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# ACHALAGLIE: analysis of the oesophageal muscle in achalasia from biopsies obtained during per-oral endoscopic myotomy (POEM) : a feasibility and safety study

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Samuel Andrault. ACHALAGLIE: analysis of the oesophageal muscle in achalasia from biopsies obtained during per-oral endoscopic myotomy (POEM) : a feasibility and safety study. Human health and pathology. 2022. dumas-03882396

**HAL Id: dumas-03882396**

**<https://dumas.ccsd.cnrs.fr/dumas-03882396>**

Submitted on 22 Mar 2023

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**NANTES UNIVERSITÉ**

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**FACULTÉ DE MÉDECINE**

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Année : 2022

N°

**THÈSE**

**POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE**

**DES HEPATO-GASTROENTEROLOGIE**

par Mr Samuel ANDRAULT

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Présentée et soutenue publiquement le 11/10/2022 à Nantes

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ACHALAGLIE : Etude de la musculature œsophagienne dans l'achalasie à partir de biopsies réalisées au cours d'une myotomie per-oral endoscopique (POEM) : étude de faisabilité et de sécurité.

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ACHALAGLIE : Analysis of the oesophageal muscle in achalasia from biopsies obtained during per-oral endoscopic myotomy (POEM) : a feasibility and safety study.

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**Composition du Jury :**

**Président** : Monsieur le Professeur Emmanuel CORON

**Membres** : Madame le Docteur Lucille Quénéhervé  
Monsieur le Professeur Jean-François MOSNIER

**Directeur de thèse** : Monsieur le Docteur Raphael Olivier

## **REMERCIEMENTS :**

*Aux membres du jury,*

**Monsieur le Président du jury, Monsieur le Professeur Emmanuel CORON,**

Vous me faites l'honneur d'accepter de présider le jury de cette thèse, veuillez trouver ici l'expression de mon profond respect et de ma reconnaissance. Je vous remercie de m'avoir encadré et transmis votre passion de l'endoscopie interventionnelle.

**Madame le Docteur Lucille QUENEHERVE,**

Tu me fais l'honneur d'être présente pour juger de mon travail, sur place de surcroît, et ce malgré ce long trajet Brest-Nantes que je ne connais que trop bien. Merci pour ton encadrement, ces formations d'endoscopie incroyables et ta bonne humeur.

**Monsieur le Professeur Jean-François MOSNIER,**

Vous me faites l'honneur d'être présent pour prendre part au jury de cette thèse. Merci d'apporter votre regard et votre expertise sur ce travail. Merci de votre disponibilité et votre bienveillance. Veuillez recevoir ici l'expression de mon profond respect.

**Monsieur le directeur de thèse, Docteur Raphaël OLIVIER,**

Merci d'avoir été mon guide dans le méandre obscur qu'est l'écriture d'une thèse. Sans toi je n'aurais sûrement jamais réussi à écrire ce travail. Je te remercie de ta patience et de ta compréhension dans ces moments qui ont parfois été difficiles. Je suis très heureux que tu fasses partie de ce jury.

*A toutes les personnes ayant contribué à ce travail,*

Merci à Céline TAKOUDJU d'avoir apporté son expertise pour relire et classer certaines manométries.

Merci à Clément, mon indic, de m'avoir récupéré ces magnifiques images en service d'anatomopathologie. La dette a été remboursée.

Merci à beaucoup de personnes d'avoir été compréhensifs pour mes absences et mon humeur de ces derniers mois.

*Merci également,*

**A mes formateurs,**

Tous les médecins qui m'ont supervisé, dans les services d'hépatogastro-entérologie du CHU de Nantes et du CH de Cholet. Merci pour vos enseignements pratiques et théoriques qui m'ont permis d'apprendre et de progresser dans ma spécialité. Merci également aux médecins des services d'oncologie médicale et de radiothérapie de l'ICO Gauducheau de m'avoir accompagné pendant 1 an de mon internat dans le vaste monde de l'oncologie médicale.

Tous mes anciens chefs de clinique et assistants, parfois anciens co-internes, merci pour votre accompagnement durant mon internat, votre gentillesse et votre disponibilité : Matthieu, Marion, Maëva, Catherine, Caroline.

Merci à Christèle de m'avoir aidé à faire mes premiers pas dans l'oncologie, et de m'avoir transmis sa passion. J'ai bien compris que je n'étais pas l'interne d'endoscopie. On aura quand même bien ri en HDJ malgré le COVID.

**A toutes les équipes paramédicales, que ce soit celles du CHU ou de l'ICO,** Merci pour ce que vous nous apportez tant sur le plan humain que professionnel. Dédicace spéciale à l'équipe de nuit des soins intensifs.

**A mes co-internes,**

Ma promo de vainqueurs : Vicky, Morgo (encore merci pour les tomates), et La Delge, l'internat aurait été beaucoup plus difficile sans vous à mes côtés.

Mes co-internes devenus grands : Juliette, Elise, Lucie, Marine, Miloud, Quentin, Oriane, et la Gond (sans rancune pour toutes ces raclées que je t'ai infligé au badminton).

Mes co-internes actuels : Briot (j'ai encore la nostalgie de ces après-midis dans le bureau avec le bon Benoît), la Bove (mon poulain, je lui ai tout appris), Raphaëlle, Amaury, Alexandre, Nour, Giulia, Douhoume, Yvre, Hugo, Céline et Madeleine. RIP Boudenne, tu nous manques.

Mes co-internes angevins : Docteur Cotilleau devenue grande, Norma, merci à vous deux de m'avoir supporté pendant 6 mois à Cholet. Dommage qu'on ne puisse pas se retrouver tous les trois.

Mes co-internes d'oncologie médicale et de radiothérapie : Clément (x2), Alexandre, Marie, Garabet, le jeune Joly, Dr Perennec.

Mesdames et messieurs, ce fut et cela restera un plaisir.

**A mes amis,**

A mon meilleur copain Lou-Lou, on ne va pas se mentir, c'est quand même pas top Kampfar.

A mon frérot Jean-Jean, le sang, le muscle. Les fléchettes sont installées à la maison et n'attendent que toi.

A mes frères de pogo : Lucas, Pierre. Merci pour tous ces Hellfest et tous ces concerts incroyables avec vous malgré la distance. J'espère continuer en Juin 2023 et pour longtemps encore.

A mes copains de l'externat, Thomas, Loumar, Béré, et surtout mon bon vieux Maxime, j'espère qu'un jour tu te bougeras un peu et que tu sortiras de Lille pour venir nous voir.

Aux copains du water-polo :

- Les anciens de Poitiers : Ramezy, Paul, Damien, Victor, Fred, Pierre, Nathan et tous ceux que je ne cite pas. Merci de m'avoir aidé à reprendre forme lors de mon externat, ce n'était pas gagné.
- Les champions régionaux de Rezé : Franck, Lilian, Sophie, Thadée, Théo, Louis, Greg, Vincent, Alexandre (x2), Benoit, Pascal, Thierry, Lucas, Rodolphe, Louison, et tous les autres. Désolé pour Septembre-Octobre, promis je me rattrape sur le reste de la saison 2022-2023 (et cette fois, premier buteur !).

Aux copains du ski : Mathilde et Agathe, Leïla, Simon, Béber, Camille et Bastien.

**A ma famille,**

Mes parents. Mon petit papa et ses sautes d'humeur, qui m'a transmis l'envie de faire médecine. Ma petite maman bavarde qui m'a transmis sa compassion. Merci de m'avoir soutenu toutes ces années. Il y a eu des moments difficiles mais qui n'ont jamais éclipsé les meilleurs.

Ma petite sœur (oui), partie bien loin vers sa belle île ensoleillée depuis maintenant de longues années. Je n'espère pas encore avoir à subir trop longtemps le harcèlement constant pour le mariage et les enfants, c'est assez culotté venant de ta part si je puis dire. Je ne te souhaite que du bonheur.

Mon petit frère, le petit scarabée de la famille. Ma petite teigne, avec ses « je m'en fous, ça marche ». Merci pour ton soutien, ta bonne humeur, pour nos sessions de geekage. Continue de t'accrocher, ce n'est pas parce qu'on tombe une fois que le combat est terminé.

Mes grands-parents, ceux toujours présents et ceux partis. Merci pour tout.

Mes cousins (et autres !), Benja et Cerise, Emilie, Romain, Solan (et bientôt un de plus !), Solène et Paul, Alice, et tous ceux que je ne cite pas, je ne vous ai pas oublié.

**A ma belle-famille,** merci de m'avoir accueilli et de me nourrir comme vous l'avez fait.

**A ma Pierrette,** Merci pour ta douceur et ta gentillesse, et surtout merci de me supporter ! J'espère profiter de nos moments pendant encore de nombreuses années.

Je dédie cette thèse à mon oncle Pascal.

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## **LISTE DES ABREVIATIONS**

ASA (score): American Society of Anesthesiology Physical Status Classification System

BMI : Body mass index.

BP : Bodily pain

ENS : Enteric nervous system

ER : Emotional role

ESD : Endoscopic submucosal dissection

FFOCT : Full-field optical coherence tomography

GERD : Gastro-esophageal reflux disease

GH : General health

H&E : Hematoxylin and eosin

ICU : Intensive care unit

HREM : High resolution oesophageal manometry

IQR : Interquartile range

LES : Lower esophageal sphincter

MCS : Mental component score

MH : Mental health

NGEU : Neuronal–glio–epithelial unit

PCS : Physical component score

PF : Physical functioning

POEM : Peroral endoscopic myotomy

PPI : Proton pump inhibitor

RP : Role physical

SF : Social functioning

VT : Vitality

# 1. INTRODUCTION

Achalasia is the most common primary oesophageal motility disorder, characterized by abnormalities of oesophageal peristalsis and abnormal relaxation of the lower oesophageal sphincter. Achalasia is a rare disease (0,5/100 000 inhabitants in France) (1) that can affect all ages and severely impact the patient's quality of life.

High resolution oesophageal manometry (HREM) is the gold standard for the diagnosis of achalasia (2) It allows to differentiate 3 subtypes according to the Chicago classification (3).

The pathophysiology of achalasia remains poorly understood. Damage to the enteric nervous system (ENS) and the oesophageal epithelial barrier, which constitute a true anatomical and functional unit also called the neuronal–glio–epithelial unit (NGEU)(4), probably plays a major role in the development of the disease. While oesophageal muscle is also involved in this pathology, data are scarce to evaluate the real pathophysiological mechanisms since it remains difficult to obtain muscular samples at early stages of the disease (5). The etiological factors possibly involved are viruses (Herpes Simplex Virus)(6–8), a dysimmune condition with antineuronal antibodies (9,10), activated eosinophils (11), hormones (12) or a genetic background (13).

Histological analysis of the oesophageal muscle in achalasia was previously limited to the lower oesophageal sphincter, accessible during Heller myotomies or esophagectomy (5,14,15). Routine endoscopy did not allow analysis of the oesophageal muscle, but only of the muscularis mucosae and submucosa. Per-oral endoscopic myotomy (POEM) is the most recent treatment for achalasia (16). It consists in making a mucosal incision, creating a tunnel by submucosal dissection, performing an incision of the inner circular muscular layer, and closing the mucosal entry.

Since the advent of POEM, the muscularis has become accessible for biopsy after creation of the submucosal tunnel. Several studies have shown that it was possible to biopsy several components of the oesophageal wall during this procedure (8,17,18), without intraoperative and postoperative complications.

Our main hypothesis is that the analysis of oesophageal mucosal and muscle biopsies, obtained safely during POEM in naïve-treatment patients with achalasia, would allow us to better characterise the achalasia pathophysiology, by analysing remodelling of the oesophageal mucosa and muscular tissue. These abnormalities could eventually constitute new therapeutic

targets and improve the stratification of patients according to the type of achalasia and their response to treatment.

Although POEM treatment is effective (19), it consists of a myotomy in a functional disease. We know that some patients, although improved after the procedure, will develop atypical symptoms. Our second objective will be to explore the life quality of the patients after the intervention.

Therefore, the aim of this study was to prove the feasibility and safety of oesophageal muscular and mucosal biopsy during POEM in achalasia patients, to evaluate the efficacy of the treatment, and to report the quality of life the patients after the procedure.

## **2. METHODS**

### **1. Patients**

ACHALAGLIE is a monocentric (Nantes University Hospital) prospective, uncontrolled, non-randomised study. Patients were enrolled from November 2019 to November 2021. The trial protocol was approved by an independent ethics committee (Comité de Protection des Personnes). Written informed consent was obtained from all patients.

Inclusion criteria were as follows: proven achalasia by standard HREM (according to Chicago Classification), age  $\geq 18$  years old. All the patients included had to be naïve of either surgical or endoscopic treatment. Pregnancy and curative anticoagulation were considered as exclusion criteria. Inclusion was done the day of the POEM (V1). All complications and adverse events were reported.

Eckardt score, manometry and clinical information, nutritional and SF-36 questionnaires were assessed at the pre-inclusion consultation (within 1 day to 4 months before the procedure). SF36-questionnaires were then assessed at V3 (between 9 and 12 months post-POEM). Eckardt score were assessed after at least 1 year of follow-up.

### **2. Outcomes**

Our primary outcome was to demonstrate that the study of the oesophageal muscle is feasible from oesophageal mucosal and muscular biopsies taken by an endoscopic paediatric

forceps during POEM in treatment-naive patients with achalasia, defined by the percentage of biopsy with an effective histological study.

The secondary endpoints were as follows:

- Evaluate the safety of the procedure, assessed on the following criteria: per and post procedure-related adverse events (bleeding, haematoma, perforation, infection). Adverse events were graded according to the American Society for Gastrointestinal Endoscopy lexicon(20). The length of hospital stay was also collected.
- Evaluate the safety of the biopsies, defined by the complications potentially attributable to the biopsies. For the complication to be imputable to the biopsies, it was necessary to certify that the location corresponded to the area of interest (e.g., a haematoma opposite the tunnel closure cannot be attributed to the biopsies).
- Evaluate the feasibility of the procedure, assessed on the following criteria: procedure failure, length of myotomy, number of clips used to close the tunnel and procedure duration. A procedure was considered complete if the myotomy and tunnel closure could be performed. A POEM was considered a failure if the procedure was not completed entirely.
- The efficacy of the treatment, defined by an Eckardt score  $\leq 3$  (21) (Annex 1) after at least one year of follow-up. A POEM was considered as a clinical failure if the Eckardt score was  $\geq 3$  at 1 year or if a new procedure was required.
- Improvement in quality of life after the procedure, according to the SF36 questionnaire (Annex 2) between 9 and 12 months after treatment (V3).
- Histological analysis of the biopsies was also reported.

### **3. POEM and biopsy procedure**

All POEM procedures were performed at the University Hospital of Nantes from November 2019 to November 2021. A high definition gastroscope (EG760Z, Fujifilm, Japan) mounted with an Endoscopic submucosal dissection (ESD) cap on the distal tip was used for all procedures. Patients were anesthetized using propofol, intubated and CO<sub>2</sub> was used for endoscopic insufflation. A submucosal injection was then created using a mix of saline and indigo carmine solution between 30 and 35cm of the dental arches. A transverse mucosal incision was performed using a second generation ESD knife allowing re-injection (Flushknife BT 2 mm, Fujifilm, Japan), and an electrosurgical generator (ERBE, Tübingen, Germany). The

gastroscope was then introduced into the submucosal space and submucosal tunnelling was performed. The tunnel was extended across the lower oesophageal sphincter (LES) and into the gastric cardia. Both circular and longitudinal muscular layers were cut to provide a 10-12 cm long full thickness myotomy using the same ESD knife. Coagrasper Hemostatic Forceps were used in case of haemorrhage. Closure of the mucosal incision was achieved using haemostatic clips (Olympus, Japan).

Biopsies were taken in an area not macroscopically injured by the procedure using a paediatric forceps.

- Three biopsies of the oesophageal mucosa were taken 3 to 6 cm above, and three at the level of the cardia, contralateral to the POEM. For each localisation, two were placed in a dry tube and immediately put in nitrogen, one was placed in formalin and sent to the anatomopathological department to be included in a paraffin block.
- After the submucosal dissection, four biopsies were taken 3 to 6 cm above, and four at the level of the cardia. For each localisation, three were placed in a dry tube and immediately put in nitrogen, one was placed in formalin and sent to the anatomopathological department to be included in a paraffin block.
- Another muscular biopsy was taken for each patient for full-field optical coherence tomography (FFOCT) analysis.

A water-soluble oesophagram was obtained the day following the procedure before initiating liquid and soft diet. Patients were discharged home on day 2 or 3 if they were able to tolerate soft diet without significant pain. Procedural data collected included American Society of Anaesthesiology Physical Status Classification System (ASA) score of the patient (22), date of procedure, full procedure, length of myotomy, number of clips used to close the tunnel, procedure-related adverse events, and procedure duration. Antibiotic prophylaxis was performed by the anesthesiologist at the time of induction before each procedure.

It should be noted that the biopsies not sent to the anatomopathology department were sent to the research laboratory (Inserm U 1235) for the analysis of NGEU, which will be the subject of further studies that we will not detail in this work.

#### **4. Statistical analysis:**

Data were collected prospectively and studied retrospectively. Quantitative variables were presented as the mean, median, percentile (interquartile range: 25% and 75%). Categorical variables were presented as percentages associated with each response modality.

The follow-up of patients in terms of quality of life and Eckardt scores has been analysed using Wilcoxon signed rank tests.

### **3. RESULTS**

#### **1. Population study:**

At baseline, 28 patients were included instead of the 30 initially planned. The baseline characteristics of these 28 patients are listed in Table 1. The most frequent indication for POEM was type II achalasia (75%). 4 patients had auto-immune diseases: 2 (7%) had asthma, 1 (4%) had psoriasis, 1 (4%) had scleroderma. 2 patients (7%) had a history of breast cancer, 1 patient was considered in remission. The most predominant symptom at diagnosis was dysphagia (86%). The median age at the time of POEM was 62 years old (IQR 25-75: 43-66). The median Eckardt score before POEM was 8 (IQR 6-9). The median weight loss since the onset of symptoms was 9 kg (IQR 25-75: 0.5-12). All patients had high-resolution manometry. Seven (25%) patients were on proton pump inhibitors (PPIs).

**Table I: Patients characteristics at baseline**

		N (%)	median [IQR 25-75]
Gender	Male	14 (50)	
	Female	14 (50)	
Weight at diagnosis (kg)			66,5 (58-76)
Height (cm)			168 (160-174)
BMI (kg/cm <sup>2</sup> )			23 (20-26,5)
Initial weight loss since onset of symptoms (kg)			9 (0,5-12)
Time since onset of symptoms (years)			
<i>Data missing for 6 patients</i>			12 (5,25-67,5)
Autoimmune disease	Total	4 (15)	
	Psoriasis	1 (4)	
	Scleroderma	1 (4)	
	Asthma	2 (7)	
Neoplasia	Breast cancer	2 (7)	
Dominant symptom at the diagnosis	Dysphagia	24 (86)	
	Regurgitation	3 (11)	
	Chest pain	1 (4)	
Eckardt score at diagnosis			8 (6-9)
Age at diagnosis (years)			60 (42-66)
Age at POEM (years)			62 (43-66)
Achalasia subtype	Type I	5 (18)	
	Type II	21 (75)	
	Type III	0	
	Unclassified	2 (7)	
Time between diagnosis and POEM (months)			8 (4-13)
PPI therapy before POEM		7 (25)	
Preoperative LES pressure (mmHg)			27,6 (19,8-34,7)

## 2. POEM descriptive data

All data are detailed in Table 2. The median procedure time was 59.5 minutes. The median length of the myotomy was 10 cm and the median number of clips used was 6. Four patients could not be refed the day after the operation, either because of complications or because of abnormalities on the esophagram.

**Table 2: POEM characteristics**

	N (%)	median [IQR 25-75]
ASA score		
I	7 (25)	
II	19 (68)	
III	2 (7)	
IV	0	
Procedure duration (min)		59,5 (50-65,5)
Length of myotomy (cm) <i>data missing for 1 patient</i>		10 (10-10)
Number of clips used		6 (5-6)
J1 post-POEM Refeeding	24 (86)	
POEM Failure	3 (11)	
Length of hospitalisation stay		1 (1-1)

### 3. Feasibility, safety and efficacy

Performing biopsies was possible in all patients. Biopsy analysis was possible in 97% (109/112) of cases. Three biopsies (one of the oesophageal body mucosae, one of the cardial mucosae and one of the oesophageal body muscle) could not be analysed due to insufficient material.

The procedure could be performed in 100% of cases. Concerning procedure safety, adverse events are depicted in Table 3. A total of 9 patients (32%) had per or post-procedures adverse events. The most common was mild bleeding per procedure (14%), requiring haemostasis by Coagrasper. One severe adverse event occurred: it was a release of the clips closing the submucosal tunnel, requiring a covered endoscopic prosthesis for closure. The patient did not require intensive care unit (ICU) hospitalisation but was hospitalised for 18 days. The median of hospital stay was 1 day (IQR 1-1).

Regarding biopsy safety, all adverse effects were related to the procedure itself rather than to the biopsies.

Eckardt score data for 24/28 (86%) patients were disponible 1 year after POEM (1 patient lost to follow-up, 3 patients did not reach 1 year of follow-up). The mean Eckardt score



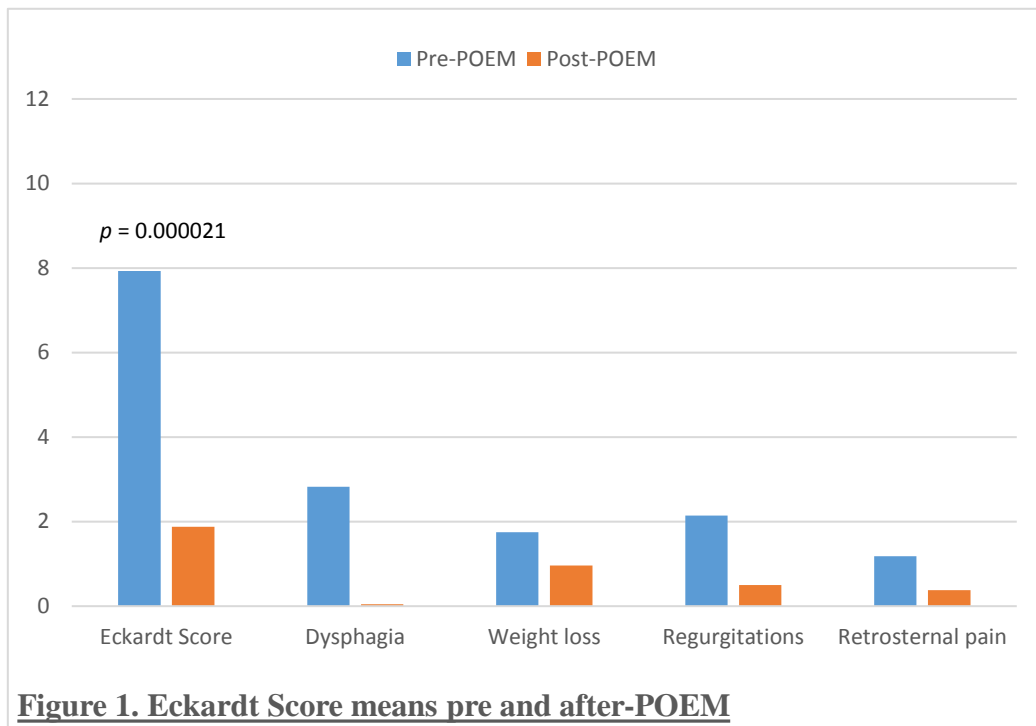
(Fig 1) before POEM was 7.9 and 1.875 1 year after POEM ( $p = 0.000021$ , data collected between 14-23 months post-procedure). The evolution of the different score items is visible in Fig 2. Out of 24 patients, 3 had an Eckardt score  $> 3$  (including the patient who needed another POEM), and 1 patient required endoscopic balloon dilatation, which translates into a POEM effectiveness of 83.3% (20/24) after more than one year of follow-up.

We had 4 clinical failure in this study (14%): one patient required another POEM 6 months after the first procedure due to the recurrence of dysphagia, and another required 2 pneumatic balloon dilatations at 1 and 6 months after POEM. Another patient needed pneumatic balloon dilatation after 19 months after the first procedure.

Data from SF36 questionnaires are shown in the Fig. 3. We found a significative difference between various items at V0 and V3: Physical functioning (PF), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), and Mental Component Score (MCS). We found a decreasing but not significant tendency for the following items : Role Physical (RP), Mental Health (MH), Role Emotional (ER), and Physical Component Score (PCS).

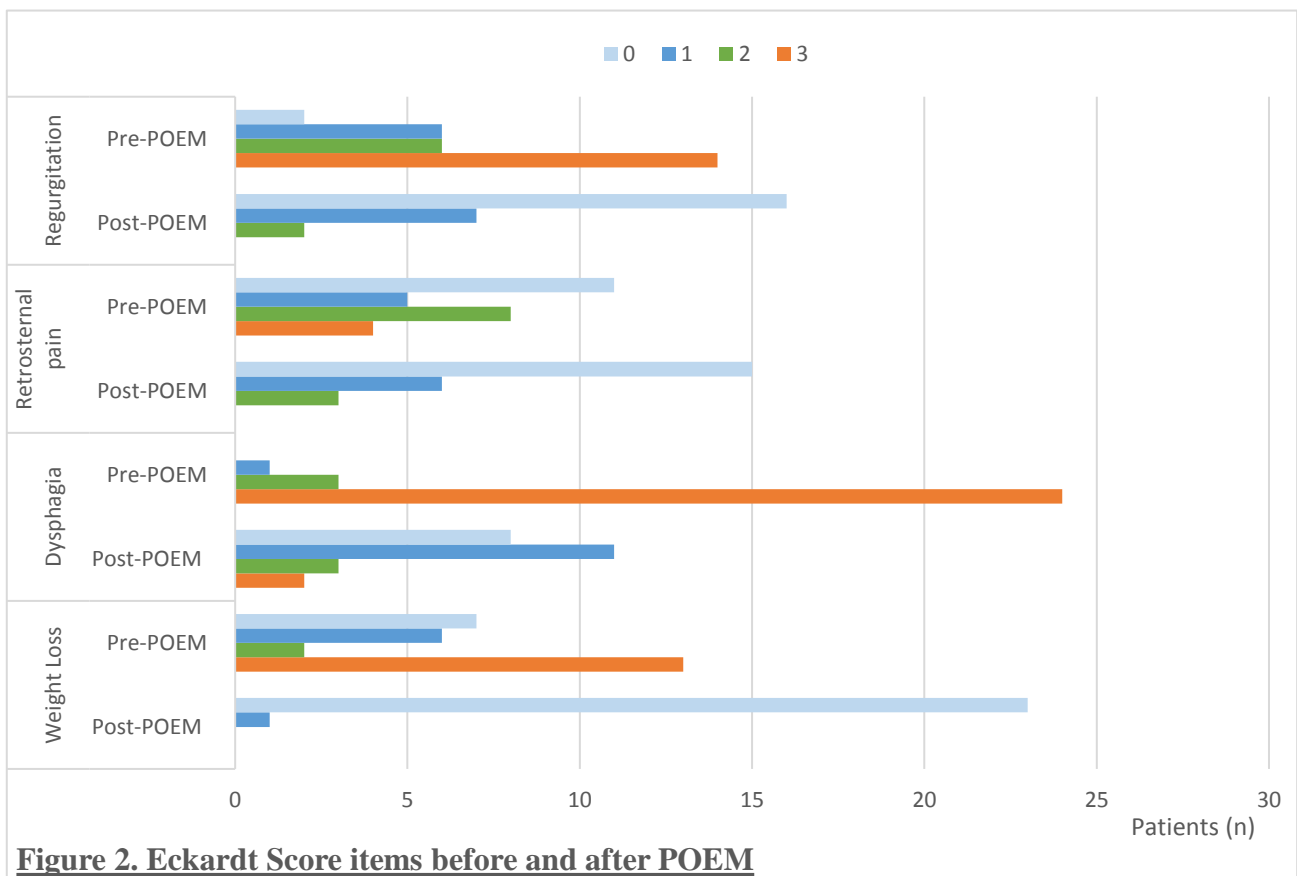
**Table 3: adverse events of POEM according to the lexicon for endoscopic adverse events**

<b>Total adverse events</b>	<b>9 (32%)</b>
<b>Severe adverse events</b>	<b>1 (4%)</b>
No closure of the sub mucosal tunnel requiring <i>endoscopic prosthesis and hospital stay &gt; 10 days</i>	1 (4%)
<b>Moderate adverse events</b>	0
<b>Mild adverse events</b>	<b>8 (30%)</b>
Cardial mucosal breach, clips used	1 (4%)
Post-procedural pain	1 (4%)
Fever post-procedure, <i>medical treatment only</i>	1 (4%)
Gastric fluid inhalation per procedure, <i>medical treatment only</i>	1 (4%)
Mild bleeding per procedure, <i>requiring coagrasper</i>	4 (14%)



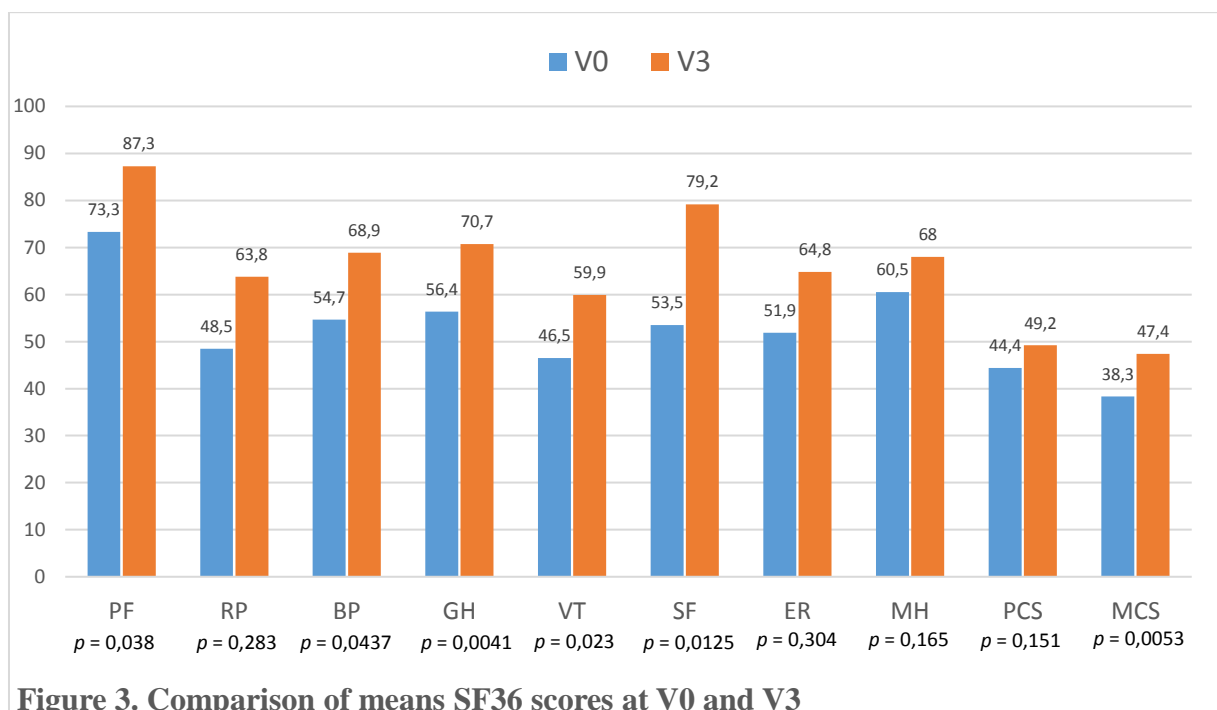
**Figure 1. Eckardt Score means pre and after-POEM**

Analyses performed on data from 24 patients (data missing for 4 patients)



**Figure 2. Eckardt Score items before and after POEM**

Analyses performed on data from 24 patients (data missing for 4 patients)



**Figure 3. Comparison of means SF36 scores at V0 and V3**  
 Analyses performed on the SF36 scores of 18 patients (10 questionnaires could not be recovered).  
*PF : physical functioning, RP : Role physical, BP : bodily pain, GH : general health, VT : vitality, SF : social functioning, ER : emotional role, MH : mental health, PCS : Physical component score, MCS : mental component score.*

#### 4. Biopsies analysis

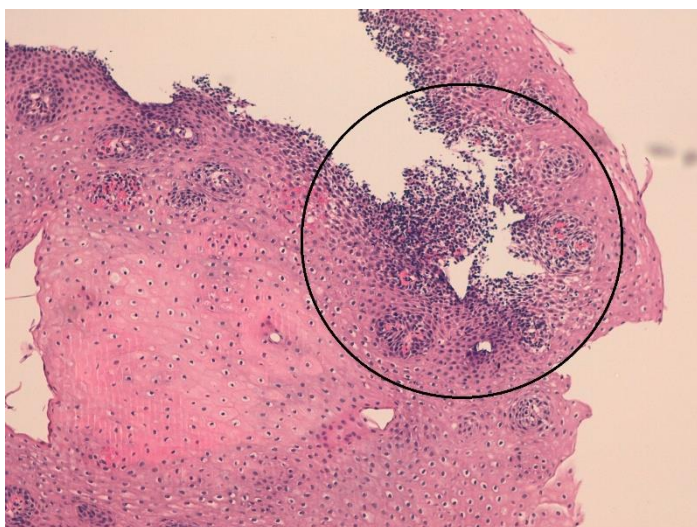
Mucosal biopsy analysis was normal in 41% of cases for the oesophageal body, and 37% for the cardial mucosa. A lymphocytic infiltrate was visible in 30% of cases for the oesophageal body, and 41% of cases for cardial mucosa. For the oesophageal body, surface parakeratosis was found in 33%, basal layer hyperplasia in 37%, epithelial wave (Pinstripe pattern) in 19%, and papillary elongation in 11% of cases. For the cardial mucosae, surface parakeratosis was found in 30%, basal layer hyperplasia in 44%, epithelial wave in 19%, and papillary elongation in 11% of cases. Eosinophils were seen in only 1 patient (4%).

Fibrosis was found in 15% of mucosal locations, and in 33% of muscular biopsies of the oesophageal body, and 32% of biopsies of the LES. No eosinophil infiltrate was visible in the muscular biopsies. Cajal cells were visible in 15% of the muscular biopsies of the oesophageal body, and 25% of biopsies of the cardial muscle. Most muscular biopsies (56% for the oesophageal body, 43% for the LES) showed no abnormalities.

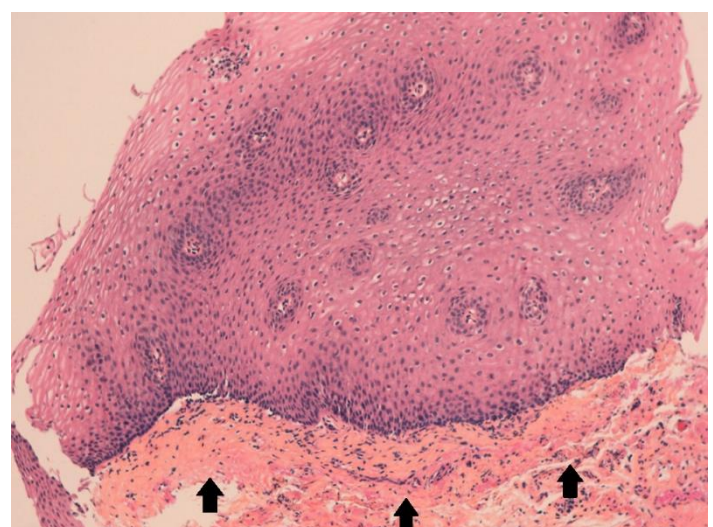
Anatomopathological results are listed in Table 4.

**Table 4: Histological analysis of biopsies according to location:**

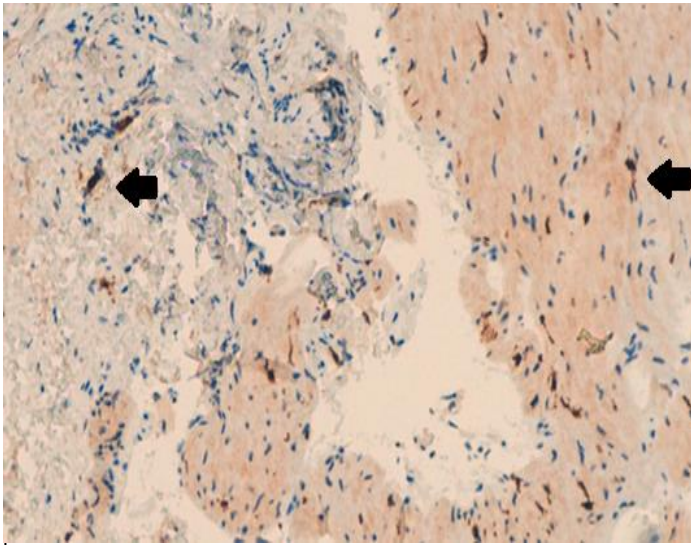
	Mucosal biopsies of the oesophagus body (N=27) (%)	Biopsies of the cardial mucosa (N=27) (%)	Muscular biopsies of the body of the oesophagus (N=27) (%)	Biopsies of the cardial muscle (N=28) (%)
No abnormality	11 (41)	10 (37)	15 (56)	12 (43)
Intraepithelial lymphocytosis	8 (30)	11 (41)	0	2 (7)
Neutrophilic infiltrate	1 (4)	2 (7)	1 (4)	1 (4)
Eosinophilic infiltrate	1 (4)	1 (4)	0	0
Mast cells infiltrate	0	0	0	3 (11)
Fibrosis	4 (15)	4 (15)	9 (33)	9 (32)
Spongiosis	4 (15)	3 (11)		
Surface parakeratosis	9 (33)	8 (30)		
Papillary elongation	3 (11)	3(11)		
Basal layer hyperplasia	9 (33)	12 (44)		
Epithelial wave	5 (19)	5 (19)		
Vacuolization			3 (11)	5 (18)
Muscular cells atrophy			2 (7)	4 (14)
Visible Cajal cells			4 (15)	7 (25)



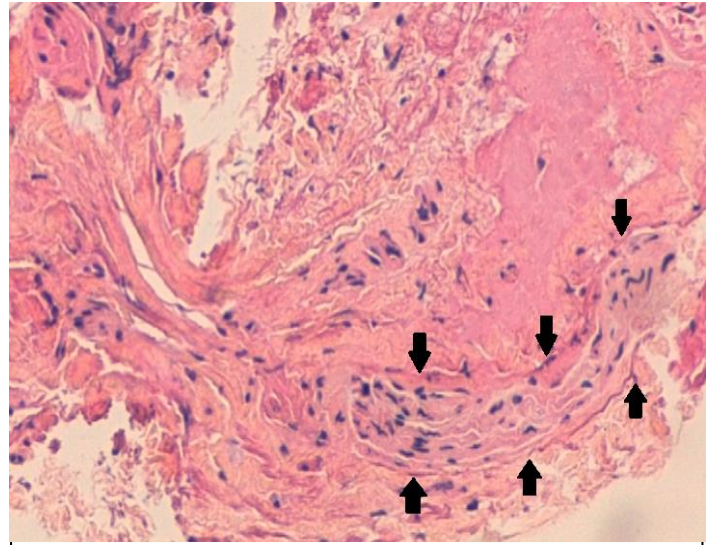
**Img 1.** Mucosal infiltration of lymphocytes and eosinophilic polynuclear cells (circle) from one patient with achalasia who underwent peroral endoscopic myotomy (H&E stain).



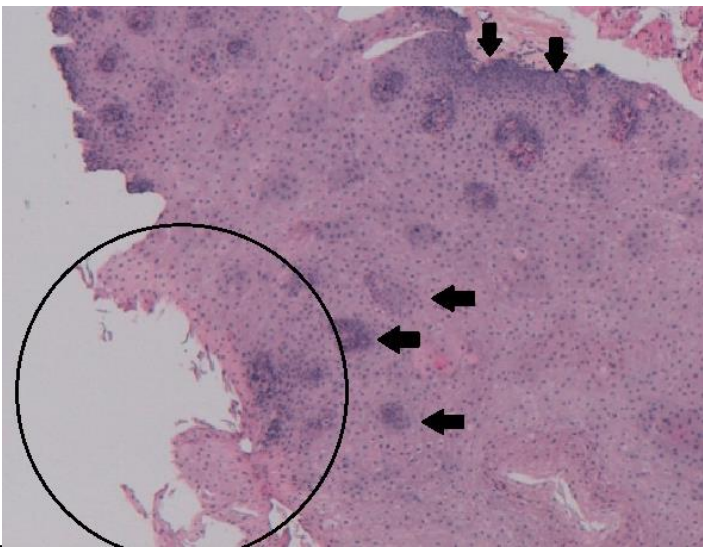
**Img 2.** Mucosal changes related to achalasia, with fibrosis of the chorion (up arrows) and basal layer hyperplasia (H&E stain).



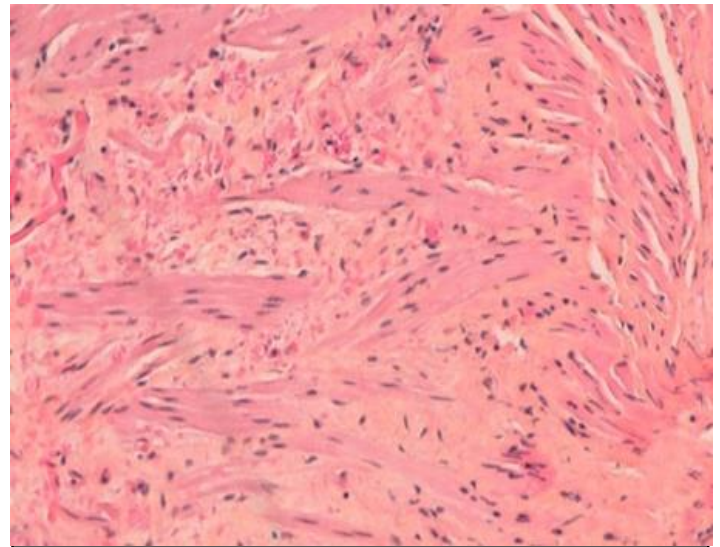
**Img 3.** Histologic findings in muscular biopsy of the oesophagus: visible Cajal cells (left arrows) (immunohistochemistry: c-Kit/CD117 antibodies)



**Img 4.** Histologic findings in muscular biopsy of the oesophagus: Interstitial fibrosis and visible myenteric nerve (up and down arrows) (H&E stain).



**Img 5.** Mucosal changes related to achalasia, with papillary elongation (left arrows), basal layer hyperplasia (down arrows) and surface parakeratosis (circle) (H&E stain).



**Img 6.** Histologic findings in muscular biopsy of the oesophagus: Interstitial fibrosis compatible with achalasia (H&E stain).

## 4. DISCUSSION

In our study, we showed that it was possible to perform many muscle biopsies (9 per patient) without a significant increase in the risk of the procedure. Only one severe complication was reported, requiring endoscopic management and prolonged hospitalisation. However, the link between this complication and the performance of the biopsy was not established, as the episode appeared to be secondary to a release of the clips closing the submucosal tunnel. The other complications, such as mild bleeding, also seem to be related to the procedure itself rather than the biopsies. This low rate of complications is consistent with what has been recently described in the literature (23). It shows that muscular biopsies are a simple procedure that can be performed routinely if the endoscopist considers it necessary.

The amount of muscle tissue taken with a paediatric forceps was sufficient in 98% (27/28) of cases. The remaining collected tissue will be used to investigate neuronal connectivity (Tuj Synpasin 1) and neuronal phenotype (nNOS/Chat), glial reactivity (GFAP S100b), and inflammation (TNF $\alpha$ ). Furthermore, 1 muscle biopsy per patient was used for FFOCT analysis, which has already been used for analysis of the gut tissue remodelling (24), but the results are still in progress.

In this study, the efficacy of POEM, defined as an Eckardt score <3 after one year (range from 14 months to 23 months) was 83.3%. This result is in concordance with the literature (19,25). We showed improvement in most items on the SF36 questionnaires before POEM and between 9 and 12 months after. The non-significant differences can be explained by numerous missing data (almost 10 patients per SF36 score item did not return their questionnaire). These results are in concordance with the data in the literature(26–28). These findings highlight the effectiveness of the technique in a global functional motor pathology of the oesophagus. Even if the LES is mainly affected, there are also inefficient contractions of the oesophageal body in achalasia, which could have impacted the quality of life of the patients at a later point in time.

Recent studies have examined muscle and mucosal biopsies from patients with early-stage achalasia taken during POEM (18,23). The main mucosal abnormalities highlighted in the literature are basal hyperplasia, papillary elongation, surface parakeratosis, spongiosis, and intra-epithelial lymphocytes (23). In addition, some studies have described the pinstripe pattern (29), a wave-like appearance of the epithelium, as a more specific aspect of achalasia. In this study, basal hyperplasia, papillary elongation, surface parakeratosis, and spongiosis were

present in 39% (21/54), 31% (17/54), 11% (6/54) and 13% (7/54) respectively. This is less than what has been described in the most recent studies (23). Wavy epithelium was present in 18% (10/54) of our mucosal biopsies. Again, this is less than previously described (29).

Some studies have suggested a link between intramucosal lymphocytes and oesophageal motor disorders (30). Lymphocytes were found in 35% (19/54) of our mucosal biopsies. These results are again fewer than in the study of Liu et al. (23).

Several recent reports have suggested a possible link between eosinophilic esophagitis and achalasia (18,31,32). Our study did not demonstrate visible eosinophils in the oesophageal muscle, and only one patient had intramucosal eosinophils. A lymphocytic infiltrate of the muscle was found in only 2 patients (4%). We did not observe the presence ganglionitis or neuritis in our study, which contrasts with what has been previously described in the literature (5,14).

Fibrosis was found in 33% (18/55) of muscle biopsies and in 15% (8/54) of mucosal biopsies, and smooth muscle cell atrophy in 11% (6/55), despite the early stage of achalasia.

These differences may be due to the very early stage of achalasia in our study. Indeed, the patients had never received endoscopic or surgical treatment, and the average duration of disease was 42 months (with a median of 12 months) versus 79 months in Liu et al. The amount of tissue removed during paediatric forceps biopsies remains small, which may have limited our analysis of the oesophageal muscle.

The strength of this study is that it set up a multi-year follow-up cohort of treatment-naive achalasia patients. The anatomopathological material collected will allow the launch of further studies and increase research data in a rare and poorly comprehended disease. To our knowledge, this is the first study to investigate muscle and mucosal biopsies taken during POEM in a Caucasian population.

However, many limitations are to be noted, especially the important number of missing data on the SF36 quality of life questionnaires, and some Eckardt scores not recovered from patients lost to follow-up. This is partly due to the Covid epidemic, which made it difficult to follow patients over a long period. The small number of patients in this study should also be mentioned, due to the rarity of the pathology and the monocentric nature of the study. Moreover, although the SF36 questionnaire has already been used in achalasia (33), it was not created to evaluate this disease, which may lead to a bias in the analysis. Furthermore, we do not have a control

group with which to compare histological results, because we were unable to recover oesophagi resected for oesophageal cancer.

These results will allow a revolution in the management of this pathology. Muscle analysis could be performed systematically, in clinical routine, to allow a more exhaustive exploration. Because of the small number of patients in our study we did not look for histological parameters of the musculature explaining the treatment failures. But the histological elements of the muscularis could be a first answer when it comes to the efficiency of the POEM treatment (inflammatory infiltrates, fibrosis...). This would then allow a selection of patients for a possible second therapeutic line (dilatation, surgery, second POEM...).

On the other hand, this opens exciting new perspectives in fundamental research with access to histological areas that were previously unreachable. The comprehension of the physiopathology of this disease could thus be significantly improved. There were no ganglions found in our study, but they were not systematically searched during the procedure. It will probably be necessary to develop new endoscopic methods of analysis and characterization to better visualize the enteric nervous system. The contribution of virtual staining such as Narrow Band Imaging (NBI) could be interesting as well as the super zoom of some endoscopes. If the analysis to date is not perfectly feasible, the technological progress to come allows us to hope for rapid changes in this field.

In conclusion, this study shows that it is possible to take a large sample of muscle biopsies with a paediatric forceps during POEM in treatment-naive patients with achalasia, without increasing the risk of the procedure, and without impacting on its effectiveness. These biopsies will allow us to initiate new studies and could even be carried out in clinical practice if the need arises.



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## 6. ANNEXES

### 1. Annex 1: Eckardt Score

Score	Weight loss (kg)	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	< 5	Occasional	Occasional	Occasional
2	5 - 10	Daily	Daily	Daily
3	> 10	Each meal	Each meal	Each meal

## 2. Annex 2: SF36 Questionnaires (French version)

### QUESTIONNAIRE D'ETAT DE SANTE SF-36

**COMMENT REpondRE :** Les questions, qui suivent, portent sur votre état de santé telle que vous la ressentez. Ces informations nous permettront de mieux savoir comment vous vous sentez dans la vie de tous les jours.

Veuillez répondre à toutes les questions en cochant la case correspondante à la réponse choisie. Si vous ne savez pas très bien comment répondre, choisissez la réponse la plus adaptée à votre situation.

**1. Dans l'ensemble, pensez-vous que votre santé est :**

- Excellente .....
- Très bonne .....
- Bonne .....
- Médiocre .....
- Mauvaise .....

**2. Par rapport à l'année dernière à la même époque, comment trouvez vous votre état de santé en ce moment ?**

- Bien meilleur que l'an dernier .....
- Plutôt meilleur que l'an dernier .....
- A peu près pareil .....
- Plutôt moins bon .....
- Beaucoup moins bon .....

3. Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours. Pour chacune d'entre elles indiquez si vous êtes limité(e) en raison de votre état de santé actuel.

Liste d'activités	Oui, beaucoup limité(e)	Oui, un peu limité(e)	Non, Pas du tout limité(e)
a. Efforts physiques importants tels que courir, soulever un objet lourd, faire du sport	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Soulever et porter les courses	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Monter <b>plusieurs étages</b> par l'escalier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Monter <b>un étage</b> par l'escalier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Se pencher en avant, se mettre à genoux, s'accroupir	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Marcher <b>plus d'un km</b> à pied	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Marcher <b>plusieurs centaines de mètres</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Marcher <b>une centaine de mètres</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Prendre un bain, une douche ou s'habiller	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Au cours de ces 4 dernières semaines, et en raison de votre état physique

	OUI	NON
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles	<input type="checkbox"/>	<input type="checkbox"/>
b. Avez-vous accompli moins de choses que vous auriez souhaité	<input type="checkbox"/>	<input type="checkbox"/>
c. Avez-vous dû arrêter de faire certaines choses	<input type="checkbox"/>	<input type="checkbox"/>
d. Avez-vous eu des difficultés à faire votre travail ou toute autre activité (par exemple, cela vous a demandé un effort supplémentaire)	<input type="checkbox"/>	<input type="checkbox"/>

5. Au cours de ces 4 dernières semaines, et en raison de votre état émotionnel (comme vous sentir triste, nerveux(se) ou déprimé(e))

	OUI	NON
a. Avez-vous réduit le <b>temps passé</b> à votre travail ou à vos activités habituelles	<input type="checkbox"/>	<input type="checkbox"/>
b. Avez-vous <b>accompli moins</b> de choses que vous auriez souhaité	<input type="checkbox"/>	<input type="checkbox"/>
c. Avez-vous eu des difficultés à faire ce que vous aviez à faire <b>avec autant de soin et d'attention</b> que d'habitude	<input type="checkbox"/>	<input type="checkbox"/>

6. Au cours de ces 4 dernières semaines, dans quelle mesure votre état de santé, physique ou émotionnel, vous a t-il gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

- Pas du tout .....
- Un petit peu .....
- Moyennement .....
- Beaucoup .....
- Enormément .....

7. Au cours de ces 4 dernières semaines, quelle a été l'intensité de vos douleurs physiques ?

- Nulle .....
- Très faible .....
- Faible .....
- Moyenne .....
- Grande .....
- Très grande .....

8. Au cours de ces 4 dernières semaines, dans quelle mesure vos douleurs physiques vous ont-elles limité(e) dans votre travail ou vos activités domestiques ?

- Pas du tout .....
- Un petit peu .....
- Moyennement .....
- Beaucoup .....
- Enormément .....

9. Les questions qui suivent portent sur comment vous vous êtes senti(e) au cours de ces 4 dernières semaines. Pour chaque question, veuillez indiquer la réponse qui vous semble la plus appropriée. Au cours de ces 4 dernières semaines, y a-t-il eu des moments où :

	En Permanence	Très souvent	Souvent	Quelquefois	Rarement	Jamais
a. Vous-vous êtes senti(e) dynamique ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Vous-vous êtes senti(e) très nerveux(se) ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Vous-vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Vous-vous êtes senti(e) calme et détendu(e) ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Vous-vous êtes senti(e) débordant(e) d'énergie ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Vous-vous êtes senti(e) triste et abattu ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Vous-vous êtes senti(e) épuisé(e) ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Vous-vous êtes senti(e) heureux(se) ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Vous-vous êtes senti(e) fatigué(e) ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



10. Au cours de ces 4 dernières semaines, y a-t-il eu des moments où votre état de santé, physique ou émotionnel, vous a gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

- En permanence .....
- Une bonne partie du temps .....
- De temps en temps .....
- Rarement .....
- Jamais .....

11. Indiquez, pour chacune des phrases suivantes, dans quelle mesure elles sont vraies ou fausses dans votre cas :

	Totalement vraie	Plutôt vraie	Je ne sais pas	Plutôt faux	Totalement faux
a. Je tombe plus facilement malade que les autres	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Je me porte aussi bien que n'importe qui	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Je m'attends à ce que ma santé se dégrade	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Je suis en excellente santé	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Veillez vérifier que vous avez bien fourni une réponse pour chacune des questions.**

**Merci de votre collaboration.**

## SERMENT D'HIPPOCRATE



Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.



## 7. ABSTRACT

**Background:** The pathophysiology of oesophageal achalasia remains poorly understood, as the amount of histological material available for fundamental research is low. Since the advent of peroral endoscopic myotomy (POEM), the muscularis has become accessible to biopsy and thus to new options for exploring this pathology. The aim of this study was to evaluate the feasibility and safety of muscularis and mucosal biopsies performed during POEM in patients with achalasia. Secondary objectives were to evaluate the efficacy and safety of the treatment, the quality of life of the patients after the procedure, and to perform a first histological analysis.

**Methods:** Patients were included at Nantes University Hospital from November 2019 to November 2021. They had to be naïve to any surgical or endoscopic treatment of their achalasia. 6 mucosal biopsies and 9 muscle biopsies were performed per procedure. All technical data of the procedure were recorded prospectively. Any complications were recorded. Patients were reassessed clinically at least one year after POEM. SF36 scores were re-evaluated between 9 and 12 months after the operation.

**Results:** 28 patients were included. Biopsy analysis was possible in 97% of cases. 9 patients (32%) presented intra or post-procedural adverse events of which only 1 was severe (4%), requiring a new intervention for oesophageal prosthesis. These events were not related to the performance of the biopsies. The clinical success rate at more than one year after the procedure was 83.3% (20/24). We found significant improvement in the majority of the SF36 questionnaire items 9 to 12 months after POEM. Fibrosis was found in 15% of mucosal locations and 33% of muscle biopsies. An eosinophilic infiltrate was found in only one patient (1%). Most muscle biopsies showed no visible abnormalities.

**Conclusion:** This study shows that it is possible to take a large sample of muscle biopsies with a paediatric forceps during POEM in treatment-naïve patients with achalasia, without increasing the risk of the procedure, and without impacting on its effectiveness.

**Keys words :** achalasia, peroral endoscopic myotomy, biopsy.

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ACHALAGLIE : Etude de la musculature œsophagienne dans l'achalasia à partir de biopsies réalisées au cours d'une myotomie per-oral endoscopique (POEM) : étude de faisabilité et de sécurité.

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## RESUME

**Introduction :** La physiopathologie de l'achalasia de l'œsophage reste mal connue, la quantité de matériel histologique disponible pour la recherche fondamentale étant faible. Depuis l'avènement de la myotomie per-oral endoscopique (POEM), la musculature est devenue accessible à la biopsie et donc à de nouvelles possibilités d'exploration de cette pathologie. Le but de cette étude était d'évaluer la faisabilité et la sécurité des biopsies de la musculature et de la muqueuse œsophagienne réalisées pendant une POEM chez des patients atteints d'achalasia. Les objectifs secondaires étaient d'évaluer l'efficacité et la sécurité du traitement, la qualité de vie des patients après la procédure, et de réaliser une première analyse histologique.

**Matériels et méthodes :** Les patients ont été inclus au CHU de Nantes de Novembre 2019 à Novembre 2021. Ils devaient être naïfs de tout traitement chirurgical ou endoscopique de leur achalasia. 6 biopsies muqueuses et 9 biopsies musculaires ont été réalisées par procédure. Toutes les données techniques de la procédure ont été relevées prospectivement. Les complications éventuelles ont été relevées. Les patients ont été réévalués cliniquement au moins un an après la POEM et les scores SF36 entre 9 et 12 mois après l'opération.

**Résultats :** 28 patients ont été inclus. L'analyse des biopsies a été possible dans 97% des cas. 9 patients (32%) ont présenté des événements indésirables per ou post-procédure dont 1 seul sévère (4%), nécessitant une nouvelle intervention pour pose de prothèse œsophagienne. Ces événements n'étaient pas liés à la réalisation des biopsies. Le taux de succès clinique à plus d'un an de l'intervention était de 83.3% (20/24). Nous avons constaté une amélioration significative de la majorité des items du questionnaire SF36 9 à 12 mois après la POEM. De la fibrose a été mise en évidence dans 15 % des localisations muqueuses, et 33 % des biopsies musculaires. Un infiltrat éosinophile a été trouvé chez un seul patient (1%). La plupart des biopsies musculaires ne présentaient aucune anomalie visible.

**Conclusion :** Cette étude montre qu'il est possible de prélever un grand nombre de biopsies musculaires pendant la POEM chez des patients naïfs de traitement atteints d'achalasia, sans augmenter le risque de la procédure, et sans impact sur son efficacité.

**Mots clés :** achalasia, myotomie per orale endoscopique, biopsie.