Author's response to reviews

Title: Diagnosis and Staging of Superficial Esophageal Neoplasm based on Pre-Endoscopic Resection System Comparable to Endoscopic Resection

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Response to Dr. Pierre de Delva

1. It is unclear from the manuscript if any patients treated with EMR were found on pathological examination to have depth of invasion beyond SM1 and therefore moved on to surgery. Although EUS invasion beyond SM1 was an exclusion criteria, EUS can be unreliable making this distinction. Therefore, there could have been patients that by EUS were treated by EMR but later found to have deeper invasion on analysis of the specimen and then moved on to esophagectomy. In that case the esophagectomy specimen should be the gold standard.

My concern is if those patients are excluded from the gold standard group, how do we know if the pre ER system will identify those patients? If those patient are included in your cohort please state so and consider reporting how many of the cohort had this occurrence. If they are not included, I suggest adding them to make sure that your cohort is as close as possible to actual clinical practice.

Could it be possible that the pre ER system would miss a patient with SM2-SM3 disease?

Response: This study was the retrospective study, and the aim was the diagnosis and staging of the pre-endoscopic resection system comparable to endoscopic resection.

In our study, we evaluated the EUS in the stage of the esophageal cancer and neoplasm, especially for the lesion in the mucosa. In our study, the EUS was also used for choose of the EMR. So all the lesions were the lesion operated with the EMR.

That’s was right that if we want to evaluate the EUS, we should also contain the lesions operated the esophagectomy, which was also another study for the evaluation of the EUS in the stage for the esophageal cancer, not just the early cancer and neoplasm. This study was aim to establish the pre-system for the treatment of the early cancer and the neoplasm. So the lesions which were suspected invading to sm were all excluded in our study.

2. You might want to add a paragraph in the discussion to describe the strength and weaknesses of the study. I wonder how replicable these results would be at centers without the endoscopic and pathologic experience of your center.

Response: the paragraph of the strength and weakness had been add as follows:

We try to improve the diagnosis criteria by adding the grading of the endoscopic appearance of the lesions after Lugol’s iodine staining (based on the intensity of the lack of staining and the margin characteristics of the lesion), and by adding the stage criteria based on the Paris Classification and EUS findings. We conclude that the pre-ER system can estimate lesion histology and stage as accurately as post-ER by combining data from the endoscopic appearance and biopsy diagnosis. And the most
important were that the use of the EUS for the stage and the Paris classification for
the including criteria. The weakness of this study was that the study on the endoscopic
appearance of the lesion after the lugol’s staining was mainly from China, and there
was also no other study on it. In this study, we want to share the experience in the
lugol’s for the diagnosis in the esophageal neoplasm.
Reviewer: Daniel Oh

The authors investigate a relevant issue in endoscopic therapy for superficial esophageal squamous cell carcinoma - the accuracy of non-invasive endoscopic techniques to determine whether an early esophageal cancer is suitable for ablative therapy or whether esophagectomy is indicated. Traditionally, the authors have used endoscopic mucosal resection (EMR) to make this determination. The combination of techniques used to replace EMR includes the appearance on EGD with Lugol's solution, Paris classification of the lesion, EUS, and endoscopic biopsy - the authors call this "the pre-ER test" or pre-endoscopic resection test.

The conclusion of the study is an important contribution to those clinicians who perform endoscopic therapy on early esophageal cancers. However, the manuscript is very difficult to interpret and would benefit from an editor or writer who could improve its readability. Second, a statistician should be included in this study since it is based on the premise of ROC and AUC calculations to justify its conclusions, and a formal statistical analysis would be helpful to determine if this is truly the best method of answering the authors' questions. Third, many of the references in this manuscript are from Chinese journals and cannot be accessed for review. With some major revisions, this study would be suitable for a major gastroenterology journal.

Response: As to the readability of this article, we had let the native polished, and again, we corrected again. We hope this would be improved. The statistic was supported by the statistician, who was also acknowledged. And the formula for the comparison of the AUCs also was added.

It was known that the prevalence of ESD parallels rates of invasive ESCC and is typically found in 25% or more of adults above the age of 35 years in populations in north central China, where risk for ESCC is among the highest in the world. And the value of the lugol’s staining in the diagnosis of the EGD was also accepted. The Chinese references were mainly the study for the lugol’s staining, and we want to share the experience.
Reviewer: Dr. Sanford Dawsey

Explain how the Paris Classification of a lesion’s macroscopic appearance is used to create the pre-ER system diagnosis, and how individual Paris Classification categories would “upgrade” or “downgrade” biopsy diagnoses in the pre-ER system diagnosis. At least one reference showing the appropriateness of such a use of these macroscopic observations would also be helpful.

Response: the Paris classification was used as one of the criteria for the chosen of the ER. All the lesions, classified as 0-I and 0-III, were excluded. After the re-evaluation of all the lesions, we think that the most important value of the Paris classification was as the exclusion criteria just as the update classification in 2005.

Explain how the EUS findings were classified, the appropriateness of such a classification with the technology used, and how individual EUS diagnostic categories would “upgrade” or “downgrade” the other data in the pre-ER system.

Response: the EUS for the stage of the esophageal cancer was explained in the article, and the reasons for the “upgrade” or “downgrade” were also explained as follows:

During the EUS operational procedure, there was “upgrade” or “downgrade” rate. The reasons were that: (1) There was different appearance of the lesions and the different image in the EUS picture. When we used the probe to exam the depth of the lesion, there was bias because of this; (2) There was inflammation in the lesion, and the invasion depth affected; (3) There was minute invasion in the lesion and it was difficult to be tested in the EUS.

Clarify how the data from the four components of the pre-ER system were combined to create the final pre-ER system diagnosis. Examples of individual cases would be helpful in this regard.

Response: the example was described in the article: Such as, the lesion was 0-II according to the Paris classification which was the indication for the ER. If the diagnosis based on the biopsy was HGIN, while endoscopic diagnosis after the lugo’s staining as the MGIN, the pre-ER diagnosis was HGIN with the EUS no invasion to submucosa. If the diagnosis based on the biopsy was MGIN, while endoscopic diagnosis after the lugo’s staining as the HGIN/ESCC, the pre-ER diagnosis was HGIN/ESCC with the EUS no invasion to submucosa.

• Clarify how the under-diagnosis, accuracy, and over-diagnosis statistics of the Endoscopic Diagnosis, Paris Classification, and EUS findings (vs. the “final gold-standard diagnosis”) were calculated.

Response: the statistics of the accuracy was described and the example was described in the article: The under-diagnosis, accuracy, and over-diagnosis rate
were calculated based on the number of the pre-ER as numerator and the gold standard as denominator. The under-diagnosis means the numerator was lesser than the denominator, while the accuracy means the same diagnosis, and the over-diagnosis means the numerator worse than the denominator.