Dr. Yuan Qi
Scientific editor
World Journal of Gastroenterology

20 October 2016
Dear Dr Yuan Qi,

Re: Manuscript reference No. 30175

Please find attached a revised version of our manuscript "Risk factors for intraoperative perforation during endoscopic submucosal dissection of superficial esophageal squamous cell carcinoma", which we would like to resubmit for publication as a Retrospective Cohort Study in World Journal of Gastroenterology.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using yellow highlight for additions, and strikethrough font for deletions. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in World Journal of Gastroenterology.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1

1. The risk factors for esophageal squamous cell carcinoma are smoking and alcohol. Pleas add data of these parameters.

Response: As reviewer's suggestion, smoking and alcohol are very important factors in development of esophageal squamous cell carcinoma. However, this study focused on endoscopic treatment of esophageal cancer. And, it is very difficult to follow the data of patients' preference data because of retrospective analysis. And, we suggested that these parameters are not necessary to make conclusion in this study.

2. In this study, authors used a dual knife or an insulation-tipped diathermic knife. How about association with kinds of knife and intraoperative perforation? How did authors select kinds of knife? If authors decided kinds of knife according to tumor location, size and depth, the risk factors for intraoperative perforation during ESD for esophageal squamous cell carcinoma may include bias.

Response: As reviewer's mention, it is very important factor of device which was used in esophageal ESD in this analysis. We basically used dual knife in most of process in ESD procedure in all cases. IT knife was used adjunctively in order to physician's judgement. Therefore, it was very difficult to compare the risk of perforation between each device. And, it was difficult to collect the data of device, which was used at the moment of perforation. Thus we added this information in Method and limitation of the study in revised version.

3. How about incidence rate of late perforation? If authors add to mention late perforation in this study, value of this study will increase.

Response: There was no case of late perforation in this study. We add this information in Table 1 and RESULTS.

4. This study retrospectively analyzed consecutive patients with esophageal cancer treated using ESD between April 2008 and October 2012. The institutional review board of our institution approved the study protocol in September 2014 (2014–119). Data from November 2012 to September 2014 was missing.

Response: We drew up protocol of this study on August 18, 2014. And, this was the retrospective study using data between April 2008 and October 2012. The institutional review board approved this study protocol in September 2014. The period from November 2012 to September 2014 is not included in the study period.

5. One of the indication criteria of ESD for esophageal cancer was that clinical depth invasion was limited within submucosal 1 (SM1). Is it acceptable in Japan? If so, you should add references (including guideline).

Response: In guidelines for diagnosis and treatment of carcinoma of the esophagus in Japan, T1a-EP and LPM have absolute indication for endoscopic resection, and T1a-MM and T1b-SM1 (<200μm) have relative indication. pT1a-MM and pT1b-SM cancer is examined the need for additional treatment such as surgery, chemoradiotherapy, radiotherapy, or chemotherapy. In our hospital, we perform ESD for esophageal cancer, which is limited within cT1b-SM1. If histological examination is T1a-MM or T1b-SM1, we consider additional treatment to the esophageal cancer. We add this guideline information to references.

6. There was a strong correlation between maximum lesion dimension and mucosal deficiency, and so maximum lesion dimension was excluded from the multivariate analysis. Which parameter was appropriate to suggest as potential risk factor for intraoperative perforation during ESD for esophageal carcinoma?

Response: Upon univariate logistic regression analysis, odds ratio of mucosal deficiency was bigger than odds ratio of mucosal deficiency (OR, 7.93; 95%CI, 1.59–39.7 vs. 1.64; 95%CI, 1.07-2.52). Mucosal deficiency was more appropriate as risk factor for intraoperative perforation during ESD for esophageal cancer.

7. In page 9. Of the 156 ESCC, 131 (83.9%) were intramucosal carcinomas and 25 (16.0%) were submucosal carcinomas. 84.0%?

Response: We made a miscalculation. We correct the date.

8. Please delete data of range of procedure time.

Response: We delete data of range of procedure time.

9. Figures are not clear. If possible. Please replace clear pictures.

Response: There are no clearer pictures. We are not able to replace pictures.

Responses to the comments of Reviewer #2

1. If the patient was supposed to have high risk of perforation, which precaution would you do?

Response: This study suggests that mucosal deficiency corresponding to 3/4th of the circumference or larger is an independent risk factor. Thus, we should shorten the range of mucosal deficiency as narrowly as possible while maintaining oncological curability, and changing the position of the patient may enable the use of gravity to help control the movements of the endoscope. And we recommend to use the clip-with-line method and the outerroute method effectively to make the endoscopic view clearer and counter traction easier.

2. Does the lesion on the left side is a risk factor of perforation?

Response: Upon univariate logistic regression analysis, predominant site (right vs. left) was not a risk factor for intraoperative perforation (OR, 2.50; 95% CI, 0.64–9.72; P = 0.186; Table 3). There were some cases which were not predominantly located in left side but should be dissected the submucosal layer under the left side mucosa. Therefore, we suggested that predominant site of left side could not be a risk factor, even though left wall was the predominant site of perforation.