Author's response to reviews

Title: Quality of life predicts survival in patients with lung cancer

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Author's response to reviews: see over
Dear Editor:
Thank you very much for giving us the chance to reply the reviewer’s comments for our paper "Quality of life predicts survival in patients with lung cancer." We have followed reviewer’s suggestion to make changes. Concerning the reviewer’s comments, our point-by-point reply has been made.

Your sincerely
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Reviewer's report
Title: Quality of life predicts survival in patients with lung cancer
Version: 1 Date: 30 January 2012
Reviewer: Akif Turna

The authors would like to thank reviewer for judicious reading of the manuscript and valuable comments which greatly improved this manuscript. We have followed your suggestion to make changes. Concerning the reviewer’s comments, our point-by-point reply has been made.

Reviewer's report:
1. Major Authors investigated the relationship between EORTC QLQ-C30 and QLQ-LC13 and survival. There are a number of issues regarding study design, analyze and reasoning. First of all, authors pooled all patients with early-stage and locally-advanced stage disease, patients with non-small and small cell lung cancer and analyzed. In order to analyze additional prognostic factor, authors should have documented the impact of conventional prognostic factors such as T, N and M factor in the first place as a validation of the prognostic prediction model. However, there is no information on this respect. The surgically treated patients should have been analyzed separately since there should be a mortality owing to surgery and QLQ scores should be better in these patients since there were no metastasis and they should have had less tumor mass causing systemic morbidity.

Reply: We have followed your suggestion by re-analyzing our data and all results are represented
stratified by surgery status. Due to only 2 patients with small cell lung cancer in our study, we cannot analyze our data stratified according to type of lung cancer (non-small or small cell lung cancer). Our previous analyses have restricted in patients with non-small cell lung cancer, but we did not notice it. Now we have made correction for the entire manuscript. As for conventional prognostic factors, originally we considered clinical stage of cancer, which is derived from T, N and M factor. We have followed your suggestion by taking T, N and M factor into account in our models. All description in the manuscript have been changed accordingly.

2. In a 'state-of-the-art survival model, firstly one should accomplish 'Kaplan-Meier' survival estimation test followed by 'log-rank' test and Cox proportional hazard test. However, in the paper, authors first indicated the importance of EORTC QLQ-C30 as a prognostic factor, and Cox test and Kaplan-Meier analysis was mentioned. There was no log-rank test given in the text.

Reply: We agree your comments that Kaplan-Meier survival functions should be estimated first and then followed by log-rank test and Cox’s proportional hazard test. There are 25 subscales of EORTC QLQ-C30 and LC-13, which means there are 25 graphs of Kaplan-Meier survival functions if we present Kaplan-Meier survival functions first. Thus we followed the analysis strategy of a similar paper for liver cancer published in Quality of Life Research by presenting the univariate and multivariate Cox’s proportional hazard models first and then presenting Kaplan-Meier survival functions for those significant scales in multivariate Cox’s proportional hazard models. These Kaplan-Meier survival functions and univariate Cox’s proportional hazard models both belong to bivariate analysis of survival data. Cox’s proportional hazard model estimates the strength of association between independent variable and time-to event whereas Kaplan-Meier survival function provides the survival probabilities for the entire follow-up period. We have followed your suggestion by presenting the results of log-rank tests.

3. The quality of life can be affected a number of factors including patient's comorbid status (diabetes, cardiac disease etc), pulmonary functions, applied therapeutic modality such as surgery/chemotherapy/ radiotherapy. These possible factors were not given and analyzed before 'quality of life' scores.

Reply: We agree your comments that quality of life can be affected by a number of factors such
as patient’s comorbid status, pulmonary functions, and applied therapeutic modality. Because some patients undergoing active treatment, they are too frail to report these information in self-report questionnaire or it is missing in medical record. Thus we did not consider them in our data analysis. We have checked previous studies which are similar to ours and we found some of them did not consider these factors either. We guess they encounter the same problem as ours. Thus, we had discussed it in our study limitation.

Third, the study lacked information regarding pulmonary function, comorbidity, genetic factors and the physical environment of these patients; hence, we cannot rule out the possibility that our findings may be confounded due to these unmeasured variables.

4. Conventional prognostic factors such as T,N and M are associated with disease exetension and its invasion. Understandably, survival of patients is associated with these factors. However, QOL is primarily associated with patient's current condition (age, performance status, comorbid diseases etc). For this reason, it is plausible to suggest that QOL could be a result of disease and patient status not a primary 'cause' of patient's survival. However, QOL seemed to be related to be survival indirectly, not by a 'causative' mechanism. Authors should have been aware of this phenomenon.

Reply: Yes, we agree with your comments. QOL is primarily associated with patient’s current condition such as age, comorbid diseases, etc. As for performance status, it belongs to one of QOL domain. For example, EORTC QLQ-C30 has a subscale of physical functioning which measures physical performance status. We are aware of the phenomenon that QOL is related to survival indirectly, not by a ‘causative’ mechanism. We have mentioned it in our fifth study limitation.

Last, this study did not establish a causal relationship between HRQOL and survival, since an unidentified factor may have been involved. HRQOL may reflect a patient’s status of disease, which has a direct effect on a patient’s survival.

5. Authors did not give the details of surgical ( how many neumonectomies /lobectomies/bilobectomies?) and oncological ( chemotherapeutic agents, dose and route of irradiation etc) therapies which theoretically should have been related with patient’s outcome.
Reply: Thank you for your suggestion. We have followed your suggestion by adding number of study subjects for each type of surgery (neumonectomies, lobectomies, or bilobectomies), type of chemotherapeutic agents (Iressa, Navelbine, Gemzar, Taxol, and Taxotere), and radiation use and their associations with survival in Table 1.

6. 'Mortality' and 'Survival' were used interchangeably in the article. However, these terms represent different outcomes.
Reply: Thank you for your suggestion. We have followed your suggestion by changing mortality as survival for the entire manuscript.

7. In the manuscript, authors did not give the criteria for adjuvant therapy following surgical therapy, inclusion and exclusion criteria for chemotherapy/radiotherapy in patients with locally advanced lung cancer.
Reply: Thank you for your suggestion. The inclusion and exclusion criteria for chemotherapy/radiotherapy in NSCLC patients are the same as those for NSCLC patients with surgery. The description about criteria for adjuvant therapy following surgical therapy and chemotherapy/radiotherapy has been added in the method section. It is as follow:

*Usually, patients who did not have completely resected stage IA and IB NSCLC would receive adjuvant therapy and patients who are not candidates for surgery or who refuse surgery, curative intent chemotherapy or radiotherapy is used.*

8. There was a need for validation of EORTC QLQ-C30 and LC-13 in Mandarin dialect and in Taiwanese.
Reply: Thank you for your suggestion. EORTC QLQ-C30 and LC-13 had been validated in Mandarin dialect in Taiwanese and the findings had been published in *Quality of Life Research*. We have cited this paper in our method section. The added sentence and citation are as follows:

*Previous study showed that overall validation results for the Chinese version of the EORTC QLQ-C30 and QLQ-LC13 confirmed it as a reliable and valid questionnaire for assessing lung cancer-specific HRQOL in Taiwan* [12].

9. The manuscript failed to show the importance of QOL scales on survival in NSCLC patients. 

Reply: Previously we thought our analysis had been done in NSCLC and SCLC patients but actually it was in NSCLC patients. Because we have focused our analysis in NSCLC patients, we can say that our study showed the prediction ability of QOL scales on survival in NSCLC patients. In addition, this is the first paper reporting the prediction ability of QOL scales on survival in Chinese patients with NSCLC stratified by surgery status. Due to this relationship may depend upon culture difference, our study finding has its own importance. Thank you for your comments.