Author’s response to reviews

Title: Correlation of three immunohistochemically detected markers of neuroendocrine differentiation with clinical predictors of disease progression in prostate cancer

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Author’s response to reviews: see over
Re: Prognostic impact of three immunohistochemically detected markers of neuroendocrine differentiation in prostate cancer

Dear Robin,

Many thank for yet another opportunity to modify this paper. I have addressed issues raised by the editorial office and Mr. A Roddam. Please find a point by point response to the observations.

Reviewer's comments

1. The sample size for a prognostic marker study is very small. This presents the authors with a number of critical problems. Firstly the small sample size does not permit the authors to investigate whether or not the markers they have investigated are related to prognosis after adjustment for other known prognostic variables, by use of for example a cox regression model. Secondly if they had been able to come up with a predictive/prognostic rule it is normal to develop this on a training set of the data and then validate its use on a validation set – again this is not possible with the current data.

Authors’ response: Agreed, title, objectives and conclusion modified

2. The authors have used 95 samples from 84 people but it does not appear that they have accounted for the correlations that will exist due to multiple samples from the same person.

Authors’ response: All calculations have been re done with denominator of 84. See table 1, 2; methods and result section.

3. The presentation of the results in Table 1 makes it very difficult to interpret. It is not clear which of the results are significant, what the p-values are.

Authors’ response: the p-values have been calculated and mentioned in the table.

4. The selective presentation of the results for CgA in Table 2 also makes it difficult to interpret the overall outcome of the study. Why not also show the results for the 2 other NE markers. Further as stated in point 1 above, it is essential to see if there are differences after adjustment for other prognostic factors.

Authors’ response: the Impact of NSE is also added, data for SYN not included as its overall expression was very low (only expressed in 8 patients).
Editorial comments
We would ask you to further revise your manuscript in response to the referees’ comments. The most important point is point two.

Authors’ response: reviewers recommendation related to Point 2 have now been incorporated and modifications made in the tables and texts.

In addition, we would ask you to modify your title. As the referee(s) have pointed out, at best your study suggests a correlation; it can't actually assess the prognostic impact of the markers.

Authors’ response: title modified
Please re-write your conclusions to be more realistic, and move the limitations to a separate section before the conclusions and expand on the impact of these limitations on the interpretation of your study findings. We would suggest language such as:

"In conclusion this study further supports the theory that focal NE differentiation within classical prostate carcinoma is predictive of poor prognosis, as it correlates with Gleason sum and clinical stage of the disease. In our study, CgA was the best predictor of NE differentiation as it correlated better than the other two markers examined, both with stage and grade of the disease. Given the relatively small sample size of this study, these correlative findings suggest that the prognostic impact of these markers merits further investigation in a larger cohort."

Authors’ response: done
Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Authors’ response: formatting done to conform to the journal style, see references.

Kind regards,

Dr M Hammad Ather