Author's response to reviews

Title: Prognostic factors associated with the survival of oral and pharynx carcinoma in Taiwan

Authors:

Ping-Ho Chen (phchen@nhri.org.tw)
Tien-Yu Shieh (tiyushi@kmu.edu.tw)
Pei-Shan Ho (psho@kmu.edu.tw)
Chi-Cheng Tsai (chchts@kmu.edu.tw)
Yi-Hsin Yang (yihsya@kmu.edu.tw)
Ying-Chu Lin (chulin@kmu.edu.tw)
Min-Shan Ko (darkzealot69@hotmail.com)
Shang-Lun Chiang (u9481015@kmu.edu.tw)
Ying-Chin Ko (vcko@nhri.org.tw)

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Author's response to reviews: see over
Dear editor,

Thank you and reviewers for concerning about our work. The comments you provided were very useful to us. Our revised manuscript "Prognostic factors associated with the survival of oral and pharynx carcinoma in Taiwan" (MS #1445697861120858) have submitted to "BMC Cancer". The present version has been extensively revised in accord with the suggestions of the reviewers.

Our revised manuscript provides a cover letter giving a point-by-point response to the concerns. Revision of the text for reviewers’ comments was in yellow highlight. We believe the present manuscript has been greatly improved. We look forward to hearing from you on the final decision regarding publication of our manuscript.

Sincerely,

Ying-Chin Ko, M.D., Ph.D.
According to reviewer’s report, we have checked and made changes in the Highlight manuscript as follows:

**Reviewer's report**
**Title:** Prognostic factors associated with the survival of oropharyngeal carcinoma in Taiwanese community
**Version:** 1
**Date:** 12 December 2006
**Reviewer:** Chris Terhaard

**Reviewer’s report:**
General
In the review the following points were considered:
1. The question posted by the authors is new, but not well defined. In general oropharyngeal carcinomas are confined to the oropharynx region. That means tonsil, soft palate, base of the tongue, but not the oral cavity. In this study the oral cavity and oropharynx tumours and even hypopharyngeal tumours were included. The second point is the term carcinoma. In the study also lymphomas are included and besides squamous cell carcinoma adenocarcinoma is also included.

**Response:** Thank for your suggestion. In this study, we used the term “oral and pharynx carcinoma” to include the oral cavity and pharynx carcinoma. (Page 1, line 1)

**Response:** We have excluded lymphoma and adenocarcinoma in this study. (Page 7, line 14-16)

2. I do not think the methods are appropriate because the oropharynx, also the hypopharynx and oral cavity are included. All kind of histology: lymphomas, adenocarcinomas, squamous cell carcinomas are included.

**Response:** Thank for your suggestion. The pharynx site was classified into oropharynx and hypopharynx. In additional, adenocarcinoma and lymphoma were also excluded in this study.

3. Are the data sound and well controlled? The most important prognostic factor stage is not included. It is a very large dataset starting with 10.245 persons; 459 patients are excluded. However, in 7% of the included patients no histological conformation of the diagnosis was available. So this 7% should be excluded. If I understand the authors well, the Hakka and Hokkien and Taiwanese aborigines are separately situated. However as stated on page 7 in Hakka regions 25% of the people is not Hakka and in Hokkien regions 15% is not Hokkien. This means that in the table 1 not all the people named aboriginals, Hakka and Hokkien are really aboriginal, Hakka or Hokkien

**Response:** Thank for your suggestion. Information pertaining to staging is unavailable to Taiwan Carcinoma Registry in Taiwan, but the subjects’ therapeutic choices can be treated as a clinical reference. We also considered the choices of therapy in multivariate Cox proportion hazards model.

**Response:** In this study, we excluded 7% subjects with no histological conformation. (Page 7, line 17-18)
Response: Thank you for your suggestion. We have revised the definition of subjects in this study as follows (Page 8, line 14-16):
Subjects were divided into three ethnic groups according to their area of residence: Aborigines community, Hakka community, and Hokkien community.

4. In general the manuscript adheres the relevant standards for reporting and data deposition, although more details about the uni- and multi-variate analysis could be given.

Response: We have revised the statistical analysis as follow (Page 10 line 6-7):
The Cox multivariate proportional hazards model examined the role of prognostic factors on survival of different ethnic group.

5. In the discussion again is said that the study goes about oropharyngeal carcinoma subjects. However, it concerns patients with oropharyngeal, hypopharyngeal and oral cavity tumours. Not only carcinomas but also lymphomas. In the discussion many possible prognostic factors that explain the difference between the Hakka and the Taiwanese aborigines and Hokkien are named. However all these factors like cytokine gene polymorphisms are not studied in this manuscript. Also no information is available about the betel-quid chewing habits. In the results no correlation between histology and therapy is given. I suppose that chemotherapy alone was reserved for lymphomas and this explains the better survival in the aborigines for chemotherapy alone compared to radiation alone or surgery plus radiotherapy or radiotherapy and chemotherapy. In squamous cell carcinoma and adenocarcinoma chemotherapy only is a palliative treatment, and prognosis should be comparable with supportive care only. Also not explained in the discussion is the interesting finding that supportive care therapy has the same death hazard as surgery alone and even better than radiotherapy plus chemotherapy in the aborigines.

Response: The Taiwan Cancer Registry records lacked of the detail life habits data. Therefore, we can't analyse in this study.

Response: Thank you for your suggestion. We have excluded the adenocarcinoma and lymphoma in this study.

6. In the summary on page 20, regarded as conclusion, explanation of the better survival of the Hakka group is given, however not based on the data of this study.

Response: In the summary on page 21, we omitted the explanation of the better survival among Hakka group.

7. The title speaks only about oropharyngeal carcinoma. As stated before, there was a wider inclusion in this study.

Response: We used the term “oral and pharynx carcinoma” to get extensive inclusion in this study.

8. Abstract tells what has been found.

Response: We have revised abstract in this manuscript. (Page 3, abstract)
9. In general the writing is acceptable, however for example on page 12, line 15, “lip sites were protective”. I do not understand the word protective. I think the authors mean a better prognosis.

Response: We have revised as follow (page 13, line 17)
Lip sites had a significantly better prognosis.

10. My suggestion should be a major compulsory revision based on a selection of patients with histological confirmation of the primary tumour, selection of only those patients with a carcinoma, excluding the lymphomas and the adenocarcinomas. Adding stage to the multi-variety analysis is very important since the treatment would also depend on the stage. I should advise as next step not to accept or reject the manuscript until the authors have responded to the major compulsory revisions.

Response: Thank you for your suggestion. We have revised greatly in this manuscript.

11. Statistical review: I suggest, that an expert will also review this. There are some questions about the multi-variate analysis.

Response: We used the Cox multivariate proportional hazards model to examine the role of prognostic factors on different ethic group survival (page 10, line 6-7).

12. More detailed comments:
Title: this study also involves oral cavity tumours, some hypoharyngeal tumours and lymphomas.

Response: We used the term “oral and pharynx carcinoma” to include the oral cavity and pharyngeal carcinoma. In oral and pharynx carcinoma, we excluded the lymphoma and adenocarcinoma.

13. Background page 4 and 5:
The same comment about oropharyngeal, oral cavity tumours and hypopharyngeal tumours.

Response: We have revised in this manuscript and used the term “oral and pharynx carcinoma” to include the oral cavity and pharyngeal carcinoma.

14. Page 6
If we start with 10.245 patients and we exclude 459 patients, 9.786 patients remain. However, 93% of the patients were diagnosed with histological confirmation. My suggestion is to exclude the 7% that did not have a histological confirmation.

Response: We have excluded no histological confirmation patients. (Page 7, line 17-18)

15. On page 7 it is not clear or the stratification between Hakka, Hokkien and Taiwanese aborigines is just only based on regions, so not on an exact definition of ethnicity, merely a difference in regions where people live. This may influence the results.

Response: We have revised a definition of ethnicity. (Page 8, line 14-16)
16. On page 8 the choice of therapy is not very detailed analysed. There may be a large difference between chemotherapy used, kind of radiation schedules used, kind of surgery etc.

**Response:** Because Taiwan cancer registry system is a large database, it lacked of detail information of therapy choice.

17. On page 8 the hypopharyngeal tumours were included. This is a quite different group with in general a very bad prognosis compared to oropharyngeal tumours.

**Response:** We separated oropharynx and hypopharynx carcinoma in this manuscript.

18. Page 10: what do you mean by oropharyngeal carcinoma survival rates, disease free survival rates?

**Response:** It means disease-specific survival rates. For oral and pharynx carcinoma survival rates, death with ICD code 140-149 (except for ICD 142 and ICD 147) were classified as death due to oropharyngeal carcinoma, and subjects who died of other causes or were still alive were considered censored observation. (Page 9, line 15-18)

19. Page 12 is showing that the survival rates in 1990-1994 are decreased comparing to former years. Do you find any reason for this in your multi-variate analysis?

**Response:** Explanation for this deterioration is not straightforward. Conceivably, the decline in survival rates may be no improvement in earlier detection or treatment effectiveness. (page 18, line 7-9)

20. On page 13 it is said that for the aborigines the mortality rates were best with chemotherapy alone. Since we know that chemotherapy alone is only palliative in squamous cell carcinoma and adenocarcinoma this means that chemotherapy alone is only given to the lymphoma patients? The difference in treatment as published on page 13 may be caused by histology and stage. So the multi-variate analysis should include stage, because stage may explain not only the treatment given, but also the results. If people from Taiwanese aborigines have higher stages, this could explain differences in treatment and in outcome.

**Response:** We have excluded adenocarcinoma and lymphoma subjects in the multi-variate analysis. Unfortunately, information pertaining to staging is unavailable to TCR in Taiwan, but the subjects' therapeutic choices can be treated as a clinical reference. Thus, we only can add the therapy variables in this multi-variate model.

21. On page 14, 15 and 16 many reasons to explain the difference found in the study are given, however all those prognostic factors are not analysed in this study. The most important is the betel-quid chewing habits, but also these habits are not scored in this study.

**Response:** The Taiwan Cancer Registry records lacked of the detail life habits data. Therefore, we can't analyse in this study.

22. Page 19, line 15
Surgical therapy alone cannot give a protective effect. I think the authors mean: has a prognostic favourable effect, namely based on patient selection.
Response: Our findings offered a prognostic favourable effect with the option of surgical therapy alone in Taiwanese aborigines, Hakka and Hokkien. (Page 20, line 16-18)

23. Page 20
Therapy with chemotherapy alone or radiotherapy alone might indicate that patients have advanced stage, however chemotherapy alone might also be given to lymphomas, giving a good prognosis.

Response: We have excluded the lymphoma in this study.

24. Table 3, results of multi-variate analysis It is not clear why chemotherapy alone is taken as the standard comparing to all other treatments, it looks more logic to take surgery alone.

Response: The surgery alone is taken as the standard comparing to all other treatments in Table 3.

25. Table 2, adjusted hazard ratio should be based on an analysis using all relevant factors, also including stage.

Response: Our data lack of stage index.

28. In the figures, number of days is taken for the X-axis, mostly months or years are used.

Response: Number of years was taken for the X-axis in the figures.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
see above (2,3,5,10,14)
Response: We have revised carefully in this manuscript.
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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
see above
-----------------------------------------------------------------------------------------------------------------
Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes
Declaration of competing interests:
Declaration of competing interests: I declare that I have no competing interest in relation to this paper.
**Reviewer’s report**
**Title:** Prognostic factors associated with the survival of oropharyngeal carcinoma in Taiwanese community
**Version:** 1  **Date:** 7 December 2006  
**Reviewer:** Eduardo De Stefani  
**Reviewer’s report:**
**General**
This is an interesting paper which provides new information. The manuscript is well written and carefully discussed. The paper could improve in its quality if the authors provide information on clinical staging according to the UICC TNM classification.

**Response:** Information pertaining to staging is unavailable to TCR in Taiwan, but the subjects’ therapeutic choices can be treated as a clinical reference. Thus, we only can add the therapy variables in this multi-variate model.

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**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**
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**Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**
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**Discretionary Revisions (which the author can choose to ignore)**

**What next?:** Accept after minor essential revisions

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**
I declare that I have no competing interests