

Manuscript No. 63080

The Evolving Roles of Magnifying Endoscopy and Endoscopic Resection for Neoplasia in Inflammatory Bowel Diseases

Reviewer #1:

Specific Comments to Authors: There are no figures or diagrams and tables insufficient, so the Manuscript seems boring to the readers in spite of the good data included.

Response: Thank you for the comment. This manuscript included Table 1, 2 and Figure 1, 2. We believe that these are sufficient to summarize the updated data regarding the utility of magnifying endoscopy and showed representative images of dysplasia in IBD.

Reviewer #2:

Specific Comments to Authors: Well written and organized mini-review that summarizes current literature on important topics: the utility of pit patterns or use of NBI to diagnose neoplastic lesions, as well as the feasibility and outcomes of endoscopic resection to remove these lesions in IBD patients. The only revision I will make refers to the "core tip" should be brief and stay focused on the purpose of this review.

Response: Thank you for this comment. We have shortened the core tip to focus on the purpose of this review as follows: Magnifying colonoscopies assessing Kudo's pit patterns or surface/vascular patterns with narrow band imaging are useful techniques to differentiate neoplasia from non-neoplastic lesions. Many investigations have demonstrated the diagnostic utility of magnifying scopes for neoplasia, as well as the feasibility and outcomes of their endoscopic resection in patients with inflammatory bowel disease. **We aim to review updated data regarding these important topics.**

Reviewer #3:

1. Specific Comments to Authors: This is a narrative review of magnifying endoscopy with chromoscopy or NBI in ulcerative colitis patients. It is important to change the title by replacing "...in inflammatory bowel diseases" for "...in ulcerative colitis" because all included studies are referred to UC patients. The same applies to other titles in "Utility of magnifying chromoendoscopy for IBD".

Response: Thank you for this suggestion. We cited some systematic review and meta-analyses assessing the feasibility and outcome of endoscopic resection for neoplastic lesions (e.g. references #28, #29). These studies include not only patients with ulcerative colitis but also those with Crohn's disease. So, we would like to use "inflammatory bowel diseases" in the title and the short running head.

2. Specific Comments to Authors: It is better to omit the observational study with reference number 9 because it includes a small number of lesions and it adds little value as it is presented between studies with higher accuracy like an RCT and a multicenter prospective study.

Response: We appreciate this comment. We transferred reference #9 to the following sentence as the new reference number (#8): Similar to non-IBD patients, neoplasia in IBD patients also show pit pattern types III_L, III_S, IV or V [7, 8]. Accordingly, we deleted the following sentence: An observational study assessing 15 neoplastic lesions (10 dysplasia and 5 early cancer) also showed that pit pattern types III_S to III_L or type IV were detected in these lesions, suggesting that close observation of pit patterns may be diagnostically useful for neoplasia in UC patients

3. Specific Comments to Authors: Later on, at the same chapter it is better to omit the

study with reference number 16 as it is too old to make a difference when discussing modern technology in image acquisition.

Response: Thank you for this comment. Reference #16 reviewed classical findings of dysplasia in IBD and was published in 1983. Many studies cited this pivotal dysplasia classification in IBD (More than 2000 articles cited this paper based on the Google Scholar). We think this important article should be cited.

4. **Specific Comments to Authors:** At the final sentence it is said that “high sensitivity to rule out neoplasia”. Sensitivity is used as a measure of the adequacy of a method to detect a lesion or condition and not as a tool to define absence of it. Probably is better to use the term NPV (negative predictive value).

Response: We appreciate this comment. Given that exams with high sensitivity have high NPV in general and not all studies included in this review article showed NPV and PPV, we used sensitivity instead of NPV.

5. **Specific Comments to Authors:** In the chapter of endocytoscopy, it is mentioned for the first time with reference no 26 the term of artificial intelligence. It would be better if a broader search for similar bibliography was added in this review.

Response: Thank you for this comment. As our original standpoints in this review, we would like to focus on the utility of magnifying endoscopy and endocytoscopy for neoplasia in IBD. We searched Pubmed using “artificial intelligence”, “dysplasia”, and “ulcerative colitis” and found only one case report (Maeda et al. *Endoscopy* 2021; 53: E273-E274), which suggests that AI may be a promising tool to detect dysplasia in ulcerative colitis. However, a recent review article discussing AI application in diagnostic GI endoscopy (Correia et al. *World J Gastroenterol* 2021; 27: 5351-5361) has already discussed this article. Thus, we think our review article should focus on other important issues regarding neoplastic lesions in IBD.

6. **Specific Comments to Authors:** A useful review needs not only to exhibit the published studies but also to provide insight and give reasonable explanations to the results and conclusions of the literature that is presented. Following this notion, it would be better to comment on the reasons and limitations that drive the low sensitivity and in some studies even low specificity of the magnifying chromoendoscopy as it is presented in table 1 causing a confusion regarding the real contribution of this method.

Response: Thank you for this comment. We concluded that Kudo’s pit patterns may have a high sensitivity to rule out neoplasia, but a limited utility to accurately diagnose neoplasia in IBD patients due to its low specificity. As we have already mentioned in the article, pit patterns type III_L and IV can be observed not only in the neoplastic lesions but also in the “regenerative mucosa” in UC patients. This is the reason why pit patterns III-V have high sensitivity and low specificity. To clarify our thoughts, we added the following sentence at the end of UTILITY OF MAGNIFYING CHROMOENDOSCOPY FOR IBD section: **Given that the regenerative mucosa can present pit patterns type III_L and IV and may decrease its specificity to diagnose neoplasia in IBD, it is suggested that providers must achieve mucosal healing prior to the scopes to overcome this disadvantage.**

7. **Specific Comments to Authors:** The same applies as to what reasons are responsible for the very low sensitivity of JNET classification of magnifying NBI in contrast to the more reliable Nishiyama classification.

Response: Thank you for this critic. We added the reference #19 to further discuss the capillary patterns (The Sano classification) of neoplastic lesions in IBD. Then,

we also revised the last paragraph in the section of UTILITY OF MAGNIFYING ENDOSCOPY WITH NBI FOR IBD to provide our insights as follows: Each study assessing the utility of magnifying endoscopy with NBI showed similar sensitivity and specificity for neoplastic lesions in UC, although the sensitivity of JNET type 3 was low. Hence, it is still unclear which of vascular or surface patterns of tumors are important to differentiate neoplasia and non-neoplastic lesions in UC. Given that each study only assessed the small number of UC-associated neoplasia, further investigations with larger sample sizes are warranted to better understand the characteristics of NBI findings of IBD-associated neoplasia and diagnostic accuracy of JNET classification as well as its limitations.

8. **Specific Comments to Authors:** At the end, it is prudent to have a language polishing.

Response: Thank you. The third author (JMS) is a native American GI doctor and he checked English expressions in this article.

Editorial Office Director:

Specific Comments to Authors: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: Thank you for these comments. We revised figure legends and tables, accordingly.