Author's response to reviews

Title: Insulin-like growth factor II mRNA binding protein 3 (IMP3) is overexpressed in prostate cancer and correlates to higher Gleason scores

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Author's response to reviews: see over
Submission of revised manuscript

Zurich, May 3rd, 2010

Dear Sir or Madam,

Please find enclosed the revised manuscript, “Insulin-like growth factor II mRNA binding protein 3 (IMP3) is overexpressed in prostate cancer and correlates with higher Gleason scores”, which we would like to resubmit to BMC Cancer for publication.

Thank you very much for reviewing our work. We found the reviewers comments and suggestions very helpful to revise and further improve this manuscript.

To verify the findings of our initial study we added 173 new cases from a second, independent cohort, which were separately from the first group stained and analysed. Thus, all calculations and tables had to be recalculated. However, the conclusion of this paper remains the same, as IMP3 is strongly expressed in a subset of prostate carcinomas, but fails to be a prognostic marker.

Please find below the responses to the issues raised by the reviewers, itemized point by point. Reviewer comments are in italics, followed by our answers:

Referee #1 (Comments to the Author):

1. Criteria to call something IMP3 positive is not very well established, so using a
20% cut off is arbitrary and not sure why it was selected.

Answer: We absolutely agree that this point has to be clarified further: Although IMP3 was fairly homogeneous expressed, in heterogeneous cases the predominant staining pattern (>80%) was counted, hence staining with subdominant staining (<20%) was not considered. This threshold is arbitrary, however only very few cases were heterogeneous.

2. Not sure what they mean by median of 0 in normal prostate, were there any normal prostate tissue IMP3 positive if so was it weak or strong.

Answer: There was no normal prostate tissue positive for IMP3 (N=31, 0 in 100%).

3. I would suggest the authors recalculate the percentages in the Result sections which have been presented inaccurately. I have recalculated it and they show that more than 80% prostate cancer cases are either negative or 1+ positive. The Figure representing 1+ shows the equivocal nature of the staining and not sure if it will be reproducible in practical real life situations. What is useful in real life situations is 3+ or 2+ staining that group is a small minority in prostate cancer so it questions the usefulness of this test.

I think given the data and further analysis of it shows that it is not sound enough to draw the conclusions that have the authors have done in my opinion.

Answer: We are grateful for this advice. As a second cohort was enclosed, all percentages were recalculated. However, the conclusions remain the same after recalculation. We agree in general that deriving a robust prognostic test from immunohistochemical data is very difficult if at all possible. Since not even the subgroup of moderate to strongly positive cases (14.1%) differs markedly in progression free survival times we do not recommend to invest further efforts in deriving a prognostic test for prostate cancer from IMP3.

Referee #2 (Comments to the Author):
1. In a Kaplan-Meier PSA relapse free survival analysis there was no significant prognostic value for IMP3 ($p=0.153$). This finding was only based on the comparison between patients with IMP3 negative and positive prostatic adenocarcinomas. To reach this final conclusion the additional analysis is suggested. For example, prognostic value of IMP3 can be further determined if the authors compare the patients with moderately to strongly IMP3 positive cancer, and weakly and negatively IMP3 staining cancer.

Answer: We are thankful for this suggestion and enclosed an additional figure, which displays the PSA relapse free survival in a Kaplan-Meier analysis for all IMP3-subpopulations in the supplementary figures (Supplementary Figure 1). Regarding this figure and the distribution of the subpopulations in the Kaplan Meier curves, there is no further prognostic information when redefining the subgroups of IMP3 expression.

2. The data presented in Figure 2 is not clear. The authors need to revise it and make a bigger and clear image or make a table to demonstrate a IMP3 expression pattern in benign prostatic tissue and caner cases.

Answer: We agree that this figure has no additional information to the data presented in the text and therefore took this figure out.

3. The references for IMP3 expression in malignancies were not complete. For example, IMP3 have been immunohistochemically studied in colonic adenocarcinoma, gastric carcinoma, esophageal carcinoma, thyroid cancer, lymphoma, small and large cell neuroendocrine carcinoma of the lung, extrapulmonary small cell carcinoma, cell carcinoma, lymphoma…

Answer: We carefully read the actual literature and added twelve relevant new references to this article.

4. IMP3….. but not in adult tissue in page 5. This may not absolutely true. For
example, it has been reported that IMP3 is strongly and diffusely expressed in germinal center lymphocytes.

Answer: We agree that this statement in its absolute manner is not correct and revised the passage.

5. There are numerous grammar errors in the manuscript. For example, “correlates to” in the title, “but failed prognostic significance” in the abstract, “IMP3 as a independent prognostic marker” in the background…

Answer: The manuscript was carefully edited and revised by the authors to adjust grammar errors and spelling.

We hope that these changes and additions render our manuscript acceptable for publication in BMC Cancer.
Please do not hesitate to contact us for any further information.
We are looking forward to hearing from you.

Kind regards,

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