Editor-in-Chief

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Title: Imaging biomarkers for the treatment of esophageal cancer

Dear Dr. Lian-Sheng Ma,

We are most grateful to you and reviewers for the helpful comments on the original version of our manuscript. We have taken all these comments into account and would like to resubmit a revised version of our paper. We have addressed all the comments of the reviewer, and we hope that the explanations and revisions of our work are satisfactory. We hope that the revised version of our paper is now suitable for publication in World Journal of Gastroenterology.

Sincerely yours,

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We are grateful to reviewer 1 (00731523) for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comments by Reviewer #1:

1. This article reviews the imaging biomarkers as a predicting tool only for response to chemo- or chemoradiotherapy not response to surgery. The title should be changed due to this concept.

    Response: Thank you for your comment. But if you read PET section, you can find prognostic importance of tumor SUV in patients who received surgery. Thus, the title should not be changed.

2. You should add a conclusion at each section. Also, it's better to discuss about the relation of these biomarkers to the pathologic type (i.e. SCC or adenocarcinoma), the location of the tumor (upeer, middle and lower third) and the clinical condition of the patient.

Response: Thank you for your comment. I added small conclusion in some of sections. But, regarding the relation with the pathologic type and the location of the tumor, there has been no published data on pathologic type and the location of the tumor. Besides our focus is whether imaging biomarkers can predict treatment response or prognosis. That's why we didn't include them in this manuscript.

We are grateful to reviewer 2 (00812852) for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comments by Reviewer #2:

The article is interesting. If it included the biomarkers on sonography both transcutanous and EUS it would be more comprehensive.

Response: Thank you for your comment. I partly agree with you. But in this article, we wanted to focus on "radiological" imaging biomarker such as CT, MRI, PET. Besides, because functional analysis of esophageal cancer using US or EUS may be limited, we didn't include this topic in the article.

We are grateful to reviewer 3 (03026970) for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comments by Reviewer #3:

1. This review concluded the features of CT / MR perfusion, texture analysis, DWI, and PET as biomarkers in predicting the treatment response or prognosis of esophageal cancer. Imaging biomarkers, featured by availability and less invasiveness, offer clinical doctors an option in esophageal cancer diagnosis. The whole passage is well-organized.

   Response: Thank you for your comment on our article.

2. There is a review in 2017 discussed the endoscopic and imaging predictors in assessing the pathologic response after chemoradiation for esophageal cancer (Endoscopic and Imaging Predictors of Complete Pathologic Response After

Chemoradiation for Esophageal Cancer).

Response: Thank you for your comment. I read the review you suggested. But this review concluded as following "While no single technique reliably predicts pCR, a combination of imaging and diagnostic modalities (endoscopic appearance, biopsy, EUS, and PET/CT) may provide a better diagnostic yield rather than any of these modalities taken alone." Our aim is to review "imaging biomarkers", not to review endoscopic and pathological factors. Besides, our aim is not to find biomarker for pCR. In this sense, our review is different from the review you suggested.

3. Besides, only 1/4 references quoted in this review were published in the last 5 years. This review is lack of novelty and needs thorough discussion.

    Response: Thank you for your comment. Because investigations of esophageal cancer using PET started more than 20 years ago, even DCE-CT and DCE-MRI studies on esophageal cancer started about ten years ago, quoted references in this paper become old. But texture analysis is still popular and recent papers were cited.

4. It was mentioned in the article that published results about relationship of CT / MR perfusion and angiogenesis are controversial. Could you please provide specific

reference and discuss it?

Response: Thank you for your comment. We added following sentences. "Sato et al. speculated that blood flow assessed with perfusion imaging reflected only the functional vessels with a lumen, and not the functionless tumor vascularity; and therefore, micro-vessel density studied immunohistochemically in vitro using surgical specimens might be inadequate for "in vivo tumor vascular physiology. These factors may lead to controversial results."

5. It is recommended to add the limitations and challenges of diffusion-weighted MRI.

   Response: Thank you for your comment. We added following sentences. "Because DWI does not need radiation exposure and contrast enhanced agents, it can be an ideal biomarker. However, standardization of data acquisition and analysis methods have yet to be established for DWI. Low spatial resolution, especially in high b-value image, should be improved for accurate detection and measurement of the tumor lesion."

6. Some abbreviations are confusing and the full name should be provided at the first appearance. Such as CRT, BF and ROI. 5.There is no "A" or "B" in the picture of

Figure 3. 6.There are several grammar mistakes in this review.

Response: Thank you for your comment. I corrected them.