Author's response to reviews

Title: Periostin is up-regulated in high grade and high stage prostate cancer

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We are very grateful for the constructive remarks and comments and appreciate that you took the time to evaluate our manuscript. We have revised and improved our manuscript according to the issues raised.

To reviewer 1

Minor essential revisions:

All addressed points were attended.

“Major compulsory revisions:

1. The authors should make the presentations of the results more consistent throughout the article to assist the readers in getting the most precise and relevant information from the study. For example, in the Abstract the description of epithelial periostin staining was “Strong epithelial periostin expression was detectable in 142 of 418 (34.0%) of prostate carcinomas”. In the Results, the descriptions were “189 (58.2%) cases had an IRS equal or below 3 (median 3)” and “Only in 7.4% of cases the IRS for the epithelial periostin expression was above 6”. The reader will have to rely on the two tables to put together the information referred to in the Abstract by adding the “Periostin epithelial high” columns of the two cohorts (6 + 136 = 142).

2. Likewise, for the benign tissues, the Abstract states that “strong epithelial periostin expression was detectable in 11 of 38 benign prostate glands (28.9%)”. In the Results, these were described as “14 (36.8%, median IRS 2) (displayed) no epithelial periostin expression”. Along with that, 24 (63.2%, median IRS 0) were said to have displayed no periglandular stromal periostin expression. The readers are once again left with a small mathematical challenge before the authors’ ideas are clearly conveyed. It will help the authors’ delivery a great deal if these data presentations are re-sorted. Further, what's the epithelial staining status of the 24 benign tissues w/o periglandular stromal staining? Also, what’s the periglandular stromal staining status of the 14 benign tissues w/o epithelial staining? In other words, how many are "double negatives"?

To 1./2. The result section was adjusted to the abstract in terms of addition of percentages etc. A passage on benign prostate glands was included describing in more detail the distribution of positive and negative stromal and epithelial periostin expression.

“3. Outside of the two cohorts, the 20 metastatic, 19 hormone resistant, and 38 benign prostate tissues were not very well described. Major conclusive remarks were made of the data gathered from these tissues, so they should be better
described. In particular as the journal does not have page limit issues, there should be more detailed descriptions of these tissues.”

To 3. A review of all pathology reports on hormone resistant and lymph node metastasis was done and the gained information was included in the manuscript.

“4. Prior to this manuscript, only one report by Tsunoda et al. was published on periostin expression in the prostate, with data gathered from a much smaller group of patients. This prior study was acknowledged and described by the authors. The difference in the observed results, however, was not explained. The study by Tsunoda et al. reported an association of prostate cancer (epithelial cell) periostin over-expression with low Gleason scores (6-7), but not with high Gleason scores (8-10). The authors of this manuscript reported an association of high epithelial periostin expression with high Gleason scores (8-10) in the test cohort but not the training cohort. A discussion of this difference in the observations between the two studies should be included in the manuscript. A discussion on the Gleason score/epithelial periostin expression association differences between the two cohorts in this study is also merited.”

To 4. A passage analyzing the differences of Tsunoda et al. and our study was included in the discussion section.

To reviewer 2

“1) In the Result section, the results of the training set and of the test set is somewhat mixed and it may be difficult to distinguish the two results.”

To 1. The section was rewritten in order to present the data in a more consistent manner

“2) I do not understand the inclusion of kappa values on the immunohistochemical staining. The staining is first evaluated by two pathologist, coming to an agreement on how to interpret each tissue core staining. This consensus is to be viewed as a "gold standard". A third assessment can be compared to this "standard" by computing of sensitivity, specificity, and predictive values, but not of kappa values.”

To 2. The use of kappa-values was considered to show the trend of agreement between the pathologists who evaluated the tissue micro array slides. We decided to skip the kappa-value for this publication as it may lead to confusion.

3) I am concerned that using one core each of 0.6 mm or 1.0 mm in tissue microarrays might not be representative of the entire cancer, and several papers have demonstrated that 3-4 cores of 1 mm should be applied. The authors should include a discussion of the consequences of using only one core of each cancer specimen.
To 3. A core diameter of 0.6mm per prostate cancer case runs the risk of selecting a not representative part of the tumour. This is especially of importance in small cohorts. During the preparation of our tissue microarray we reviewed each case very carefully and chose one representative H&E slide to plot the best tumour tissue. We hope to minimize the error of using only one core/tumour. This information has been added to the discussion.

“4) There are a few language errors, especially in the discussion (e.g. p. 9, line 5 "EMT is correlated with tumor progression represents..."; p. 10, l. 7-8 "even if a prognostic value of periostin was existent...")”

“5) Please explain the sentence (p. 10, l. 6-7) "Given th p-value of <0.05 it was not surprising that there was no effect in the test cohort.""

To 4./5. The sentences were corrected.

To the editor and the reviewers

We hope that you find an adequate implementation of the major compulsory and the minor essential revisions in the revised manuscript. We would be happy if these changes render our manuscript acceptable for publication.