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June 25, 2013

Dear Dr. Jin-Lei Wang,
Director, Editorial Office
Baishideng Publishing Group Co., Limited

Please find enclosed the edited manuscript in Word format (file name: 2484-review.doc)

Title: Simultaneous follow-up of mouse colon lesions by colonoscopy and endoluminal ultrasound biomicroscopy

Author: Rossana C. Soletti, Kelly Z. Alves, Marcelo A. P. de Britto, Dyanna G. de Matos, Mônica Soldan, Helena L. Borges, João C. Machado

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2484

We have revised the manuscript entitled "In vivo endoluminal ultrasound biomicroscopic imaging in a mouse model of colorectal cancer". The changes incorporate the reviewers' suggestions. We found the comments very helpful and constructive. Most of the comments are implemented in the modified manuscript and an explanation how they were incorporated, or not, follows after each reviewer's detailed comment and are typed in italic.

Reviewer comments:
In this manuscript, the authors describe the evaluation of the potential use of colonoscopy and endoluminal ultrasonic biomicroscopy (eUBM) to track the progression of mouse colonic lesions. This is a clinically very interesting study. However, the study has some limitations, which should be addressed by the authors.

1. The authors described 'At the first eUBM exam, a small elevation in the mucosa layer is seen, indicating an early adenoma. At this time, colonoscopy

Programa de Engenharia Biomédica – COPPE
Universidade Federal do Rio de Janeiro
Av Horácio Macedo 2030
Centro de Tecnologia, Bloco H, Sala H327
Cidade Universitária
21941-914 – Rio de Janeiro – RJ
☎ (+55-21) 2562-8630/8629 – FAX (+55-21) 2562-8591 – secretaria@peb.ufrj.br

Endereço Postal
Caixa Postal 68510
21941-972 – Rio de Janeiro – RJ

was unable to visualize the lesion. Six weeks later, eUBM showed that the adenoma had increased in size, and the lesion was then observed in the colonoscopic image. in results. Recently, the colonoscope which is commonly used is a high-resolution scope. I think that you used bronchofiberscope for the reason that was not detected with a colonoscopy. So you should describe it in limitation.

The small elevation in the mucosa layer observed with eUBM and registered in Figure 3 was not detected by colonoscopy. Perhaps, this fact was due to the poor bronchofiberscope image quality and could be overcome with high-resolution scopes designed specifically for work with rat and mouse models of colonic diseases (Olson and Halberg, 2011). These high-resolution scopes are usually rigid telescopes and a working channel is formed in a space between an operating sheath and the telescope external wall. Although the bronchofiberscope used in the present work is unable to produce high-resolution images, it has the advantage of being flexible. According to the authors' experience, this facility of the bronchofiberscope is important to position the eUBM mini-probe tip close to a lesion, which improves the lesion visualization, or at the center of the colon lumen in order to generate circular eUBM images of the colon.

2. In this study, the authors distinguished tumor and non-tumor by change over time without performing a biopsy. If we perform a biopsy or use NBI system, we can distinguish it instantly. How do you think about this procedure to have by a diagnosis for weeks? So you should describe it in discussion.

The potential of the eUBM technique to differentiate malignant from non-malignant lesions is yet to be implemented. Nowadays, the technique of narrow band imaging (NBI) has the capacity to diagnose colon lesion malignancy in real time based in mucosal and superficial vascular structures imaging enhancement (Lee and Enns, 2009). However, eUBM has the potential to detect lesion penetration depth through submucosal layers. Both methodologies have their advantages and limitations and could be performed simultaneously to complement each other.

3. The authors described eUBM is useful for CRC screening. The mice bowel lumen is small, but a human is wide. Do you think to a really bowel luminal wide human effectively?

The authors agree that the eUBM technique may also be used in human CRC screening, as long as dimensional scale corrections of ultrasound probe and frequencies are made considering the size proportions between humans and mice.

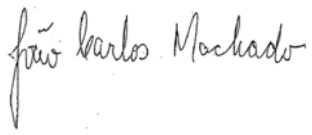
4. Do you think that it is useful about not only the pedunculated lesion but also flat or depressed lesion?
The present work results confirm the eUBM capacity to detect depressed lesions, as depicted in Figure 2B. In addition, the authors have already detected flat lesions in animal models of CRC and current work is being conducted using p53 knockout mice, which develop flat lesions with a higher incidence than wild type mice (Chang et al., 2007), to evaluate the method sensitivity.

Minor
1. The authors described 'Colonoscopy identified all colonic tumors but failed to diagnose lymphoid infiltrates and increased mucosal thickness and failed to differentiate lymphoid infiltrates from small adenomas.' in results. In Table 2, L2-7 is not checked in colonoscopy.
Lesion L2-7 was not checked because colonoscopy was unable to detect the lesion due to colonic hemorrhage or faeces. Instead, we checked in "Obs", which is described in table legend as "impossible to analyze due to colonic hemorrhage or faeces".

2. In Table 2, the lesion of animal 10 is L1-11. I think it is L1-10.
Yes, we corrected "L1-11" to "L1-10".

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

Sincerely yours,



Prof. Dr. João Carlos Machado, PhD
Biomedical Engineering Program – UFRJ
Universidade Federal do Rio de Janeiro
Av. Horácio de Macedo, 2030, sala 327
Ilha do Fundão
Rio de Janeiro, RJ, Brazil
21941-972
E-mail: jcm@peb.ufrj.br