

38556-Answering Reviewers

Reviewer 1:

Question 1: There have been changes in the way ESTD is performed over time (eg. advices, current type, use of CO2) - What are the reasons for the high number of R0 resection failures. (12 in the vertical margin and 3 in the lateral margin).

Reply: Thank you for your comment. As is reported, incidence rate of positive margin after ESD is 3%-17%^[1-3], in our study, positive margin rate is 15.76%(35 in horizontal margin, 10 in vertical margin, and 4 both in horizontal and vertical margin). The tumor area and invasion depth are reported to related to the positive margin^[4], the larger the tumor area, the deeper the tumor invasion, the higher the rate of positive margin. In our study, we included the 137(44.05%) lesions of large tumor area with tumor circumference $\geq 3/4$, so this maybe the reason why we have a high number of R0 resection failures. We have discussed this as is suggested in the discussion part, thank you very much again.

Question 2: Discuss about the macroscopic aspects and lymphovascular invasion.

Reply: Thank you for your comment. After ESTD, the specimens were fixed in 10% formalin about 24-48 h, then sliced into many slips at a 2-mm intervals, and stained with Hematoxylin-Eosin, each slip was observed carefully under microscopy. The tumor invasion depth was detected by a special microscopy with a ruler above the its eyepiece, which can specify the distance into micron. Lymphovascular invasion is reported to associated with lymph node metastasis in early esophageal cancer^[5], and according to ESGE guideline^[6], presence of lymphovascular invasion in ESD specimen is defined as non-curative resection, so we also detected the lymphovascular invasion status using immunohistochemistry, CD2-40 staining for lymphatic endothelium and CD34 staining for vascular endothelium. Thank you very much again.

Question 3: It is necessary to discuss the incidence of infections. Is the prophylactic antibiotic necessary?

Reply: Thank you for your comment. We have discussed the incidence of infections as is suggested in the discussion part of revised manuscript. The choice of whether to use antibiotics before ESD is controversial, because currently available guidelines about gastrointestinal endoscopy do not mention ESD or ESTD. As is reported^[7], the incidence of bacteremia after esophageal ESD is low (1%), and according to Chinese Guidelines for Use of Antibiotics, prophylactic antibiotics were not recommended for ESD, except for large mucosal dissection and high risk of perforation procedures. In our study, we used prophylactic antibiotics only in lesions with circumference $\geq 3/4$, this has been added in the *Method* part of revised manuscript, thank you very much again.

Question 4: Should the protection of the airways be done in all cases?

Reply: Thank you for your comment. Because the esophageal ESTD procedure is susceptible to the patient's breath status, and the operation was accompanied by many times of gas injection and water injection, the trachea cannula is necessary to protect airways in order to improve the resection rate and prevent regurgitation and aspiration. Thank you very much again.



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Reviewer 2:

Question 1: High complete resection rate and high positive margin rate was contradictory.

Reply: Thank you for your comment. The definition of complete resection rate is different from en bloc resection, in our study, the en bloc resection rate is high (99.04%) , but the complete resection rate is only 81.28%, we analyzed the reason in the discussion part of revised manuscript why the positive margin is high in our study. Thank you very much again.

Question 2: There were no data on the pathological discordance between the pre- and post-ESTD specimens in the Abstract; therefore, the conclusions should be modified (page 2, line 17-19).

Reply: Thank you for your comment. The conclusion is modified as is suggested. Thank you very much again.

Question 3: Continuous variables should be rounded to the first decimal place.

Reply: Thank you for your comment. This has revised as is suggested. Thank you very much again.

Question 4: The average hospitalization expense should be converted into dollars.

Reply: Thank you for your comment. The average hospitalization expense has been converted into dollars in revised manuscript. Thank you very much again.

Question 5: Further management for 10 patients with obstinate stricture should be described (page 12, line 1-2).

Reply: Thank you for your comment. The further management for 10 patients with

obstinate stricture was added in the revised manuscript. Thank you very much again.

Question 6: Gender difference was of no importance in this study (page 13, line 18-20).

Reply: Thank you for your comment. We have deleted the discussion about gender difference as is suggested in revised manuscript. Thank you very much again.

Question 7: The bleeding rate of 8.04% in this study was not low compared with that of ESD in the previous studies (0%-6%). Please specify the reason why the authors considered ESTD as a safe treatment method for these diseases (page 14, line 17-21).

Reply: Thank you for your comment. In our study, the intraoperative bleeding was defined as blood volume >50 ml and bleeding that could be effectively stopped in ESTD procedure; postoperative bleeding was defined as the symptoms of hematemesis or/and melena, with hemoglobin levels being decreased by more than 20 g/L within 30 days after ESTD procedure. While in other studies^[1,8-11], the bleeding was defined as the significant bleeding that need blood transfusion or postoperative hemostatic treatment. Because the difference of definition, the total bleeding rate in our study is 8.04%, but the rate of significant bleeding that need postoperative hemostatic treatment in our study is low (1.61%). Besides, the esophageal perforation rate in our study is also relatively low (1.93%), no ESTD related disability or death were observed and no recurrence tumors presented in the follow-up period, so we think the ESTD procedure is relatively safety. We have revised the discussion about bleeding rate in the revised manuscript. Thank you very much again.

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