

*Dr. Subrata Ghosh*

*Dr. Andrzej S. Tarnawski*

*Editor-in-Chief*

*World Journal of Gastroenterology*

*Dear Dr. Ghosh & Dr. Tarnawski*

Herein we would like to resubmit our manuscript entitled “Clinical Relevance of FDG-PET/CT and Magnifying Endoscopy with Narrow Band Imaging in Decision-making Regarding the Treatment Strategy for Superficial Esophageal Squamous Cell Carcinoma” to the Journal of ***World Journal of Gastroenterology***. We thank the editors and the reviewers for their thorough review of our manuscript. We made revisions as the below letters.

Manuscript NO: 51631

Thank you very much for reviewing our manuscript and offering valuable advice.

We would like to give a point-by-point reply to reviewer’s comments, and

revised the manuscript accordingly.

**Reviewer's code:** 03726743

### **SPECIFIC COMMENTS TO AUTHORS**

In the manuscript entitled, "Clinical Relevance of FDG-PET/CT and Magnifying Endoscopy with Narrow Band Imaging in Decision-making Regarding the Treatment Strategy for Superficial Esophageal Squamous Cell Carcinoma", the authors examine the significance/utility of PET/CT and also magnifying endoscopy with NBI in the evaluation of ESCC and how these relate to depth of invasion and thus treatment strategy. This is an interesting and multi-disciplinary subject, and the manuscript is generally fairly well written. The sample size seems adequate. Perhaps the major concern is what exactly the take home message is, and how this is different than or goes beyond prior reports. Despite reading the manuscript several times, I still could not come away with a succinct conclusion. The only thing I was able to catch on to was that if PET is positive, the lesion is deep (too deep for ESD). What exactly ME with NBI adds to this is unclear, though I think the combination of the two had the best performance (?). Additional

and more specific comments and suggestions, many of which can be easily resolved and all of which are intended to improve the manuscript, are provided below:

Title: -Quite long. Consider omitting the word “superficial”, as this is implicit.

Abstract: - It would be helpful if the opening statement could be a bit clearer. For example, instead of “...but it is difficult to evaluate pathological factors related to additional treatment after endoscopic resection (ER).”, why not just say “...but determining the appropriate method of resection, endoscopic (ER) vs. surgical (SR), is often challenging.” (or something to this effect). -A comma is not needed in the Aim subsection, as the second clause is not independent. -The Methods subsection should clearly state what the primary endpoint was and what additional (secondary) endpoints there were. In other words, its understood that a database was retrospectively analyzed...but for what (variables)??

Tables: -Nicely organized, but a single figure which helps summarize the key points or provides a practice algorithm would greatly strengthen the manuscript.

Response:

Thank you very much for your constructive suggestions. First, we revised the

title as you recommended. And we revised the background in the abstract according to your suggestion (p. 6, line 5-7, 10-15), and we removed the comma from the Aim subsection (p. 7, line 1-4). We also, added endpoints in the METHODS section (p7, line 12-16, p18, line 12-15). Finally, we added Figure 2 which helps summarize the key points or provides a practice algorithm according to your suggestion. (p. 28, line 13-15)

**Reviewer's code:** 03474649

#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript is original and clinically relevant topic especially in Asian population in which Esophageal cancer has high incidence. The study has two major disadvantages and this limitation is mentioned by the authors at the end of discussion section. First is retrospective design of the study and second is lack of esophageal ultrasound correlation. But the combination of FDG PET/CT scan findings with magnifying endoscopy with narrow band imaging is major originality of this study and makes it valuable. The study is quite well written. On the other hand, the authors reported high FDG uptake in 29 (35.4%) lesions, which is relatively low number. But, the diagnostic

performance reflects higher values in terms of sensitivity, specificity and accuracy. This values are incomprehensible. They reported uptake in 29 patients but sensitivity 78-87-93. It should be explained more clearly. In the abstract, in the first sentence of results the authors used “FDG-PET showed positive uptake in 29 (35.4%) lesions”. In the explanation of PET results, terms of positive uptake not commonly used. Uptake can be described as high / low uptake or SUV values. In the manuscript, the authors explained the meaning of "positive uptake" and "visibility". In the abstract section these two words needs brief explanation.

Response:

Thank you very much for your constructive suggestions.

In this study, as you mentioned, the number of FDG-PET positive cases were as small as 35.4%, but most of them were SM (T1b) cases. As described in the text, we examined the detection accuracy when assuming FDG-PET positivity as SM2-3. Although the number of SM cases were small, most of them showed FDG high uptake, so we think that is the reason why the diagnostic performance reflects higher values in terms of sensitivity, specificity and

accuracy.

We added the explanation of the meaning of "positive uptake" and "visibility" in the abstract section and method section as you have pointed out (p. 7, line 9-11, p16, line 6-10).

**Reviewer's code:** 03362724

### **SPECIFIC COMMENTS TO AUTHORS**

Results helps clinicians for their decisions. I want to learn: 1. You accept PET positive any focal FDG uptake above the expected background. But what is the expected background ? Did you find any background values? and, Where did you get this value as a reference value? 2. You mentioned that FDG uptake was correlated with circumferential extension, depth of tumor invasion, infiltrative growth pattern, histological grade, vascular invasion, and lymphatic invasion. Could you search any threshold for SUVmax value for these parameters? 3. As I understood, you excluded the patients with distant metastasis. Was there any difference in SUVmax values and pathological findings between the patients with local lymph node metastasis?

Response:

Thank you very much for your constructive suggestion.

1. This study was a retrospective study. Each data of PET-CT were evaluated before treatment. So, SUV max could not be measured based on the standardized site in all cases, and the reference sites were also different. For this reason, FDG uptake was evaluated based on whether accumulation was visible or not. We added sentence in method section. (p. 16, line 5-10)
2. Because of above background, it was difficult to evaluate the threshold for SUVmax value for these parameters. However, wrote in (p20, line 17 – p21, line 10), there were significant significance between the circumferential extent, depth of tumor invasion, infiltrative growth pattern, vascular invasion, and lymphatic invasion and SUV max values. In the prospective study, these problem will be solved.
3. In this study, the subjects were patients who had undergone endoscopic or surgical treatment. No one showed FDG uptake. So it was difficult to evaluate the difference in SUVmax values and pathological findings between the patients with local lymph node metastasis.

Finally, we added two sentences in method section (p17, line16-18) to show the skill of endoscopists who evaluate the classification with NBI magnification, and to help understanding the result of this study, we added a sentence (p. 20, line 15-17) in result section.