Author's response to reviews

Title: IGF-1 Receptor and IGF Binding Protein-3 Might Predict Prognosis of Patients with Resectable Pancreatic Cancer

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Author's response to reviews: see over
Editor-in-Chief

*BMC Cancer*

Dear Editor-in-Chief,

Re; MS: 8981993794382421

IGF-1 Receptor and IGF Binding Protein-3 Might Predict Prognosis of Patients with Resectable Pancreatic Cancer

We greatly appreciate your invitation for us to re-submit our manuscript 8981993794382421 entitled “IGF-1 Receptor and IGF Binding Protein-3 Might Predict Prognosis of Patients with Resectable Pancreatic Cancer” by Hirakawa T, *et al.* We would like to thank the reviewers for detailed comments and suggestions for improvement in our manuscript. We have carefully considered the referees’ comments and have made point-by-point responses as described below. Also, we highlight all changes in the revised manuscript. This manuscript is not being considered in whole or in part by any other journal. All authors are aware of the content of this manuscript. We believe the revised paper will interest the readers of BMC Cancer.

This manuscript has not been published nor submitted for publication elsewhere. All authors of this research paper have directly participated in the planning, execution, or analysis of the study, and that all authors are in agreement with the content of the manuscript. The all of authors have no conflicts of interest to disclose.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki (1975). This study was approved by the Osaka City University ethics committee. Informed consent was obtained from all patients prior to entry.

We appreciate the critical reviews and hope you will seriously consider this report for publication in BMC Cancer.

Sincerely,

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I. We have responded to the Referee #1 comments, as follows.

Referee #1
Thank you very much for the careful reviews of the Referee #1. We correct several points according to the descriptions by the reviewer, as described below. We indicate the changes point by point and highlighted them in the revised paper.

Major Revisions:

1. Description of the Cox model in the Methods section: What is the observation period? Which variables were the time variables used in the Cox model? Which factors were adjusted for in the multivariate model?

   The observation period is overall survival time that was set in days as the period from the time of resection until the time of death. The time variables used in the Cox model is overall survival time. Lymph node metastasis, and expression of IGF1R and IGFBP3 were adjusted for in the multivariate analysis with respect to overall survival. (page 5 line 11-13).

2. Description of results: The authors use the word "correlation" or "were correlated". However, strictly speaking they did analyze correlation, but examined associations.

   We changed correlation to association.

3. Results: "The prognosis of patients with IGF1R-negative and IGFBP3-negative PDAC was significantly correlation with overall survival (p=0.218)" The p-value is not < 0.05... why is stated that there was a significant correlation?

   We corrected as follows. The prognosis of patients with IGF1R-negative and IGFBP3-positive PDAC was not significantly associated with overall survival (p=0.218). (page 8 line 5-7).

4. Discussion: "The prognosis of patients with IGF1R-positive and IGFBP3-negative PDAC was poorer than that of other groups, especially in patients with stage II tumors."

   This statement is in contrast to the following sentences: "The IGF1R-positive/IGFBP3-negative subgroup was the group with the best prognosis."

   We rewrote as follows, The IGF1R-positive and IGFBP3-negative subgroup was the group with the worst prognosis. (page 9 line 30).

5. The comparisons in the bottom diagrams of figures 2&3 are not well explained. Please give the rationale for these comparisons (IGF1R-negative or IGFBP3-positive vs. IGF1R-positive and IGFBP3-negative and IGF1R-negative and IGFBP3-positive vs. IGF1R-positive or IGFBP3-negative).

   In the left bottom diagram of Figures 2&3, we analyzed the significance of IGF1R-positive and IGFBP3-negative group with respect to overall survival, which might clarify the significance of IGF1/IGF1R signaling in PDAC. The data suggested that IGF1R signaling is closely associated with tumor aggressiveness in PDAC.

   On the other hand, the function of IGFBP3 is controversial. Although IGFBP3 is the major IGF carrier protein, some paper reported that IGFBP3 has IGF-independent antiproliferative and proapoptotic effects. The significance of co-expression of IGFBP3 and IGF1R in PDAC remains obscure. We then analyzed the significance of IGF1R-negative and IGFBP3-positive group with respect to overall survival (in the right bottom diagram of Figures 2&3), which might clarify whether IGFBP3 is IGF1/IGF1R signaling-independent or not. Although IGFBP3 expression alone tended to be associated with overall survival (p=0.079), co-expression of IGF1R-negative and IGFBP3-positive PDAC was not associated with overall survival (p=0.218). These data
suggested that the function of IGFBP3 might be dependent on IGF1R expression. (page 10 line 2-13).

II. We have responded to the Referee #2 comments, as follows.

Referee #2
Thank you very much for the careful reviews of the Referee #2. We correct several points according to the descriptions by the reviewer, as described below. We indicate the changes point by point and highlighted them in the revised paper.

1) On page 8, result section under Survival heading: Please check 6th and 7th line. "The prognosis of patients with IGF1R negative and IGFBP3 negative PDAC was significantly correlated with overall survival (p=0.218)". Please revise this sentence as p value is above 0.05 and therefore not statistically significant. Please check p value on line 10 (i.e. p=0.0181) as the p value in Figure three and in Figure 3 legend for prognosis in IGF-1R patients with stage II tumours is shown as p=0.008.

We corrected as follows, The prognosis of patients with IGF1R-negative and IGFBP3-positive PDAC was not significantly associated with overall survival (p=0.218). (page 8 line 5-7).

2) On page 9, discussion section, last line: Please check and correct the sentence "The IGF-1R positive/IGFBP3 negative subgroup was the group with the best prognosis". It should have been be with the worst prognosis!

We corrected as follows, The IGF1R-positive/IGFBP3-negative subgroup was the group with the worst prognosis. (page 9 line 30).

3) Figure 3. Please check the two IGF-1 and IGFBP3 subgroups labelling on these two subgroup figures as both figures had identical labelling (i.e. IGF1R-ve/IGFBP+ve versus IGF1R+ve/IGFBP-ve).

In the left bottom diagram of figures 2&3, IGF1R-negative or IGFBP3-positive groups included 3 groups, the IGF1R-negative & GFBP3-positive group, the IGF1R-negative & IGFBP3-negative group, and the IGF1R-positive & IGFBP3-positive group. Since this expression was confusing, we rewrite IGF1R-negative or IGFBP3-positive groups to "other groups".

Also in the right bottom diagram of figures 2&3, IGF1R-positive or IGFBP3-negative included 3 groups, the IGF1R-positive & GFBP3-positive group, the IGF1R-positive & IGFBP3-negative group, and the IGF1R-negative & IGFBP3-negative group. We rewrite IGF1R-positive or IGFBP3-negative groups to "other groups". (Figure 2 and 3).

4) Also please refer to your specific figures when discussing your results in the discussion section.

We referred figure number in the discussion section.