

Dear editor,

Thank you very much for your decision letter and advice on our manuscript (Manuscript ID 52383) entitled “ Effect and Safety of Mark-guided versus Standard Peroral Endoscopic Myotomy: A Retrospective Case Control Study”. We also thank the reviewers and editor for the helpful comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

We hope that the revision is acceptable for the publication in your journal.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Prof. Li-sheng Wang

Reviewer 1

This is an interesting single center retrospective study on marked-guided v/s standard POEM for achalasia. The authors concluded that both techniques are equally safe and effective with <<less procedure duration, reflux symptoms and PPI use>>in marked group. This negative actually study is potentially interesting for publication. Some major issues:

1. English language corrections are necessary.

Response: Thank you very much. The manuscript is edited by native speaker of English.

2. There is plagiarism in the introduction. Please focus on the aim of this study, which is if marked-guided POEM is superior to standard POEM. Actually this is a negative study. All other comparisons eg balloon dilatation v/s POEM, LHM v/s POEM reflux after POEM are not relevant to this study. Also no comment on the ethical issues of studies comparing balloon dilatation to POEM myotomy, is made? Also the issue of post-POEM GERD is on base of pHmetry and not on symptoms. Severe complications after POEM appeared during the learning curve and in in-experienced hands!!!!Please follow the credentials and make comments.

Response: Thank you for insightful comment. We have deleted the comparison between balloon dilatation vs. POEM and LHM vs. POEM which are not relevant in this study. We fully agree with that post-POEM GERD is on base of pH metry, however, we used to use GERDQ to identify GERD after POEM in our clinical center, which is our limitation in this study (We have explained in the discussion). Therefore, we presently use pH metry to identify post-POEM GERD for your insightful comment. We also agree with severe complications after POEM appeared during the learning curve and in in-experienced hands, thus, the endoscopists need to receive formal POEM training and perform at least more than 50 POEM procedures supervised by a tutor in our clinical center.

3. The authors found a statistical significance in << *reflux symptoms and PPI use was significantly less in the mark-guided POEM group than standard POEM group*>>.

Are there any obvious logical explanations why in marked-guided group there is less reflux? Please give any potential reason or explanation of this result.

Response: Thanks for your suggestion. We consider that the advantages of mark-guided POEM are sufficient sub-mucosal injection, limiting mucosal injury, building sub-mucosal tunnel straightly and decreasing accidentally the inner circular muscle damage because of way lost in the tunnel, indeed these factors are associated with the efficacy and safety of POEM[1].

4. Obviously in uncomplicated achalasia cases without sigmoid esophagus mark-guided POEM will be easier to guide the submucosal tunnel direction. Did the authors have any experience with this technique in sigmoid type II achalasia with megaesophagus or in failed Heller cases with changed anatomy? In these complex achalasia cases marked-guided POEM could be helpful.

Response: Thank you for insightful comment. We have performed the mark-guided POEM in more than 30 sigmoid type II achalasia patients until now and successfully relieve the symptoms of dysphagia, regurgitation and chest pain. But, we are sorry to tell you that we do not have many experience use the mark-guided POEM to treat unsuccessful laparoscopic Heller myotomy cases, therefore, we will do further research in this important area. Thank you again.

Reviewer 2

I read with a great interest the article by Li et al. This is a novel technique that could be helpful especially for initial experience for POEM. I performed hundreds of POEM s/p previous treatment (botox, dilation, Heller and previous poem) and I never lost my way in the tunnel. Again this could be helpful for beginners. I think it will be helpful to compare the performance of beginners with this technique, it may show positive results. I could not find the video

Minor comments:

1. English and grammar correction

Response: Thank you very much. The manuscript is edited by native speaker of English.

2. Why the author use to knives, this will add >\$600 to the procedure

Response: Thank you for insightful comment. We are sorry to tell you this is the endoscopist preference. However, most cases were performed using Dual Knife and Triangle Knife. First, Dual Knife was used to cut mucosal and build tunnel. Second, Triangle Knife was used to dissect circular muscle bundle. Standard POEM using Triangle Knife was described by Inoue *et al.* in the 2010[2]. But, we consider that Triangle Knife is not suitable to cut mucosal and build tunnel because of accidental mucosal injury.

#### Reference

1. Liu, X.Y., et al., *A risk-scoring system to predict clinical failure for achalasia patients after peroral endoscopic myotomy*. Gastrointest Endosc, 2019.
2. Inoue, H., et al., *Peroral endoscopic myotomy (POEM) for esophageal achalasia*. Endoscopy, 2010. **42**(4): p. 265-71.