Answering Reviewers

Reviewer #1: This study evaluates the NICE and JNET classification for differential diagnosis of colorectal cancer and precancerous lesions, aiming to clarify the potential difficulty in their clinical application. In order to do so, eighty-seven patients were photographed during nonmagnifying conventional white-light colonoscopy, nonmagnifying NBI, and magnifying NBI, with a total of 125 lesions. Each lesion was evaluated by six endoscopists from the same istitution using the NICE and JENT classifications. Then the sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) was calculated for each category of the two classifications. In the end, the study identifies a lower sensitivity of JNET classification Type 2B lesions for the diagnosis of high-grade dysplasia or superficial submucosal invasive carcinoma. The study has several limitations that are indicated correctly in the manuscript, therefore this kind of clinical evaluation could stimulate further and multicentric studies.

Answer reviewer #1: Thanks a lot for your comments, and we also hope to validate the two new NBI classifications in a multicenter prospective study.

Reviewer #2: Validated study on the two NBI classification systems (NICE and JNET) for colorectal early cancerous and precancerous lesions between highly experienced (HEE) and less experienced (LEE) endoscopists in one center in China. The authors concluded that there is good agreement for NICE Type 1 and 3 and JNET Type 1, 2A and 3 lesions, but for JNET Type 2B lesions still needs further examinations. The article is very interesting for publication. Some Issues for further clarification: 1.In the core tip the authors proposed for NJET type 2b further study with endoscopic ultrasonography. However, it is well known that for type 2b early colorectal lesions mainly mucosal or submucosal lesions EUS is not usefull!. Please report any relevant literature if any on EUS for early colorectal mucosal lesions. Moreover such an

examination for 2b lesions in LST types is troublesome and unreliable. 2.The main conclusion of this study is that the diagnostic ability for type JNET 2b lesions is poor. However, the authors cannot make clear the great significance of such result in the conclusion. The type JMET 2b lesions is the most important for treatment strategy that is curative ESD v/s EMR. This is the main stone of treatment algorithms in Japan that is why the Japanese experts introduce the type 2a and 2b. Obviously the type 2b lesions are the most important for curation and the most difficult to be diagnosed endoscopically. It is very surprising that also HEE cannot diagnose with accuracy these lesions. So please add these comments in the discussion. 3. Minor English grammatical mistakes.

Answer reviewer #2: Thank you for your comments, and your questions have been very helpfully in improving the quality of our study. These are the answers about your questions:

1. The normal colonic wall has a five-layer structure in the images of EUS. The first and second layers are the mucosal layers, the third layer corresponds to the submucosal layer, the fourth layer is the muscularis propria, and the fifth layer is the serosa. EUS can produce axial images of the colorectal lesion, which could help to objectively diagnose the depth of lesion invasion. So, the EUS is a useful technique for the diagnosis of invasion depth and the selection of treatment in patients with early colorectal cancers, including the superficial submucosal invasive (SM-s) carcinoma and deep submucosal invasive (SM-d) carcinoma. The EUS not only can be used to diagnose the invasion depth of flat lesion like LST, but also can be used to subtype evaluation the LST lesions. Our topic is about NBI classification, so the usefulness of EUS was not described in detail in this article. Relevant literature is as follows:

Chao G , Ye F , Li T , et al. Estimation of invasion depth of early colorectal cancer using EUS and NBI-ME: a meta-analysis[J]. Techniques in Coloproctology, 2019, 23(3).

Yamada T , Shimura T , Ebi M , et al. Subset Analysis of a Multicenter,

Randomized Controlled Trial to Compare Magnifying Chromoendoscopy with Endoscopic Ultrasonography for Stage Diagnosis of Early Stage Colorectal Cancer[J]. Plos One, 2015, 10(8):e0134942.

Mukae M , Kobayashi K , Sada M , et al. Diagnostic performance of EUS for evaluating the invasion depth of early colorectal cancers[J]. Gastrointestinal Endoscopy, 2015, 81(3):682-690.

2. I will add these significant comments about JNET 2b lesion in the discussion

3. The manuscript has been edited by a native English speaking medical editor at MedE Medical Editing Group. And we will corrcct these grammatical mistakes before resubmitting.c