Author's response to reviews

Title: Evaluation of dual-wavelength excitation autofluorescence imaging of colorectal tumours with a high-sensitivity CMOS imager: a cross-sectional study

Authors:

Yoko Kominami (kominami@hiroshima-u.ac.jp)
Shigeto Yoshida (yoshida7@hiroshima-u.ac.jp)
Shinji Tanaka (colon@hiroshima-u.ac.jp)
Rie Miyaki (miyaki@hosp.city.hiroshima.med.or.jp)
Yoji Sanomura (y-sanomura@hiroshima-u.ac.jp)
Min-Woong Seo (mwseo@idl.rie.shizuoka.ac.jp)
Keiichiro Kagawa (kagawa@idl.rie.shizuoka.ac.jp)
Shojo Kawahito (kawahito@idl.rie.shizuoka.ac.jp)
Hidenobu Arimoto (arimoto-h@aist.go.jp)
Kenji Yamada (k-yamada@sahs.med.osaka-u.ac.jp)
Kazuaki Chayama (chayama@hiroshima-u.ac.jp)

Version: 2
Date: 30 June 2015

Author's response to reviews: see over
June 30, 2015

Prof. Maqdalena Morawska, MD

Executive Editor, BMC Gastroenterology

Dear Prof. Maqdalena:

Thank you very much for the careful review of our manuscript entitled "Evaluation of dual-wavelength excitation autofluorescence imaging of colorectal tumours with a high-sensitivity CMOS imager" by Y. Kominami et al. The manuscript has been carefully rechecked and appropriate changes have been made in accordance with the reviewers’ suggestions.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a more balanced and better account of the research. We hope that the revised manuscript is now suitable for publication in your journal.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Yoko Kominami, M.D.

Please address correspondence to
Shigeto Yoshida, M.D., Ph.D.
Department of Endoscopy and Medicine
Hiroshima University
1-2-3 Kasumi, Minami-ku
Hiroshima 734-8551, Japan
Tel: +81-82-257-5939
Fax: +81-82-257-5939
E-mail: yoshida7@hiroshima-u.ac.jp
Evaluation of dual-wavelength excitation autofluorescence imaging of colorectal tumours with a high-sensitivity CMOS imager: a cross-sectional study

[MS: 1873254520161665]

Yoko Kominami

Replies to reviewer

Responses to the Reviewer: Dr. Zhen Tian’s Comments

Major compulsory revisions:

I have two major concerns. One is about the efficacy gain of this dual-wavelength excitation autofluorescence imaging method. The other is about the reliability of the findings.

For my first concern: the authors claim that the big disadvantage of the AFI method is its high false-positive rate and low specificity of 35%. 15-32% of colorectal adenomas were missed by colonoscopy. That’s the major motivation for the authors to develop a new imager and propose to use dual wavelength excitation method. While, in their results, 86.2% of the Adenoma/M-ca ratio images were considered as high signal group. Compared to the 15% value mentioned above for AFI, the new method doesn’t show much improvement in sensitivity (true positive rate). On the other hand, the authors didn’t do any experiments and analysis on the false positive rate and true negative rate for the new method. Without these values, I cannot reach the conclusion that the new method outperforms the AFI method in order to justify the relevance of this manuscript.

Reply: Our results indicate that autofluorescence imaging may be able to detect SSA/P and adenoma and adenocarcinoma, and differentiate these neoplasms from hyperplastic
polyps. Our findings also suggest that this system could be useful to image tumours directly, and for the clinical detection of colorectal tumours. However, our study was an ex vivo study, and we did not evaluate the clinical utility of endoscopic imaging for the detection and differentiation of colonic polyps.

According to the reviewer's helpful suggestion, we added the following to the Discussion:

“However, there was a limitation to this study in that it was performed ex vivo; thus, we did not evaluate the clinical utility of endoscopic imaging for detection and differentiation of colonic polyps. Further in vivo studies should be performed when our dual-wavelength excitation autofluorescence endoscopy technique, which operators can easily perform in real-time, is developed.”

[revised manuscript: page 9, lines 205-209]

For my second concern: The ratio images were categorized into high signal images and no signal images by only one gastroenterologist. What’s the intensity threshold the gastroenterologist used to differentiate the high signal images and no signal images? Whether a very different category result may be achieved by another gastroenterologist? If a similar result cannot be repeated by another gastroenterologist, then the analysis and conclusion based on this result is not reliable.

Reply: According to the reviewer's helpful suggestion, we added the following sentences to the Methods: “Interobserver agreement

Another gastroenterologist categorized the same ratio images as high-signal group and no-signal group. Interobserver agreement between the two gastroenterologists was then analysed to determine kappa values” and “The interobserver agreement of the
classification of the ratio images, i.e., the agreement between two gastroenterologists, was tested using the kappa statistic.”

[revised manuscript: page 6, lines 136-139, 141,142]

In addition, we added the following to the Results: “Regarding the interobserver variability of the ratio images, the kappa value between two gastroenterologists was 0.902, and the agreement was excellent.”

[revised manuscript: page 7, lines 160,161]

In addition, we added the following to the Discussion: “The interobserver agreement of the classification of the ratio images could be an issue; however, in our classification, excellent agreement was observed, with high kappa values.”

[revised manuscript: page 9, lines 203-205]

**Minor essential revisions:**

Line 157: “Clinicians are able image colorectal lesions in detail”. There should be a grammar mistake. Consider revising this sentence.

Reply: Thank you very much for this suggestion. In response to the reviewer’s comment, we had the entire manuscript checked by a native speaker again and we revised the sentence in the Discussion:

Original: “With the development of endoscopy, clinicians are able image colorectal lesions in detail, including microscopic changes; however, this level of sensitivity relies on the skill and experience of the operator.”
Revision: “With the development of endoscopy, clinicians are able to image colorectal lesions in detail, including microscopic changes; however, the level of sensitivity relies on the skill and experience of the operator.”

[revised manuscript: page 7, lines 166-168]

Line 200: “can be emitted light using ...” should be “can emit light ...”

Reply: Thank you very much for the reviewer’s suggestion. In response to the reviewer’s comment also, we had the entire manuscript checked by a native speaker again and we revised the sentence in the Discussion:

Original: “In our study, both adenoma/M-ca and SSA/P colorectal tumours can be emitted light using the dual-wavelength excitation method, which suggests that inexperienced operators can easily identify lesions using this technique without oversight.”

Revision: “In our study, both adenoma and adenocarcinoma and SSA/Ps can emit light using the dual-wavelength excitation method, which suggests that inexperienced operators can easily identify lesions using this technique without oversight.”

[revised manuscript: page 9, lines 215-217]

Responses to the Reviewer: Dr. Elena V Filonenko’s Comments

Reviewer's report:

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct).
The manuscript is dedicated to evaluation of dual-wavelength excitation autofluorescence imaging of colorectal tumours with a high-sensitivity CMOS imager.

I have issues I would like addressed:

1. 34 and further as the text goes. In order to facilitate comprehension of the work the group of lesions should be renamed: adenoma/M-ca into adenoma+M-ca or adenoma and M-ca, SSA/Ps into SSA+Ps or SSA and Ps.
   
   Reply: According to the reviewer's kind suggestion, we renamed the group of lesions adenoma/M-ca to adenoma and adenocarcinoma. However, Sessile serrated adenoma is abbreviated as SSA/P in the Japanese classification of colorectal cancer established by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). If possible, we would like to continue to indicate sessile serrated adenoma and sessile serrated polyp as SSA/P.

2. 34 vs 91 and further as the text goes. In the text both “Ps” and “P” are used, one variant should be chosen.

   Reply: SSA/P means sessile serrated adenoma and sessile serrated polyp.

   In line 34, SSA/Ps used as a plural form of sessile serrated adenoma/polyp, and in line 91, specimens of SSA/P used as a plural form of specimen of SSA/P. If possible, we would like to continue to use this term.

3. 36-37. The specimens were irradiated with excitation light at 365 nm and 405 nm, and autofluorescence images were obtained using a new, high-sensitivity CMOS imager. It is
necessary to represent the wavelength in which autofluorescence registration was performed using high-sensitivity CMOS imager.

Reply: According to the reviewer’s suggestion, we revised the following sentence in the Abstract.

Original: “The specimens were irradiated with excitation light at 365 nm and 405 nm, and autofluorescence images were obtained using a new, high-sensitivity CMOS imager.”

Revision: “The specimens were irradiated with excitation light at 365 nm and 405 nm, and autofluorescence images measured with a 475 ± 25-nm band pass filter were obtained using a new, high-sensitivity CMOS imager.”

[Revised manuscript: page 2, lines 35-37]

4. 91. The sentence should be written as “adenocarcinoma (M-ca), adenoma, and sessile serrated adenoma (SSA), polyp (P) specimens”.

Reply: According to the reviewer's kind suggestion, we renamed the group of lesions adenoma/M-ca into adenoma and adenocarcinoma. However, sessile serrated adenoma is abbreviated as SSA/P in the Japanese classification of colorectal cancer established by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). If possible, we would like to continue indicating sessile serrated adenoma and polyps as SSA/P.

5. 101. The study included 98 patients. However, authors indicated that there were 64 men and 36 women, (n=100)

Reply: Thank you very much for your suggestion. We made a mistake about the number of patients. According to the reviewer’s suggestion, we revised the following sentence in the Methods.
Original: “The patients were treated at Hiroshima University Hospital between October 2012 and March 2014, and included 64 men and 36 women aged 65.1 ± 11.3 years (mean ± standard deviation [SD]).”

Revision: “The patients were treated at Hiroshima University Hospital between October 2012 and March 2014, and included 62 men and 36 women aged 65.1 ± 11.3 years (mean ± standard deviation [SD]).”

[Revised manuscript: page 5, lines 102-104]

6. 171. There is misspelling: “u” in the word “florescence” is missed.

Reply: Thank you very much for your suggestion. In response to this comment, we had the entire manuscript checked by a native English speaker again.

[revised manuscript: page 8, lines 181]

7. 220. Literature older than 5 year is 75,7% of given references, thus do not reflect the reality of modern colon cancer diagnosis (inc. fluorescence diagnosis), and given statistics may not correspond to up-to-date situation.

Reply: Thank you for your kind suggestion. We added references less than 5 years old:

[references: 9, 10 and 11]