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Editors-in-Chief

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To the Editors:

Thank you for giving us an opportunity to revise and re-submit our manuscript, entitled "Prediction of colorectal tumor grade and invasion depth through narrow-band imaging scoring" (Manuscript No: 40550).

We have made the necessary revisions to the manuscript and have responded to all comments in a point-by-point manner below. We believe that the manuscript has been significantly improved by these revisions and hope that it is now acceptable for publication in your journal. We have also included the Article Highlights and Audio Core tip as requested.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Reviewer #1:

#### SPECIFIC COMMENTS TO AUTHORS

In this manuscript the authors reported the results on the use of statistical model for predicting tumor grade and depth invasion of colorectal cancer through narrow-band imaging scoring. They described a good number of clinical cases with interesting results. This article may be the starting point for other prospective works by other research groups to confirm the usefulness of the method.

**Response:** Thank you for your positive comments.

Reviewer #2:

#### SPECIFIC COMMENTS TO AUTHORS

Authors retrospectively analyzed endoscopic images with NBI for colorectal neoplasia, to determine the algorithm to predict tumor grade and invasion depth.

1) Although authors used a statistical model, the interpretation of images inevitably harbors inter-observer variability. In this study, two experts evaluated the images, but in the regard of inter-observer variability, the reproducibility evaluated by other endoscopists should be validated. In the regard of validation, the model constructed with the cohort of this paper should be validated with another cohort of colorectal polyps.

**Response:** Thank you for your comment. We agree that the model should be validated further by other endoscopists to ensure reproducibility. Also, our proposed model will require validation in other cohorts of patients with colorectal polyps. Our future work will address these validation studies, and we have noted this issue in the limitations section of the Discussion.

2) In the Tables 1 and 2, authors indicated predictability of NBI images for tumor grade and invasion depth. In contrast, in the Tables 3 and 4, authors showed the correlation between NBI images and tumor architectures. The two topics are quite different and readers would be confused because of the ambiguity of the main objective of this study.

**Response:** Thank you for your comment. The main objective of our study was the creation of a statistical model in which narrow-band imaging scores could be used to predict the tumor grade and invasion depth of colorectal tumors.

Several expanded NBI classifications have been proposed in Japan to date. However, beginners find it difficult to evaluate these different NBI findings, and the diagnostic objectivity is poor when compared to that of the traditional pit pattern classification. The main objectives of this research were to identify diagnostically useful NBI findings from among several of the known expanded NBI findings and to simplify diagnosis while increasing objectivity by assigning scores. To this end, we included lesions for which the detailed pre-surgical NBI investigations corresponded with the detailed pathological tissue histology results after surgical or endoscopic removal. We assessed the correlations of NBI findings with both "quality/invasion depth" and "pathological tissue architecture" and found that both correlations could be used to predict the outcome of a cancer.

3) Assignment of endoscopic resection or surgery does not solely depend on the depth of invasion. There are other factors including venous or lymphatic invasion, presence of budding. So, prediction of only depth of invasion would not work enough in clinical settings.

**Response:** This comment is absolutely correct. Prior to surgery, we evaluated only the invasion depth. Postoperatively, however, we evaluated pathological specimens (e.g., other tissue types,

vascular invasion) and determined whether additional surgery was necessary. This model was to increase the sensitivity of a cancer diagnosis and reduce the likelihood of a missed diagnosis, increase the positive hit ratio for deep invasive cancers, and prevent unnecessary surgical operations. Therefore, a lesion diagnosed as a deep invasive cancer based on a NBI observation would be subjected to a diagnostic surgical operation, whereas a lesion diagnosed as a cancer but not judged to involve deep invasion would be subjected to a pit pattern diagnosis to assess the invasion depth (this process requires lesion staining and other techniques but yields a superior diagnostic performance vs. NBI) and a lesion diagnosed as adenoma would be subjected to endoscopic treatment.

Reviewer #3:

### **SPECIFIC COMMENTS TO AUTHORS**

This manuscript by Maeyama Y et al. demonstrated a usefulness of a novel scoring system using magnifying narrow-band imaging for predicting tumor grade and invasion depth. This results can be beneficial in future research and clinical practice. However there are points of concern.

1. Authors should clarify the criteria for initially included 161 lesions with NBI imaging among all observed lesions during this study period. Pedunculated type polyps were also included?

There is a discrepancy of the number of the all included lesions, 160 in the abstract, and 161 in other parts.

**Response:** Thank you for your constructive comments. We included only those lesions for which a local one-to-one correspondence was observed between the pre-treatment NBI findings and

post-treatment pathological tissue findings. We have revised the Methods and Figure 1 to better clarify this point. None of the pedunculated-type polyps met the criteria for category and therefore, no such lesions were included. Possibly, pedunculated polyps move and rotate during endoscopic observations, making it difficult to identify the site at which to obtain magnified NBI images and, consequently, to compare the data with postoperative histological findings.

We also thank you for pointing out the discrepancy in the number of lesions. This has been corrected in the abstract.

2. “tumor grade” and “advanced cancer” should be defined clearly in the manuscript.

**Response:** Tumor grade was classified based on the scoring system in Table 2. We have indicated this point in a note to Table 2. "Adenomas" and "cancers" were distinguished based on the manner in which the ducts were organized and the nuclear forms in histopathological samples.

Lesions in which cancer was found to infiltrate beyond the muscular layer were considered to be advanced cancer. This explanation has been added to the Results section.

3. The sample size is enough and appropriate to make a solid conclusion in this topic?

**Response:** Thank you for your comment. We understand your concern. However, this research was initially exploratory in nature. To this end, the study design did not include random assignment or pre-specified hypotheses requiring sample size calculations. However, the conclusions drawn from our data analyses are solid from a statistical point of view.

4. More detailed statistical analysis in order to achieve the scoring in Table 2 should be mentioned. How does the value of each scores come to?

**Response:** Thank you for your comment. As mentioned in the Methods subsections titled “Development of a model for predicting tumor grade and invasion depth” and “Statistical analyses”, as well as in the legend to Figure 4, the scoring system in Table 2 was constructed based on the parameter estimates and their standard errors in the multivariate logistic regression model. Specifically, z-scores based on parameter estimates and corresponding standard errors were calculated. Next, integer scores based on the relative magnitudes of z-scores were assigned to risk factor level. This information has now been included in Table 2.

5. Does the value of each scores have any importance regarding sensitivity? Scoring-based systems should be interpreted into scale with different sensitivity and specificity. If the scoring system based on yes-or-no basis, there would be similar to other common classifications. Although the value of each scores reveals relative importance of each variable in the scoring systems, only total score determines sensitivity and specificity of the systems.

**Response:** Thank you for your comment. The logistic regression was fitted after obtaining the total score from each patient’s clinical records. Cut-off values were then determined based on the Youden index. Accordingly, each score contributes to the sensitivity of the model, and we have determined the final sensitivity/specificity of the screening test (i.e., our scoring system).

6. Please mention the outlines of place of this classification (similarity, difference, and clinical significance) between the previously known classifications such as NICE and JNET classifications.

**Response:** Although multiple previous studies addressed the utility of NBI for the endoscopic diagnosis of colorectal tumors, endoscopic findings were only expressed in numbers and letters and within categories, whereas the actual clinical application was challenging due to the high subjectivity and the requirement for a high level of skill and training to reach a correct diagnosis. This is also true for the NICE and JNET classifications. In this study, NBI findings which incorporated surface and vascular pattern findings were assigned scores based on statistical methods. Furthermore, a statistical model for predicting the grade and depth of invasion of a colorectal tumor was created, and its utility was investigated. We have added this information to the Discussion section.

In this prediction model, the sensitivity and specificity can be adjusted by changing the total score, depending on the purpose of the NBI examination in an actual clinical setting. We think that the use of a high sensitivity setting during careful qualitative diagnostic examinations will enable features such as the detection of numerous tumors, while a high specificity when determining the depth of invasion will allow the avoidance of excessive surgeries; furthermore, a pit pattern diagnosis of the remaining lesions will ensure an effective and accurate diagnosis.

7. In Table1, the univariate analysis of every variables in order to obtain the multivariate analysis should be shown.

**Response:** Thank you for your suggestion. We have accordingly included the univariate analysis in Table 1.