

## **Reply to reviewer's comments**

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First of all, we deeply appreciate the effort of the reviewer for reviewing our manuscript carefully. We hereby resubmit a response to the reviewer's comments formatted in the point-by-point style. We highlighted with underline where we revised within the manuscript and described the number of page and line.

### **RESPONSE TO REVIEWER**

**(1) First**, this manuscript proposed a validation of JNET classification for endoscopists. It is a very interesting study with a review of rare original articles and of the enormous serie of the authors. After reading this article, we are convinced that this classification is very interesting, probably easier to use for endoscopists but not completely convinced that it is better than the NICE classification. See the commentaries in the attached file.

*As follows (1-1, 1-2, 1-3) are from Specific Comments to Authors in the attached file.*

**(1-1) First** : you say in the discussion that » The JNET classification is considered to have a higher diagnostic performance than the NICE classification ». The table 4 shows however that some important end-points of a classification are in favour of the NICE classification: Sensitivity (deep submucosal invasive cancer vs other neoplasia): JNET 51% and NICE 92%, PPV (neoplasia vs non neoplasia): JNET 74.5 vs NICE 85%

The most important difference in favour of JNET classification is the higher confidence rate of the JNET. That demonstrates rather that this classification is clearer and easier to use than the NICE classification for the endoscopists?

**Response: Thank you for your suggestion. Yes, we agree your opinion. In accordance with your suggestion, we have revised that paragraph as follows:**

The JNET classification is considered to have as high diagnostic performance as the NICE classification. However, there have been no studies directly comparing the JNET classification with the NICE classification. For comparison with the NICE classification, we evaluated the diagnostic performance with high confidence prediction and the high confidence rate in regards to two differentiations; “Neoplasia vs. Non neoplasia” and “Deep submucosal invasive cancer vs. other neoplasia” (Table 4). In both differentiations, the high confidence rate in the JNET classification was significantly higher than that of the NICE classification. It may demonstrate the JNET classification is clearer and easier to use than the NICE classification for the endoscopists. Magnifying observation may increase the high confidence rate of endoscopic diagnosis.

**(1-2) Second,** you did not discuss the difference between the both classifications: the parameter « color » is present in the NICE and absent in the JNET. It was interesting to discuss why this parameter were superfluous.

**Response: Thank you for your question. As we heard, while JNET members were making JNET classification, they discussed about the parameter « color ». When we observed colorectal lesions with magnification, we cannot compare its color with surrounding membrane in a view. Thus, they decided to exclude this parameter from the JNET classification. This issue is interesting; however, we guess it should be written not in our manuscripts, but in making process of the JNET classification and manuscripts about the comparative study.**

**(1-3) Third, Malignant neoplasia (type 2B, 3) VS. Benign neoplasia (type 2A).** You explained that it is a very important point because « endoscopist can appropriately determine whether to perform en bloc resection or not». You exposed that. The accuracy, specificity, and NPV of this diagnosis are 80.7-96.1%, 84.7-98.2%, and 87.0-97.7% respectively. Could you give values of accuracy, specificity, NPV and PPV of NICE classification to differentiate type 2 and type 3? The response at this question is not in the table 4 where we have responses to the questions questions : 1 versus non 1 and 3 versus non 3.

**Response: Thank you for your question. The table 4 refers to your question.**

**In table4, “Neoplasia vs. Non neoplasia” means NICE 1 versus NICE2, and “Deep submucosal invasive cancer vs. other neoplasia” means NICE 2 versus NICE3.**

**In accordance with your suggestion, we have added legends with table 4 as follows:**

**\* Neoplasia vs. Non neoplasia; JNET 1 vs 2A,2B and NICE 1 vs 2**

**\*\*Deep submucosal invasive cancer vs. other neoplasia; JNET 2A,2B vs 3 and NICE 2 vs 3**

(2) **Second**, authors said, and we completely agree, that the goal of a classification will enable endoscopists to identify almost all neoplasia, to appropriately determine whether to perform en bloc resection or not, and to avoid unnecessary surgery. Authors could have said in their series, how many unnecessary surgeries had been performed and how many necessary surgeries had not been performed.

**Response: Thank you for your suggestion. It is important to avoid unnecessary surgeries. In our study, two unnecessary surgeries had been performed and 22 necessary surgeries had not been performed. For such cases, we performed the surgeries after endoscopic resection if necessary.**

**In accordance with your suggestion, we have revised “3. *Deep submucosal invasive cancer (Type 3) from other neoplasia (Type 2A, 2B)*” as follows:**

The diagnostic performance in differentiating deep submucosal invasive cancer from other neoplasia is associated with the necessity of surgical resection. As for this distinction, the specificity was extremely high being 99.8-100.0%. The JNET classification enables endoscopists to avoid unnecessary surgery for non-invasive neoplasia. **In our study, the unnecessary surgeries were only two cases.** On the other hand, 10.6-23.9% of type 2B lesions were D-SMCs, and 0.0-5.1% of type 3 lesions were S-SMCs. Additional magnifying chromoendoscopy is recommended in cases where it is difficult to differentiate between shallow and deep submucosal invasive cancers.

**(3) Third** the future direction should be to compare in a same endoscopic and histopathologic center the accuracy of the classifications JNET and NICE, for example by a randomization of the endoscopic "expert", blind each other: one classes with JNET and the other with NICE. Then confrontation with histopathologic examination.

**Response: Thank you for your suggestion. We agree your opinion and are interested in such a comparative study. But we did not such a trial yet. So, we have revised the limitation as follows:**

The limitation in this review is that there were only 3 articles about the diagnostic performance of the JNET classification. The previous studies were all retrospective single center studies. A large-scale prospective multicenter validation study of the JNET classification is awaited in the future. About the comparison the JNET classification with the NICE classification, though it is better to compare in the same endoscopic and histopathologic center, we did not such a comparative trial yet.

**We wish to express our strong appreciation to you for your beneficial comments on our manuscript. We feel the comments have helped us significantly improve the manuscript.**

**Sincerely**

**Daizen Hirata**