in the disease's pathophysiology.(14) This nerve cell dysfunction may be triggered by an autoimmune reaction targeting the nerves of the myenteric plexus through mechanisms that involve both cell-mediated and possibly antibody-mediated processes. (Figure 5) Additionally, various pathological factors, including viral infections, idiopathic autoimmune responses, and genetic predispositions, have been proposed as potential contributors to the pathophysiology.(12)

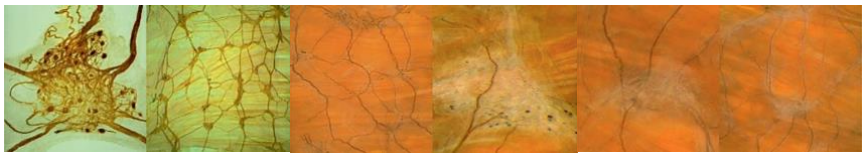


Figure 5: **Myenteric plexus (left) and normal ganglion cell (right) undergoing changes due to autoimmune destruction over time**. Adapted from *Nature Reviews Disease Primers, 2022, Volume 8, Issue 1, Page 4*

Some viruses, including varicella-zoster, herpes simplex, measles, and human papillomavirus, can interfere with the normal regulation of esophageal motility and LES function in certain achalasia patients, although this is not the case for all individuals infected with these viruses. Research indicates that about 80% of achalasia patients had varicella-zoster virus DNA present in their saliva.(12)(Figure 6)

Furthermore, studies suggest that eosinophils and mast cells could be key players in the development of achalasia and related esophageal motility disorders. The presence of these cells in the esophagus may lead to increased production of inflammatory cytokines, which contribute to the fibrotic changes in the esophageal wall, eventually leading to esophageal dysfunction and the symptoms seen in achalasia.(12) A 2013 study of 96 achalasia patients who underwent laparoscopic Heller myotomy (LHM) revealed eosinophilic infiltration in the esophagus. However, other research has not consistently confirmed a direct link between eosinophils and the onset of achalasia.(15)

Research indicates a higher prevalence of autoimmune diseases among individuals with achalasia. For instance, 47.80% of patients have type I diabetes, and 19.60% have thyroid disorders. Further, achalasia is also more frequently associated with autoimmune conditions such as Crohn's disease, rheumatoid arthritis, psoriasis, autoimmune uveitis, and Sjögren's syndrome. Additionally, autoantibodies targeting sarcomeres have been identified in the serum of achalasia patients, particularly those with the HLA-DQA10103 and DQB10603 alleles. The study revealed that thyroid disorders were the most common autoimmune comorbidity, and Down syndrome was the most frequently observed genetic disorder linked to achalasia. Familial achalasia, achalasia related to genetic disorders, and cases connected to autoimmune diseases were documented in 0.63%, 0.99%, and 2.40% of cases.(12)

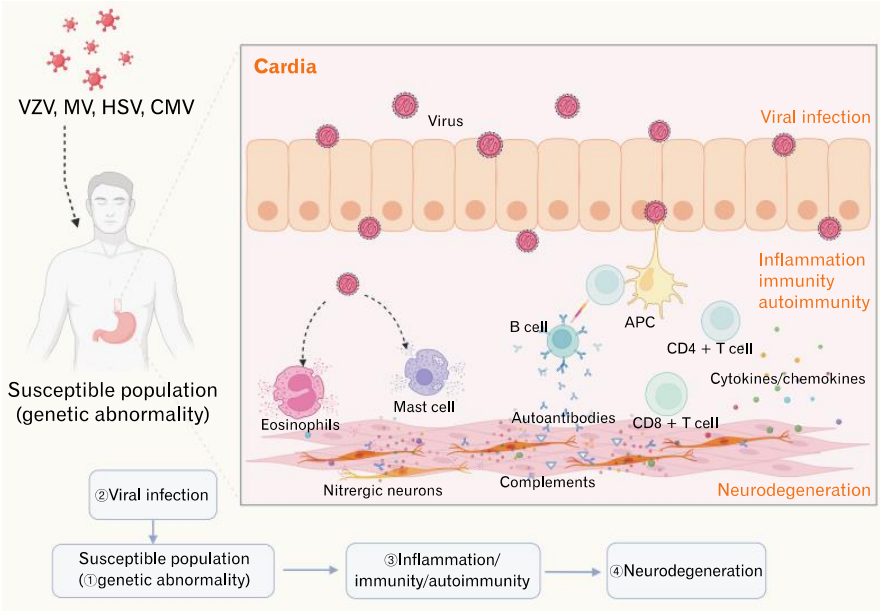


Figure 6: **Infectious hypothesis of achalasia: Individuals with a genetic predisposition may be affected by viruses or other environmental factors** Adapted from the Journal of NGM, 2023, Volume 29, Issue 2, Page 147

1.6 Esophageal Carcinoma

Esophageal cancer affects over 450,000 individuals worldwide each year, with increasing incidence rates. According to a study by Torres-Aguilera et al. (16) it ranks as the eighth most common cancer globally, with nearly 80% of cases found in non-industrialized regions, particularly Asia and Africa. According to the National Cancer Institute, in 2016 there were approximately 16,910 new cases and 15,910 deaths attributed to this malignancy. The prognosis for esophageal cancer remains bleak, with five-year survival rates hovering between 15% and 25% in most countries, leading to high mortality rates. There are two main forms of esophageal cancer: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA).(17) These cancers differ significantly in terms of incidence, ethnic prevalence, and geographic distribution. ESCC is the dominant type globally, particularly in developing countries. Conversely, EA now accounts for up to 50% of esophageal cancer cases in Western countries and is rapidly increasing in incidence. Esophageal cancer, like other gastrointestinal malignancies, has identifiable risk factors However, screening for this type of cancer is challenging and often unreliable, resulting in a high frequency of late-stage diagnoses. Although rare, achalasia can increase the risk of developing esophageal cancer, with studies indicating prevalence rates ranging from 0.4% to 9.2%. The association between achalasia and esophageal cancer was first documented in 1872, and subsequent case reports and studies have continued to investigate this link, yielding critical yet inconsistent data. The risk of ESCC among achalasia patients varies significantly, with some studies suggesting it may be up to 50 times higher compared to a control population matched by age and gender.(17) A recent meta-analysis reviewing 40 studies with 11,978 patients reported an incidence rate of squamous cell carcinoma at 312.4 cases per 100,000 patient-years. The prevalence of ESCC in achalasia patients was identified as 26 cases per 1,000, with an increase in absolute risk of 308.1 cases per 100,000 patients annually.(16) Most esophageal cancers associated with achalasia are ESCC. However, cases of adenocarcinomas linked to Barrett’s esophagus have also been observed. These often result from prolonged acid exposure in the esophagus following achalasia treatment, potentially leading to Barrett’s esophagus development. For instance, a study in the Netherlands found that 8.4% of 331 Achalasia patients who underwent pneumatic dilation developed Barrett’s esophagus over a follow-up period of up to 25 years.(16)

1.7 Diagnostic

Diagnosing achalasia involves recognizing general symptoms and performing various diagnostic tests to verify the disorder. Collecting a comprehensive medical history is a critical step in this diagnostic framework.

According to a study by Savarino et al.(18), patients with symptoms such as dysphagia, which affects both solids and liquids, as well as nighttime regurgitation of undigested food and saliva. These issues can cause weight loss and occasionally lead to bronchitis or recurrent pneumonia. Achalasia could also manifest in those struggling with severe obesity, possibly because decreased sensitivity in the esophagus dulls the perception of swallowing difficulties. Additionally, mistaking the regurgitation of food for vomiting can lead to the wrong conclusion, making it seem like a stomach issue rather than a problem originating in the esophagus.(18) Additionally, chest pain, which is consistent across all achalasia subtypes but notably severe in Type 3, has unclear origins. Possible causes include acidic fermentation of food residues, esophagitis from prolonged food exposure, erratic muscle spasms, or increased esophagus sensitivity. Children's symptoms mirror those of adults, but they also include additional indicators such as coughing or choking during meals, recurrent aspiration pneumonia, eating difficulties, refusal of food, and growth disorders.(18)

Other benign conditions, such as gastroesophageal reflux disease (GERD), benign esophageal strictures, eosinophilic esophagitis, diffuse esophageal spasms, hypercontractile esophagus, and neoplastic esophageal diseases, are more common causes of dysphagia and regurgitation than achalasia. Therefore, the diagnosis of achalasia usually follows the exclusion of other structural or mucosal causes through diagnostic procedures like upper endoscopy and/or a barium swallow X-ray.(18)

1.7.1 Medical history/Eckardt symptom score

During the collection of a patient's medical history, special emphasis should be placed on the primary symptoms such as dysphagia, regurgitation, chest pain, and weight loss. However, these symptoms are not exclusively indicative of esophageal motility disorders.(19) Dysphagia with liquids and chest pain may suggest motility issues, but they can also be caused by physical obstructions.(19)

The severity of these symptoms is assessed using the Eckardt symptom score, a subjective measurement that helps evaluate the intensity of a patient's symptoms and can guide discussions on the potential need to intensify treatment. In addition to these primary symptoms, other aspects such as the onset of symptoms, family history, and any comorbidities are crucial for a comprehensive understanding of the disease's progression.(20)

The Eckardt Symptom Score (ESS) is the most commonly utilized tool for gauging the severity of achalasia. It quantifies the intensity of four primary symptoms: dysphagia, regurgitation, chest pain, and weight loss. Each symptom is rated on a scale from 0 to 3, reflecting its frequency (ranging from none, occasional, daily, to with every meal) or the degree of weight loss (measured in increments of 5 kg). The maximum possible cumulative score is 12 points.(Table 1)(21) Although the ESS was not originally designed for monitoring treatment outcomes, it is frequently used in clinical practice for this purpose. A post-treatment ESS score of less than 3 is typically considered a clinical success in terms of symptom relief.(22) However, there are some inconsistencies to note, such as the fact that regurgitation and chest pain might be related to post-treatment reflux, and weight gain may not be a reliable indicator in cases with short follow-up intervals.(23)

Table 1: Calculation of the Eckardt Symptom Score

Score	Dysphagia	Regurgitation	Retrosternal Pain	Weight Loss
0	none	none	none	none
1	occasional	occasional	occasional	<5
2	daily	daily	daily	5-10 kg
3	each meal	each meal	each meal	>10 kg

Additional diagnostic procedures that are valuable in confirming achalasia, monitoring its progression, or guiding treatment include:

- HRM
- Endoscopy
- Barium swallow X-ray
- CT scan/endoscopic ultrasound
- Functional Lumen Imaging Probe (FLIP)

1.7.2 High-resolution manometry (HRM)

Prior to the introduction of HRM into clinical esophagology in the early 2000s, conventional line-tracing manometry was the go-to technique for evaluating esophageal motility. These older manometry systems utilized catheters hand-made from materials like silicone or polyvinyl chloride, incorporating anywhere from three to eight lumens that ended with pressure sensors, although the optimal placement of these sensors lacked standardization. The primary goal of these measurements was to ascertain the pressure of the LES, yet achieving precise readings was complicated by the axial movements of the sphincter during respiration and swallowing.(24)

The evolution to modern technologies brought forth solid-state catheters that span the full length of the esophagus, enabling the simultaneous visualization of the sphincter and the EGJ during assessments. This advancement has streamlined the procedure, enhancing patient comfort and reducing procedure times. HRM not only provides more precise and consistent readings by trained motility specialists, but it has also been shown, in a clinical study of 247 patients with dysphagia, to offer a superior diagnostic yield for achalasia and facilitate earlier diagnoses compared to conventional methods.(24)

The Chicago Classification (20) aimed to establish a standardized manometry protocol globally to ensure consistent procedures, enhance diagnostic accuracy, and promote cooperative research.

For patients undergoing manometry, a minimum fast of 4 hours is required, though small amounts of clear liquids may be consumed. The protocol involves initially positioning the

patient sitting, followed by a repeat while lying down. The procedure starts with a rest period to pinpoint anatomical features like the UES and LES, and continues with various swallow and provocation tests.

If standard HRM protocols do not conclusively reveal a severe motility disorder, or if results are inconsistent with clinical observations or fail to account for the patient's symptoms, further HRM evaluations might be necessary. These may include solid test swallows, meal assessments to check for EGJ obstruction, and postprandial monitoring for signs of rumination or belching. Pharmacological challenges may also be used during the protocol to confirm EGJ obstruction. If results remain unclear, additional diagnostics such as a timed barium esophagogram (TBE) and FLIP might prove helpful.(20)

Primary HRM metrics assessed include swallow-induced LES/EGJ relaxation measured by integrated relaxation pressure (IRP), esophageal contraction strength via the distal contractile integral (DCI), contraction wavefront integrity at an isobaric contour of 20 mmHg, and the timing of swallow-induced inhibition as determined by distal latency (DL). Notably, the average IRP threshold is higher when the patient is in a supine position compared to an upright position, while the thresholds for DCI and DL are consistent regardless of the patient’s posture.(20)

The assessment of esophageal dysmotility follows a structured approach, beginning with the investigation of outflow obstruction disorders and subsequently focusing on esophageal peristalsis. This approach is grounded in the idea that issues at the EGJ can influence the motility of the esophageal body, making it essential to address EGJ dysfunction before evaluating the esophageal body's motility. In this evaluation, a critical metric is the IRP, which measures the EGJ's relaxation by measuring the pressure differential between the esophageal body and the upper stomach during swallowing. If the IRP remains consistently high during standard and provocation swallowing tests, it suggests an esophagogastric motility disorder. When the esophageal body's motility is otherwise normal, this condition is termed esophagogastric junction outflow obstruction (EGJOO). However, if the esophageal body shows absent or spastic peristalsis, the condition is identified as achalasia.(23)

Additionally, HRM can distinguish between three specific subtypes of achalasia based on the distinct contraction patterns of the esophageal body.(Figure 7) For a deeper exploration of these subtypes, consult the chapter dedicated to achalasia classification.

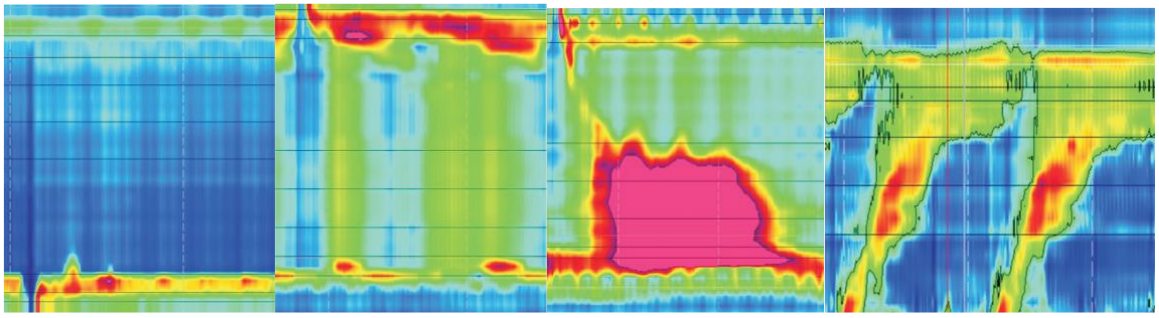


Figure 7: **From left to right: Achalasia Types 1, 2, and 3, and "EGJOO in intact peristalsis" in HRM.** Adapted from *Journal of NGM, 2023, Volume 29, Issue 4, Page 422*

1.7.3 Endoscopy

While HRM remains the gold standard for diagnosing achalasia, endoscopy is invaluable for early detection, particularly in differentiating it from other structural diseases and pathologies such as membranes, rings, esophageal cancer, and proximal gastric carcinomas, which can present with similar symptoms.(25) The leading cause of secondary achalasia is malignancy, accounting for over half of all cases, followed by benign lesions and iatrogenic injuries.(26, 27) Numerous studies have investigated the possible link between achalasia and eosinophilic esophagitis (EoE), finding that individuals who suffer from both conditions often experience poorer outcomes and have a less favorable response to treatment. Consequently, for patients who present with dysphagia, it is advisable to perform an endoscopic examination with multiple esophageal biopsies to exclude the presence of EoE.(28)

Endoscopic evaluation in achalasia typically reveals several classic findings: retained saliva, a wrinkled appearance at the EGJ, dilation of the esophageal lumen, and residual food within the esophagus. (Figure 8) The Japanese Society for Esophageal Research has outlined specific diagnostic criteria, including: (27)

1. Dilatation of the esophageal lumen
2. Abnormal retention of food and/or liquid remnants in the esophagus
3. Whitish change and thickening of the esophageal mucosal surface

4. Functional stenosis of the esophagogastric junction (endoscope passes through the stenotic segment, although the esophagogastric junction fails to be dilated by insufflation)
5. Abnormal contraction waves of the esophagus(29)

Figure 8: **Dilatation of the esophageal lumen, abnormal retention of food, thickening of the mucosal surface, functional stenosis of the EGJ, and abnormal contraction wave.** Adapted from *Clinical Endoscopy, 2023, Volume 56, Issue 5, Page 538*

The esophageal mucosa may look normal in the early stages of achalasia or in type III cases, which can cause a lot of time to pass before the problem is diagnosed. Indeed, only about half of achalasia patients exhibit the classic endoscopic signs, meaning that a normal endoscopy does not exclude the diagnosis.(27)

Recently, additional endoscopic features have been recognized as indicative of achalasia. These include fine superficial ridges, known as the "pinstripe pattern,"(Figure 9) seen in 60.7% of patients, and esophageal dilation or residual food, observed in 41.1% of cases.(30) Moreover, primary achalasia is characterized by the absence of esophageal palisade vessels (EPVs) and the presence of rosette-like folds in the lower esophagus during deep inspiration(27). In one study, EPVs were absent in 28 out of 34 patients, and rosette-like folds were observed in 33 out of 34 cases.(31) These represent valuable diagnostic indicators for achalasia in specific patient populations.

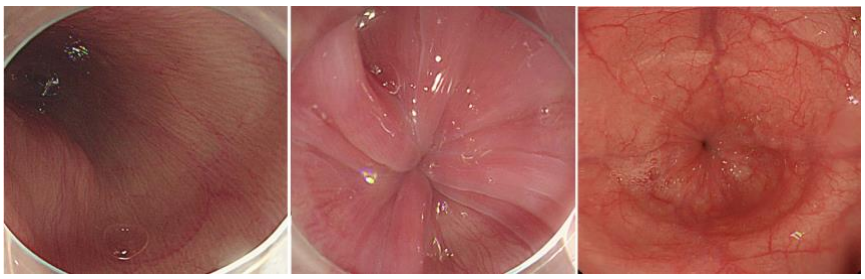


Figure 9: **Pinstripe pattern, rosette-like esophageal folds, and champagne glass sign.** Adapted from *Clinical Endoscopy, 2023, Volume 56, Issue 5, Page 539*

1.7.4 Barium Swallow

The barium swallow test, a standard clinical procedure, is utilized to visualize the movement of a bolus through the esophagus into the stomach using barium sulfate as a contrast agent. Historically, its diagnostic utility was limited, particularly prior to the development of the TBE.(32) Traditional radiographic indicators like the bird-beak sign, air-fluid level, corkscrew or rosary bead appearance were often unreliable and typically only appeared in advanced stages of achalasia.(19)

Over the last twenty years, the utility of barium radiography has been greatly improved with the advent of TBE. During this procedure, patients are instructed to quickly consume approximately 200 ml of barium contrast while standing. A sequence of X-ray images is then captured at set intervals—typically at 1, 2, and 5 minutes post-ingestion.(Figure 10) By measuring the height and width of the barium column remaining in the esophagus, healthcare professionals can more precisely determine the extent of esophageal blockage.(23) TBE has demonstrated its value not only as a dependable diagnostic approach but also as a useful method for tracking treatment progress during subsequent care.(33)

Typically, under normal conditions, barium should pass entirely through the esophagus within 1 to 2 minutes after being swallowed. If barium remains, it suggests a potential passage problem, with taller columns indicating reduced esophageal clearance. In a major study, the presence of a 5 cm barium column after 1 minute or a 2 cm column after 5 minutes was found to be highly sensitive in diagnosing achalasia in patients experiencing swallowing difficulties. This method showed sensitivity rates of 86% and 80% and specificity rates of 71% and 86%.(32)

Recent research has further refined the role of TBE in differentiating between subtypes of EGJOO and achalasia (Types I, II, and III). The study found that Types I and II achalasia were associated with greater barium retention at both 1 and 5 minutes post-ingestion compared to Type III and EGJOO, suggesting that TBE is less sensitive in conditions where esophageal motility is impaired but not completely absent, as seen in obstructive disorders.(23)

When assessing treatment effectiveness, changes in the barium column's height or surface area have been found to correlate more accurately with therapeutic outcomes than height measurements alone. The introduction of computer-assisted TBE image analysis has further improved diagnostic accuracy. A retrospective study compared TBE and HRM. The dilated diameter index showed that automated TBE analysis had a sensitivity of 95% and specificity of 93% for diagnosing achalasia and a specificity of 85% and sensitivity of 87% for diagnosing EGJOO. Some researchers have proposed incorporating solid components, like a barium pill, marshmallow, or bread, into the standard TBE protocol. Although this method is not yet standardized, studies comparing liquid barium with barium pills have shown a notable increase in diagnostic yield for both achalasia and EGJOO. (23)Moreover, TBE is also utilized in cases where esophageal perforation is suspected, such as following pneumatic dilation procedures.(34)

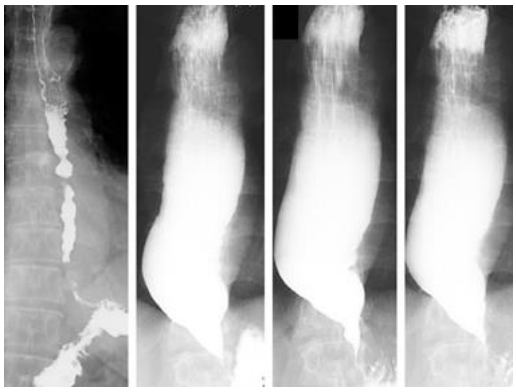


Figure 10: **Hypercontractile/spastic disorders; timed barium esophagogram showing abnormal barium retention at 1, 2, and 5 minutes after barium ingestion.** Adapted from *Digestion, 2023, Volume 105, Issue 1, Page 13*

1.7.5 The functional lumen imaging probe (FLIP)

FLIP is an advanced tool utilizing high-resolution impedance technology to analyze the relationship between pressure and the geometry of the esophagus. FLIP's capability to simultaneously evaluate cross-sectional area and pressure enables it to create a three-dimensional model that is particularly useful for assessing the dynamics of esophagogastric junction (EGJ) opening, especially in the context of achalasia.

Typically performed during a sedated endoscopy, the FLIP procedure is brief, lasting under five minutes. The procedure involves the transoral insertion of a catheter equipped with a

balloon filled with 20 mL of saline into the esophagus. The catheter may shift during the procedure as the esophagus contracts, necessitating real-time adjustments. The balloon is then gradually inflated in 10 mL increments until it reaches 70 mL, with adjustments made based on the narrowing observed on the display.(35)

A key measurement obtained from FLIP is the distensibility index (DI), which assesses the flexibility of the LES. The DI is calculated by dividing the narrowest cross-sectional area within the sphincter by the corresponding balloon pressure over a set period.(36) (Figure 11) In individuals with achalasia who have not received treatment, the DI is usually around 1 mm^2/mm Hg or lower, whereas it averages about 6 mm^2/mm Hg in the general population.(37)

FLIP has proven to be an effective diagnostic tool for achalasia, often aligning closely with the results obtained through manometry. It is particularly valuable in cases where manometry does not provide a definitive diagnosis, despite strong clinical indications of achalasia. Studies have shown that FLIP panometry is both sensitive and accurate in detecting achalasia, comparable to HRM. For instance, in a study of 145 patients, 70 were diagnosed with achalasia using HRM, and all 70 showed reduced EGJ distensibility on FLIP as well. FLIP also offers an alternative for patients who cannot undergo or complete standard manometry, as it can be performed during sedated endoscopy.

Ongoing research is investigating the potential of FLIP to either replace or reduce the need for traditional manometry and barium esophagograms in achalasia management. Because FLIP can be performed during the initial endoscopic evaluation, it offers a potentially cost-effective approach. Currently, FLIP is a useful option for patients who are unable to tolerate manometry and may serve as an important diagnostic tool in challenging cases both pre- and post-treatment.(34)

In one study, patients who showed clinical and radiological signs of achalasia but did not meet the diagnostic threshold of an IRP greater than 15 mm Hg on HRM were assessed using FLIP. The reduced EGJ distensibility observed during FLIP led to treatment for achalasia, which subsequently resulted in symptom improvement.(38)

Another study focused on evaluating treatment outcomes in achalasia patients following pneumatic dilation or LES myotomy. The people who had worse symptomatic outcomes had

a lower EGJ-DI, often below the level of 2.8–2.9 mm2/mm Hg, compared to those who had better outcomes. This suggests that DI could serve as a more objective measure of treatment success, potentially offering a more reliable indicator than the subjective ESS commonly used to monitor therapeutic progress.(37)

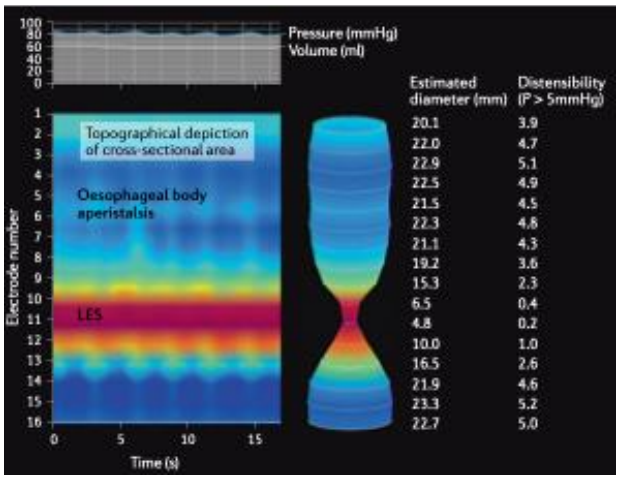


Figure 11: **FLIP measurement: Low distensibility index (DI) with assumption for achalasia.** Adapted from *Nature Reviews Disease Primers, 2022, Volume 8, Issue 28, Page 9*

Additional imaging techniques, such as CT scans or endoscopic ultrasound, have limited application in the diagnosis of achalasia.(39) They are primarily used to rule out pseudoachalasia or other structural disorders when there is a strong clinical suspicion.(40)

1.8 Classification of Achalasia

Achalasia is a complex and heterogeneous disorder characterized by variations in its underlying causes, pathophysiological mechanisms, and clinical manifestations across its subtypes. A hallmark of the disease is the impaired relaxation of the LES. The patterns of esophageal motility differ significantly among the three subtypes of achalasia, which are identified using HRM.(41) These subtypes include Type I, where LES relaxation impairment is accompanied by absent peristalsis; Type II, characterized by pan-esophageal pressurization; and Type III, marked by premature (spastic) distal esophageal contractions. In some cases, peristalsis may still be preserved, yet achalasia remains evident.(42)

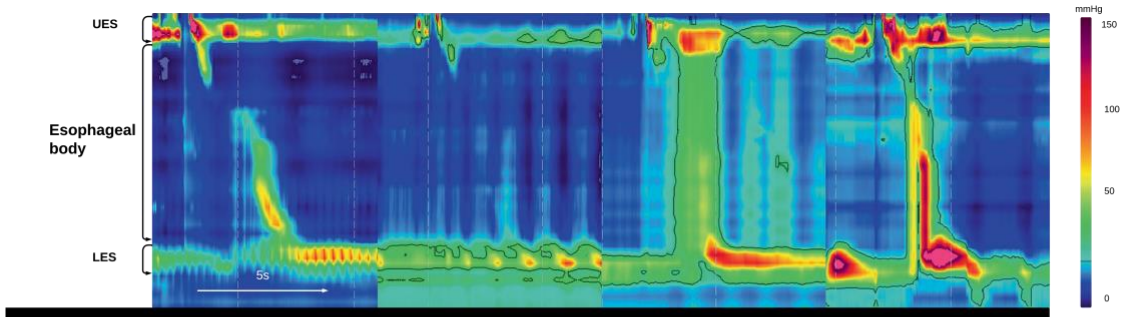
Like in the Chicago protocol summed up (20) Type I achalasia is identified when there is a high median IRP at the LES, no watery swallows at all (defined by a distal contractile

integral, or DCI, of less than 100 mmHg·s·cm), and less than 20% of swallows causing pan-esophageal pressurization. An elevated median IRP, complete failure of wet swallows, and panesophageal pressurization in 20% or more of swallows identify Type II achalasia, often considered an earlier stage with a better prognosis. Type III achalasia, resembling spastic achalasia, is thought to represent a distinct pathological process. Unlike the other subtypes, this variant shows fewer indications of progressive neuronal loss in the distal esophagus and the LES.(43)

Achalasia Subtype Profiles from chicago protocol 4.0: (20) (Figure 12)

- **Type I Achalasia:** This subtype makes up 20–40% of all cases of achalasia. It has an abnormal median IRP and no peristalsis at all
- **Type II Achalasia:** is defined by an abnormal median IRP, complete failure of peristalsis, and pan-esophageal pressurization in a significant proportion of swallows. Type II represents 50-70% of cases.
- **Type III Achalasia**: is the least common type, making up less than 5% of cases. It is diagnosed when an abnormal IRP is seen along with esophageal spasms (premature contractions in 20% or more swallows) that don't have peristalsis

The contraction patterns of esophageal muscles also vary among the subtypes. In normal peristalsis, the circular and longitudinal smooth muscles contract in sync. However, in Type I achalasia, both muscle types show significant impairment, with little or no longitudinal muscle activity. Conversely, Type II achalasia retains robust longitudinal muscle contractions, which are crucial for pan-esophageal pressurization. Type III achalasia is marked by a pronounced lack of coordination between the circular and longitudinal muscle contractions, resulting in distinct motility patterns across the subtypes.(44)



Category	Normal	Typ 1	Typ 2	Typ 3
Definition	IRP exceeds normal limits Normal peristalsis or Less than 5% failed swallows	IRP exceeds normal limits Complete absence of peristalsis No pressurization	IRP exceeds normal limits More than 10% peristalsis Over 20% premature peristalsis Compartmentalization	IRP exceeds normal limits Absence of body peristalsis with pressurization
LES Relaxation	Normal	Impaired	Impaired	Impaired
Smooth Muscle Function	Both circular and longitudinal muscles function correctly	Neither circular nor longitudinal muscles contract; esophagus is dilated	Circular muscles do not contract; limited longitudinal muscle contraction	Circular and longitudinal muscles contract but lack coordination and are asynchronous
Esophageal Emptying	Normal esophageal emptying	Severely limited; rely on gravity and patient maneuvers to boost intrabolus pressure	Suboptimal emptying; consider post-esophageal pressurization	Esophageal emptying may be sufficient; consider post-esophageal pressurization and compartmentalized

Figure 12: **Normal HRM and Achalasia Types 1–3 in comparison.** Adapted from *Nature Reviews Disease Primers, 2022, Volume 8, Issue 28, Page 5*

The mechanisms for esophageal emptying vary across different Achalasia subtypes. Savarino et al. (18) report that in Type I achalasia, gravity is the main thing that helps the esophagus to empty. However, some people learn how to raise the pressure inside their chest beyond what is needed to close the LES. Type II achalasia relies on pan-esophageal pressurization against a closed LES for occasional emptying, supported by the continued function of proximal striated muscle contraction, longitudinal muscle activity, and partial contractions of the distal circular muscles. Interestingly, impedance studies indicate that esophageal transit in Type III achalasia, though segmented and uncoordinated, can still be functionally effective. Multi-rapid swallow (MRS) tests show that Type I achalasia is marked by the absence of LES relaxation; Type II may lead to increased LES pressure; and Type III can display almost normal LES relaxation.(18)

In instances where HRM findings do not correspond with the patient's symptoms, additional diagnostic tools such as a timed barium esophagram or FLIP can be valuable. For patients with suspected pseudoachalasia, particularly those who are older and have experienced

significant short-term weight loss, endoscopic ultrasound or cross-sectional imaging should be considered as part of the diagnostic evaluation.(34)(Figure 13)

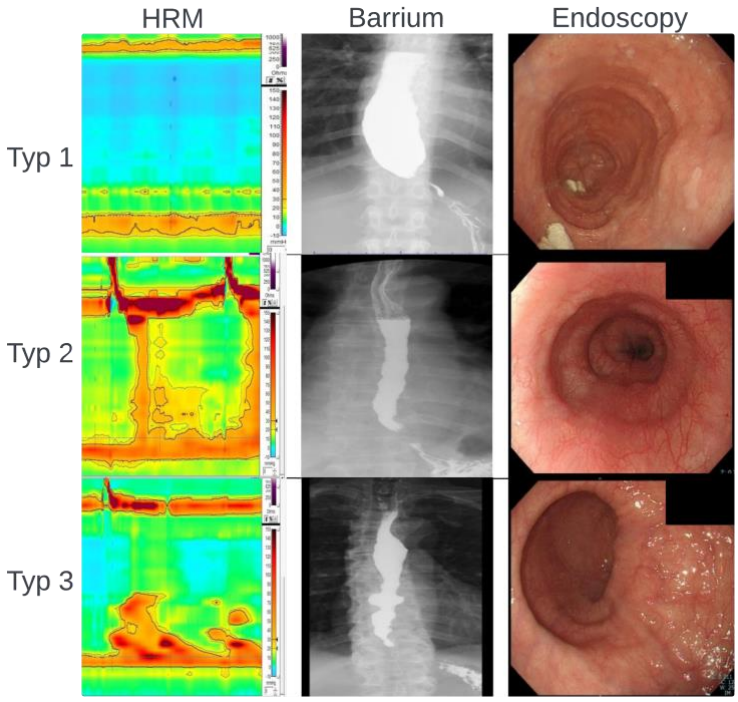


Figure 13: **HRM, barium swallow, and endoscopy findings from Achalasia Types 1, 2, and 3.** Adapted from *Journal of Smooth Muscle Research, 2023, Volume 59, Page 19*

1.9 Therapy

Common therapies in practice can be divided into surgical/endoscopic and pharmacological approaches. Over the decades, a variety of treatment methods have been tested. Since most are not recommended in practical treatment, the focus will be on the essential ones. All others should only be used within a controlled study framework.

1.9.1 Unconventional therapy options

1.9.1.1 Pharmacology

Over the past decade, the therapeutic landscape for achalasia has undergone substantial changes. Oral medications, once a common treatment, have now largely fallen out of favor due to their limited efficacy. Among the most commonly studied drugs are calcium channel blockers, such as sublingual nifedipine and nitrates, like sublingual isosorbide dinitrate. (45) The effectiveness of these medications varies, and their use is frequently associated with serious side effects such as headaches, low blood pressure, peripheral swelling, and the rapid

development of drug tolerance.(45) These side effects often lead to poor patient compliance, particularly in the short-term. With the introduction of more dependable and long-lasting treatment options, the reliance on oral medication for managing achalasia has decreased, and it is no longer recommended as the first-line treatment.(46, 47)

1.9.1.2 Botolinum injection

In addition to standard achalasia treatments like pneumatic balloon dilation, Heller myotomy, and peroral endoscopic myotomy (POEM), botulinum toxin injection has emerged as the most extensively studied alternative therapy. This method should be considered a primary option for patients who are not suitable candidates for pneumatic dilation or surgical myotomy due to significant comorbidities.(45) For older patients in generally good health, the choice of treatment should align with the type of achalasia, the patient's preferences, and the expertise available, mirroring the approach taken with younger individuals.(48)

Botulinum toxin is injected into four sections of the lower esophageal sphincter during an upper endoscopy (Figure 14), with a total of 100 units administered. Initial symptom relief is experienced by 79% of patients within 30 days, dropping to 70% at the 3-month mark, 53% at 6 months, and just 41% after a year. Although this treatment shows promising short-term results, its effectiveness significantly wanes over time, with almost half of the patients requiring additional injections within 6 months to maintain symptom control.(45)

1.9.2 Pneumatic Dilatation (PD)

PD involves the use of a non-radiopaque polyethylene balloon, which comes in graded sizes of 3.0, 3.5, and 4.0 cm, typically employed in a stepwise fashion.(Figure 14) A newer option, the 30-mm hydrostatic balloon dilator (EsoFLIP), is also available.(45) This device utilizes impedance planimetry to allow real-time measurement of the esophageal lumen diameter during endoscopy, eliminating the need for fluoroscopy, although its current application is limited to the 30-mm size.(45) The reported success rates of PD within the first six months range widely from 52% to 99%.(49)

The American College of Gastroenterology (ACG) guidelines advocate for a graduated approach to pneumatic dilation in achalasia patients. The process begins with a 30-mm balloon, followed by a 35-mm balloon, and if necessary, a 40-mm balloon for patients who do not respond to the smaller sizes (34) After six months, the remission rates are similar for the 30-mm and 35-mm dilations, at 81% and 79%, respectively, while the 40-mm dilation shows a higher remission rate of 90%. However, while short-term success rates can reach up to 88%, they tend to decline over time, with only 54% of patients maintaining remission after five years. Research has demonstrated that a series of three dilations is significantly more effective than one or two sessions, with increasing efficacy as balloon diameters grow, peaking in a stepwise progression up to 40 mm.(34) Notably, the risk of perforation increases with larger balloons, with 9.3% of perforations occurring during the use of the 35-mm balloon compared to 1.1% with the 30-mm balloon. Interestingly, no perforations were reported with the 40-mm balloon, though data for this size is limited.(50) When employing a graded dilation approach, the overall perforation risk drops to 0.97%. Factors that predict a positive clinical response to PD include being over 45 years old, female, having a narrow esophagus, and having Type II achalasia.(51)

After the procedure, it is essential to assess the patient for any injuries or potential perforations. Patients should be observed in the recovery area for signs of complications. A follow-up shortly after the procedure will help gauge therapeutic success based on symptom resolution. If perforation is not suspected, a routine esophagram post-PD is generally unnecessary. For patients whose symptoms persist, a subsequent dilation with the next larger balloon size is recommended, or alternative treatments such as POEM or laparoscopic Heller myotomy (LHM) may be considered. An objective evaluation of treatment effectiveness is then carried out after 4–6 weeks.(34)

1.9.3 Laproscopic Heller Myotomie (LHM)

The introduction of minimally invasive surgery in the early 1990s brought about a major change in the treatment of achalasia, with laparoscopic techniques quickly becoming the preferred method for performing myotomy on the LES. This innovation marked a significant transition from the traditional reliance on pneumatic dilation to the widespread use of LHM as the main treatment approach for achalasia.(52) LHM has surpassed other surgical methods, such as transabdominal, transthoracic, and thoracoscopic approaches, largely due

to its lower invasiveness and a reduced risk of GERD.(53) The current LHM procedure involves cutting through the two muscle layers of the EGJ, extending the incision 2–3 cm onto the upper stomach.(Figure 14) Despite its efficacy, LHM carries a risk of postoperative GERD similar to that seen after pneumatic dilation. To mitigate this, a fundoplication is often added, typically an anterior partial fundoplication (Dor, 180°) or a posterior partial fundoplication (Toupet, 270°). The success of LHM heavily depends on the surgeon's experience, with the procedure's learning curve requiring at least 20 surgeries—a challenge given the rarity of achalasia cases. These factors, in addition to the need for general anesthesia, are notable drawbacks of this treatment method.(54)

Initial success rates with LHM are impressive, averaging 89% over a median follow-up period of 35 months. However, like many treatments, its effectiveness can wane over time. Despite this, a long-term study involving a large patient cohort revealed that more than 80% of patients remained symptom-free two decades post-surgery.

Patients with type II achalasia tend to have the most favorable outcomes following LHM, mirroring the results seen with pneumatic dilation. Type III achalasia patients also benefit significantly from LHM, as well as from POEM. This advantage may stem from the myotomy's ability to sever muscle fibers above the LES. Additionally, some manometric studies suggest that the LES is longer in type III achalasia compared to the other subtypes, making an extended myotomy, both upward and downward, particularly effective.(54)

The most frequent complication linked to LHM is mucosal perforation, which occurs in 2.5–7% of cases. Fortunately, the majority of these perforations are detected and repaired during the procedure, usually without causing long-term issues, although they may lead to a longer hospital stay for the patient. Another concern following LHM is the potential development of GERD, even when a fundoplication is performed.(54) A review of various studies revealed that 8.8% of patients experienced GERD after myotomy with fundoplication, whereas this rate increased to 31.5% when fundoplication was not performed.(55)

A European study from the past few years found that 23% of patients developed GERD within five years of undergoing LHM, which was not significantly different from the 15% incidence following pneumatic dilation. Additionally, a large-scale study (52) involving

1,001 patients who received LHM with Dor fundoplication at a specialized center reported that only 9.1% developed GERD, as confirmed by 24-hour pH testing.(54)

LHM can be considered for patients who need rescue treatment following a failed myotomy or when additional pneumatic dilation proves ineffective. Although these subsequent procedures carry a higher risk of failure and a greater chance of developing postoperative GERD, LHM remains a reliable and effective approach for managing symptoms in patients with persistent achalasia.(56)

1.9.4 Peroral endoscopic myotomy (POEM)

The first POEM was successfully performed in Japan 2008, marking a significant advancement in the treatment of achalasia.(Figure 14) This technique was designed to merge the advantages of a minimally invasive endoscopic procedure with the durability of a surgical myotomy.(27) POEM is carried out in four key stages: accessing the submucosal space, creating a submucosal tunnel, performing the endoscopic myotomy, and finally, closing the entry point in the mucosa.(27)

The length of the myotomy typically ranges from 7 to 13 cm, depending on the extent of esophageal involvement. For patients diagnosed with type III achalasia, the myotomy is often extended beyond this range to effectively target and relieve spastic segments within the esophageal body. Typically, the procedure involves a selective myotomy, dividing only the circular muscle layer while preserving the longitudinal muscle layer.(27) This approach helps maintain some structural integrity of the esophagus while still providing the necessary relief from symptoms. Additionally, the preservation of the longitudinal muscle may contribute to a reduced risk of complications, such as esophageal perforation. This technique ensures that the functional outcome is optimized for patients with varying severities of achalasia.(57)

However, despite efforts to preserve the longitudinal muscle fibers, they are sometimes inadvertently damaged, which can lead to gas escaping from the esophagus. After completing the myotomy, the entry incision is sealed using several hemostatic clips. Since the esophagus lacks a serosal layer, some degree of gas leakage during the procedure is almost inevitable. To manage this positive pressure ventilation and CO2 insufflation are used to minimize the leakage.(27)

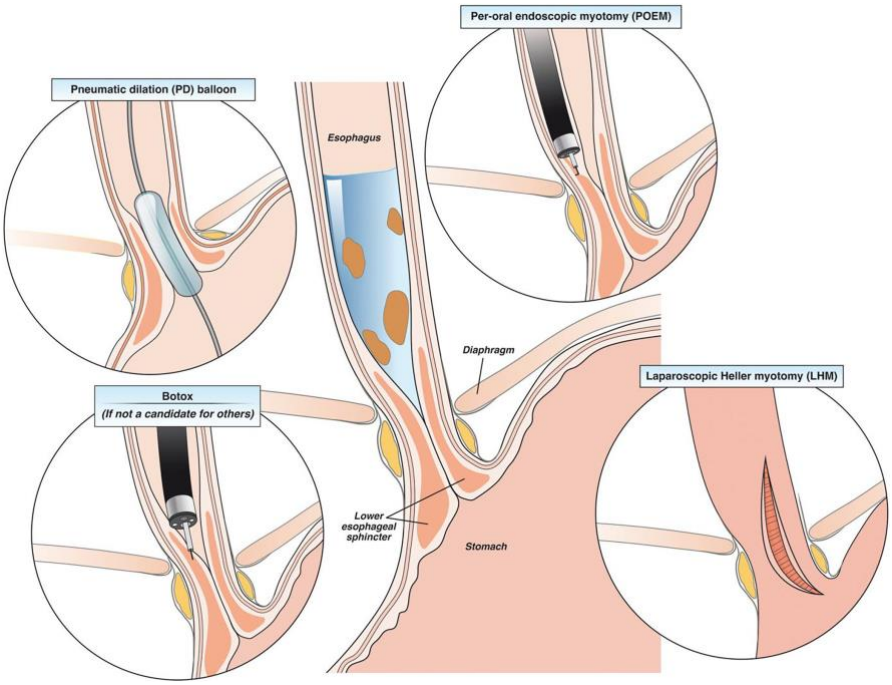


Figure 14: **Main treatment options for achalasia.** Adapted from *Gastroenterology, 2022, Volume 162, Issue 6, Page 1632*

Following POEM, 22.8% of patients experienced minor gas-related complications, according to a multicenter retrospective study. The most frequent complication observed was pneumoperitoneum, affecting 15.5% of patients, followed by subcutaneous emphysema (4.9%), pneumomediastinum (1.8%), and pneumoretroperitoneum (0.6%). However, these minor gas leaks usually don't interfere with the perioperative process and tend to resolve spontaneously.(27) Serious complications, such as mucosal injuries, bleeding, or hemothorax, are relatively uncommon, occurring in about 2.4% of cases.(27) GERD is a more frequent concern, with prevalence rates ranging from 29.4% to 39.7%. Proton pump inhibitors typically effectively manage symptomatic GERD.(27) Recently, an endoscopic fundoplication procedure performed simultaneously with POEM has been developed, which has shown a notably lower incidence of GERD compared to the traditional POEM technique after one year of follow-up.(58)

1.9.5 Esophagectomy

For patients with advanced achalasia who continue to suffer from persistent symptoms despite various treatments, esophagectomy should be considered, particularly when other therapies have not worked or are unavailable. As achalasia progresses, the esophagus

becomes increasingly dilated and deformed, exacerbating the food blockage and leading to significant saliva and food retention.(59)

For individuals with ongoing symptoms and a markedly dilated and distorted esophagus—particularly if previous pneumatic dilation efforts have failed-surgical myotomy should be considered. If an initial myotomy does not resolve the issue, a subsequent procedure might be necessary. Should both attempts prove ineffective, esophagectomy becomes the logical next step.(60) This surgery is the only approach that effectively re-establishes food passage, addresses nutritional issues, and reduces the risk of aspiration pneumonia and esophageal cancer. End-stage achalasia, seen in roughly 5% of patients, is characterized by a dramatically enlarged (>6 cm) and sigmoid-shaped esophagus.(23) Although there is ongoing debate about the management of end-stage achalasia, recent research has explored laparoscopic cardioplasty as a potential option for select patients. Nonetheless, esophagectomy remains the preferred standard treatment for this condition.(59) The duration between the onset of symptoms and the decision to proceed with esophagectomy can vary significantly, ranging from a few months to over 20 years. Most patients who undergo this procedure have already tried multiple endoscopic and surgical treatments, with recurring severe symptoms being the primary motivation for surgery. Esophagectomy can be performed via a transthoracic approach (78.7% of cases) or a transhiatal approach (21.3%). Complication rates are relatively high, ranging from 19% to 50%, including a 10% incidence of pneumonia, a 7% rate of anastomotic leaks, and a 2% mortality rate. Despite these risks, most patients experience significant improvement, with many being able to eat without restrictions and gaining weight during an average follow-up of 43 months.(61) When all other treatments have been exhausted, esophagectomy should be considered sooner for patients who are good candidates and have severe symptoms, especially when the esophagus is severely dilated and previous treatments have failed.(40)

1.9.6 Gastroesophageal reflux disease (GERD)

One of the major issues following procedures like POEM, and to a lesser extent LHM or PD, is the reflux of stomach contents into the esophagus, a condition known as GERD. This problem is particularly prominent after POEM, prompting a significant focus on this complication.

Therapy

GERD is primarily managed with proton pump inhibitors (PPIs), which have shown effectiveness in addressing reflux esophagitis after POEM. Persistent cases of GERD are rare, with large studies indicating a response rate to PPIs of 81.4% and 87% in patients with erosive esophagitis following POEM. Non-compliance with PPI therapy often leads to ongoing issues, highlighting the importance of following prescribed treatments.(62)

While short-term GERD data post-POEM are well-documented, long-term studies are less comprehensive. A major study tracking 610 patients over 2 to 6 years noted a few cases of Barrett's esophagus and peptic strictures, though these were infrequent. Long-term follow-up suggests that GERD symptoms might improve over time, with 35% of patients showing normalized pH-metry results. This improvement may be due to changes in the gastroesophageal junction, as shown by EndoFLIP studies indicating increased LES pressure, reduced cross-sectional area, and compliance months after POEM.(63)

A significant study from Japan observed a decrease in symptomatic GERD from the first year to five years after POEM, indicating a generally favorable progression and suggesting that conservative treatments are often effective.(64)

In a comparative study of POEM and LHM, the incidence of reflux esophagitis dropped from 57% to 44% between the first and second year after POEM, while it rose in the LHM group over the same period. This aligns with earlier research showing a gradual increase in acid reflux following LHM in long-term follow-ups.(64)

Following POEM, endoscopic fundoplication has been investigated as a treatment for GERD. A multicenter retrospective study on transoral fundoplication without incisions in 12 patients demonstrated a significant reduction in the need for bi-daily PPIs, alongside improvements in daily symptoms, GERD-related quality of life, and acid exposure time.(64)

Similarly, a randomized study involving 60 patients reported comparable outcomes. Despite promising results, all procedures were performed by a single, skilled physician. No major improvements in esophagitis were noted, and many patients continued to require reduced PPI doses for symptom control.(65)

2 Methods

2.1 Study design

This study is a retrospective, single center data analysis. The primary objective of this study was to evaluate the treatment outcomes of patients who presented at the Esophagus outpatient Clinic of the Medical University Graz between January 2012 and February 2023 and to compare them with the latest treatment recommendations. The focus was on endoscopic procedural techniques, particularly botulinum injection and PD, as these were the most frequently used methods. LHM and POEM results were also examined. The various treatment methods were assessed in terms of their course, duration of effectiveness, and complications. Additionally, a database was created for further research projects. To identify patients within the specified period, a keyword search was carried out in openMedocs (the hospital information system from Graz) for the gastroenterological outpatient clinic, endoscopy, and internal medicine wards. The following keywords were used: achalasia, POEM, PD, Heller myotomy, and Botox injection. The data was pseudonymized and initially stored in an Excel file as the foundation of a database.

2.2 Causality Assessment

The patients were categorized into two groups. The first group comprised those for whom other potential diagnoses were excluded using endoscopy. Afterward, HRM was employed as the gold standard diagnostic tool. The second group included patients who either had inconclusive HRM results or were unable to tolerate the procedure. In such cases, Botox injections were used as a trial therapy until the diagnostic protocol introduced FLIP. A positive response to Botox indicated a probable diagnosis of achalasia. Cases with insufficient or unusable documentation were excluded. As a result, two groups were established based on expert evaluation: achalasia and non-achalasia, as shown in Table 2.

2.3 Inclusion Criteria

Patients were eligible for inclusion if achalasia had been confirmed through endoscopy, HRM, or other diagnostic tools when necessary. They had to be at least 18 years of age and

have attended the achalasia outpatient clinic during the observation period. Additionally, patients must have undergone one of the following therapeutic interventions: Botox injection, PD, LHM or POEM.

2.4 Exclusion Criteria

Patients were excluded if achalasia was considered only as a differential diagnosis and endoscopy or HRM indicated a more likely motility disorder, such as pseudoachalasia, eosinophilic esophagitis, or jackhammer esophagus. Another exclusion criterion was insufficient documentation.

2.5 Collected Data

Data were extracted from outpatient visit records, medical reports, and examination findings. When available, the following parameters were recorded:

- Patient demographics: age, height/weight, gender
- Pre-existing conditions, family medical history
- Onset of symptoms and data of diagnosis
- Main symptoms categorized using the Eckardt Symptom Score
- Compensation mechanisms
- Achalasia subtype
- Treatment modalities
- Cancer Development

Patient histories were evaluated for the presence of thyroid disorders, rheumatoid arthritis, autoimmune uveitis, psoriasis and Crohn’s disease.

Compensatory mechanisms are frequently employed by patients with achalasia. These strategies include actions such as "consuming additional fluids with meals," "taking extended pauses between bites," and "standing up during eating."

The treatment modalities were categorized into:

- Pharmacological therapy
- Botox injections
- PD
- LHM
- POEM

For Botox injections, the total dosage was recorded. For pneumatic dilation therapy, the number of dilations and balloon sizes were recorded. For POEM, the length of the myotomy was documented.

2.6 Outcome

The primary objective of the study was to evaluate the effectiveness of the therapies based on the following criteria:

- Treatment success
- Time to relapse
- Complications

Patient outcomes were categorized into successful or unsuccessful treatments. Treatment success was defined using the ESS, with a successful outcome being an ESS of less than 3. Long-term therapies (PD, LHM, POEM) were also required to maintain a relapse-free status for more than six months. Relapse was identified when symptoms worsened over time, accompanied by an EES greater than or equal to 3. Additionally, the duration during which the therapy maintained an EES of less than 3 and the period during which patients did not require further treatment were analyzed.

Secondary endpoints included comparing the quality of treatment outcomes with existing literature, assessing the incidence of other autoimmune diseases, cancer development in the different groups, and indications of risk factors that may be associated with achalasia, with the aim of summarizing the data to develop a registry for achalasia patients.

2.7 Statistics

Data were analyzed using both descriptive and inferential statistics. For numerical data, measures of central tendency and dispersion, including the mean, standard deviation, median, interquartile range (IQR), minimum, and maximum values, were calculated. Categorical data were presented as absolute frequencies (counts) or relative frequencies (percentages).

The normality of the data was assessed using the Kolmogorov-Smirnov test, supplemented by graphical evaluations with QQ plots and trend-adjusted QQ plots. A 95% confidence interval was used for all estimates, and statistical significance was defined as a p-value of less than 0.05.

To evaluate the independence between two categorical variables, the Chi-square test was conducted. Kaplan-Meier analysis was employed to estimate the time to remission or the occurrence of relapse. All statistical analyses were performed using SPSS (version 29) and Microsoft Excel.

2.8 Statement of Ethics

The study was approved by the research ethics committees of the Medical University of Graz (EK 35-344 ex 22/23). The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its amendments. Patient consent was not required due to the retrospective design of the study.

3 Results

3.1 Patient characteristics

The study included both male and female patients aged 18 years and older, resulting in the identification of 158 individuals. In all these cases, the diagnosis of achalasia was suspected based on the presence of one or more key symptoms or similar events, such as bolus obstruction. Following a thorough diagnostic evaluation, 125 patients were confirmed for further analysis (Table 2).

Between 2012 and 2023, 125 patients diagnosed with achalasia were managed at the Esophageal Outpatient Clinic of the Medical University Graz. Of these patients, 72 (58%) were male and 53 (42%) were female, with a median age of 70 (IQR 29) years. Three distinct age distribution peaks were observed, occurring around the ages of 33, 54, and 74 years. The median body mass index (BMI) among the cohort was 24 (IQR 5). In the patient histories, eight individuals were identified with thyroid disorders, four with rheumatoid arthritis, and one with Crohn's disease. Documentation was unavailable for 38 patients.

In this study, 38 (30%) patients utilized compensatory mechanisms regardless of their ESS. Specifically, 35 patients consumed extra fluids during meals; 2 took prolonged pauses between bites; and 1 stood while eating.

In this cohort, the median time to diagnosis was 12 months (IQR 48).

The distribution of achalasia subtypes within the patient population was as follows: 35 (28%) patients were classified as Type I, 62 (50%) as Type II, and 21(17%) patients of Type III. A concise overview is provided in Table 3.

Table 2: Exclusion process

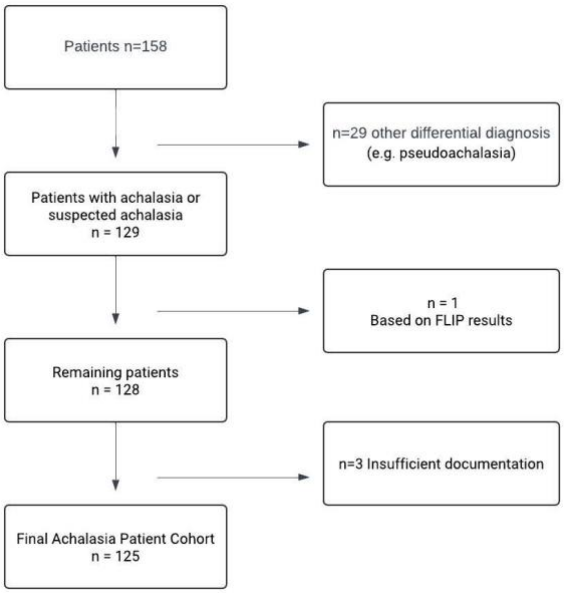


Table 3: Patient characteristics

Category	Value
Age	
- Median (IQR)	70 (29)
- Range	23 - 97
Sex	
- Male	72 (58%)
- Female	53 (42%)
BMI	
- Median (IQR)	24 (5)
- Range	14.3 - 38.6
Autoimmune Diseases	
- Total	13 (11%)
- Thyroid	8 (6%)
- Rheumatoid Arthritis	4 (3.0%)
- Crohn's Disease	1 (1%)
Compensation Mechanisms	
- Total	38 (30%)
- Drinking	35 (28%)
- Pauses	2 (2%)
- Standing Up	1 (1%)

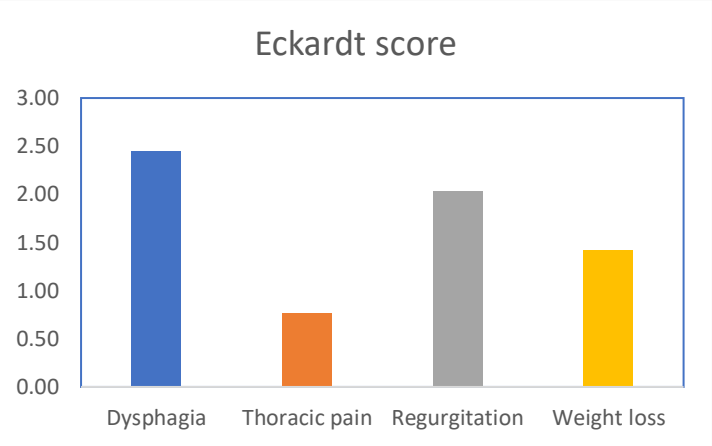
Patient characteristics

Time to Diagnosis (months)	
- Median (IQR)	12 (48)
- Range	1 - 120

Achalasia Types	
- Type 1	35 (28%)
- Type 2	62 (50%)
- Type 3	21 (17%)
- Unknown	7 (6%)

At the time of diagnosis, the median ESS was 6 (IQR 3). Most patients exhibited symptoms of dysphagia with an average score of 2.5, and regurgitation, with an average score of 2.0. Chest pain, with an average score of 0.8, and weight loss, with an average score of 1.4, were less commonly reported at diagnosis. A visual representation is provided in Table 4. These latter symptoms increased primarily in patients who experienced prolonged diagnostic periods or declined therapy.

Table 4: Average symptom score of the study population separated by symptoms



Four cases documented pharmacotherapy, with one patient receiving a calcium channel blocker and four receiving sublingual nitrates. These medications were intended only as a temporary measure until a more definitive treatment could be implemented and did not result in significant symptom relief.

3.2 Botolinum injection

A total of 123 applications were administered during the study period. On average, 300 units were injected into the four quadrants. Symptomatic improvement, reflected by an ESS below 3, was observed in 104 cases direct after the application (85%), while approximately 14 cases (12%) showed no response to the therapy. The median time to recurrence was approximately 12 months, as shown in Table 5 and Figure 15. After six months of treatment, 78% of patients were still in remission, with 56% at the 12-month mark and 32% remaining in remission after 24 months. In the chi-square test examining the type of achalasia and the effectiveness of the therapy, the p-value was 0.961. This suggests that no statistically significant association was found between the effectiveness of the therapy and the types of achalasia. No side effects or complications, such as bleeding, mediastinitis, mucosal tears, or misplacement of injections, were reported.

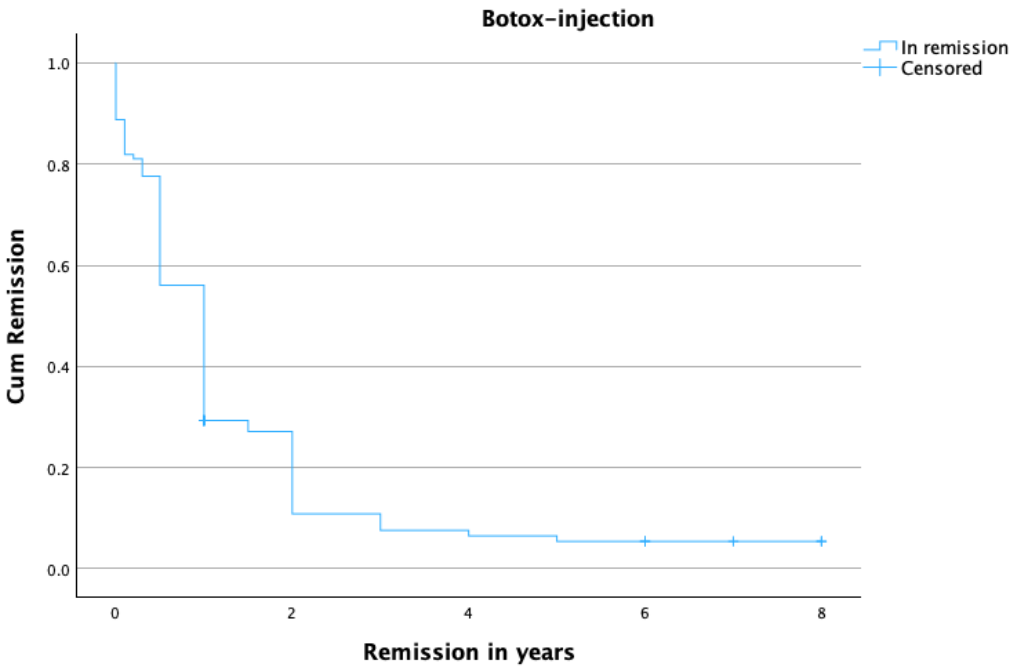


Figure 15: Remission in years of Botox-injections

Table 5: Remission in month and Patients at risk of Botox-injections

Remission in month		
mean	17	
Std. Error	0.2	
median	12	
Follow-up in years		
follow-up	25	
range	25	
patients at risk	month	patients
	0	116(100%)
	6	90 (78%)
	12	65 (56%)
	24	32 (28%)
	36	17 (15%)

3.3 Pneumatic Dilatation

A total of 94 balloon dilation therapies were conducted. In the past decade at the outpatient clinic, the generally preferred approach involved performing at least two dilations, beginning with a 3 cm balloon. Balloon sizes of ≤ 2.5 cm and ≥ 4 cm were largely abandoned over a decade ago, with only one recent exception involving a 4 cm balloon. When the initial dilation yielded little improvement, additional dilations were performed using the next largest balloon size, typically up to two more times. The number of subsequent dilations varied depending on factors such as the patient's underlying health conditions, the occurrence of complications, and the expertise of the physician. For statistical purposes, this series of dilations was considered a single procedure, recorded under the largest balloon size eventually used.

In terms of balloon size distribution, 47 cases (52%) utilized a 3 cm balloon, 26 cases (29%) employed a 3.5 cm balloon, 11 cases (12%) used balloons of ≤ 2.5 cm, and 6 cases (7%) involved balloons of ≥ 4 cm. The procedure was successful in 84 cases (89%), achieving a reduction in symptoms with an ESS of less than 3, which persisted for at least six months. However, in 10 cases (11%), the treatment was unsuccessful. One year into the treatment,

84% of patients remained in remission, while 66% were still in remission at the five-year point and 57% after ten years. The median interval before recurrence was 6 years seen in Table 6 and Figure 16. It is worth noting that approximately 50% of these procedures were performed after 2017, with all of these patients still in remission. Among the 10 unsuccessful procedures, 7 were conducted using only a ≤ 3 cm balloon without escalating to a larger size despite inadequate results. Furthermore, 4 of these 7 unsuccessful cases involved only a single dilation.

Minor mucosal tears were observed in 17 cases (18%), all of which resolved without the need for further intervention and were considered a deliberate outcome of the dilation procedure. In one instance, a perforation occurred, necessitating surgical intervention that led to an esophagectomy. This complication arose during a 4 cm balloon dilation. Following PD, 7 patients (7%) developed GERD and have since required long-term treatment with PPIs. The best outcomes were associated with the use of balloons ≥ 4 cm, where patients underwent three dilation sessions, with a maximum balloon size of 4 cm, and in one case, 4.5 cm. These patients have remained in remission for 11 years or more.

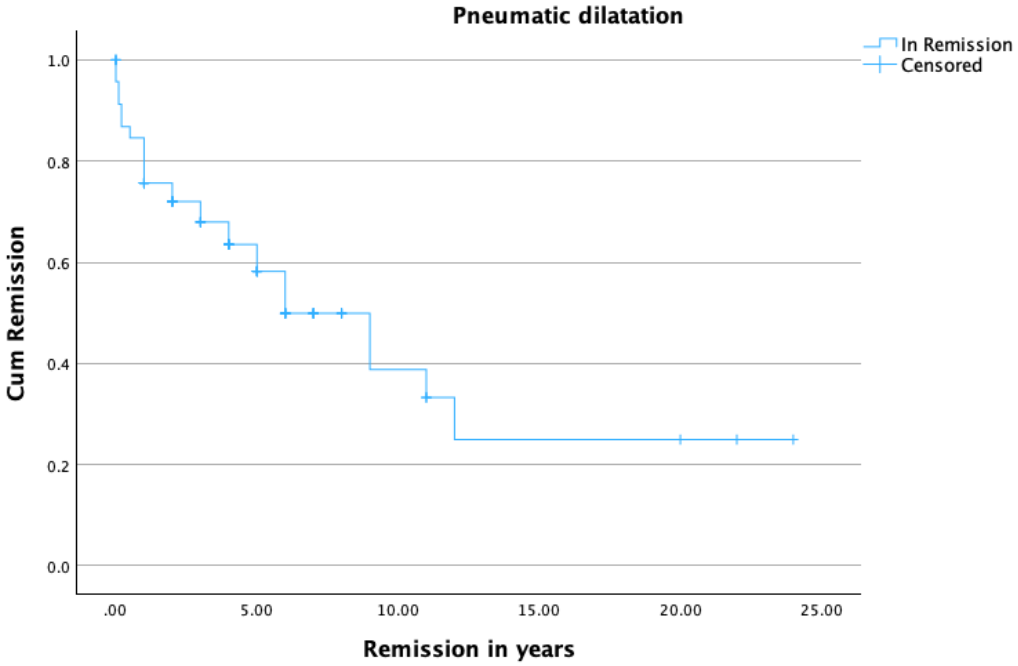


Figure 16: Remission in years for PD

Table 6: Remission in years and Patients at risk of PD

Remission in years		
mean	10	
Std. Error	1.5	
median	6	
Follow-up in years		
follow-up	24	
range	24	
patients at risk	year	patients
	0	93(100%)
	1	78 (84%)
	5	61 (66%)
	10	53 (57%)

3.4 POEM

POEM was first performed in 2010 but was only incorporated into the therapeutic protocols in Graz by 2021. Therefore, it is currently difficult to estimate the recurrence rate. The procedures themselves were carried out in Linz, with follow-up care provided in Graz. A total of 15 patients underwent this treatment. In one case, the patient experienced a recurrence a few weeks after the initial procedure, necessitating a repeat myotomy a few months later. The initial treatment was successful in 14 patients. One of these patients required an additional POEM procedure. To date, all patients remain in remission. The Median follow up time was 2 years and the range 2 years as well. The average myotomy length was 10 cm (SD 4 cm). Complications included gastroesophageal reflux disease (GERD) in 5 patients (33%), aspiration in 1 patient, and cervical emphysema in 1 patient. The aspiration and cervical emphysema led to an extended hospital stay.

3.5 Heller-Myotomy

Heller myotomy was the pioneering surgical approach for long-term treatment of achalasia, but its use has diminished since the advent of POEM in 2008. During the investigation interval, there were 19 patients treated with 21 procedures. Initially, all patients showed a positive response with an ESS less than 3 within the first six months. Sixteen of these operations were done using the modern laparoscopic method, paired with a partial Dor

fundoplication, while the remaining five cases employed either a transabdominal or thoracoscopic approach. These approaches were grouped together in the analysis because they yielded similar results. One year into the treatment, 100% of patients remained in remission, while 89% were still in remission at the five-year point and 80% after ten years. The median interval for the treatment was about 30 years, as seen in Table 7 and Figure 17.

So far, 11 patients (58%) have not experienced a recurrence. However, four patients (24%) required esophagectomy after many years because of the progression to end-stage achalasia. Three patients (18%) needed further treatment following their initial Heller myotomy—one had two more Heller myotomies, another underwent POEM, and one was treated with Botox injections. 8 patients (45%) experienced complications. Among the complications, there was one case (6%) of vagus nerve injury, one case (6%) of perforation requiring additional surgery, and six cases (33%) of GERD. It's worth noting that the transabdominal and thoracoscopic approaches are more likely to cause reflux, which is why they are no longer commonly used. When focusing solely on the laparoscopic Heller myotomies, the rate of GERD requiring PPI treatment drops to three cases (15%).

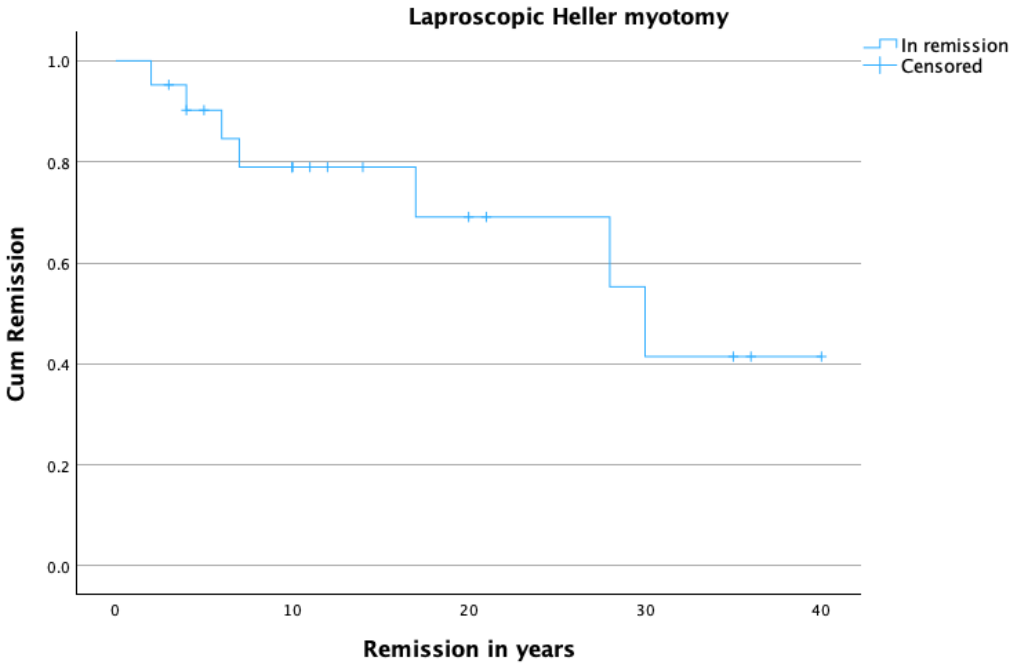


Figure 17: Remission in years for LHM

Table 7: Remission in years and Patients at risk of LHM

Remission in years		
mean	26	
Std. Error	3.6	
median	30	
Follow-up in years		
follow-up	46	
range	46	
patients at risk	year	patients
	0	19 (100%)
	1	19 (100%)
	5	17 (89%)
	10	15 (80%)
	20	14 (73%)
	30	11 (58%)

3.6 Carcinoma rate

During the observation period, one patient developed squamous cell carcinoma, and three others developed Barrett's mucosa. All three patients had previously developed GERD. Each of these patients had been treated with different methods: one with POEM, one with Heller myotomy, and one with pneumatic dilation. Currently, none of these cases have progressed to adenocarcinoma.

4 Discussion

Achalasia is a rare motility disorder of the esophagus.(12) Between 2012 and 2023, 125 patients were treated in the outpatient clinic at Medical University Graz. Over the past decade, significant advancements have been made in diagnostic techniques and screening methods. Some of these changes are the widespread use of HRM instead of conventional manometry, the standardization of technologies like the TBE, and the introduction of new techniques like FLIP. There are also new endoscopy methods like chromoendoscopy, narrow-band imaging for cancer screening and a novel treatment approach called POEM. These advancements, along with increased awareness of this rare condition, may explain the reported rise in new cases over the last ten years. Nonetheless, it is likely that more patients are developing achalasia today compared to 50 years ago, and we may expect a further increase in cases in the future.

In our cohort, there was a predominance of male patients, with 72 (58%) men and 53 (42%) women, supporting other studies suggesting that male gender may be a risk factor for achalasia.(11)

The literature reports an increased prevalence of autoimmune diseases among patients with achalasia. In our cohort, 10% of patients also developed an autoimmune condition. Specifically, eight patients were diagnosed with thyroid disease, four with rheumatoid arthritis, and one with Crohn's disease. Notably, only the incidence of rheumatoid arthritis in our patient group is higher (three times) than that observed in the general population.

The literature frequently alludes to significant delays before achalasia is accurately diagnosed, with variability between studies. For instance, Eckardt reports (66) an average delay of approximately 5 years, while Sato's findings (67) suggest a delay of around 6.5 years. In contrast, within our network, the median time to diagnosis was notably shorter, at just 12 months. This improvement can be attributed to the strong collaboration between primary care physicians, the initial diagnostic steps taken at the Medical University of Graz, and peripheral hospitals. These healthcare providers typically initiated procedures such as endoscopy or a barium swallow and referred suspected motility disorder cases to the specialized clinic in Graz.

Currently, symptom assessment and therapy success are measured using the ESS, a somewhat subjective measure. Studies suggest that dysphagia severity alone may be a better parameter than the overall score. Components like chest pain and weight loss often skew the results. (68) This is reflected in our data, where weight loss and chest pain had little diagnostic value. With a median of 6 in ESS dysphagia and regurgitation accounted for 4.5 points. Weight loss and chest pain were only significant if patients remained untreated for extended periods. Existing studies suggest that the DI measured by FLIP could provide a more objective assessment of treatment success, potentially serving as a more reliable metric than the subjective ESS.(37)

An ESS score above 3 is not an absolute indicator for therapy, but a significant increase in symptoms should prompt reevaluation and potential retreatment. Though evidence is limited, data suggests untreated achalasia may lead to quicker esophageal dilation progression.(69) culminating in end-stage achalasia, currently affecting up to 5% of patients, often requiring esophagectomy. Six of the 125 treated patients faced this outcome—one due to perforation, one from ESCC, and four as the last result after treatment failure.

Use of nitrates and calcium channel blockers was rare in our cohort and the use of these medications to alleviate symptoms proved ineffective in our patients. Guidelines no longer recommend calcium channel blockers, nitrates, or phosphodiesterase inhibitors for achalasia.(40) Consequently, their use was discontinued in 2019.

Our findings indicate that all four therapeutic approaches effectively reduce symptoms. 56% of patients treated with Botulinum toxin injections were in remission after 12 months, without any complications that extended their hospital stay. This is a notably longer remission period than reported in the literature, where only 40% of patients were in remission after 12 months.(54) Botulinum injections were also used diagnostically before the introduction of HRM and additional diagnostics like FLIP in Graz. However, today, they should only be considered for patients at high surgical risk due to poor overall health.(48)

73% of patients who underwent Heller myotomy achieved a remission period of 20 years following a single procedure. Comparable long-term outcomes have been observed in other studies, with some patients maintaining remission for more than 20 years.(52) In two cases, patients maintained an ESS of 4 over several years, with secondary measures delaying

further intervention. One patient suffered long-term damage due to a vagus nerve lesion, and another required reoperation due to perforation. Our patients' complications were similar to those observed in the POEM group. Combined with Dor fundoplication, 15% of cases in the laparoscopic group developed GERD, a rate not statistically significantly higher than with pneumatic dilation. The "new" surgical technique of POEM appears to offer similarly favorable remission rates as Heller myotomy.(57) Therefore, the choice between these procedures should primarily depend on the expertise available at the treating center. A significant drawback of POEM, observed both in our group and in the literature, is that 30-40% of patients develop GERD.

Recent research indicates that the incidence of endoscopic reflux post-POEM might decline over time. It is essential to rigorously follow PPI therapy due to the risk of long-term GERD complications after POEM, such as the development of peptic strictures and Barrett's esophagus.(64) Initial approaches are being tested that allow for endoscopic fundoplication, which could be an option for patients unresponsive to PPI therapy.(70)

Currently, all 15 patients with and median follow up of 2 years in our POEM group are in remission. One patient developed cervical emphysema, and another developed pneumonia due to aspiration, both resulting in prolonged hospital stays. One patient required a repeat myotomy due to poor response to the initial POEM. Despite this, the therapy achieved a 93% success rate within the first six months. The first patients were operated on only in 2021, so long-term results should be reassessed in 3-5 years. Because of the high incidence of GERD, all post-myotomy patients should be included in a screening program to monitor for reflux esophagitis and its consequences.(40)

Considering the implications of GERD development, PD holds a unique position. While one-year recurrence-free rates are generally good, five-year or longer recurrence-free intervals vary significantly across studies. For example, a large retrospective study in China reported a 60% recurrence-free rate after five years(71) while other studies report rates as high as 82% or more.(50) These outcomes depend on factors like achalasia subtype(34) and treatment protocol.(50)

PD was performed 94 times, with 84 procedures considered successful. In unsuccessful cases, the dilation was done with a 3 cm balloon with no subsequent diameter increase, and

four of these were only dilated once. This implies the use of smaller balloons or insufficient frequency of dilation, which aligns with the literature's data.(50) In 94% of cases, balloons of 3.5 cm or less were used. Long-term studies indicate that the best outcomes are achieved with three dilations using progressively larger balloon diameters, aiming for at least 4 cm on the third dilation. Our best treatment outcomes were also observed with the largest balloon size, resulting in remission lasting at least 11 years. However, patient constitution must also be considered. The same balloons used for adults are currently used for children, leading to a higher incidence of perforations.(72) The results from our patient group are quite promising, with 66% of patients remaining recurrence-free after five years. However, it's important to note that about 50% of treatments were performed after 2017, and all patients remain in remission, making long-term effectiveness difficult to assess. The observation period should be regularly repeated to make definitive statements A good interval for repetition would be 3-5 years with the POEM group. Future patients should follow a protocol similar to the one outlined in the Moonen study (50) provided there are no contraindications. This involves a structured regimen of three dilations, starting with a 3 cm balloon and progressively increasing to a 4 cm balloon.

There was one case of perforation that necessitated esophagectomy. This aligns with existing data, even though no perforations occurred with 4 cm balloons in a large meta-analysis. Seven patients developed GERD as a complication, one of whom also developed Barrett's esophagus.

In our analysis, Barrett's esophagus developed after POEM, Heller myotomy, and PD in one case each, along with one case of ESCC. The metaplasia occurred in patients who developed GERD following therapeutic interventions for achalasia. Currently, there is no screening program in place in Graz. Because of the high risk of illness and low 5-year survival rates (15–25%) for ESCC and EA, it is very important to think about ways to prevent these cancers. There is division in the ongoing discussion about routine surveillance for esophageal cancer in Achalasia patients. Some experts argue that the current evidence does not support regular endoscopic surveillance, while others recommend monitoring every three years, especially for those with a history of the condition spanning 10-15 years or more.(16) As Han (27) pointed out, conducting thorough esophageal examinations in Achalasia patients presents a technical challenge, as food often obscures the mucosa,

complicating detailed evaluations. As a result, random biopsies may lack accuracy. Traditionally white-light endoscopy has been used in most studies on ESCC surveillance in Achalasia patients. It is still not clear how well newer techniques like chromoendoscopy, narrow-band imaging, and confocal microscopy work. Weighing the pros and cons, it might be more beneficial to focus on identifying high-risk individuals and establishing a targeted surveillance approach.(27) For example, regular endoscopic screening could be more suitable for patients with additional ESCC risk factors such as male gender, history of smoking, age over 60 and heavy alcohol consumption.(16) Additionally, all patients who have undergone a myotomy (35) or have developed GERD, as seen in our results, should be included in the screening program. Due to the potential long-term risks associated with GERD, including the possibility of Barrett's esophagus advancing or the development of peptic strictures, ongoing monitoring and careful management are essential. This approach is key to identifying any early signs of progression, allowing for prompt intervention and helping to avoid serious complications like esophageal cancer.

Integrating these patients into a well-organized follow-up plan not only addresses GERD-related issues, but also ensures ongoing evaluation of achalasia treatment effectiveness. By tailoring follow-up care to each patient's unique needs and risk factors, healthcare providers can better prevent complications and improve the overall health and quality of life for those dealing with achalasia.

4.1 Limitation

Throughout the observation period from 2012 to 2023, there have been significant advancements in both the diagnostic techniques and classification of achalasia. The standardization of HRM, the introduction of the FLIP, and the division into three distinct subtypes have all led to important therapeutic implications. Given the expertise of the treating physicians, the course of the disease, and the therapeutic responses observed, it is reasonable to conclude that all included patients were indeed suffering from achalasia. However, there remains a possibility that classification errors occurred before HRM was widely implemented. In several cases, the manometry protocol was documented without specifying the subtype, and the IRP was not recorded, nor was universally recognized terminology like "100% failed contractions" used. This could have led to potential misinterpretations.

A further challenge lies in the retrospective nature of this data analysis, which complicated the collection of data. The earliest patients were diagnosed as far back as the 1970s, resulting to the advent of digital records, leading to gaps in the available documentation. Moreover, in the past decade, new insights into the pathophysiology and risk factors for the disease have emerged, which were not previously recognized and thus are not comprehensively documented. Examples of these include family medical history, the presence of other autoimmune diseases, and occupational history. To avoid future omissions, a prospective study approach would be more appropriate.

Additionally, not all patients received treatment exclusively in Graz. This includes individuals who underwent POEM or, three cases, likely received LHM treatments outside Graz. As a result, details about their treatment, complications, and other related data were not always fully available, leading to some instances of lost follow-up.

The Botox injections and the main focus of this thesis on PD were carried out either in Graz or in other hospitals within the same network. However, the exact duration of the treatment's effect until remission was not always clearly ascertainable. There is a possibility that some patients experienced worsening symptoms before their outpatient visits, which were not documented. To determine this with precision, accurate documentation or regular follow-ups would be required.

In our patient population, there could be additional cases of Barrett’s mucosa and ESCC beyond those already identified. The current findings were incidental and not based on a systematic method. To thoroughly evaluate our cohort, a more structured and prospective approach is needed.

With a cohort of 125 patients, the study has a relatively small sample size. So, it's not easy to draw any firm conclusions about remission rates, complications, especially in the Heller and POEM groups, and the growth of carcinoma. Nevertheless, the data from this study align with findings from other meta-analyses, supporting the reliability of the presented results.

4.2 Conclusion

Over the span of 10 years, with 125 treated patients, achalasia is recognized as a rare but serious disease at the Medical University Graz. The treatment outcomes were generally

positive, with remission and complication rates that were on par with or better than those reported by other centers. However, to draw more definitive conclusions, the observation period, particularly for the pneumatic dilatation and POEM groups, should be extended and re-evaluated in another 3-5 years. Future efforts in the pneumatic dilatation group could potentially yield better results by implementing a three-dilatation strategy, which includes the use of a 4 cm balloon.

Based on the available results, younger patients would particularly benefit from treatment options such as LHM or POEM, as they tend to experience a significantly longer remission period. However, this requires sufficient expertise at the treatment center. PD continues to be a safe and effective alternative. On the other hand, Botox injections should be reserved for patients who are not suitable candidates for surgery due to their general health condition.

To better understand the prevalence and outcomes of Achalasia in Austria, establishing a registry would be highly beneficial. This study has laid the groundwork, but additional prospective studies are necessary, which could be conducted through the Esophagus Specialty Outpatient Clinic. At present, there is no established screening protocol for esophageal adenocarcinoma (EA) and esophageal squamous cell carcinoma (ESCC) in Graz. This issue is currently being debated within the medical community. A prospective approach for a screening program could target specific groups, including patients with risk factors for esophageal squamous cell carcinoma (ESCC), such as smokers, males over 60, those who have undergone myotomy, and patients who developed GERD following treatment.

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