February 6, 2014

Title: Laterally Spreading Tumors: Limitations of CT Colonography
ESPS Manuscript NO: 7990

Dear Editor,

Please find enclosed the edited manuscript in MS Word format (file name: 7990-edited.doc). The manuscript has been improved according to the suggestions of reviewers:

1. The format has been updated
2. Revisions have been made according to the suggestions of the reviewers. The details of the revisions are shown in the attached pages.
3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely,

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Reviewer No. 504766

Q1: *Abstract 1. Aim and Conclusion: It is recommend changing the term "sensitivity" to "detection rate". Authors use the term "detection rate" in keywords,*
A1: I appreciate your valuable comment. According to your recommendation, I changed "sensitivity" to "detection rate"

Q2: *Results (P8), and Table 2. 2. Aim: Authors should stress prospective method. Because this is strength of this study.*
A2: I accepted the Reviewers' suggestions. I have now emphasized that this is a prospective study throughout the manuscript.

Q3: *Discussion 3. No control group can be cause information bias. It is necessary to mention this important point as limitation.*
A3: Thank you so much for valuable comment. As pointed out by the Reviewer, this is one of the weak points in this manuscript. We added the following sentences to the Discussion section.

"It is also acknowledged that there is no appropriate control group for this study. Consequently, sensitivity as well as specificity cannot be calculated based on the study data."

Q4: *Fecal tagging is essential technique for bowel preparation in screening CTC. Need to discuss the lack of fecal tagging as study limitation.*
A4: I appreciate this critical suggestion raised by the Reviewer. Nowadays, fecal tagging is an essential technique to identify more adenomas in screening CTC, as pointed out by the Reviewer. I completely agree with this opinion. In this study, however, optical colonoscopy was performed just prior to the CTC investigation in all patients. Instead of using fecal tagging, we were able to cleanse the mucosal surface with washing and aspirate nearly all of the liquid in the lumen, particularly in the area where the target LST existed. This real cleansing may provide a better image than electric cleansing by fecal tagging. We discussed this issue in the final paragraph of the Discussion section.

Q5: *Last paragraph: Please change the term "sensitivity" to "detection rate".*
A5: As the reviewer mentioned, "sensitivity" might be equivocal. We replaced "sensitivity" with "detection rate" in the entire manuscript.

Q6: *References 6. References 14-16: Reference numbers seem to be incorrect. The sentence "A previous report using a computer-aided diagnosis system showed that the detection rate for flat T1 cancers is 83.3% [14]." seems to cite [15]. The sentence "According to the latest report, novice CTC readers obtained sensitivity equal to that of experienced readers after practicing an average of 164 CTC studies[15]. " seems to cite [16].*
A6: I very much appreciate the correction made by the Reviewer. The manuscript is revised according to all of these suggestions. In addition, other incorrect citations have now been corrected.

Q7. *Reference [15] (Eur Radiol 2008;18:1666-73.) This is inappropriate for citation because the study participants were preoperative cases. I recommend exchanging this to another paper (ex. Park SH, et al. Sensitivity of CT colonography for nonpolypoid colorectal lesions interpreted by human readers and with computer-aided detection. AJR Am J Roentgenol 2009;193:70-8.).*
A7: I appreciate the valuable comments. Reference 16 is the correct citation, and we added the reference

as recommended by the reviewer.

Q8: *Figures 8. Figures 1-3: Please add MPR images in each lesion. It would be more informatics and easy to understanding for readers.*
A7: **A19**: I appreciate this valuable comment. This suggestion definitely reinforces the manuscript. Corresponding MPR or axial images were added as Figure 1C, Figure 2C and Figure 3C.

Reviewer 2 (No. 69608)
Q9: *Page 6 line 7: please indicate slice width (there is only reconstruction interval), and if possible pitch and tube rotation time.*
A9: I appreciate the valuable comments. This suggestion reinforces the manuscript. The information suggested by the reviewer is now added to the Methods section. The slice width was 1.2 mm and pitch was 0.9.

Q10: *Page 6 line 11, please specify who instructed the two radiologists and his experience in CTC reading. Indicate whether the 100 training cases were endoscopically verified or not.*
A10: I appreciate these critical comments. The second author (KU) who is an expert in the field of CT colonography instructed both examiners for the two days, and subsequently two examiners performed at least 100 CTC readings. According to a well-known ACRIN trial, each participating radiologist was required to submit confirmation of having interpreted at least 500 CT colonographic examinations or having participated in a specialized 1.5-day training session on CT colonography. Our education program for CTC reading was somewhat less than this, but considered adequate. We have now clarified who instructed CTC reading in the Methods section. Furthermore, we deleted the following sentences from the discussion, as our education program is somewhat different.
"However, the results from novice readers were almost consistent with those by an expert reader (data not shown). A different decision was made in only one case."

Q11: *Page 6 line 15: was 2D reading used only for problem solving or to examine the whole colon after 3D reading? If 2D reading was used only for problem solving, this could be a limitation of the study, because flat lesions are often better depicted on 2D images than on 3D. If this is the case, then the issue should be mentioned in "Discussion"*
A11: I appreciate the valuable comments. We agree with the reviewer's comment that flat lesions could be identified on 2D images alone. In CTC reading with the primary three-dimensional search method, 3D images as well as 2D images are always used, and we applied the primary three-dimensional search method in the present study. To more clearly emphasize the primary three-dimensional search method, we added "initially".

Q12: *Page 8: examples of lesions are redundantly described both in manuscript text and figure legends*
A12: We appreciate the valuable comment. As pointed out by the reviewer, this description was redundant. We have removed this redundant description.

Q13: Page 8: it could be of interest to mention the number of false positive LSTs reported by the two CTC readers.
A13: I appreciate the valuable comments. Unfortunately, the data on "false positives" are not available

because we did not have a control group where patients did not have any LSTs. We agree that the present study would be more informative if a control group was set at the start of the study. In the future, we would like to conduct a study to calculate sensitivity as well as specificity. The lack of a control group is acknowledged in the Discussion section.

Q14: *Page 9 line 15: "Given that a flat morphology was defined as a broad-based lesion with a height of less than one half of its width [11]". Reference 11 seems inappropriate, as it does not contain that definition.*
A14: We apologize for incorrect citations. Reference 12 is the correct citation. We replaced reference number 11 with 12. We have checked and verified all references.

Q15: *Page 10: References 14, 15 and 16 seem to be cited in the wrong place in the text.*
A15: We apologize for incorrect citations. These have been corrected.

Q16*: Page 10, line 15. Data regarding the experienced reader performance should not be discussed unless they are fully presented in the paper.*
A16: We appreciate the valuable comment. We did not demonstrate data on expert (KU) reading in the Results section. As pointed out by the reviewer, we should therefore not mention expert reading. We deleted the following sentences from the paragraph.
"However, the results from novice readers were almost consistent with those by an expert reader (data not shown). A different decision was made in only one case."

Q17: *Page 10: Currently, faecal tagging is mandatory for CTC bowel preparation. In the study CTCs were performed without tagging. This limitation must be clearly stated.*
A17: I appreciate the critical suggestion raised by the reviewer. Nowadays, fecal tagging is a mandatory technique to identify more adenomas in screening CTC, as pointed out by the reviewer. I completely agree with this opinion. In this study, however, optical colonoscopy was performed just prior to the CTC investigation in all patients. Instead of using fecal tagging, we were able to cleanse the mucosal surface with washing and suck nearly all liquid in the lumen, particularly in the area where the target LST existed. This real cleansing may provide a better image than electric cleansing by fecal tagging. We discussed this issue in the final paragraph of the Discussion section.

Q18: *Page 10: "Bowel preparation was excellent for all patients…" How did you evaluate it? Mention it in the Result section.*
A18: I appreciate the valuable comment. As the reviewer pointed out, a description of bowel preparation was lacking in the Results section. We added "Bowel preparation was excellent for all patients" into the first part of the Results section.

Q19: *Figures: 2D axial or MPR CTC images of the lesions could be added*
A19: I appreciate the valuable comments. This suggestion reinforces the manuscript. Corresponding MPR or axial images were added as Figure 1C, Figure 2C and Figure 3C.