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 (ycko@nhri.org.tw)

Version: 5 Date: 8 March 2007

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 oral and pharynx carcinoma in Taiwan

Version: 4 Date: 7 February 2007

Reviewer: Chris Terhaard

Reviewer's report:

General: The manuscript has been revised according to most of the suggestions. An important improvement is the selection of patients with only histological confirmation of malignancy excluding the adenocarcinoma and lymphoma. Also the title has been changed including oral and pharynx carcinoma. An extensive multivariate analyses has been shown in table III.

The importance of this manuscript, and the reason why this should be published, is the statement that ethnic groups in Taiwan may be an independent factor for the C3 survival for oral and pharyngeal carcinoma. However, in this study, the definition of ethnic groups depends on the area of residence, so it means that in the Taiwanese aborigines community, the Hakka community and the Hokkien community not all the patients will be aborigines, Hakka and Hokkien respectively. That is the reason why some care should be taken, considering the results.

Response: Thank you for your suggestion. We have made a clear explanation of our ethnic groups as follow:

(Page 9, line 4-12)

Since there is no item of ethnicity or race on the TCR system in Taiwan, previous studies could only use residential areas as the proxy. In 1996, Lu et al. estimated a mortality pattern of aborigines in Taitung County [13], Taiwan according to their ethnic origins and found a very similar pattern when compared to the mortality pattern of Taiwanese residential communities, which are classified according to residential data in Ko’s study [7]. Likewise, in our latest published study, we compared the ethnic differences (Aborigines, Hakka, and Hokkien) in incidence and mortality of oropharyngeal cancer in Taiwan according to their residential areas [9]. Hence, in this study, the possible misclassification of our ethnic groups should not be a serious problem.

Reference:
13. Lu TH, Chen AD, Lee MC, Chen IK, Hwang LJ, Chou MC: Mortality pattern of
The second problem is that there is no information according to staging, and staging is known to be the most important prognostic variable for the disease free survival. As a surrogate treatment has been considered as a variable that is closely correlated with staging. Patients with a good prognosis will receive surgery alone and for patients with a poor prognosis, surgery combined with postoperative radiotherapy or chemo radiotherapy might have been used.

As shown in this manuscript treatment was an independent variable for the disease free survival, however in fact this may only resemble staging. As shown in table 1, the Hakka people where significantly more often treated by surgery alone compared to the other two groups. This may point out that the Hakka had less advanced stage, compared to the other two groups. This might be a reason of the difference in the disease free survival. This has been outlined by the authors in their discussion.

Response: Thank you for your suggestion. There is no information about tumor stage in this study, but the subjects’ therapeutic choices can be treated as a clinical reference. We made some explanation as follows:

(Page 21, line 4-8)

In our recently published data, we use the Taiwan cancer registry system to examined the survival prognostic factors among liver cancer subjects [38]. Data suggested an earlier clinical staging of cancer was eligible for surgical resection alone or surgical reception + RT/CT. Without therapy or treated with CT alone, RT, ST alone may indicate they were diagnosed in advanced stages of the disease.

Reference:
Response: We have revised in Figure I, II and III.

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have no competing interests
Reviewer's report

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

Version: 4 Date: 7 February 2007

Reviewer: Victor Moreno

Reviewer's report:

General
This is a descriptive study of prognostic factors of oral cancer. The statistical methods used are reasonable but could be improved. The design, however, has several limitations that minimize the interest.

------------------------------------------------------------------------
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
– Cases dead for other causes of oral cancer were censored, but there is no information about the quality of the death certificates. It is standard in survival analysis of cancer registry data to assume all deaths related to cancer and adjust the expected mortality using relative survival analysis. This could also explain the differences between ethnic groups if they have overall different mortality rates.

Response: Thank you for your suggestion. We have revised as follows:
(Page 7, line 13-16)
The mortality database, submitted standardized and immediate certificates for each case, mandatory for physicians by the Department of Health. So the vital statistics published by the National Health Department of Taiwan are very complete, with a physician confirmed rate of 99%.

– The most relevant prognostic factor, tumor stage, is not available. Only treatment modality can be used as proxy. Since the differences between ethnic groups are small, these could be completely explained by tumor stage. Residual confounding cannot be ruled out as an explanation of the differences.

Response: Thank you for your suggestion. There is no information about tumor stage in this study, but the subjects’ therapeutic choices can be treated as a clinical reference. We made some explanation as follow:
(Page 21, line 4-8)
In our recently published data, we use the Taiwan cancer registry system to examined the survival prognostic factors among liver cancer subjects [38]. Data suggested an earlier clinical staging of cancer was eligible for surgical resection alone or
surgical reception + RT/CT. Without therapy or treated with CT alone, RT, ST alone may indicate they were diagnosed in advanced stages of the disease.

Reference:

– The sample is hospital based and no information is given about the representativity of the general population.

Response: Thank you for your suggestion. We made some explanation as follows:

(Page 7, line 2-10)
Taiwan Carcinoma Registry (TCR) is a population-based cancer registry with the collection of information on cancer patients newly diagnosed in hospitals with 50 or more beds throughout the country. The registry is financially supported by the National Department of Health of Taiwan. The registry center has an epidemiologist as the director, a postdoctoral research fellow and eight cancer registrars. The registry has an advisory board including 18 members with specialties in pathology, oncology, radiotherapy, cancer registry, and public health. The cancer registry proved advantageous in evaluating the quality of medical care and the preciseness of cancer site diagnosis. In Taiwan, over 95% of registered cases were histologically confirmed.

– The number of cases for each ethnic group 302, 556 and 8181 have proportions 3%, 6% and 90%, which do not agree with the population proportions 2%, 12% and 86%. Are oral cancer incidence rates different for these ethnicities? If cancer incidence is similar these proportions show evidence of selection bias in the sample and this would mean the results have low validity.

Response: Thank you for your suggestion. We made some explanation as follows:

(Page 16, line 17-19)
From our latest published study, significantly lower incidence and mortality rate of oral and pharyngeal cancer were found in the Hakka communities, when compared to the Hokkien communities [9].

Reference:

– Follow-up is said to be “active”, but there are no data about lost of follow-up. This suggests that in fact only death certificates were linked and no confirmation was sought whether those not found dead were really alive and in the territory. If this is the case, follow-up was "passive" and survival rates might have been overestimated. Also this problem could be differential for ethnicities or periods, and explain why more recent cases have worse prognosis.
Response: Thank you for your suggestion. We made some explanation as follows:
(Page 7, line 11-17)

Our study population (N = 10,245) comprised of all subjects diagnosed with PLC in 1985–1994, recruited via the TCR system and matched accordingly to the mortality database. The subjects’ survival days post-diagnosis were ascertained by active validation of their vital status until December 31, 2002.
– In this revision adenocarcinomas and lymphoma have been excluded, but cases NOS and other, are still there, which introduce misclassification and heterogeneity.

Response: Thank you for your suggestion. We made some changes as follows:
(Page 7, last line; Page 8, first line)
We combined the carcinoma, NOS and other carcinoma into other carcinoma.

– It is not clear from the methods section if the investigators really know the ethnic of the patients or only their residence and they impute ethnic. They say that mainland Chinese could not be traced, which is ambiguous. If this is the case, all analysis regarding ethnicity, the point of the paper, in fact are related to residence.

Response: Thank you for your suggestion. We made some explanation as follows:

(Page 8, line 13-19)
The population of Taiwan approaches 24 million which consists of Hokkien (73%), mainland Chinese (13%), Hakka (12%), and Taiwanese aborigines (2%). The Hokkien and Hakka populations of Taiwan migrated from Mainland China approximately 400 and 600 years ago, respectively. There are 10 aboriginal tribes in Taiwan, and most of them live in rural and remote mountain areas. The Mainland Chinese are those people who came to Taiwan in a wave around 50 years ago, who lived in Hokkien communities, and integrated with the local population.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because too small an advance to publish

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report. Declaration of competing interests:
I declare that I have no competing interests