Author's response to reviews

Title: Malignant transformation of oral potentially malignant disorders: a retrospective cohort study

Authors:

Pei-Shan Ho (psho@kmu.edu.tw)
Yi-Hsin Yang (yihsya@kmu.edu.tw)
Pai-Li Chen (scalpel58@seed.net.tw)
Saman Warnakulasuriya (s.warne@kcl.ac.uk)
Tien-Yu Shieh (tiyush@kmu.edu.tw)
Yun-Kwan Chen (yukkwa@kmu.edu.tw)
Chung-Ho Chen (chench@kmu.edu.tw)
I-Yueh Huang (iyuhu@kmu.edu.tw)

Version: 5 Date: 1 April 2009

Author's response to reviews: see over
Title: Malignant transformation of oral potentially malignant disorders: a retrospective cohort study

Reviewer: Meir Gorsky

1. **Too many authors for such study**
   Ans: This paper is a cross disciplinary study. All involved in planning, clinical research and manuscript writing were included. Their individual roles are stated at the end of the manuscript.

2. **Generally too old references**
   Ans: Thank you for your advice, we have added some recent references to the revised paper.

3. **Poor English editing**
   Ans: The paper has been re-checked and edited.

**Background**

4. **I suggest that the authors should refer to newer studies for their references.**
   Ans: Thank you for your advice, and we have added some new references in the revision.

5. **Ref. 14 refers to Oral Lichen Planus rather than to Oral Submucous Fibrosis.**
   Ans: We are deeply sorry, because miss-link of Endnote software caused some error in the reference. Now we have corrected it on page 4.

6. **Ref. 16 is incorrect.**
   Ans: Thank you, we have corrected the miss-link of Endnote software.

7. **Studies referred to as 6,7 are not Lumerman’s.**
   Ans: Thank you, we have corrected it on page 4.

8. **In the second paragraph ref. do not refer to Napier and Speight.**
   Ans: Thank you, we have corrected it on page 4.

9. **“The Aim….” Why OPMD’S twice?**
   Ans: Thank you, we have corrected it on page 5.

Materials
10. Leukoplakia is a clinical term prior to performing histological examination. Therefore, it is wrong using the term “leukoplakia with dysplasia”. A better term would be “dysplastic hyperkeratosis”, clinical white lesion diagnosed as dysplasia” or some thing similar.

Ans: Thank you for your suggestion. Now in the whole paper, we have replaced “leukoplakia without dysplasia” with “hyperkeratosis or epithelial hyperplasia” and replaced “leukoplakia with dysplasia” with “epithelial dysplasia”.

11. Wrong way of citing papers in the reference.

Ans: Thank you, we have corrected it.

Results

12. Follow up of 38 months seems too short since transformation leukoplakia may take over mean of 7 years. (Ref. 4)

Ans: From the Kaplan-Meier curve we found that the majority of these malignancies happened in about 24-36 months after the OPMDs were diagnosed. We agree a long follow up period is desirable but data available so far we believe is worth reporting.

13. No need to repeat Table 1 in the text.

Ans: Thank you, we have corrected it on page13.

14. I suggest to start table 2 with “malignant transformation” and than “rate of transformation”.

Ans: Thank you, we have corrected it on page18.

Discussion

15. Poor discussion.

Ans: Thank you for your advice, we have added some additional points to the discussion section from page10 to page13.

16. Ref. 4 is not Schepman’s study, Ref. 21 is not Bouquot’s.

Ans: Thank you, we have corrected it on page10.
MATERIAL AND METHODS

• One very important detail that is missing in this section is whether the study has a retrospective or prospective design, i.e. did the Authors collected data before or after planning the study?

Ans: This study is a hospital-based follow-up study. All the information was collected from existing clinic records. All exposure information of our study subjects were recorded prospectively but follow up data was retrospective. This is clearly stated.

• More detail should be provided regarding the selection of the group. Authors clearly indicated inclusion and exclusion criteria, but it is not clear whether all subjects seen at the Kaohsiung clinic in the period considered were included in the study group or if they undergo any selection. This is particularly important in view of the sex distribution that seems to indicate some kind of selection bias.

Ans: All subjects with OPMDs attending the oral and maxillofacial surgery clinic at Kaohsiung Medical University Hospital during the period were included. This is stated.

The exclusion criteria were as follows and clearly stated in methods:

1. The patients with OPMDs who had not been followed-up for more than 6 months
2. Those patients who had any sites of cancer before the diagnosis of OPMDs.
3. The patients who were ever diagnosed as oral precancer and received medical therapy.
4. The duration from OPMDs to oral cancer was less than 6 months.

More detailed information about the selection criteria is described in the methodology section on page 6 of the paper.

• Authors should give more information on verrucous hyperplasia, as readers can be unfamiliar with such a recently described lesion

Ans: Verrucous hyperplasia is a common OPMD in Taiwan. and in Yu’s paper in 2008, the histological criteria for a diagnosis of OVH were: (1) epithelial hyperplasia with parakeratosis or hyperkeratosis and verrucous surface, and (2) no invasion of the hyperplastic epithelium into the lamina propria as compared to adjacent normal mucosal epithelium.
More detailed information about the case selection criteria has been described in the methodology section on page 6 of the paper.

- In Chung et al. 2005 no clear diagnostic criteria for the diagnosis of verrucous hyperplasia are defined, apart from affecting areca chewers. More detail on the diagnosis of such lesions are needed.

  Ans: We cited Chung’s paper in 2005 is to provide a reference about this OPMD but we agree his was based on clinical diagnosis. We have therefore removed this reference from the methods and materials section, and added a new reference (Yu et al) that states the diagnosis criteria of VH. More detailed information about the diagnostic criteria of verrucous hyperplasia has been provided in the methodology section on page 6 of the paper.

- a major problem of the present report is the absence of any information about treatment. What happened to this group of patients in the period described? Did they under any form of treatment? Did treatment affect outcome?

  Ans: No medical or surgical treatment was provided except habit intervention. This is stated.

RESULTS
- The number of females in this group investigated is really small. Too small in my opinion. It seems that something happened during the selection of the group.

  Ans: In our study, we collected study subjects consecutively according to our inclusion criteria. There was no bias in selection. The sex ratio of oral precancerous lesions in Taiwan is quite large. For all precancer lesions attending hospitals, only about 12% are female patients. The sex-ratio also showed different patterns in different types of precancerous lesions. Compared to other types of oral mucosa lesions, there is a higher female ratio in lichen planus, which is about 40%. In this study, we did not include oral lichen planus subjects. So this should be the reason for fewer female subjects included in our study. More detailed information has been described in the discussion section on page 12 of the paper.

DISCUSSION
- Please discuss the possible selection bias causing the unusual sex ratio.
Ans: In our study, we collect study subjects consecutively according to our inclusion criteria during the study period. So the unusual sex-ratio in our study is because oral mucosal disease is a male predominant disease in Taiwan. And the pattern is related to much higher cigarette smoking, alcohol drinking and areca quid chewing habit in Taiwanese males than in Taiwanese females. However, our study is a hospital-based study, and it is possible that the sex-ratio may relate to the differences in medical utilization between males and females. The problem of the access to medical resource between genders is now discussed. More detailed information has been described in the discussion section on page 12 of the paper.

• Please discuss the difficulties in comparing past and future data regarding “verrucous hyperplasia” in absence of clear clinical and histological diagnostic criteria.

Ans: Thank you for your advice, we apologize for this misunderstanding because of confused description in methodology section. In our study, all lesions were pathologically confirmed. And we have added more detailed information about the diagnosis criteria of verrucous hyperplasia in the methodology section on page 6 of the paper.
Title: Malignant transformation of oral potentially malignant disorders: a retrospective cohort study

Reviewer: Jesper Reibel

1. **Background, last paragraph: Something is missing or surplus in line 2 and 3**
   Ans: Thank you for your advice, we have corrected it on page 5.

2. **A total of 152 subjects were included. Are these subjects selected in some way or do they represent successive patients in the period 1986-2004? Inclusion criteria?**
   Ans: We have answered this with reference to referee 2’s comments.

3. **Discussion, Line 4 from start “epithelial” should be “epithelia”**
   Ans:

   Ans: Thank you for your advice, we have corrected it on page 10.

4. **Discussion, last paragraph: reference in the text are not numbered**
   Ans: Thank you for your advice, we have corrected it on page 13.

5. **Author’s contribution: initial “TH” does not appear in the author list.**
   Ans: Thank you for your advice. This was a typographical error of this author’s initial name and we have corrected it on page 13.

   However, as stated above I cannot review the manuscript in any detail due to the reference errors.

   Reference errors were corrected in this revision.