Reviewer's report

Title: Quality of Life Assessment: An Independent Predictor of Survival in Non-Small Cell Lung Cancer

Version: 2 Date: 21 January 2011

Reviewer: Richard Fielding

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Quality of Life Assessment: An Independent Predictor of Survival in Non-Small Cell Lung Cancer.

Thank you for asking me to look at this amended manuscript.

The authors have attempted to address my prior concerns and responded quite literally but they do not seem to have realised the implications of their data, or of the amendments they have introduced. Some issues remain inadequately addressed and the amendments raise other issues that I think need to be attended to requiring a major re-orientation of the paper. I urge the authors to undertake this and I think their data should be published. However, it is important that they interpret this correctly and that the paper reflects this. Consequently, there are several points that I elaborate below. All of these issues I consider compulsory amendments.

1. P4 para 1: Background: I do not see any mention of the literature that finds no association between QoL and survival, yet this is quite extensive (point 4, Review 1), I think it needs to made clear in the Background that there is no unanimity on the predictive power of QoL, nor is there a good theoretical reason why QoL should have any predictive power (as the authors briefly allude to without actually saying so: “It is currently unclear why QoL may be prognostic”). This needs to be brought out. Otherwise the impression is given not of a balanced and undecided starting point to this paper (does or does not QoL predict outcomes?), but of a pre-ordained one (QoL does predict outcomes), a “me too” paper. The authors must elaborate reasons for the disagreement in the literature in their Discussion, but there needs to be more balance and justification (I acknowledge that this is a bit of a goal post move but I think the paper would be strengthened considerably if it were to include this) in the Background, if this paper is to contribute to the existing literature.

2. P4. Para 2: “and it has been hypothesized” please provide a reference.

3. P9. Para 2: “The function scales to be significantly correlated with age were physical (r = -0.06; p = 0.04), emotional (r = 0.07; p = 0.01) and social (r = 0.07; p = 0.01). Physical scale was negatively correlated while emotional and social scales were positively correlated.” These two sentences are unclear – please re-phrase.

4. P9 last sentence, P10 first sentence: “Among the symptom scales,
nausea/vomiting \( (r = -0.09; p = 0.001) \), pain \( (r = -0.16; p = 0.001) \) and insomnia \( (r = -0.12; p = 0.001) \) were negatively correlated with age while dyspnea \( (r = 0.08; p = 0.007) \) was positively correlated. All these correlations were very weak (with \( r \) less than 0.20 in either direction).

The phrasing of this sentence implies that older patients had less nausea, pain and insomnia and more dyspnea. Is that correct? If so, it is an interesting result, and worthy of comment, as one would expect the opposite (at least for pain and insomnia). The small correlations are, as pointed out, very weak and probably reflect the large sample size. With smaller samples they would be insignificant. Be careful not to "milk" your data too heavily.

5. P11 last paragraph. Relocate the last two sentences from the “Results” to the “Discussion” section where they are more appropriate, (although see comments on the Discussion below which I think needs a thorough re-write).

6. Discussion: The authors valiantly defend the idea that “there is a statistically significant relationship between specific elements of QoL, as measured by the QLQ-C30, and survival in lung cancer patients” (P12, para 1: there *is* a statistical relationship, but their data really do not support this interpretation except in the most superficial, and I believe misleading way. It would be great to have an indicator like QoL for prognosis, but this study’s results fit very well the overall pattern of previous findings – namely that, once adjustment is made, only the physical status of the patient predicted survival, and the global QoL score likely reflects the contribution of physical status to the global score. These QoL scores do not, despite our desires for them to do so, stand up to scrutiny as an independent predictor – this is an example of confounding by reverse causality. That does not make the study unpublishable, but it does demand that the authors be more objective in interpreting their findings.

7. P13/14 New paragraphs. These need to be re-written more clearly. The authors need to do two things. First, revisit the many studies they cite in the Background section that they claim “show an independent relationship between QoL and survival” and consider these, together with the new studies referred to in the additional paragraphs. They then need to look to see which of these studies were vulnerable to confounding by reverse causality (RCC), and which were not, and then examine which found independent associations between QoL and survival and which found only physical or “global” scores predicted survival. If they do this, a clear pattern emerges: Those studies most vulnerable to reverse causality confounding, usually also the weakest controlled studies, are the ones reporting the strongest independent effects for QoL; those least vulnerable to reverse causality confounding, usually the better controlled, tend to show that, if anything, only physical and perhaps Global scores predict survival. If RCC is responsible, then adequate adjustment makes the prognostic effect disappear - that is what these authors found.

8. As these new paragraphs stand, they imply that the authors either fail to grasp the import of the literature (and their own findings) or are unwilling to acknowledge these problems, as the rather timid last sentence P14, para 1
suggests. The Discussion needs much more work to be better balanced.

9. P14, para 2: This now needs to be amended in the light of the newly added paragraph. The current wording of the opening sentence (subgroup analyses) is misleading because it only applies to unadjusted analyses. I suggest you delete it.

10. You cannot say in one sentence that most likely these effects are due to confounding (as you do) and then in the next paragraph say “there was an independent effect” arguing as they do that there are elements of “QoL that exert physiological effects” on survival may be the case, but this contradicts what the literature suggests is the case – if the authors are going to go down this route, then they must argue a much more substantive case that overturns the bulk of evidence for confounding being responsible.

11. P15. Para 1: Similarly, you need to re-word this paragraph to reflect the more circumspect interpretation of what your data reflects. The whole tone of this paper needs to be adjusted because the most probable interpretation of your data is that it reflects disease progression. It would be more interesting to discuss what the implications of this are for use of QoL assessment as a clinical indicator. If it does not offer prognostic value, that is not a disaster. QoL wasn’t designed for that. Instead, the QoL measure serves a very important role as a standardized format for acquiring data on patient QoL to monitor symptom progression and identify problems for patients that might be addressed therapeutically. This is the major value from such measures but receives almost no mention.

12. Conclusions: This needs to be amended to accommodate newly added components. Your data does not support your claim that QoL has prognostic utility. The second sentence appears unrelated to the study or paper generally and should be deleted.

Supplementary indicators of confounding:

a. Table 1: I note from Table 1 that for all QoL scales the Mean scores are well below the Median values, suggesting some extreme outliers – some patients with very poor QoL – similarly for symptom scores, generally the Median scores were lower than the Mean values. A small number of extreme outliers suggests the data are non-normally distributed and this may violate the assumptions underlying the Cox regression, indicating a difference that is significant where no such difference really exists.

b. Table 2: The different patterns between loco-regional and metastatic disease – very few differences except for pain and fatigue, and new versus previously treated patients – previously treated much worse profile overall – suggests advanced disease = worse QoL. We know this from page 10 where survival for previously treated patients was about half that of newly diagnosed patients. You mention this but do not take these indicators “on board” when arguing your case.

c. Table 5: This table shows us that when fully adjusted for the influence of other
factors, only physical QoL, gender, stage and prior treatment predicted survival.

Minor compulsory amendments

1. do not include the initials of authors cited in the newly added sections of the Discussion. “Fielding” should be “Fielding & Wong” where it appears.

**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 researched and published in this area myself. Otherwise, I have no competing interests.