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Manuscript Type: Manuscript NO.: 74700, Clinical and Translational Research

Title: Non-Optical Polyp-Based Resect and Discard Strategy: A Prospective Study

RE: Response to Reviewers;

Dear Prof. Subrata Ghosh, Dr. Andrzej S Tarnawski

Editors-in-Chief,

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled " Non-Optical Polyp-Based Resect and Discard Strategy: A Prospective Study" to the World Journal of Gastroenterology. We appreciate the time and effort you and the reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the editors and reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect all the comments provided by the reviewers.

Please find our answers to the requested changes below.

Thank you for considering our manuscript for publication in your journal.

Sincerely,

Daniel von Renteln, M.D.

2021-11-28

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Reviewer					#1:
Scientific	Quality:	Grade	B	(Very	good)
Language	Quality:	Grade	A	(Priority	publishing)
Conclusion:		Minor			revision

Specific Comments to Authors: Manuscript titled “Non-Optical Polyp-Based and Discard Strategy: A Prospective Study” has been assessed for publishing on World Journal of Gastroenterology according to the journal rules. Authors conducted a prospective trial to determine whether a polyp based resect and discard strategy (PBRD) can reach the required quality benchmark and how it would perform compared to optical polyp diagnosis (OPB). Findings of manuscript are original because authors reported a high rate of surveillance agreement rate between PBRD and pathology based surveillance. Furthermore serious decrease in histopathological assessment will provide a cost benefit for all private insurance systems or government based health care systems. It is utmost importance to find a cheap and accessible way to prevent gastrointestinal tract cancer. Although screening with colonoscopy and screening with endoscopy -especially in East Asia- lowers the prevalence, incidence and mortality of these cancers, there is still way to go. So this study is another confirmation of screening colonoscopy is important and try to find an answer regarding which strategy to use when we find polyp during colonoscopy. I think the manuscript made valuable contributions regarding the colon cancer screening so it can be published after minor revisions. Comments are listed at the bottom.

1) High grade dysplasia is not a separate pathologic type. Dysplasia is usually reported with polyp pathologic type. For example, “tubulovillous adenoma and low grade dysplasia” or “Villous adenoma and high grade dysplasia”. Authors reported that 1.4% of polyps were “high grade dysplasia”. When all other pathologic types were summed the total rate was % 100 but it is misunderstood that high grade dysplasia is another pathologic type from Table 2. I think this must be corrected. Author can present this data in a separate section in Table 2.

Answer: Thank you very much for bringing this point into our attention. We made the correction in Table 2 on page 24-25.

2) When they used the PBRD strategy used by endoscopist according to 2012, agreement rate was 76%. The rate is not very high that can be recommended for clinical practice. Authors made a statement that this approach is a safe approach that can be easily applied in clinical practice by endoscopists but I think this statement cannot be made until it is approved. 98% agreement rate is the rate of

post hoc analysis. In clinical practice; this post hoc analyse approach is impossible so I think authors must change the statement as “may” and suggest further studies using this approach that they create

Answer: Thank you for your comment. We agree that the PBRD strategy is a safe approach and the results of the post-hoc analysis is likely to be producible, but its implementation in routine practice must be tested through further research in real-time practice. Therefore, we changed the main text as follow:

1. Page 14, lines 172-178:

As our adaptation of the PBRD strategy to reflect the updated 2020 USMSTF guideline resulted in a significantly higher agreement compared with the 2012-based PBRD model (98.0% [95% CI, 0.97–0.99] vs. 90.7% [95% CI, 0.89–0.92]; $P < 0.0001$), we believe that the PBRD strategy may be a safe alternative that can be easily applied by endoscopists pending further research confirming efficacy in real-time endoscopic practice, and Gastroenterology society endorsements.

2. Page 17, line 232-233:

Therefore, the PBRD strategy may be a feasible alternative to resect and discard that can be used without specialized equipment, training, or optical diagnosis skills. 3) I suggest authors to change the figure legend. They may change Figure 3A as Figure 3 and Figure 3B as Figure 4 because two figures are exactly different from each other.

Answer: Thank you for your suggestion. We revised the figure legends as suggested and changed Figure 3, panel A to figure 3, and Figure 3, panel B to Figure 4.

4) What is the benefit of same day surveillance recommendation instead of pathology based surveillance recommendation? Cost benefits regarding the decreased histopathologic assessment is the target but I think there is no benefit other than patient satisfaction because patient do not have to wait the pathology results. Of course it will be very valuable outcome when patient oriented approach is considered but authors may discuss this issue except the cost benefit.

Answer: Thank you for your comment. The review of the root cause of the post-colonoscopy colorectal cancer (PCCRCs) shows that the majority of PCCRCs (70%–90%) are attributable to potentially avoidable human factors. We believe that these administrative or decision-making errors can be augmented if the appropriate surveillance interval for next colonoscopy examination is not communicated well during the same session with patients. For example, endoscopists may forget unresected lesions left in situ, and consequently,

consider the colonoscopy as normal and assign a longer surveillance interval or even may not schedule a repeat colonoscopy. Therefore, the proportion of surveillance examinations not being done in due time would be increased rendering to an increase to interval and non-interval cancers. As suggested, and to address this point, we modified the main text as follow:

Page 14-15, lines 180-188:

A significant proportion of post-colonoscopy colorectal cancers (PCCRCs) are due to administrative or decision-making errors.²⁹ Fail-safe mechanisms are therefore needed to ensure the assignment of an appropriate surveillance interval during the index session for follow-up examination. For instance, histopathology might not be followed up adequately, or patients might fail to receive their surveillance interval after pathology results are available. This would exacerbate loss to follow-up and increase the chance of PCCRC. The PBRD strategy could offer a simple solution for endoscopists to communicate the appropriate time for the next surveillance colonoscopy without requiring histopathology evaluation.

Reviewer					#2:
Scientific	Quality:		Grade	C	(Good)
Language	Quality:	Grade	B	(Minor	language polishing)
Conclusion: Minor revision					

Specific Comments to Authors: This prospective study aimed to test the polyp-based strategy using polyp size and number to assign the next surveillance interval for small polyps (<10 mm). This is an interesting study and the results can be applied to routine clinical practice. Please see the below questions/comments

1. How did the authors select the polyps to include in the Polyp-Based Resect and Discard Strategy, and which ones to include in the Optical Diagnosis-Based? This information can be added to the supplementary Figure 1.

Answer: Thank you for your comment. The inclusion and exclusion criteria were explained in page 8, Method, lines 26-36. As shown in supplementary figure 1., we excluded all patients with missing histopathology evaluation, missing determination of surveillance intervals by PBRD strategy, and missing in bowel preparation data. All exclusion criteria was explained in supplementary figure 1.

2. The confidence level in the optical diagnosis may contribute to the endoscopists' judgment in the surveillance interval assignment. The authors should report and discuss the level of confidence (low and high) of optical diagnosis.

Answer: thank you for your comment. In this study, 648 (69.5%) of polyps received a high-confidence optical prediction of the histology by the endoscopists (Table 2). We modified the text as follow:

Page 12, line 122-123:

A total of 842 (90.2%) polyps ≤ 10 mm were optically diagnosed using NICE; of those, 648 (69.5%) were classified with high confidence (Table 2).

Page 14, lines 166-170:

In our study, 70% of polyps were optically classified with high confidence, similar to the rates reported by other studies.^{27,28} Increasing the rate of high-confidence optical diagnosis would contribute to the acceptance of this technique in routine endoscopic practice, particularly for non-academic endoscopists.

3. Even though the incidence of malignancy is low in small polyps, it would be helpful to provide the data of malignant or advanced adenoma detected on pathology as advanced histology affects the surveillance intervals and management.

Answer: thank you for pointing this out. In the modified PBRD strategy based on the 2020 guideline, the determination of the next surveillance interval is based on the number and size of the detected polyps. We found that 5.4% of detected colorectal lesions had advanced pathology, including adenomas with villous and high-grade dysplasia components (Table 2). We found that none of the patients that could have received shorter surveillance interval by post-hoc model of PBRD strategy had a polyp with advanced histology. We also found that only 3/145 patients that could have received shorter surveillance intervals by endoscopists had polyps with advanced histology. Based on your suggestion, we modified the text as follow:

Page 12, lines 116-118:

None of the patients that should have received shorter surveillance intervals through the post-hoc PBRD model had a polyp with advanced histology. Only 3/145 patients that should have been assigned to shorter surveillance intervals by endoscopists had polyps with advanced histology.

4. Does the location of the polyps (right side vs. left side) affect the decision to apply the PBRD strategy?

Answer: Thank you for your comment. No, only the size and number of polyps, bowel preparation level and family history of CRC are included in the Criteria of the PBRD strategy (Table 1).

5. The macroscopic and microscopic diagnosis of sessile serrated adenoma/polyp can be challenging. Despite the WASP classification, the diagnostic dilemma remains due to the variations of polyp morphology. Which characteristics does the author use for diagnosing sessile serrated adenoma/polyp?

Answer: Thank you very much for bringing this point into our attention. The participating endoscopists in our study optically classified polyps as neoplastic and non-neoplastic and did not classify polyps as sessile serrated lesions. We corrected the data in Table 1.

6. The authors proposed that it might be beneficial to limit the use of the PBRD strategy to diminutive polyps only, which would reduce the risk of assigning polyps with high-grade dysplasia or serrated adenomas to longer surveillance intervals, as advanced pathology occurs more frequently in polyps of 6–9 mm than in those of 1–5 mm. Have the authors performed subgroup analysis to compare the benefit of PBRD in polyps of 1–5 mm in size vs. those of 6–9 mm in size?

Answer: Thank you for your comment. In this study, we did not perform a sub-analysis for those patients with small polyps because the PBRD strategy consider both diminutive and small polyps, meaning if a patient has more than 2 small polyps, the next surveillance interval must be determined based on the results of the histopathology examinations.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

Please ask the authors to revise.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Answer: Thank you. We have revised the text attentively for the scientific language.

(2) *Company editor-in-chief:*

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, 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. 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. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the

author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Answer: Thank you for your valuable comments. We have revised the manuscript accordingly and provided the figures as a single PPT file. All figures are original and has been created and conformed by the first authors and all authors of the manuscript, respectively. We appreciate the invaluable comments of the editors and reviewers and thank you for considering our manuscript for being published in your journal.