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Relationship between Lower Esophageal Sphincter muscles thickness and their response to pneumatic dilation in patients with achalasia

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RESEARCH ARTICLE

Relationship Between Lower Esophageal Sphincter Muscles Thickness and Their Response to Pneumatic Dilation in Patients With Achalasia

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Abstract

Background: **Prognostic factors play a major role in managing achalasia patients treated with pneumatic dilatation (PD) and understanding the pathophysiology of the disease. In this regard, the muscular thickness of the lower esophageal sphincter (LES) has drawn attention in recently published studies.**

Methods: **Patients with newly diagnosed achalasia were included consecutively in this study, and Endoscopic Ultrasound (EUS) was used to determine the thickness of longitudinal and circular muscles of LES. To determine the recurrence of symptoms, patients were followed up for one year using the Eckardt questionnaire. The relationship between pre-treatment LES muscle thickness and symptom recurrence was investigated.**

Results: **Seventeen of nineteen treated patients were enrolled in this study and the data of sixteen patients was analyzed. Although not statistically significant, those with thinner LES had recurrent symptoms (p-*value* = 0.08). Patients with a thicker LES (5.1 mm vs. 4.6 mm) initially responded better to pneumatic dilatation (p-*value* = 0.03). After initial therapy, severe pain (daily pain) was strongly associated with symptom recurrence.**

Conclusions: **Severe retrosternal chest pain and a thin LES appear to be surrogate markers for advanced disease and poor outcomes. Pre-treatment integrated relaxation pressure (IRP) seems to be a promising predictor of PD prognosis. Due to the study's heterogeneous population, the findings cannot be generalized to all achalasia patients, and larger-scale studies are necessary to confirm these findings.**

Keywords: Endoscopic sonography, Esophageal achalasia, Lower esophageal sphincter, Esophageal manometry, Integrated relaxation pressure

1. Introduction

Achalasia is a relatively rare disorder of esophageal movement with an incidence rate of 1−2 per 100,000. The disease is equally prevalent in both genders and primarily observed between the ages of 30−60 years.[1,2] Achalasia's presentations owe to the absence of sufficient lower esophageal sphincter (LES) relaxation during deglutition and esophageal body aperistalsis. These phenomena are due to mixed infectious, autoimmune, and familial components resulting in the selective loss of inhibitory neurons in the myenteric plexus of the distal esophagus leading to the dominance of excitatory neurons.[2,3] Achalasia is characterized by progressive dysphagia to solid and liquid foods, regurgitation, weight loss, chest pain, and heartburn, contributing to the high morbidity of this disease.[2,4]

All available treatments for this chronic morbid condition are palliative to alleviate symptoms and prevent further esophageal dilatation.[4−6] Pneumatic dilatation (PD) is one of the most often used and

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approved therapies for achalasia, with over 80% effectiveness reported in various studies; however, regardless of the therapy strategy, 25−30% of patients will relapse in a 5-year follow-up.[5,7−9] Understanding the predisposing factors that increase the risk of achalasia recurrence helps physicians to employ therapeutic modalities more efficiently to reduce the relapse risk. Patients younger than 40 years, male sex, LES pressure after dilation greater than 10−15 mmHg, and continued symptoms following one or two treatments are known as predictive factors of a poor clinical outcome of treatment.[10]

There are few studies given the muscular thickness of LES as a determining factor of success rate in achalasia treatment.[11−14] According to the peroral endoscopic myotomy (POEM), cardiac muscularis propria thickness was shown to be a predictive factor for treatment failure in patients with achalasia in one study.[11] However, another investigation indicated that patients with a thin muscularis propria may be susceptible to relapse.[12] Considering PD as a treatment of achalasia, similar contradictory results were observed. Although no correlation was noticed between the cross-sectional area of esophageal muscle and the outcome of achalasia after PD in the study by Sinn et al.[13], Li et al.'s study revealed that the thickness of LES outer longitudinal muscle is associated with poor midterm treatment outcomes following PD.[14]

In view of this scarce and controversial literature on the role of LES muscle thickness in ascertaining the outcome of achalasia treatment, we aim to investigate the thickness of the muscular layers of the LES by endoscopic ultrasound and its association with treatment response in achalasia patients treated by PD.

2. Methods

2.1. Study population

All patients aged 18 to 75 newly diagnosed with achalasia, based on radiological and manometric criteria who were visited between November 2018 to May 2019, at Imam Khomeini Hospital Complex, affiliated to Tehran University of Medical Sciences, with no prior treatment for the achalasia, were included in this study. Patients who had a history of advanced cardiovascular illness, cancer and radiotherapy, esophageal and gastric surgery, esophageal and gastric cancer, previous treatment for achalasia, or refused endoscopic treatment were excluded. Also, an evaluation of esophagus and stomach for determining pseudo-achalasia was conducted in order to exclude patients with tumors or lymphadenopathy. In addition, patients with esophagitis and GERD were excluded from this study. An esophagogram was performed in order to exclude patients with megaesophagus.

Patients' demographic information, including age, sex, underlying disease history, smoking, alcohol, and opium consumption, disease characteristics, such as achalasia type, duration, and severity of symptoms, and endoscopic or manometric features of the disease were collected. We also recorded complications such as hemorrhage and esophageal rupture. All participants gave their informed consent after the study was authorized by the independent medical ethics council of Tehran University of Medical Sciences with the code of IR.TUMS.IKHC.REC.1398.204.

After measuring esophageal muscle thickness using EUS and dilatation therapy with a size 3 balloon, patients were followed for at least one year for recurrence of clinical symptoms. The patients with recurrence of the disease were planned for repeated dilatation up to three times, each time with a bigger balloon size. The initial response was defined as those whose symptoms resolved within the first month of treatment (Eckardt score of 3 or less). If there was no initial response, dilatation was repeated with a size 3.5 balloon, and the response to treatment was examined one month later. In cases of second recurrence, a size 4 balloon was used for the treatment of achalasia. All patients whose symptoms improved considerably with treatment (Eckardt score of 3 or less) were monitored for one year by phone calls every 4−6 months for recurrence. The criterion for recurrence was defined as an Eckardt score greater than 3. Patients were requested to return one year later for a Timed Barium Esophagogram (TBE) and repeat manometry.

2.2. Initial diagnostic tests

Initial patient histories and underlying diseases were recorded for all patients. The severity of the condition was then determined using the Eckardt questionnaire. This questionnaire assigns a score from 0 to 3 to four symptoms of dysphagia, regurgitation, chest pain, and weight loss. The scores for dysphagia, regurgitation, and chest pain depend on the intensity and frequency of occurrences per day or week (0 asymptomatic, 1 sometimes, 2 daily, 3 with each meal) and for weight loss, 0 is for no weight loss, 1 is for 0−5 kg, 2 is for 5−10 kg, and 3 is for weight loss of more than 10 kg. A total of 0−12 points assigned to the severity of patients' symptoms, based on the Eckardt symptom score items.

High-resolution manometry was performed using a catheter with 36 sensors spaced 1 cm apart while the patients were positioned supine (High-Resolution Impedance Manometry (HRIM); Medical Measurement System, the Netherlands). Fasting for 8 h prior to the procedure was recommended to the patients. Achalasia was classified using the third edition of the Chicago Classification, and analyses were performed using Chicago classification parameters, LES baseline pressure, and median integrated relaxation pressure (IRP).

2.3. Measuring the thickness of lower esophageal sphincter muscles

During the study, the measurement of the thickness of LES muscles was performed only at one time, and the balloon dilatation and esophageal muscle thickness assessment was conducted on one day. Patients were advised to consume a small meal 48 h before the EUS procedure and were kept fasting from the previous evening. Using a Japanese Hitachi instrument with a 10 MHz probe, an experienced physician performed the measurements in EUS. First, the location of LES was identified by inserting a probe into the stomach and then withdrawing it from the cardia. Then, the thickness of the LES was measured twice, and each time the average of multiple measurements was taken into account. Finally, the smallest value between these two measurements was entered into the study as the esophageal thickness. Efforts were made to avoid taking a tangential view during the measurements. To rule out pseudo-achalasia, the esophagus and stomach were then inspected for mass and lymphadenopathy.

2.4. Dilatation with a balloon

For dilatation, a Regiflex balloon was employed. The procedure was performed while the patient was lying on the left side and under sedation. The endoscope was used to insert the guidewire into the duodenum, after which the endoscope was removed, and the balloon was inserted into the esophagus via the guidewire. Endoscopy was used to confirm the proper positioning of the balloon. Afterward, the balloon slowly inflated to a maximum pressure of 15 psi and held for 60 s or until the ischemia center was visible, and then, the balloon was deflated. Finally, another endoscopy was performed to observe the dilatation site. If perforation was suspected, patients were observed for up to 6 h, and esophagography was performed if needed.

2.5. Timed Barium Esophagogram (TBE)

The TBE was used when clinical symptoms of disease recurrence and manometry results were in contrast, one year after the initial procedure in all patients. In this technique, the patient, who had been fasted since the previous evening, ingested 150–250 cc of barium, depending on the patient's tolerance, and then, had radiography at 1, 3, and 5 min. The radiography in minute 3 was done to determine whether the radiography in minute 5 was necessary. The presence of barium at a height greater than 5 cm in minute 5 radiography indicates inadequate esophageal evacuation. If it had similar results with clinical symptoms and manometric conditions, it was indicative of disease recurrence.

2.6. Data analysis

The Kolmogorov–Smirnov test was used to determine the normality of the data. If the quantitative data in the two groups were normal, the student t-test was used to compare the means; if the data were non-normal, the Mann–Whitney U test was applied. The Chi-square or Fisher's exact test was used to compare qualitative group data. Using the Spearman correlation test, the relationship between research variables was analyzed. If the data were normalized, they were presented as mean ± standard deviation; otherwise, they were shown as median (IQR). All analyses were performed using the SPSS version 26 software. A significance level of 0.05 was considered in all cases, and two-domain tests were used.

3. Results

3.1. Demographic features

A total of 22 patients were diagnosed with achalasia for the first time, 19 of them received PD treatment, and 17 patients enrolled in this study. One patient refused performing the second EUS. As a result, the data of 16 patients was analyzed (Fig. 1). Of the 17 study participants, 11 patients (64%) were female and 6 patients (36%) were male. The mean age of the study participants was 52 years. Seven patients (41%) were classified as class I achalasia, whereas 10 cases (59%) were classified as class II achalasia. Table 1 represents the baseline characteristics of the study participants, and also manometric and endosonographic data of each patient. The patients with class I achalasia were slightly older than the patients with class II achalasia, however, the difference was not statistically significant.

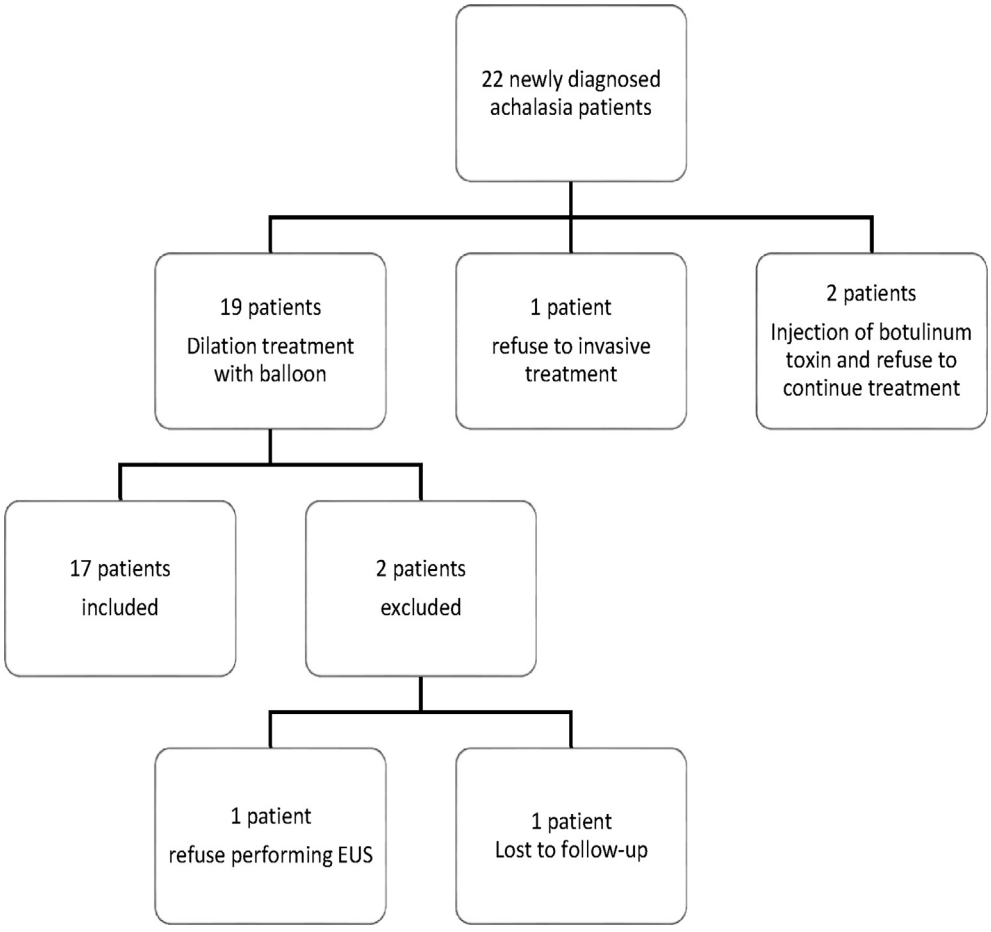

Fig. 1. Flowchart of patient inclusion.

Table 1. Demographic information of patients involved in the study and a comparison of type one and two of achalasia.

	Studied patients (n = 17)	Type I (n = 7)	Type 2 (n = 10)	P-value
Duration of disease (months)	12 (1−60)	12 (3−36)	11 (1−60)	0.95
Age (years)	52 (18−68)	57 (38−60)	47.5 (16−68)	0.096
Female gender (percent)	11/17 (64%)	4/7 (57%)	7/10 (70%)	0.49
Body mass index (BMI) (kg/cm^2)	23.9 (±5.04)	22.9 (±3.01)	19.1 (±18.87)	0.32
Symptom severity	8.9 (±1.81)	9 (6−11)	10 (6−12)	0.36
Chest pain	1 (0−3)	0 (0−2)	2 (0−3)	0.10
Regurgitation	3 (1−3)	3 (2−3)	3 (1−3)	0.60
Dysphagia	3 (2−3)	3 (2−3)	3 (3−3)	0.66
Weight loss	2 (0−3)	3 (0−3)	2 (0−3)	0.36
Post-treatment symptom severity				
Chest pain	1.5 (±1.3)	0.7 (±1.03)	2.3 (±1.03)	0.038
Regurgitation	0 (0−3)	0 (0−0)	0 (0−3)	0.08
Dysphagia	0 (0−1)	0 (0−1)	0 (0−1)	0.62
Weight loss	1 (0−3)	0 (0−3)	2 (0−2)	0.25
Smoking	0.17	0	0	
Diabetes	2.17			
Hypertension	1.17			
Manometric features before treatment				
IRP (mmHg)	20.8 (16−80)	23.3 (16−80)	19.5 (17−43)	0.67
LES baseline pressure (mmHg)	41 (21−69)	40.5 (30−69)	44 (21−64)	0.94
LES thickness (mm)	4.9 (3.6−6.6)	4.9 (4.2−5.7)	4.9 (3.6−6.6)	0.58
External muscle thickness (mm)	2.6 (1.1−3.8)	2.5 (2.2−3.3)	2.65 (1.1−3.8)	0.95
Internal muscle thickness (mm)	2.1 (1.6−2.9)	2.3 (1.9−2.9)	2.1 (1.6−2.8)	0.74

IRP: Integrated Relaxation Pressure, LES: Lower Esophageal Sphincter.

3.2. Patients follow-up

Six patients discontinued treatment after the first or second dilatation, and two patients relapsed despite three dilatations, which required surgical intervention. After one year, only ten patients were referred for an in-person visit (5 recovered patients and 5 with disease recurrence).

Nine of the seventeen investigated patients responded to the first balloon dilation, of which seven did not show recurrence of the disease until the end of the follow-up duration. Of the eight individuals who did not respond well to the first dilatation, two patients refused to perform the second dilatation and six cases underwent a repeated dilatation, which resulted in well initial response (two of whom recovered by the end of the study, and the other four relapsed). If we define patients with the initial response as asymptomatic cases for at least one month, 15 patients after one or two dilations achieved initial response (Eckardt score 3 or less). Of which, 6 patients (40%) had symptoms and were classified as recurring in less than one year, whereas 9 patients (60%) did not have recurrence until the end of one-year follow-up (see supplementary figure 1).

3.3. Factors associated with recurrence

Table 2 summarizes the correlation between study variables and achalasia recurrence. Of the four symptoms documented, only chest pain was significantly associated with recurrence. Regarding the thickness of LES muscle, it was thinner in recurring patients (both overall and individually for internal and exterior muscles), the difference was not statistically significant ($p\text{-value} = 0.06$). However, those who responded to the initial dilation had thicker LES muscles ($p\text{-value} = 0.031$).

Of the seventeen patients studied, the manometry study of three patients was unsatisfactory (all three patients were in the initial-response category); thus, the manometry studies of 14 patients were included in the analysis. Although not significant ($p\text{-value} = 0.055$), the IRP before treatment was higher in patients with recurrence.

Twelve of the seventeen patients underwent re-manometry, with one patient's test being unsatisfactory. Re-manometry was performed for two patients one month after the previous dilatation (due to early recurrence) and between 9 and 12 months after the last dilatation in the remaining patients. Since manometry was not done within the same time frame for all patients following therapy, no analysis was conducted using the second manometry data.

Two patients were classified as class II at the start of the trial. However, both patients showed class I manometric characteristics at one-year follow-up. Both patients were in the recurrent group, and one was still symptomatic after three dilatations. A greater proportion of patients with class I achalasia responded to treatment than patients with class II achalasia, although this difference was not statistically significant.

Table 2. Relationship between research variables and recurrence of achalasia.

	Without recurrence	With recurrence	Statistical significance
Symptoms			
Chest pain	0 (0–3)	2 (0–3)	0.01
Regurgitation	3 (2–3)	3 (3–3)	0.23
Dysphagia	3 (2–3)	3 (3–3)	0.8
Weight loss	2 (0–3)	2 (1–3)	0.41
LES thickness			
Longitudinal muscles (mm)	2.75 (2.2–3.8)	2.35 (1.1–3)	0.12
Circular muscles (mm)	2.3 (1.9–2.9)	2.1 (1.6–2.7)	0.473
Total thickness (mm)	5.15 (4.2–6.6)	4.55 (3.6–5.1)	0.06
Pre-treatment manometry			
IRP (mmHg)	30 (16–80)	17.95 (17–21.7)	0.055
Resting LES pressure (mmHg)	46 (30–69)	38 (21–57)	0.26
Achalasia type			
Type I	6	1	0.119
Type II	3	5	
Barium column height (cm)			
1st minute	10 (1.6–15)	10 (10–17)	0.62
3rd minute	7.5 (0–12)	10 (9–15)	0.37
5th minute	4 (0–11)	8 (7–9)	0.36

IRP: Integrated Relaxation Pressure, LES: Lower Esophageal Sphincter.

3.4. Association between esophagography and response to treatment

Ten patients (58%) referred for esophagography after one year, although three patients presented with a 6-month delay. All of them responded well to the treatment. Two out of the five patients that were asymptomatic and showed no recurrence had a barium column height above 5 cm in esophagography. One of them had a Eckardt score of 0 with barium column height of 7 cm and the other patient had a Eckardt score of 1 barium column height of 11 cm with a maximum barium width of 3 cm and 4 cm, respectively. Patients who had improved symptoms were more likely to have esophagography after one year, compared with patients with recurrence of the disease, (50% versus 71%), although this difference was not statistically significant. In addition, there was no significant association between disease recurrence, and initial treatment response or barium column height.

3.5. Other parameters

Other than recurrence, severe pain (score 2 or 3) was negatively correlated with the overall thickness of the LES and IRP before the treatment (Spearman correlation coefficients of −0.66 and −0.42, respectively) (Fig. 2). Although all patients with severe pain had a disease duration of fewer than 3 years, there was no association between disease duration and pain or any other examined characteristics (Fig. 3).

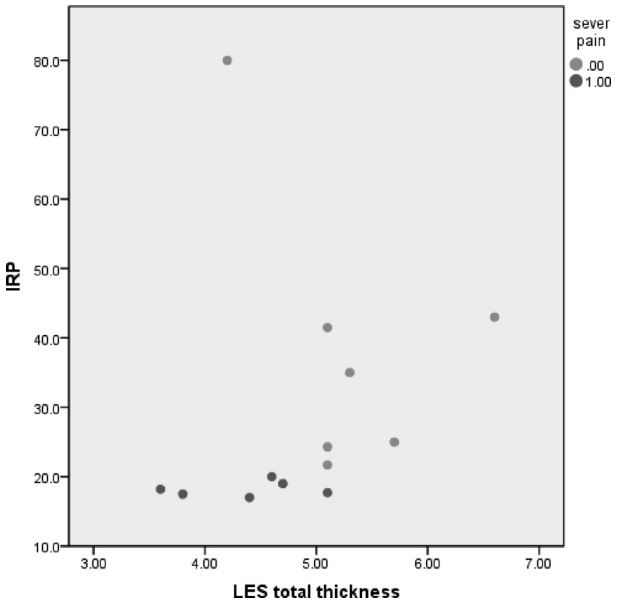

Fig. 2. The relationship between LES total thickness and severe pain and IRP before treatment.

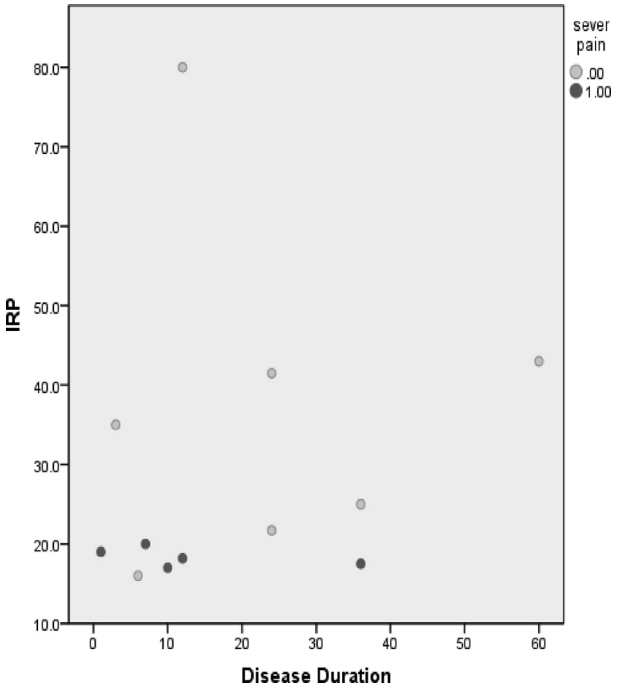

Fig. 3. The relationship between severe pain and disease duration.

4. Discussion

The high recurrence rate (40%) was one of the most significant differences between our study and previous studies. In this regard, the following considerations are crucial: 1- we used a milder PD protocol for each PD session, in contrast to other centers that treated patients more aggressively for each PD session.[15] It is not uncommon, especially in European centers, to repeat PDs at intervals of 2−4 weeks until the patient becomes completely asymptomatic, and all these dilatations are considered one session. We repeated PDs only for patients with ES > 3 or severe dysphagia. 2- The endoscopic dilation approach was employed without using a fluoroscope. Although this method had similar efficacy in several studies to using a fluoroscope, its efficacy in therapy is probable.[7] 3- This recurrence rate is similar to some other studies, such as the earlier Iranian investigation and the European study comparing PD and POEM, despite the disadvantages highlighted above.[16,17] 4 - Greater prevalence of pain and shorter duration of disease onset (half of the patients referred before one year) compared to other studies may have contributed to this study's lower success rate.

In contrast to the findings of Lee et al., which demonstrated a direct relationship between external muscle diameter and disease recurrence, our study shows an inverse relationship between esophageal muscle thickness and response to PD treatment, and

it is consistent with the findings of two recent studies.[11,12] This association in POEM treatment may be due to the ease of myotomy in patients with thicker LES. However, no research has established a relationship between LES thickness and dilatation treatment response. In this study, a thicker LES was associated with an acceptable response to the "first dilatation", regardless of the duration of the response, in contrast to "first PD session" which is typically studied in other studies.

LES thickness may be a surrogate marker for effective contractions in the longitudinal muscles of the esophagus, even if these contractions do not lead to esophageal pressurization. According to last decade's studies on esophageal longitudinal muscle involvement in achalasia, healthy contractions in the external muscles help maintain esophageal strength and clearance.[18,19] In this study, the small sample size and low statistical power made the 0.4 mm difference in longitudinal muscle thickness between the recurrence and non-recurrence groups statistically insignificant.

Pain has been associated with recurrence in several studies.[20] In some cases, its relationship with type 3 achalasia is considered the cause of this association. Pain severity and disease recurrence were clearly linked in our study, regardless of whether the patients had type 1 or 2 achalasia. The level of pain was the same in both types of achalasia.

Although muscle thickness and IRP were not substantially related to the existence or absence of pain in this study, they were related to pain severity. This connection can be understood in two ways: 1- Pain severity is proportional to the amount of stress and tension on the esophageal wall. As esophageal thickness diminishes, stress on the esophageal wall increases, and thus, so does pain. 2- Pain is a sign of the progression rate of a disease.

Pain develops in many disorders in which the volume of the organ or mass increases rapidly without allowing the capsule or surrounding tissue to adjust. The esophageal wall adapts to the obstruction in two ways. The path of fibrosis due to multiple reasons, such as mechanical traction, abrasion, or mast cell infiltration and esophageal muscle strengthening. A quicker progression of fibrosis results in tissue inflexibility, pain, and a thinner esophageal wall. In contrast, slower fibrosis permits more muscle strengthening, resulting in less pain and a more desirable response to treatment.

In our study, there was no association between pain severity and disease duration; however, patients with moderate to severe pain (Scores 2 and 3) reported symptoms for less than a year before their diagnosis. In some studies, there is no relationship between pain and other study parameters, which may be due to the low pain scores in such studies.

Inconsistent prognostic values of muscle thickness or pain in achalasia patients reported by several researches may be related to the intensity of treatment or a lower rate of treatment failure in other studies. Prognostic factors not only allow us to identify patients with more aggressive diseases but also help us to understand the pathophysiology of the disease. Since more intensive treatments may mask the value of prognostic factors, it would be possible to identify prognostic factors if only the minimum therapy necessary is administered and the disease is allowed to run its natural history.[21]

There were some limitations regarding this study. First, the small sample size was limited, which prevents multivariable analysis. Second, the follow-up period was short. Third, using an uncommon and less strict treatment protocol than other studies. Fourth, we were not able to evaluate treatment response with a TBE and we simply relyed on the Eckardt score. And fifth, the results cannot be generalized to all achalasia patients due to the difference between our study population and other studies. Also, one other limitation of this study was that the twice measurement of LES thickness was not performed by the same experienced clinician in some cases, which can result in potential bias. However, these results can be used to understand better the connection between the clinical and the paraclinical features of achalasia.

Research ethics and patient consent

All procedures and methods were carried out in conformity with applicable rules and guidelines in Iran. The study was authorized by the independent medical ethics council of Tehran University of Medical Sciences with the code of IR.TUMS.IKHC.REC.1398.204).

The authors acknowledge that the article does not contain any personal information about the participants that reveals their identity or makes more data available.

In conducting our study, we have obtained ethical approval from the appropriate research ethics board, ensuring that we adhere to ethical guidelines and protect the rights and welfare of our participants. We have taken all necessary measures to maintain confidentiality, obtain informed consent, and minimize any potential harm or discomfort to the participants involved.

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Conflict of interest

In our study, we want to make it clear that there are no conflicts of interest that could compromise the objectivity and integrity of our research.

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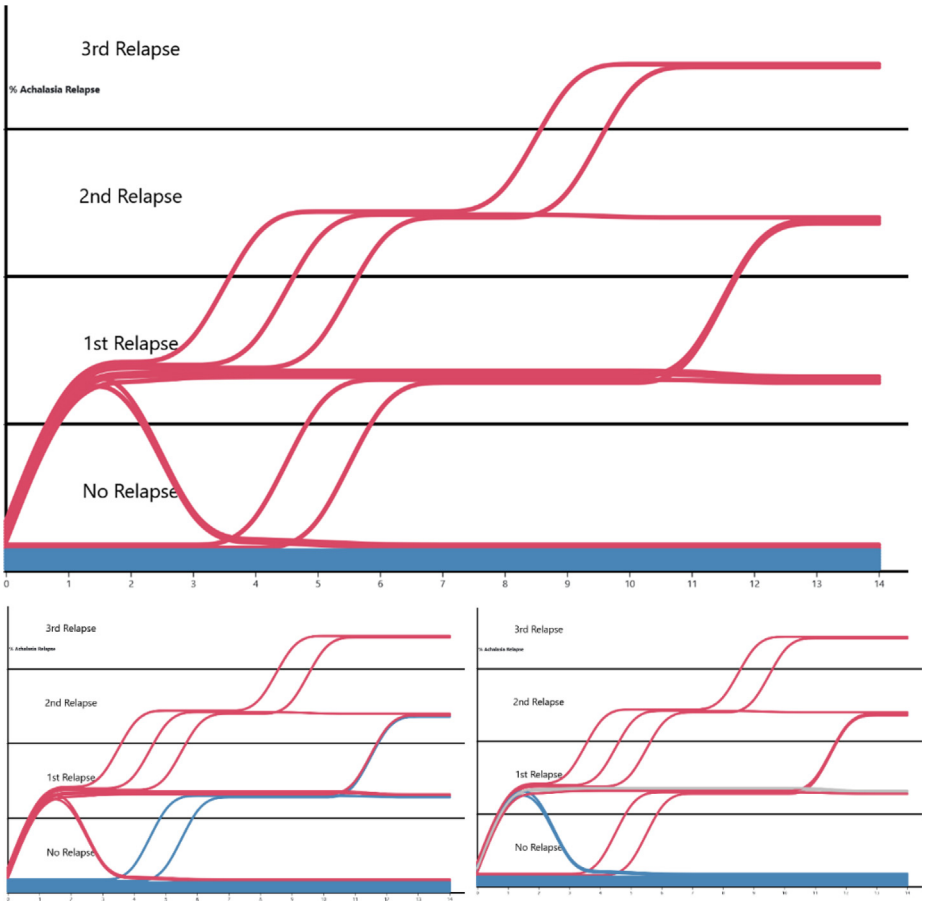
Appendix



Supplementary Figure 1. Patients' follow-up course. There are three classification types of patient responses to PD treatment over time on the x-axis (in months). The Y-axis represents the number of relapses. The final patient classification is displayed on the right side of the graphs. Patients with three therapy sessions and those with treatment failure are on the top of each chart. The bottom area of each graph represents patients who responded to treatment. Patients who did not continue therapy after one or two relapses are in the middle of the charts. In these graphs, ascending lines represent recurrences. Patients who remain symptom-free following treatment until the end of the year are categorized as non-relapsing and are connected to the zero line. A: classify patients depending on their total recurrence rate. The blue line represents patients that responded well to the initial dilatation. The Red line indicates relapses or lack of therapy response. B: categorization according to initial answer (improvement for at least one month). The blue line represents a steady improvement, whereas the red line represents early relapses (less than one month) or no responses. C: separation based on relapse following initial response stability. Blue indicates no relapses, red indicates relapses, and the gray line indicates patients who declined to continue treatment.

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