

Comments from the Science editor

provide English translation of the informed consent and IRB approval

Thank you for your comments. Although we can make the English version of the IRB approval, the document does not have the approval signature, which was only included in the original version. The guidelines recommend uploading only documents written in the official language of the authors' country. Therefore, we have uploaded the original version, which is in Japanese.

Comments from Reviewer #1

(1) Title: could the authors kindly add the type of study.

Response:

Thank you for your suggestion. We added "Retrospective case-control study" to the title.

(2) Abstract: Background: some abbreviations are presented with no full text for first reference as NBI

Response:

Thank you for your comment. We have carefully rechecked and amended the abbreviations in the abstract section (page 3, line 54) and core tips (page 5,

line 99).

(3) Aim: please mention the scores in summary and their fundamental aim instead of stating "these classifications for neoplastic etc"

Response:

Thank you for your suggestion. According to the journal guidelines, the aim sub section of the abstract should clearly state the purpose of the study in not more than 20 words (page 3, lines 59-60). Therefore, we mentioned in the result section that JNET type 2A and pit pattern type III/IV were indicators of low-grade dysplasia, JNET type 2B and pit pattern type V₁ low irregularity were indicators of high-grade dysplasia to shallow submucosal invasive cancer, and JNET type 3 and pit pattern type V₁ high irregularity/ V_N were indicators of deep submucosal invasive cancer, together with their respective scores (pages 3-4, lines 72-77).

(4) Kindly state the type of study in the abstract (?case control).

Response:

Thank you for your suggestion. As you pointed out, this study was conducted

as a retrospective case-control study. We only described it as a “retrospective study”, so we have added the type of study in the abstract section (page 3, line 63). And we have revised the relevant parts of the core tips (page 5, line 98) and introduction section (page 7, line 149) from “retrospective study” to “retrospective case-control study”.

(5) In the authors' statement: "The inter- and intra-observer agreements among experts were fair to moderate for UCAN and moderate to substantial for SN", please add the statistical results and the checklist you used for validation if any.

Response:

Thank you for your suggestion. We have amended the result section in the abstract to present the statistical results directly (page 4, lines 83-87). The checklist used for validation is listed in the statistical analysis section (page 10, lines 235-238).

(6) It is not clear which checklist the authors used for the inter and intra-observer validation process. please explain.

Response:

Thank you for your comments. As above, the checklist used for validation is listed in the statistical analysis section (page 10, lines 235-238).

(7) Introduction: please mention the definition of "sporadic neoplasms" SN clearly with citation.

Response:

Thank you for your suggestion. SN, unlike UCAN, is a neoplastic lesion that develops without the influence of UC. According to reference No. 3, contrary to the immunostaining findings that are characteristics of UCAN, expression of p53 is low in SN. In addition, Ki-67-positive cells are mainly distributed at the superficial region of the tumor, and tumor cells differentiate towards the basal side of the mucosa, also known as "top-down". We have added the sentence for the pathological criteria for SN in the pathological assessment section (page 9, line 209-213).

(8) Methodology and results: In limitations of the study the authors stated " Second, only dysplastic lesions evaluated using both the JNET and pit pattern classifications were included. While inflammation and regenerative changes might be evaluated as neoplastic patterns by both JNET and pit pattern classifications, our study could not include non-

neoplastic lesions.". This point is very important and was not clear in the abstract or the methodology sections as the authors always stated only the word "neoplasms" which could be benign or malignant but as mentioned here it is dysplastic-only lesions, please modify.

Response:

Thank you for your suggestion. As you said, we have included only the neoplastic lesions in this study. We have mentioned it in the Materials and Methods section (page 7, line 155). We have revised "dysplastic" to "neoplastic" lesions in the discussion section (page 16, line 378, 380).

(9) Discussion: Could the authors explain the disparity between their results " JNET type 2B and pit pattern type VI low irregularity had low PPV in the diagnosis of HGD to sSM. Because JNET type 2B and pit pattern type VI low irregularity include lesions from LGD to dSM, these types have low PPV even in non-UC patients." and another reference: "If a lesion is classified as JNET type 2B, pit pattern diagnosis should be used as an adjunct for depth diagnosis." a quote from the reference: Kobayashi S, Yamada M, Takamaru H, Sakamoto T, Matsuda T, Sekine S, Igarashi Y, Saito Y. Diagnostic yield of the Japan NBI Expert Team (JNET) classification for endoscopic diagnosis of superficial colorectal neoplasms in a large-scale clinical practice database. United European Gastroenterol J. 2019 Aug;7(7):914-923. doi: 10.1177/2050640619845987. Epub 2019 Apr 26. PMID: 31428416; PMCID: PMC6683640.

Response:

Thank you for your comment. We have added citation No.32 to describe pit pattern classification in the discussion section (page 15, line 350). According

to reference No.32, the pit pattern type V₁ low irregularity is also a category that includes adenoma to dSM. According to the same reference, distinction between V₁ low irregularity and V₁ high irregularity using the magnifying chromoendoscopy was able to differentiate between sSM and dSM with high sensitivity and specificity. Adding pit pattern diagnosis to the lesions classified as JNET type 2B and distinguishing V₁ low irregularity from V₁ high irregularity improves the accuracy of invasion depth. According to reference No. 25, the JNET type 2B is a category that includes adenoma to deep submucosal invasive carcinoma. Therefore, lesions of the JNET type 2B need an additional pit pattern diagnosis.

(10) Could the authors discuss if the selected sample of patients with their baseline characteristics could have any role in this low diagnostic accuracy aside from the ulcerative colitis?

Response:

Thank you for your question. This study was conducted using limited resources and involved a small sample size, as you pointed out. Quantitative diagnosis is

generally accurate when differentiating between neoplasms and non-neoplasms. Therefore, when only neoplastic lesions are examined, the diagnostic accuracy might be low, as in this study. Among neoplastic lesions, differentiating between a typical JNET 2A without irregularities and 2B with irregularities is easier than differentiating between a 2B and 3, both of which have irregularities in vessel and surface patterns. We believe that the small number of typical LGDs in this study was responsible for the unsatisfactory diagnostic accuracy. As a result, the lack of typical LGDs and the exclusion of non-neoplastic lesions, in addition to the patients' background of UC, may have contributed to the low diagnostic accuracy. We have added a sentence addressing this issue to the discussion of study limitations (page 16, lines 374-375).

Comments from Reviewer #2

Thank you for your comments.

Thank you again. We hope you will consider these comments and revisions favorably.