

World Journal of *Gastroenterology*

World J Gastroenterol 2020 October 14; 26(38): 5745-5910



OPINION REVIEW

- 5745** Role of betaine in liver disease-worth revisiting or has the die been cast?
Mukherjee S
- 5749** Management of an endoscopy center during the outbreak of COVID-19: Experience from West China Hospital
Gao Y, Ye LS, Du J, Zhang QY, Hu B

REVIEW

- 5759** Molecular mechanisms of viral hepatitis induced hepatocellular carcinoma
D'souza S, Lau KC, Coffin CS, Patel TR

MINIREVIEWS

- 5784** Role of artificial intelligence in the diagnosis of oesophageal neoplasia: 2020 an endoscopic odyssey
Hussein M, González-Bueno Puyal J, Mountney P, Lovat LB, Haidry R
- 5797** Gastrointestinal complications after kidney transplantation
Gioco R, Corona D, Ekser B, Puzzo L, Inserra G, Pinto F, Schipa C, Privitera F, Veroux P, Veroux M
- 5812** Is vitamin D receptor a druggable target for non-alcoholic steatohepatitis?
Cao Y, Shu XB, Yao Z, Ji G, Zhang L

ORIGINAL ARTICLE

Basic Study

- 5822** Acetyl-11-keto- β -boswellic acid inhibits proliferation and induces apoptosis of gastric cancer cells through the phosphatase and tensin homolog / Akt/ cyclooxygenase-2 signaling pathway
Sun MX, He XP, Huang PY, Qi Q, Sun WH, Liu GS, Hua J

Case Control Study

- 5836** Endogenous motion of liver correlates to the severity of portal hypertension
Gelman S, Sakalauskas A, Zyklus R, Pranculis A, Jurkonis R, Kuliavienė I, Lukoševičius A, Kupčinskis L, Kupčinskis J
- 5849** Longitudinal decrease in platelet counts as a surrogate marker of liver fibrosis
Gotlieb N, Schwartz N, Zelber-Sagi S, Chodick G, Shalev V, Shibolet O

Retrospective Study

- 5863** Endoscopic ultrasound-measured muscular thickness of the lower esophageal sphincter and long-term prognosis after peroral endoscopic myotomy for achalasia
Liao Y, Xiao TY, Wu YF, Zhang JJ, Zhang BZ, Wang YD, Wang S, Liu X, Sun SY, Guo JT

Observational Study

- 5874** Monitoring hepatitis C virus treatment rates in an Opioid Treatment Program: A longitudinal study
Sanvisens A, Rivas I, Faure E, Espinach N, Hernandez-Rubio A, Majó X, Colom J, Muga R
- 5884** Comparative study between bowel ultrasound and magnetic resonance enterography among Egyptian inflammatory bowel disease patients
Kamel S, Sakr M, Hamed W, Eltabbakh M, Askar S, Bassuny A, Hussein R, Elbaz A

META-ANALYSIS

- 5896** Tacrolimus and mycophenolate mofetil as second-line treatment in autoimmune hepatitis: Is the evidence of sufficient quality to develop recommendations?
Abdollahi M, Ekrami NK, Ghofazadeh M, Boezen HM, Somi M, Alizadeh BZ

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Gordon Stanley Howarth, PhD, BSc, RCPA is a tenured Professor in Gastrointestinal Physiology at the School of Animal and Veterinary Sciences, University of Adelaide (Australia). Professor Howarth was appointed as an inaugural scientist at South Australia's Child Health Research Institute in 1989. He was awarded a Cancer Council South Australia Research Fellowship in 2005, subsequently being awarded the nationally-competitive Sally Birch Cancer Council Australia Senior Research Fellowship in Cancer Control (2009) and a South Australian Cancer Council Collaborative Senior Research Fellowship in 2012. Professor Howarth has published more than 170 journal articles on novel nutraceutical treatments for gastrointestinal disease and holds an Affiliate Professor appointment in the Gastroenterology Department of Adelaide's Women's and Children's Hospital. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for WJG as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Liang Zhang; Production Department Director: Yun-Xiaojian Wu; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

October 14, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Retrospective Study

Endoscopic ultrasound-measured muscular thickness of the lower esophageal sphincter and long-term prognosis after peroral endoscopic myotomy for achalasia

Ye Liao, Ting-Yue Xiao, Yu-Fan Wu, Jing-Jing Zhang, Bao-Zhen Zhang, Yi-Dan Wang, Sheng Wang, Xiang Liu, Si-Yu Sun, Jin-Tao Guo

ORCID number: Ye Liao 0000-0001-9026-8438; Ting-Yue Xiao 0000-0002-1479-3799; Yu-Fan Wu 0000-0003-4290-8263; Jing-Jing Zhang 0000-0003-1357-9384; Bao-Zhen Zhang 0000-0001-7871-8213; Yi-Dan Wang 0000-0003-1566-3459; Sheng Wang 0000-0002-1531-7655; Xiang Liu 0000-0001-7538-6786; Si-Yu Sun 0000-0002-7308-0473; Jin-Tao Guo 0000-0001-5722-6359.

Author contributions: Liao Y and Guo JT were involved in the study conception and design; Guo JT, Wang S, Liu X, and Sun SY performed the research; Liao Y, Xiao TY, Wu YF, Zhang JJ, Zhang BZ, and Wang YD analyzed the data; Liao Y wrote the manuscript; Guo JT and Sun SY performed critical revision of the article for important intellectual content; all authors performed the final approval of the article.

Supported by National Natural Science Foundation of China, No. 81900601, Natural Science Foundation of Liaoning Province, No. 207541024; and Outstanding Scientific Fund of Shengjing Hospital, No. 201702.

Institutional review board statement: This study was

Ye Liao, Yu-Fan Wu, Jing-Jing Zhang, Bao-Zhen Zhang, Yi-Dan Wang, Sheng Wang, Xiang Liu, Si-Yu Sun, Jin-Tao Guo, Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Ting-Yue Xiao, Department of Science and Education, Shenyang Sixth People's Hospital, Shenyang 110006, Liaoning Province, China

Corresponding author: Jin-Tao Guo, MD, PhD, Doctor, Professor, Research Fellow, Department of Gastroenterology, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Shenyang 110004, Liaoning Province, China. guojt@sj-hospital.org

Abstract

BACKGROUND

People with achalasia typically have a thick lower esophageal muscularis propria (LEMP), and peroral endoscopic myotomy (POEM) has been effective in treating most patients. LEMP thickness may be associated with the outcomes and prognosis after POEM. However, more evidence is needed regarding the relationship between LEMP thickness and patient prognosis after POEM.

AIM

To assess the association between LEMP thickness, measured using endoscopic ultrasound (EUS), and long-term prognosis, especially relapse, after POEM for achalasia.

METHODS

All medical records, including EUS data, of patients who underwent POEM to treat achalasia at Shengjing Hospital of China Medical University from January 2012 to September 2018 were retrospectively reviewed. LEMP thickness was measured by EUS, and a thickness of ≥ 3 mm was defined as thickened. The severity of patient symptoms was evaluated using the Eckardt score. Relapse was defined as a 3-point rise in the Eckardt score after a period of clinical remission. The relationship between patient characteristics, muscle thickness, and recurrence was analyzed.

RESULTS

reviewed and approved by the Institutional Review Board and the Ethics Committee of China Medical University.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: June 4, 2020

Peer-review started: June 4, 2020

First decision: July 29, 2020

Revised: August 13, 2020

Accepted: September 10, 2020

Article in press: September 10, 2020

Published online: October 14, 2020

P-Reviewer: Gobejishvili L, Morling JR, Musquer N

S-Editor: Zhang L

L-Editor: Wang TQ

P-Editor: Zhang YL



Eighty-two patients (32 males and 50 females, aged 17-78 years) and 85 POEM procedures were included. In total, 76.8% (63/82 patients) of patients had a thickened muscularis propria. Older age and longer disease course were associated with muscularis propria thickening ($P < 0.05$). The mean postoperative follow-up time was 35.4 ± 17.2 mo (range, 8-87.5 mo) in 60 patients. Five patients with Eckardt scores > 3 refused further management after their symptoms were relieved. The relapse rate was 12.73% (7/55 cases). Five patients, four of whom had muscularis propria thickening, had disease recurrence within 12 mo after the procedure. Achalasia relapsed in one patient who had a thickened muscularis propria after 24 mo and in another patient who did not have a thickened muscularis propria after 30 mo. Patients with recurrence were typically younger and had a shorter disease course ($P < 0.05$). The relapse rate in patients with a non-thickened muscularis propria tended to be higher (18.2%, 2/11 patients) than that in patients with a thickened muscularis propria (11.4%, 5/44 patients), although no significant difference was found. Age (hazard ratio = 0.92; 95% confidence interval: 0.865-0.979; $P < 0.05$) and being male (hazard ratio = 7.173; 95% confidence interval: 1.277-40.286; $P < 0.05$) were identified as risk factors for symptomatic recurrence by multivariable analysis using the Cox model.

CONCLUSION

Patients with a thickened muscularis are typically older and have a longer disease course. Younger age and the male sex are associated with increased recurrence. Patients with a thin muscularis propria may be prone to relapse, although further validation is needed.

Key Words: Peroral endoscopic myotomy; Achalasia; Endoscopic ultrasound

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This study investigated the clinical significance of lower esophageal muscularis propria (LEMP) thickness in achalasia patients. We retrospectively enrolled 82 patients who underwent peroral endoscopic myotomy (POEM) at our center. The results showed that endoscopic ultrasound-measured LEMP thickness may help diagnose achalasia and predict long-term prognosis after POEM. Patients with a thickened muscularis were typically older and had a longer disease course. Younger age and male gender were risk factors for recurrence. Achalasia was more likely to relapse after POEM in patients with a thin LEMP, although further validation is needed.

Citation: Liao Y, Xiao TY, Wu YF, Zhang JJ, Zhang BZ, Wang YD, Wang S, Liu X, Sun SY, Guo JT. Endoscopic ultrasound-measured muscular thickness of the lower esophageal sphincter and long-term prognosis after peroral endoscopic myotomy for achalasia. *World J Gastroenterol* 2020; 26(38): 5863-5873

URL: <https://www.wjgnet.com/1007-9327/full/v26/i38/5863.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v26.i38.5863>

INTRODUCTION

Achalasia is currently the most common primary esophageal motility disease^[1]. While its etiology remains uncertain, achalasia is characterized by the destruction of inhibitory ganglion cells in the myenteric plexus, causing severe myopathy in smooth muscles and leading to aperistalsis and impaired relaxation of the lower esophageal sphincter (LES)^[1,2]. In addition, thickened lower esophageal muscularis propria (LEMP) has been observed in individuals with achalasia *in vivo* and during autopsies^[3-7]. LEMP hypertrophy may be a response to esophageal functional obstruction or a primary lesion^[2]. Hence, LEMP thickness is thought to be associated with the disease state.

Existing treatments for achalasia, including pharmacotherapy, clostridium botulinum injection, endoscopic balloon catheter dilation, and Heller myotomy, target the compulsory release of the stenosis segment of the LES. Peroral endoscopic

myotomy (POEM) has emerged as an increasingly utilized treatment approach, especially in patients with multiple comorbidities who cannot undergo laparoscopic or open surgical interventions^[8,9]. POEM is considered safe for patients as young as 3 years old, with no upper age limit, according to several efficacy studies with a maximum follow-up period of 3 years^[10-13].

Despite its safety, patients who undergo POEM are at risk for disease recurrence^[14-16], although there is no recognized predictor. However, treatment history, type of mucosal damage, and reflux symptoms were included in a newly developed risk prediction scoring system^[17]. Considering that the POEM procedure is performed directly on the muscularis propria and LEMP thickness is associated with the postprocedural balloon catheter dilation outcome^[7], LEMP thickness is thought to be associated with POEM outcome. However, no correlation between muscle thickness and prognosis at 1 year after POEM has been reported^[18,19], and few studies with longer follow-up periods include assessment of the relationship between LEMP thickness and POEM outcomes.

Therefore, this study aimed to examine the relationship between LEMP thickness, measured by endoscopic ultrasound (EUS), and patient characteristics including long-term prognosis after POEM for achalasia at our health center in the past 7 years.

MATERIALS AND METHODS

Patients

All medical records of patients who underwent POEM to treat achalasia at Shengjing Hospital of China Medical University from January 2012 to September 2018 were retrospectively reviewed. The inclusion criteria were diagnosis of achalasia and record of LEMP thickness measured by EUS examination before POEM. The exclusion criteria were as follows: (1) History of gastrointestinal open surgery; (2) Gastrointestinal malignancy; (3) Coagulopathy or other systemic disorders that precluded safe use of general anesthesia; and (4) Unwillingness to provide informed consent.

From the patient medical charts, demographic information, disease duration defined by time of symptom onset to POEM procedure, symptoms, Eckardt scores^[20], degree of esophageal dilation based on the upper gastrointestinal tract X-ray, endoscopy findings, thickness of LEMP according to EUS findings, and treatment outcomes were collected for analysis.

Ethics

This study was approved by the Institutional Review Board and the Ethics Committee of China Medical University. All patients voluntarily chose their therapeutic course and provided written informed consent for the POEM procedure. Written informed consent was obtained from the parents or guardians of patients younger than 18 years of age.

Symptom evaluation

Clinical symptoms of all patients were evaluated according to the Eckardt score before and after the procedure. The Eckardt score is the sum of the symptom scores for dysphagia, regurgitation, retrosternal pain (with a score of 0 indicating the absence of symptoms, 1 indicating occasional symptoms, 2 indicating daily symptoms, and 3 indicating symptoms at each meal), and weight loss (with 0 indicating no weight loss, 1 indicating a loss of < 5 kg, 2 indicating a loss of 5-10 kg, and 3 indicating a loss of > 10 kg)^[20]. Therefore, scores could range from 0 to 12, with 0 representing no symptoms.

EUS evaluation

All EUS evaluations were performed by experienced technicians using a 360° Radial-Array Ultrasound Gastroscopy (EG-3870URK; PENTAX Medical, Tokyo, Japan) and an ultrasound scanner (EUB 6500; Hitachi, Tokyo, Japan). The thickness of the muscularis propria at the esophagogastric junction (EGJ) was assessed before POEM, and a thickness of ≥ 3 mm was considered thickened. The cutoff value for the muscular thickness was determined according to the ordered sample cluster method based on age, disease duration, preoperative Eckardt score, and postprocedural outcome. The completeness of the myotomy was verified by EUS after POEM.

Endoscopic procedure of POEM

POEM procedures were performed by three experienced therapeutic endoscopists.

Patients fasted for 24–48 h and were forbidden from drinking water for 4–6 h before the procedure. If gastroscopy or EUS revealed any liquid or food residue in the esophagus, a decompression tube was indwelled for at least 24 h before POEM, and nutrients were introduced intravenously. During the procedure, patients were placed in the left recumbent position under general anesthesia with tracheal intubation. The POEM procedure was performed as follows: (1) A submucosal injection (Boston Scientific, United States) of a mixture of saline and methylene blue was administered into the esophageal wall at 12–15 cm above the EGJ; (2) A submucosal tunnel passing over the EGJ was created using a hook knife (KD-620LR; Olympus Corp., Tokyo, Japan) or a triangle tipped knife (KD-640L; Olympus) extending 3 cm into the proximal stomach; (3) Inner circular myotomy began 2–3 cm below the tunnel entry and ended at the cardia; and (4) After careful hemostasis using hemostatic clips (FD-410LR; Olympus), several metal clips [ROOC-D-26-195; Micro-Tech (Nanjing) Co., Ltd., Jiangsu, China] were applied to close the mucosal entry. CO₂ was used as the endoscope air supply. Prophylactic antibiotics and proton pump inhibitors were administered intravenously for at least 2 d after the procedure.

Assessment of therapeutic response and follow-up

Follow-up for all patients was conducted by telephone calls or clinic visits, and clinical symptoms were assessed using the Eckardt score. The procedure was considered effective, and the patient was in clinical remission if the postoperative Eckardt score was ≤ 3 . Relapse was defined as a rise in the Eckardt score to > 3 after a period of clinical remission^[15]. For patients who underwent the procedure twice, the first set of data was used to analyze the disease recurrence rate.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 software (IBM, Armonk, NY, United States). Normally distributed continuous variables are expressed as the mean \pm SD and were compared using a *t*-test. Categorical data were compared using the chi-square test and are expressed as numbers (percentages). The association between age and disease duration was analyzed by univariate logistic regression analysis. Recurrence-free survival was investigated using the Kaplan–Meier estimate of time-to-event and compared using a log-rank test. After confirming that the possible risk factors satisfied the proportional hazard hypothesis, the Cox proportional hazards model was used to evaluate risk factors for clinical recurrence. $P < 0.05$ was considered statistically significant. The ordered sample cluster analysis was performed using DPS version 7.05 software (Zhejiang University, Hangzhou, China)^[21].

RESULTS

Muscle features of the lower esophageal sphincter in patients with achalasia

Eighty-two patients (32 males and 50 females aged 17–78 year with a mean age of 46.5 ± 14.9 year) and a total of 85 procedures were included. The average disease duration was 102.4 ± 127.2 mo (range, 1–516 mo). All patients denied having a previous diagnosis of esophageal disease. Six patients had a history of an endoscopic procedure. Of all patients, 63 (76.8%) had a thickened LEMP.

Data on the correlation between patient background and LEMP thickness are shown in **Table 1**. Significant differences in age (48.4 ± 14.4 years *vs* 40.4 ± 15.2 years, $P < 0.05$) and disease duration (126.63 ± 138.49 mo *vs* 37.79 ± 35.52 mo, $P < 0.05$) were observed between the thickened and non-thickened LEMP groups, and both variables were associated with thickened LEMP. Specifically, older patients with longer disease duration were more likely to have a thickened LEMP. In addition, there was a positive correlation between patient age and duration of the disease (**Figure 1**).

The degree of esophageal dilation in 53 patients was evaluated, while the rest of the patients underwent barium esophagography at other medical centers and were not included. Of these, 21 (39.6%), 24 (45.3%), and 8 (15.1%) patients exhibited degrees I, II, and III dilations, respectively.

Therapeutic effect of POEM and long-term prognosis

The overall POEM success rate was 94.12% (80/85 procedures). There was only one reported case of post-procedure infection, which was resolved using conservative treatment. The EUS data confirmed complete myotomy after POEM in 62 cases. Sixty patients had follow-ups between 8 and 87.5 mo (mean: 35.4 ± 17.2 mo)

Table 1 Comparison of characteristics between patients with non-thickened and thickened lower esophageal muscularis propria

	Thickness of LEMP		P value
	< 3 mm (n = 19)	≥ 3 mm (n = 63)	
Age (yr)	40.4 ± 15.2	48.4 ± 14.4	0.04
Sex (male/female)	6:13	26:37	0.448
Disease duration (mo)	37.79 ± 35.52	126.63 ± 138.49	< 0.001
History of endoscopic surgery (+/-)	1:18	5:58	0.619
Dilation grade (I/II/III)	6:4:1 (11)	15:20:7 (42)	0.667
Preoperative Eckardt score	6.53 ± 2.04	6.68 ± 1.90	0.758

LEMP: Lower esophageal muscularis propria.

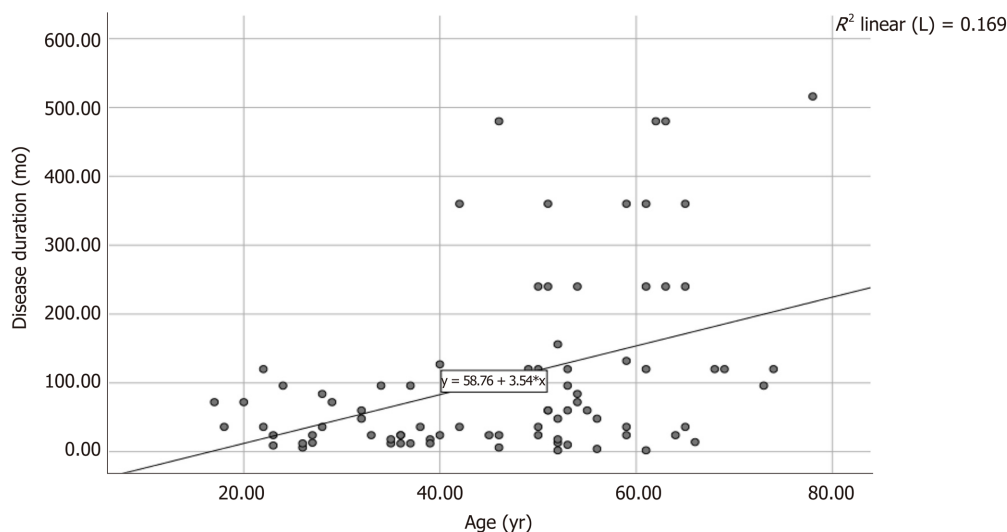


Figure 1 Correlation between age and disease duration in individuals with achalasia ($P < 0.05$, $R^2 = 0.169$).

after the procedure. Five patients with Eckardt scores > 3 refused further follow-up after their symptoms were relieved. There were no significant differences in age, sex, disease duration, preoperative Eckardt score, or LEMP thickness between the effective ($n = 55$) and ineffective ($n = 5$) groups. The relapse rate was 12.73% (7/55 cases). Five patients, four of whom had a thickened LEMP, had symptom recurrence within 12 mo after the procedure. One patient who had a thickened LEMP relapsed after 24 mo while another, who did not have a thickened LEMP, relapsed after 30 mo. Overall, the effectiveness (absence of relapse) of POEM was 87.3% up to 87 mo postoperatively (Figure 2).

Patients with symptomatic recurrence were younger and had shorter disease duration. The relapse rate in patients without a thickened LEMP tended to be higher than patients with a thickened LEMP (2/11 patients *vs* 5/44 patients). However, no significant difference was found. Data on patient characteristics according to POEM outcomes are shown in Table 2 and Figure 3. Younger age (hazard ratio = 0.92; 95% confidence interval: 0.865-0.979; $P < 0.05$) and male gender (hazard ratio = 7.173; 95% confidence interval: 1.277-40.286; $P < 0.05$) were found to be associated with recurrence according to Cox regression analysis (Table 3).

DISCUSSION

Although several previous studies have demonstrated that LEMP thickness is associated with POEM procedure duration and outcomes, the present study adds to the literature by specifically examining the relationship between LEMP thickness and

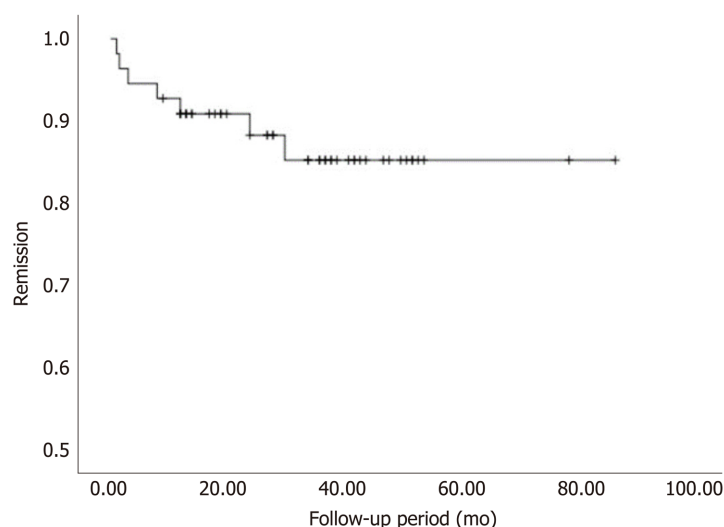
Table 2 Comparison of characteristics in patients with different outcomes after peroral endoscopic myotomy

	Not effective (n = 5)	Clinical success/effective (n = 55)		P value
		No relapse (n = 48)	Relapse (n = 7)	
Age (yr)	33.8 ± 11.97	48.02 ± 14.73	34.00 ± 13.05	0.021 ^a
Sex (male/female)	3:2	16:32	4:3	0.280
Disease duration (mo)	82.8 ± 60.36	117.29 ± 131.41	35.57 ± 30.42	0.001 ^a
Preoperative Eckardt score	6.60 ± 2.40	6.65 ± 1.74	7.57 ± 2.23	0.209 ^a
Verification of myotomy by EUS (Yes/No) ¹	3:2	39:11	6:1	0.539
LEMP (thickened/ non-thickened)	4:1	39:9	5:2	0.832

¹Based on procedure number.^aP < 0.05, between relapse and no relapse. LEMP: Lower esophageal muscularis propria; POEM: Peroral endoscopic myotomy; EUS: Endoscopic ultrasound.**Table 3 Risk factor analysis for recurrence using the Cox proportional hazards model**

Variable	Univariate		Multivariate	
	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
Age	0.943 (0.893-0.995)	0.033	0.920 (0.865-0.979)	0.008
Male sex	2.829 (0.629-12.712)	0.175	7.173 (1.277-40.286)	0.025
Disease duration	0.984 (0.963-1.006)	0.144	NA	0.402
Preoperative Eckardt score	1.296 (0.855-1.965)	0.222	-	-
LEMP ≥ 3 mm	0.606 (0.117-3.128)	0.550	-	-

CI: Confidence interval; LEMP: Lower esophageal muscularis propria; NA: Not assessed; -: Not included for analysis; CI: Confidence interval.

**Figure 2 Kaplan-Meier analysis of recurrence after peroral endoscopic myotomy.**

long-term outcomes, including disease relapse after POEM. The results from the present retrospective chart review and statistical analysis suggest that non-thickened LEMP may be associated with increased disease recurrence. In addition, there is a correlation between older age, longer disease duration, and thickened LEMP.

In previous reports, no significant correlation has been found between the severity of achalasia evaluated by Eckardt score and LEMP thickness^[19,22]. However, age, pneumatic dilation history, and male sex have been reported as predictors of a

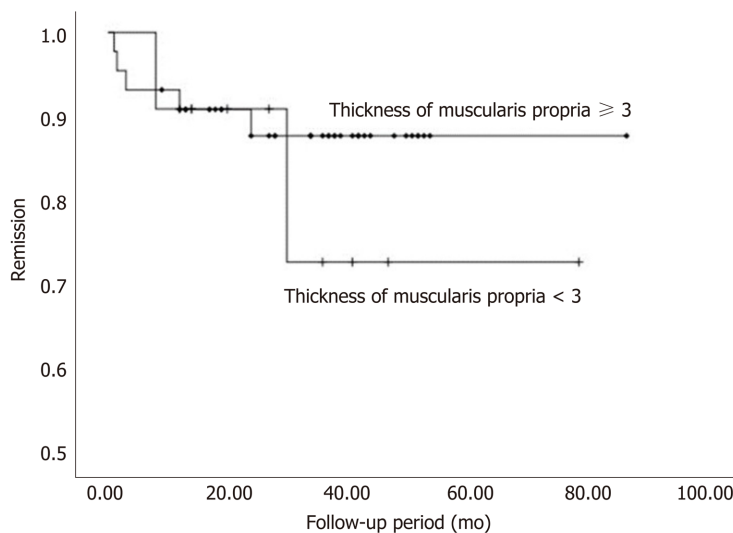


Figure 3 Kaplan–Meier estimate of time to recurrence according to muscularis propria thickness.

thickened LEMP in several studies^[6,19,22,23]. Similarly, the present study showed a positive association between age and muscle thickness. In addition, the present analysis found an association between disease duration and LEMP thickness, as patients with a thickened LEMP had a significantly longer disease course. The results may be attributed to differences in patient characteristics among the studies as we also found a positive association between age and disease duration. Thus, the thickened LEMP could be due to prolonged exposure to reactive hyperplasia since longer disease duration means longer stimulation time. The reversibility of the LES hypertrophy after POEM provides supporting evidence for this theory^[18].

The thickness of the LEMP may be associated with procedural outcomes and postoperative prognosis. We were not able to statistically evaluate the relationship between POEM-related complications and muscle thickness due to the small sample population. Previous studies have shown, without statistical significance, that there tended to be a positive association between muscle thickness, procedure duration, and complication rate^[24]. As for postoperative prognosis, symptomatic recurrence has been reported to occur between 2-5 years after POEM^[14]. A medium-term recurrence rate of 18% was reported in a 2-year follow-up study. Although no explanations for recurrence were given, there was an association between younger age and increased rate of relapse^[16]. Watanabe *et al*^[18] reported no significant difference in clinical outcomes between patients with thick and those with thin LEMP in a 1-year follow-up study, observing no cases of recurrence. Li *et al*^[15] reported a cumulative recurrence rate of 13.7% at 5 years post-POEM that correlated with disease duration and interventional treatment history. In the same study, age and symptom severity showed no correlation with achalasia relapse.

Since the analysis of the present study confirmed a relationship between patient characteristics and LEMP thickness, the effect on recurrence was also analyzed. Although there was no statistical significance, there was a slightly higher relapse rate in patients with non-thickened LEMP. The lack of statistical significance may be due to the treatment of the muscle thickness measurements as discontinuous data. Patients with a younger age and shorter disease duration had an increased rate of relapse. This may be explained by the better healing ability in younger individuals and the fact that patients with shorter disease duration did not have adequate reactive hyperplasia of the LES after esophageal functional obstruction. Our results may suggest that POEM in patients with a certain LEMP thickness caused by reactive hyperplasia has a lower disease recurrence rate.

Cox analysis showed that disease duration was not associated with recurrence, whereas age remained an effective predictor. This may be explained by the co-linear relationship between age and disease duration. Male sex was also a risk factor for recurrence, although the large confidence interval may indicate that this was a result of a sampling error. Besides, the extent of myotomy was not associated with POEM prognosis^[25]. Therefore, our result is still reliable, although we are not able to discuss the effect of the degree of myotomy on prognosis after POEM as all patients enrolled underwent myotomy of the same degree in this study. Our result, which shows that

younger age is associated with increased recurrence, concurs with the findings of Werner *et al*^[16] but contradicts those of Li *et al*^[15,16]. Therefore, the association between age, disease duration, and relapse after POEM remains unclear, and further large-scale validation studies are needed.

The Chicago classification, based on high-resolution manometry, is a predictor of achalasia treatment outcomes. Subtype II has the best prognosis, whereas the prognosis of subtype I is slightly poorer and subtype III can be difficult to treat^[26]. Patients within the achalasia subtypes tend to have similar LEMP thicknesses^[19,24]. The difference in prognostic efficacy between LEMP thickness and subtype is still unclear. However, some participants in our study were not available for manometry. To include a larger sample size in the present study, we did not evaluate the relationship between Chicago classification and POEM prognosis, nor did we compare the subtypes with LEMP thickness. We expect future studies to reveal the relationship between achalasia subtypes, LEMP thickness, and POEM prognosis.

LEMP thickness may help in diagnosing achalasia. A thickened LEMP in patients with achalasia was first observed in an autopsy^[4] and with the development of EUS, measurement of the intrinsic muscle layer thickness *in vivo* is feasible^[8,27-30]. Using a 7.5-MHz ultrasound endoscope, Devière *et al*^[3] reported a thickened LEMP in individuals with achalasia compared with healthy controls. Conversely, Ponsot *et al*^[31] argued that those results may have been attributable to puckering of the EGJ and found that the LEMP was not thicker in patients with achalasia than in healthy controls. In the 30 years since these studies, the number of studies that use different EUS techniques and include more participants have increased. Our results agree with many of these studies, where most of the individuals in the present study had a thickened LEMP^[5-7]. This suggests that LEMP thickness may be of value in achalasia diagnosis. However, because the identification of the differences in LEMP structure between patients with achalasia and healthy individuals is not easy, the use of muscle thickness in diagnosing achalasia is still controversial.

Our study has several limitations. First, it was done retrospectively and without a healthy control group for comparison of LEMP thickness according to age and other patient characteristics. Second, there was no protocol for measuring the esophageal wall thickness and variations in measurements have been noted in previous studies. Third, evaluation of disease severity and recurrence using the Eckardt score can be highly subjective where physicians may tend to report more marked symptom improvement than patients^[32]. Fourth, the cross-sectional area (CSA) of the muscularis propria may be a better indicator to estimate the degree of hypertrophy since a disassociation between muscle thickness and the CSA in some individuals with a dilated esophagus was observed. Patients with a dilated and distended esophagus may have a thin LEMP but a high CSA because of distension of the esophageal wall^[5]. Fifth, although the normal value of LEMP thickness is unknown, the cutoff of 3 mm is higher than that in previous studies^[3,23,24]. This suggests that our patient population may not be the best representative of Achalasia patients in general, a fact that might undermine the external validity of the results. However, considering the difference of age and disease duration in patients with different LEMP thicknesses, we believed that the 3 mm cutoff in this study is reasonable. In addition, the pathophysiology of achalasia is not fully understood and the role of muscular features in the progression and prognosis of the disease is still undetermined. Therefore, future studies should focus on clarifying the etiology of the disease to explain the mechanisms associated with its pathophysiology.

CONCLUSION

Most patients with achalasia have a thickened muscularis propria determined by EUS measurement. Therefore, it is likely that EUS can help diagnose achalasia. Patients with a thickened muscularis are typically older and had a longer disease course. Younger age and male gender are associated with recurrence in the present study. Patients with a thin muscularis propria may have a higher risk of symptomatic recurrence, but validation through further large-scale studies is needed.

ARTICLE HIGHLIGHTS

Research background

Peroral endoscopic myotomy (POEM) procedure is an effective treatment for achalasia as it cuts open the lower esophageal muscularis propria (LEMP) directly. LEMP thickness of achalasia patients may be associated with the outcomes and prognosis after POEM.

Research motivation

Patients who undergo POEM are at risk for disease recurrence. Several predictors have been reported while the relationship between LEMP thickness and long-term prognosis after POEM is unclear.

Research objectives

In this retrospective study, we analyzed the relationship between LEMP thickness, patient characteristics, and long-term prognosis after POEM in individuals who underwent POEM for achalasia at our health center in the past seven years.

Research methods

All medical records, including EUS data, of patients who underwent POEM to treat achalasia at Shengjing Hospital of China Medical University from January 2012 to September 2018 were retrospectively reviewed. The severity of patient symptoms was evaluated using the Eckardt score. Relapse was defined as a 3-point rise in the Eckardt score after a period of clinical remission. The relationship between patient characteristics, muscle thickness, and recurrence was analyzed.

Research results

Older age and longer disease course were associated with muscularis propria thickening ($P < 0.05$). Patients with recurrence were typically younger and had a shorter disease course ($P < 0.05$). The relapse rate in patients with a non-thickened muscularis propria tended to be higher (18.2%, 2/11 patients) than patients with a thickened muscularis propria (11.4%, 5/44 patients), although no significant difference was found. Age (hazard ratio = 0.92; 95% confidence interval: 0.865-0.979; $P < 0.05$) and male sex (hazard ratio = 7.173; 95% confidence interval: 1.277-40.286; $P < 0.05$) were identified as risk factors for symptomatic recurrence by multivariable analysis using the Cox model.

Research conclusions

Patients with a thickened muscularis are typically older and have a longer disease course than those without a thickened muscularis. Younger age and male sex are associated with increased recurrence. Patients with a thin muscularis propria may be prone to relapse, although further validation is needed.

Research perspectives

A large-scale prospective study should be conducted to gain more evidence for the relationship between achalasia subtypes, LEMP thickness, and POEM prognosis.

ACKNOWLEDGEMENTS

We thank Professor Si-Yu Sun, the co-corresponding author of this article, for his support and guidance to this study, as well as all other doctors who participated in this study.

REFERENCES

- 1 **Familiari P**, Greco S, Volkanovska A, Gigante G, Cali A, Boškoski I, Costamagna G. Achalasia: current treatment options. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1101-1114 [PMID: 26186641 DOI: 10.1586/17474124.2015.1052407]
- 2 **Park W**, Vaezi MF. Etiology and pathogenesis of achalasia: the current understanding. *Am J Gastroenterol* 2005; **100**: 1404-1414 [PMID: 15929777 DOI: 10.1111/j.1572-0241.2005.41775.x]
- 3 **Devière J**, Dunham F, Rickaert F, Bourgeois N, Cremer M. Endoscopic ultrasonography in achalasia. *Gastroenterology* 1989; **96**: 1210-1213 [PMID: 2647577 DOI: 10.1016/0016-5085(89)91644-2]

- 4 **Ferguson TB**, Woodbury JD, Roper CL, Burford TH. Giant muscular hypertrophy of the esophagus. *Ann Thorac Surg* 1969; **8**: 209-218 [PMID: 4980385 DOI: 10.1016/s0003-4975(10)66231-5]
- 5 **Mittal RK**, Kassab G, Puckett JL, Liu J. Hypertrophy of the muscularis propria of the lower esophageal sphincter and the body of the esophagus in patients with primary motility disorders of the esophagus. *Am J Gastroenterol* 2003; **98**: 1705-1712 [PMID: 12907322 DOI: 10.1111/j.1572-0241.2003.07587.x]
- 6 **Dogan I**, Puckett JL, Padda BS, Mittal RK. Prevalence of increased esophageal muscle thickness in patients with esophageal symptoms. *Am J Gastroenterol* 2007; **102**: 137-145 [PMID: 17266691 DOI: 10.1111/j.1572-0241.2006.01003.x]
- 7 **Li SW**, Tseng PH, Chen CC, Liao WC, Liu KL, Lee JM, Lee YC, Chuah SK, Wu MS, Wang HP. Muscular thickness of lower esophageal sphincter and therapeutic outcomes in achalasia: A prospective study using high-frequency endoscopic ultrasound. *J Gastroenterol Hepatol* 2018; **33**: 240-248 [PMID: 28475827 DOI: 10.1111/jgh.13816]
- 8 **Wang S**, Liu X, Ge N, Wang G, Guo J, Liu W, Hu J, Sun S. The relationship between the interruption of the lower esophageal sphincter and relief of dysphagia after per-oral endoscopic myotomy for achalasia. *Endosc Ultrasound* 2020; **9**: 252-258 [PMID: 32611850 DOI: 10.4103/eus.eus_30_20]
- 9 **Tan S**, Zhong C, Ren Y, Luo X, Xu J, Fu X, Peng Y, Tang X. Efficacy and Safety of Peroral Endoscopic Myotomy in Achalasia Patients with Failed Previous Intervention: A Systematic Review and Meta-Analysis. *Gut Liver* 2020 [PMID: 32616678 DOI: 10.5009/gnl19234]
- 10 **Inoue H**, Sato H, Ikeda H, Onimaru M, Sato C, Minami H, Yokomichi H, Kobayashi Y, Grimes KL, Kudo SE. Per-Oral Endoscopic Myotomy: A Series of 500 Patients. *J Am Coll Surg* 2015; **221**: 256-264 [PMID: 26206634 DOI: 10.1016/j.jamcollsurg.2015.03.057]
- 11 **Li CJ**, Tan YY, Wang XH, Liu DL. Peroral endoscopic myotomy for achalasia in patients aged ≥ 65 years. *World J Gastroenterol* 2015; **21**: 9175-9181 [PMID: 26290645 DOI: 10.3748/wjg.v21.i30.9175]
- 12 **Chen X**, Li QP, Ji GZ, Ge XX, Zhang XH, Zhao XY, Miao L. Two-year follow-up for 45 patients with achalasia who underwent peroral endoscopic myotomy. *Eur J Cardiothorac Surg* 2015; **47**: 890-896 [PMID: 25193955 DOI: 10.1093/ejcts/ezu320]
- 13 **Chen WF**, Li QL, Zhou PH, Yao LQ, Xu MD, Zhang YQ, Zhong YS, Ma LL, Qin WZ, Hu JW, Cai MY, He MJ, Cui Z. Long-term outcomes of peroral endoscopic myotomy for achalasia in pediatric patients: a prospective, single-center study. *Gastrointest Endosc* 2015; **81**: 91-100 [PMID: 25088923 DOI: 10.1016/j.gie.2014.06.035]
- 14 **Teitelbaum EN**, Dunst CM, Reavis KM, Sharata AM, Ward MA, DeMeester SR, Swanström LL. Clinical outcomes five years after POEM for treatment of primary esophageal motility disorders. *Surg Endosc* 2018; **32**: 421-427 [PMID: 28664434 DOI: 10.1007/s00464-017-5699-2]
- 15 **Li QL**, Wu QN, Zhang XC, Xu MD, Zhang W, Chen SY, Zhong YS, Zhang YQ, Chen WF, Qin WZ, Hu JW, Cai MY, Yao LQ, Zhou PH. Outcomes of per-oral endoscopic myotomy for treatment of esophageal achalasia with a median follow-up of 49 months. *Gastrointest Endosc* 2018; **87**: 1405-1412.e3 [PMID: 29108981 DOI: 10.1016/j.gie.2017.10.031]
- 16 **Werner YB**, Costamagna G, Swanström LL, von Renteln D, Familiari P, Sharata AM, Noder T, Schachschal G, Kersten JF, Rösch T. Clinical response to peroral endoscopic myotomy in patients with idiopathic achalasia at a minimum follow-up of 2 years. *Gut* 2016; **65**: 899-906 [PMID: 25934759 DOI: 10.1136/gutjnl-2014-308649]
- 17 **Liu XY**, Cheng J, Chen WF, Liu ZQ, Wang Y, Xu MD, Chen SY, Zhong YS, Zhang YQ, Yao LQ, Zhou PH, Li QL. A risk-scoring system to predict clinical failure for patients with achalasia after peroral endoscopic myotomy. *Gastrointest Endosc* 2020; **91**: 33-40.e1 [PMID: 31421076 DOI: 10.1016/j.gie.2019.07.036]
- 18 **Watanabe D**, Tanaka S, Kawara F, Abe H, Ariyoshi R, Nakano Y, Takao T, Morita Y, Toyonaga T, Umegaki E, Kodama Y. Clinical impact of peroral endoscopic myotomy for esophageal motility disorders on esophageal muscle layer thickness. *Endosc Int Open* 2019; **7**: E525-E532 [PMID: 31041369 DOI: 10.1055/a-0838-5268]
- 19 **Oumrani S**, Barret M, Roseau G, Brieau B, Leblanc S, Coriat R, Prat F, Chaussade S. Do we need endoscopic ultrasonography for the workup of patients with esophageal motility disorder? *Clin Res Hepatol Gastroenterol* 2019; **43**: 608-613 [PMID: 30880097 DOI: 10.1016/j.clinre.2019.02.005]
- 20 **Eckardt VF**, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. *Gastroenterology* 1992; **103**: 1732-1738 [PMID: 1451966 DOI: 10.1016/0016-5085(92)91428-7]
- 21 **Tang QY**, Zhang CX. Data Processing System (DPS) software with experimental design, statistical analysis and data mining developed for use in entomological research. *Insect Sci* 2013; **20**: 254-260 [PMID: 23955865 DOI: 10.1111/j.1744-7917.2012.01519.x]
- 22 **Sotoudehmanesh R**, Mikaeli J, Daneshpajoo M, Modirzadeh A, Mehrabi N. Endoscopic ultrasonography findings in patients with achalasia. *Esophagus* 2011; **8**: 187-190 [DOI: 10.1007/s10388-011-0286-4]
- 23 **Minami H**, Inoue H, Isomoto H, Urabe S, Nakao K. Clinical application of endoscopic ultrasonography for esophageal achalasia. *Dig Endosc* 2015; **27** Suppl 1: 11-16 [PMID: 25573637 DOI: 10.1111/den.12432]
- 24 **Watanabe D**, Tanaka S, Ariyoshi R, Abe H, Kawara F, Toyonaga T. Muscle layer thickness affects the peroral endoscopic myotomy procedure complexity. *Dis Esophagus* 2018; **31** [PMID: 29617752 DOI: 10.1093/dote/doy009]
- 25 **He C**, Li M, Lu B, Ying X, Gao C, Wang S, Ma C, Jin C. Long-Term Efficacy of Peroral Endoscopic Myotomy for Patients with Achalasia: Outcomes with a Median Follow-Up of 36 Months. *Dig Dis Sci* 2019; **64**: 803-810 [PMID: 30478767 DOI: 10.1007/s10620-018-5373-0]
- 26 **Vaezi MF**, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol* 2013; **108**: 1238-49; quiz 1250 [PMID: 23877351 DOI: 10.1038/ajg.2013.196]
- 27 **Sahai AV**. EUS is trending! *Endosc Ultrasound* 2018; **7**: 353-355 [PMID: 30168481 DOI: 10.4103/eus.eus_22_18]
- 28 **Sun S**, Wang C, Wang S. Remember, interventional EUS is performed using an elevator-containing scope as well. *Endosc Ultrasound* 2018; **7**: 73-75 [PMID: 29667618 DOI: 10.4103/eus.eus_14_18]
- 29 **Pesenti C**, Bories E, Caillol F, Ratone JP, Godat S, Monges G, Poizat F, Raoul JL, Ries P, Giovannini M.

- Characterization of subepithelial lesions of the stomach and esophagus by contrast-enhanced EUS: A retrospective study. *Endosc Ultrasound* 2019; **8**: 43-49 [PMID: 30264741 DOI: 10.4103/eus.eus_89_17]
- 30 **Hu J**, Ge N, Wang S, Liu X, Guo J, Wang G, Sun S. The Role of Endoscopic Ultrasound and Endoscopic Resection for Gastric Glomus: A Case Series and Literature Review. *J Transl Int Med* 2019; **7**: 149-154 [PMID: 32010601 DOI: 10.2478/jtim-2019-0030]
- 31 **Ponsot P**, Chaussade S, Palazzo L, Amouyal P, Gaudric M, Couturier D, Paolaggi JA. Endoscopic ultrasonography in achalasia. *Gastroenterology* 1990; **98**: 253 [PMID: 2403430 DOI: 10.1016/0016-5085(90)91337-6]
- 32 **Larssen L**, Medhus AW, Hjermstad MJ, Körner H, Glomsaker T, Søberg T, Gleditsch D, Hovde O, Nesbakken A, Thølfen JK, Skreden K, Hauge T. Patient-reported outcomes in palliative gastrointestinal stenting: a Norwegian multicenter study. *Surg Endosc* 2011; **25**: 3162-3169 [PMID: 21487867 DOI: 10.1007/s00464-011-1680-7]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

