Author's response to reviews

Title: The Association of Quality of Life with Potentially Remediable Disruptions of Circadian Sleep/Activity Rhythms in Patients with Advanced Lung Cancer

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Author's response to reviews:

March 31, 2011

Dear Editor,

Greetings,

Thank you for your correspondence in connection with our manuscript (MS: 1834286941369072) entitled “The Association of Quality of Life with Potentially Remediable Disruptions of Circadian Sleep/Activity Rhythms in Patients with Advanced Lung Cancer” for consideration in “BMC Cancer”.

We have addressed the reviewers’ concerns in our revised manuscript, which is being resubmitted to “BMC Cancer”. Attached below, for your perusal, is a detailed description (highlighted in red and CAPS) of how we have addressed the reviewers’ comments in our revised manuscript.

We thank you once again for your interest in our manuscript. Please let us know if you have any further questions and we will be more than happy to clarify.

We look forward to hearing back from you soon.

Yours Sincerely,
Reviewer's report:

- Major Compulsory Revisions

The authors have made some modification based on my suggestions. However, many points were either ignored or answered inappropriately. Please refer to the following table where I make a point by-point list to show my previous comments, authors’ responses and my comments on authors’ responses.

<table>
<thead>
<tr>
<th>My previous comments, authors’ responses, and my comments for authors’ response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My previous comment</td>
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<tr>
<td>Many actigraphy parameters were presented in this article. It is very difficult for a reader who is not so familiar with these parameters to immediately grasp the main findings of this study. Although the authors have mentioned the meaning of the individual parameters whenever they appeared, I think it would be better to describe, under heading of actigraphy, these parameters in details in terms of their definition and clinical meaning. By doing so, a lot of space of the result section can be saved. For a paper involving many variables, brevity and clarity is definitely needed.</td>
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<tr>
<td>Authors’ response</td>
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<tr>
<td>Appendix 1 addresses Dr. Chen and Waterhouse concern that the text had too dense with statistical and circadian jargon.</td>
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<tr>
<td>My comment on authors’ response</td>
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<tr>
<td>No Appendix 1 was found in the revised manuscript.</td>
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<tr>
<td>RESPONSE--APPENDIX 1 IS ATTACHED AT THE END OF THE MANUSCRIPT</td>
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<tr>
<td>2. My previous comment</td>
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<tr>
<td>On page 11, line 18, when describing the differences of quality of life between</td>
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</table>
study population and general/reference population, I suggest not to use the word “significantly” to prevent confusion with “statistical significance”. controls (Table 2)."

Authors’ response
We removed significant from page 11 line 18.

My comment on authors’ response
The word “significantly” was not removed as indicated in authors’ response (See page 12 line 1 in the revised manuscript).

RESPONSE-REMOVED SIGNIFICANT IN LINE ON PAGE 12 LINE 1. REPLACED THE ORIGINAL -- BOTH IN AND OUTPATIENTS REPORTED SIGNIFICANTLY LOWER SCORES FOR ALL EORTC-QLQ-C30 DOMAINS WHEN COMPARED TO POPULATION-BASED CONTROLS BY “BOTH IN AND OUTPATIENTS REPORTED LOWER SCORES FOR ALL EORTC-QLQ-C30 DOMAINS WHEN COMPARED TO POPULATION-BASED.

3. My previous comment
Only statistical findings should be presented in result section. Judgmental statement or explanation should be saved for discussion. Therefore, the first sentence under the heading “Correlation of QoL and actigraphy among inpatients” may be deleted.

Authors’ response
(No response)

My comment on authors’ response
The author did not revise the manuscript according to this comment and did not provide any justification.

RESPONSE-SENTENCE REMOVED FROM MANUSCRIPT

4. My previous comment
The last three parts of the result section (COPD vs. actigraphy, relationship of quality of life scores to one another and to circadian organization, effect of prognostic factors on quality of life) are less relevant to the main focus of this paper. I would suggest delete these parts and related figures to make the paper more focused.

Authors’ response
Hopefully, oncologists will be a receptive audience for this data. Almost to the doc, oncologists who treat lung cancer patients will think that COPD is a confounding variable for any investigation of circadian organization. We think this tiny section should remain.

The section on the relationship with QoL and other prognostic variables is interesting in itself, but as Dr. Chen pointed it not directly relevant to the paper, so it was removed.
My comment on authors’ response

The authors have modified the manuscript according to my suggestion. For the portion that they choose to keep, they also provided a good reason.

5. My previous comment
Tables and figures:
(1) Again, parameters listed in Table 6 should be defined and explained first.
(2) Table 4 and 5 can be combined into one table and reverse the column and row to make it consistent with other tables.
(3) A big table presenting the correlation between all the sleep parameters and quality of life domain/symptom scores may be needed. Consequently, figure 2 can be deleted because it failed to provide neither comprehensive nor clearer information than a table.

Authors’ response
We have revised all of the tables to reflect Drs Chen and Waterhouse’s comments and I have added a large table to collate all of the statistically significant correlations between QoL parameters and sleep parameters for outpatients in table 6.

My comment on authors’ response
(1) The authors responded in the first comment that an appendix is created, but this appendix was not attached in the revised manuscript. APPENDIX IS NOW ATTACHED TO END OF MANUSCRIPT.
(2) The authors did not modified Table 4 & 5 as suggested and did not provide reasons for not making any change. TABLES 4 AND 5 COMBINED INTO A NEW TABLE 4.
(3) The authors added a new table to summarize the significant correlations between QOL and sleep parameters in outpatients. It is not clear why only presenting data on outpatients, what about inpatient
RESPONSE--ADDED A SENTENCE TO THE BEGINNING OF THE CORRELATIONS OF QUALITY OF LIFE AND ACTIGRAPHY AMONG INPATIENTS ‘AMONG INPATIENTS WE ONLY FOUND SEVERAL STATISTICALLY SIGNIFICANT ASSOCIATIONS WITH ACTIGRAPHY PARAMETERS’. TO EMPHASIZE THAT THERE WERE ONLY FOUR STATISTICALLY SIGNIFICANT ASSOCIATIONS BETWEEN ACTIGRAPHY AND QUALITY OF LIFE AMONG INPATIENTS, WHICH SUGGEST NO NEED FOR A SEPARATE TABLE

In addition, only selected sleep parameters were presented in this table; significant correlations on some parameters (e.g., night-day sleep balance) were missing [DR. CHEN POINTS OUT THAT THIS TABLE DID NOT INCLUDE DATA FROM THE DAY-NIGHT BALANCE SPENT ASLEEP WHICH IS FOUND FOR A NUMBER OF QOL PARAMETERS—THEY ARE NOW IN THE TABLE 5]
Figure 2 was not removed as suggested and no justification was provided [THE CURVES IN FIGURE 2 COMMUNICATE THAT THE CORRELATIONS BETWEEN ACTIGRAPHY PARAMETERS AND QOL DOMAINS ARE RELATIVELY MODEST AND THAT A PATIENT’S QOL DEPENDS ON OTHER FACTORS—MANY PEOPLE UNDERSTAND THIS BUT I THINK IT IS HELPFUL TO SEE THE DATA GRAPHICALLY DISPLAYED].

6. My previous comment

In discussion section, the author stated that “There was a counter-intuitive finding that no significant relationship was found between self-reported insomnia and any objectively measured actigraphy parameter.” (page 19, line 11-12) This statement is conflict with the study result described on page 13-14 where a negative correlation between insomnia and 24-hour autocorrelation ($r = -0.48$, $p = 0.003$) was indicated.

Authors’ response

Dr Chen is a very careful reader, in our discussion we focused on the finding that outpatients did not report insomnia as a problem, however, inpatients did. Hospital routines seem to be designed to suddenly increase the number of untoward awakenings at night, consequently, we can hypothesize that these patients feel sleepier than they did a week ago, while outpatients have become adapted to their progressive sleep fragmentation. So we have inserted the following in the Discussion.

“An interesting finding was the lack of a significant relationship between a self-reported insomnia among outpatients and any objectively measured actigraphy parameter. This finding is surprising considering that actigraphy data showed that virtually every patient’s sleep was fragmented and unconsolidated and these patients self report of their sleep quality, as measured by a validated sleep questionnaire, was indistinguishable from insomniacs.49,50 This non sequitor between universal objective signs of very poor sleep and the perception of insomnia among advanced lung cancer is interesting. It seems as though, in cancer patients as in the healthy elderly, the perception of nocturnal sleeplessness and the reality of it are at odds. Inpatients did report an association between an actigraphy parameter and insomnia, we can speculate that hospital routines involve a sudden increase in number of untoward nighttime awakenings that results in the patients feeling much sleepier than they did in the prior week.”

My comment on authors’ response

The clarification that the lack of a significant relationship between a self-reported insomnia and objectively measured actigraphy parameter only existed in outpatients was helpful. However, there was no clear description about these non-significant findings in the Result section.

WE EMPHASIZE THE FINDINGS OF A LACK OF ASSOCIATION BETWEEN INSOMNIA AND CIRCADIAN ORGANIZATION IN RESULT SUBSECTION ENTITLED OUTPATIENTS THE RESULT ‘THERE WAS NO ASSOCIATION...”
BETWEEN INSOMNIA AND ANY PARAMETER DESCRIBING CIRCADIAN FUNCTION."

7. My previous comment
This paper did not discuss the main study results (i.e., the sleep disturbance and the correlation between actigraphy parameters and quality of life in advanced lung cancer patients) in terms of how they differ from or conform to findings from others’ work.

Authors’ response
Overall there is not much data linking parameters measuring circadian activity with QoL data. However, Berger et al and Bogdan et al provide interesting results which appear to be consistent with ours. Bogdan failed to find a relationship between a self report of insomnia and parameters of circadian rhythms and Berger reported that breast cancer patients’ circadian activity differs from controls. Both references and comments on their work were inserted in the appropriate sections of the discussion.

My comment on authors’ response
The revision is satisfactory.

8. My previous comment
Compared to general population, the study population had lower scores on health/functioning domain of Ferrans and Power QLI but not on the other three domains (i.e., social/economic, psychological/spiritual, and family domains). This finding is interesting and the authors suggested that there is a resilience of human spirit when facing the lethal disease. From the perspective of measurement, the author may also want to discuss the phenomenon of “response shift” for quality of life.

Authors’ response
I am reluctant to discuss Dr. Chen’s idea of response shift in this discussion. However, we are evaluating the effects of tumor response or lack of response, and the administration of melatonin on patients in a subsequent paper. We will have data that will directly address issues of response shift and I would prefer to discuss that issue with some data in hand.

My comment on authors’ response
The authors may misinterpret what I meant by “response shift”. “Response shift” is a measurement phenomenon and has nothing to do with treatment response. According to Sprangers & Schwartz (1999, p. 1508), the response shift is “a change in the meaning of one’s self-evaluation of a target construct as a result of: (a) a change in the respondent’s internal standards of measurement (scale recalibration, in psychometric terms); (b) a change in the respondent’s values (i.e. the importance of component domains constituting the target construct); or (c) a redefinition of the target construct (i.e. reconceptualization)".
DR CHEN’S DESCRIPTION OF RESPONSE SHIFT SHOWS IT IS A VERY BIG DEAL IN QUALITY OF LIFE RESEARCH. THE TEMPTATION IS TO SPECULATE ON HOW THE TOOL OF ACTIGRAPHY CAN BE USED TO CONTROL FOR A PATIENT’S CHANGE IN VALUES OR PERSONAL STANDARDS AS THEY RESPOND TO THE CHALLENGES OF PROGRESSIVE DISEASE. BUT IT IS FAR FROM THE KEY POINT OF THIS PAPER THAT THERE ARE SIGNIFICANT AND PERSUASIVE RELATIONSHIPS BETWEEN A PATIENT’S SELF REPORT OF QUALITY OF LIFE DATA AND A PATIENT’S CIRCADIAN ORGANIZATION. ON THE OTHER HAND, DR. CHEN HAS POINTED OUT THAT WE MUST INVESTIGATE WHETHER ACTIGRAPHY CAN BE USED TO QUANTIFY RESPONSE SHIFTS IN QOL DATA USING LONGITUDINAL DATA.

9. My previous comment
There are many writing errors that make the reading of the manuscript a little bit difficult. For example, on page 9 in describing the grades of COPD, the FEV1% for moderate COPD should be 50% to 80% (not 89%). CORRECTED

On page 12, line 3, “… patients with stage II and IV disease.” should be “…patients with stage III (?) and IV disease.” CORRECTED

Other examples of grammatical errors or confusing sentences can be found on page 12-line17 &21, page 12-last sentence, page 13-line 5 to 6, page 14-line 18 to 22. In addition, the use of abbreviations in this manuscript is inconsistent. The organization of the result section can be improved too. I strongly suggest that a professional editing is needed before submitting this manuscript for further review.

Authors’ response
(No response)

My comment on authors’ response
None of the above errors have been modified.

RESPONSE -- WE HAVE SENT THE MANUSCRIPT TO A SCIENCE WRITER WHO HAS WORKED AT JOHNS HOPKINS TO REVIEW AND IMPROVE THE MANUSCRIPT. WE DO NOT CLAIM TO BE A WORDSMITH, BUT SEVERAL UNINTERPRETABLE SENTENCES HAVE BEEN FIXED OR REMOVED, AND THE MANUSCRIPT BEEN TWEAKED FOR NUMEROUS PUNCTUATION AND GRAMMAR PROBLEMS.