Author's response to reviews

Title: Predictive Value of Metabolic 18FDG-PET Response on Outcomes in Patients with Locally Advanced Pancreatic Carcinoma Treated with Definitive Concurrent Chemoradiotherapy

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Author's response to reviews: see over
Dear Editor,

To start with, we would like to thank you for considering our study and manuscript as evaluable by the reviewers. We received the comments of all 3 Reviewers and revised the manuscript, final version of which was also uploaded to the system. We appreciated and would like to thank for the feelings and kind recommendations that will increase the value and impact of our study. All 3 Reviewers criticized our manuscript in several aspects, some of which are nearly the same and some are unique. We revised our study in that view and performed some modifications and additions in order to address all issues suggested, and presented them in a point-by-point manner in the responses to reviewers section below. Finally, since we do not live in a natively English speaking country, both initial and revised manuscripts were evaluated by commercial language editing company namely “Biosciencewriters”. However, we are ready to get help from any language editors you recommend for any linguistic problem the Reviewers might experience in our manuscript. We hope we could satisfy the Reviewers’ suggestions which we believe that added too much to our current version of manuscript.

Best Regards,

**Attachment:** Response to reviewers

On behalf of all co-authors,

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Response to Reviewers

Reviewer 1

We appreciate and would like to thank Reviewer 1 for his/her kind recommendations of paramount importance which we believe will significantly increase the quality of our current revised version of the manuscript.

Minor Essential Revisions

1- Comment: When during the 12 weeks post-radiation PET was done? They report that they gave the gemcitabine on 3 week cycles for 4-6 course or 12-18 weeks. So were all PETs done at completion or during the gemcitabine?

Response: All FDG-PET-CTs were performed at 12 weeks post C-CRT period. Therefore, all patients received 2 to 4 cycles of gemcitabine prior to first PET evaluation. When compared according to median SUV\textsubscript{max} change, there were no significant differences between the groups with lesser or greater response in terms of gemcitabine cycles received. Lesser and greater responders received average 3.2 (range; 2-4 cycles) and 3.0 cycles (range; 2-4 cycles) of gemcitabine, respectively. This issue has been clarified and added to the “Results” section as recommended.

Regarding the possible impact of total cycles of adjuvant gemcitabine received by the patients on OS, LRPFS, and PFS, we also compared two response groups according to cycles of gemcitabine received. Again, there were no significant differences between two groups. Lesser and greater responders received average 4.6 (range; 4-6 cycles) and 4.9 cycles (range; 4-6 cycles) of gemcitabine, and present survival outcomes were preserved for each group, respectively. This issue has also been clarified and added to the “Results” section to an effort to clarify doubts about the possible impact of gemcitabine cycles on survival outcomes.

Major Compulsory Revisions

2. Comment 2. Their division of responding and non-responding patients seems arbitrary. They said they split patients “response greater versus lesser than the mean difference.” It is not clear that this is the best division. In fact, they point out that this divided their patients into 21 patients with a better PET response and 11 with a poorer response. How about using the median difference, which would divide these into two equal groups or ROC analysis to pick the cut point?
Response 2. As recommended, patients were re-grouped according to the median SUV\textsubscript{max} change, which distributed patients in a more balanced way (16 in each), and all statistics were revised according to this new patient distribution between two response groups. Therefore, results are presented and discussed according to these new findings.

3. Comment 3. They used the SUV\textsubscript{max} as their measure of activity, but this really just represents a single pixel over the whole tumor. It can be subject to significant noise. Furthermore, it may be hard to generalize SUV\textsubscript{max} from one scanner to another since the pixel size and resolution can vary. Did they also try to use SUV\textsubscript{peak} or some variation of SUV\textsubscript{mean}? This would be very helpful. Some investigators have also tried other approaches such as total metabolic volume (SUV x volume), but this still requires one to set some boundaries on the tumor.

Response 3. As pointed by the Reviewer, various metabolic parameters are currently investigated in various tumor types to obtain a better predictive parameter for treatment outcomes. However, although SUV\textsubscript{max} may potentially represent a single pixel over the whole tumor volume, it is the most commonly investigated parameter at other tumor sites. Additionally, as signified by the Reviewer, it may be hard to generalize SUV\textsubscript{max} from one scanner to another since the pixel size and resolution can vary. As all of our eligible patients had their pre- and post-treatment PET scans at our institution with the single available PET scanner, we believe that all technical and measurement conditions were the same for all patients, and therefore, present patients group should theoretically be not affected by such variations. Herein, we chose SUV\textsubscript{max} based on the available data at other tumor primaries to an effort to be parallel with the majority of existing literature. In case of SUV\textsubscript{mean}, which by definition takes the average of all SUV values over the whole tumor does not give any spatial information about SUV variations over the large tumor volume. However, we reanalyzed our data by obtaining the SUV\textsubscript{mean} values, and significance of our present observations was preserved again with just few changes in the numerical values. As other two reviewers made no comment on this specific issue, we are anxious whether addition of such new parameter may confuse them. However, if indicated we are ready to add these results in another revision, too. In this setting, we believe that, various parameters deserve to be investigated in another study with larger patients cohort. Enlightened with this valuable recommendation, we are planning to study this subject comparatively in a larger trial that will include at least 100 patients to achieve more
reliable outcomes. We would like to give our special thanks to the reviewer for this nice idea.

4. **Comment 4.** The definition of locally advanced and unresectable pancreatic cancer is often confusing and varies from physician to physician. How did they define it? All they state is that “Disease extent was determined by radiological studies and laparoscopy/laparotomy.” What imaging studies were done, e.g. did they do CT with a pancreatic protocol, MRI, EUS? How many patients were judged unresectable by imaging alone vs at laparotomy?

**Response 4.** As pointed by the Reviewer, excluding the medical inoperability criteria, the definition of unresectable LAPC is still an issue of large variance between different gastrointestinal surgeons. The selection of patients for resection is heavily dependent on local treatment philosophy and criteria to accept patients for resection. Moreover, attitudes and indications are changing continuously. At our institution unresectable tumors are defined as “Tumor involving the celiac axis or the superior mesenteric artery” that is the same definition in AJCC staging system for exocrine pancreas tumors. Our definition for locally advanced carcinoma involves patients with $T_4N_{0-1}M_0$ disease, which corresponds to Stage III patients according to AJCC staging system. These two issues have been clarified in the “Methods” section of this current version.

Our current standard institutional protocol for radiologic evaluation of patients with pancreatic carcinoma includes abdominal CT, MRG and/or MRCP. We also restage patients with FDG-PET-CT for RTP prior to C-CRT. All eligible patients underwent laparoscopic or laparotomic examination and biopsy of primary tumor mass, enlarged or metabolically active regional lymph nodes, and isolated single organ metastasis respecting the current standard institutional staging procedure for pancreatic carcinoma. This issue has been clarified in the “Methods” section as recommended.

5. **Comment 5.** Table 1 should be deleted, since they just give the EORTC PET response criteria and is not needed in this manuscript. Given the limited number of patients in the study a table summarizing the results in each patient would be helpful. This could include the baseline and post-treatment SUV, the PFS and OS and resection results. This way others could plot and analyze the data as they saw fit.
Response 5. Table 1 was deleted as recommended, and a table was added to current version of the manuscript summarizing the specified parameters recommended by the Reviewer (Table 2).

Reviewer 2

We appreciate and would like to thank Reviewer 3 for his/her worthwhile review and kind comments which we believe will significantly increase the value of the current revised version of the manuscript.

Major compulsory revision

1. Comment 1. The authors claim that the PET-response had independent prognostic importance when other factors were taken into account in multivariate analysis, using the Cox model. However, they do not state which other factors were taken into account (are all the really important ones included?), how these factors were scored in the analysis, how the analysis was carried out (e.g., forward or backward selection), and which factors were in the final model. This information is crucial when evaluating whether PET-response really has independent prognostic significance. When the multivariate analysis is done it must be taken into account that there are only 26 events (failures) in total, and that therefore only a limited number of different factors can be analyzed in a Cox model at the same time. Also, the assumptions underlying the Cox model (proportional death intensities) must be demonstrated to hold. Statistical assistance is advised.

Response 1. Table 1 which included the specified potential prognostic factors has been added to this revised version of the manuscript, and groups were compared to demonstrate whether there exist any difference in between which may favor one group over the other one. Respecting the recommendation by the Reviewer, an expert on medical statistics revised the data. As a result, as anticipated by the reviewer, in the “statistical analysis” part of the “materials and methods” section, we included other factors we used to demonstrate the relationship of $\text{SUV}_{\text{max}}$ difference (greater or lower than median) and these known prognostic variables with survival. We did not give any information regarding the details how we performed the Cox Regression analysis (forward or backward selection methods) in the initial manuscript since we were not used to do that. Regarding the small size of the study and uncertainty of these factors, we had chosen enter selection method. By consulting our data with the statistician, we recognized that preferring enter selection method would be
reasonable. Therefore, we tried to supply the issues stated by the reviewer. Nevertheless, if needed more, we are happily ready to address them as well in the second revision.

**Minor essential revision**

1. **Comment 1.** The numbers in Table 2 to not add up. With a total number of patients of 32, 16 males and 8 females is too little

   **Response 1.** Regarding the recommendations given by the Reviewer 1, Table 1 in the initial manuscript was deleted, and a new table with the same name was created. This new table includes all findings in the previous Table 1 as well as other information related to the factors of prognostic significance as necessitated by the Reviewer 1. All numerical data presented in the Table 1 were given with more attention.

**Reviewer 3**

We appreciate and would like to thank Reviewer 3 for his/her nice feelings about our efforts on the subject, and for the comments of paramount importance which we believe will significantly increase the impact and relevance of results presented in our this current revised version of the manuscript.

**Major Revisions**

1. **Comment:** I believe the most significant issue I have with the manuscript is one that is difficult to fully address in the setting of pancreas cancer where early progression is common. The authors use an arbitrary cutoff of \( \text{SUV}_{\text{max}} \) reduction above \( (n=21) \) and below \( (n=11) \) the mean to create 2 comparative groups at the time of the 12 week follow up scan. In the lesser responsive group 6 of the 11 patients show local progression by the 12 week scan. The authors are essentially then comparing a group of non-progressors \( (n=21) \) to a group which contains those that have already progressed \( (n=6) \) and a minority \( (n=5) \) of patients that have not progressed. The finding of a difference in local control, progression free and overall survival is therefore not surprising.

   **Response 1:** The same issue has also been pointed by Reviewer 1. Best way to distribute patients in a more balanced way is to use median value rather than the mean value. Therefore, as recommended by reviewer 1 and indirectly by Reviewer 3, patients were re-stratified according to the median \( \text{SUV}_{\text{max}} \) that resulted in 16 patients in each group.
Thereafter, all statistics have been revised according to this new parameter, and results are presented and discussed according to these findings, as recommended. In summary, although the OS, LRPFS, and PFS changed numerically statistical significance between groups did not change, stressing the validity of predictive significance of metabolic response following C-CRT.

One possible way to prevent or minimize the biasing effect of early progressive patients on outcomes may be to censure them during statistical analysis. However, being aware of the fact that metabolic changes during treatment or at follow-up periods may alert for disease progression or unresponsiveness to treatment earlier than the anatomic changes, we did not perform such an analysis. Alternatively, in this revised version we also categorized patients into 3 groups; Group 1: Response \( \geq \) median SUV\(_{\text{max}}\) (N=16); Group 2: Response \( \geq \) median SUV\(_{\text{max}}\) (N=11); and Group 3: early progression (N=6), respectively. Results of these analyses are also presented in this revised manuscript and a new figure called “Figure 3” depicting the survival curves of these 3 groups.

2. Comment 2. Also, the timing of gemcitabine post chemoradiation is not definitively addressed. How many cycles of gemcitabine did patients receive prior to the 12 week scan? Was there a difference among patients?

Response 2. All FDG-PET-CTs were performed at 12 weeks of post C-CRT period. Therefore, all patients had received 2 to 4 cycles of gemcitabine at the time of PET evaluation. When compared, there were no significant differences between two groups with lesser or greater SUV response in terms of gemcitabine cycles received. Lesser and greater responders received average 3.2 and 3.0 cycles of gemcitabine, respectively. This issue was clarified and added to the “Results” section as recommended.

3. Comment 3. The change in SUV is deemed significant on multivariate analysis but the other factors analyzed on multivariate analysis are never mentioned. Did they include age, sex, original SUV, tumor volume, ECOG, tumor location, stage…?

Response 3. In first step, we compared two patients groups as depicted in Table 1, to demonstrate whether there exists any difference in between regarding the factors with potential prognostic significance. Then, we performed univariate analysis in which the SUV\(_{\text{max}}\) change relative to median value appeared as the unique factor with prognostic significance on OS, PFS, and LRRFS. In multivariate analysis, besides SUV\(_{\text{max}}\) change, age, gender, tumor localization (pancreatic primary), ECOG, nodal stage, pre-treatment
SUV, and Hb levels were included. Results of these analysis revealed that SUVmax change retained its significance on either of survival end-points. These issues have been clarified in this revised manuscript.

4. **Comment 4.** In general I felt that the lengthy references to FDG-PET as a tool for delineating malignant from benign pancreatic masses, as well as the benefit of FDG-PET for GTV delineation where tangential to the main thrust of the manuscript and I feel the 2nd paragraph of the introduction, and the 1st 3 paragraphs of the discussion where off point.

**Response 4.** Regarding the main objective of the study, it may be appropriate to omit or shorten these paragraphs as recommended. However, as other two reviewers have some comments that are favorable or needing some minor revisions we apologize and ask for whether it is acceptable to retain these paragraphs.

5. **Comment 5.** The 3rd paragraph of the introduction omits several studies outlining the utility of PET in predicting clinical outcomes in pancreatic cancer including those by Lee, SM; Schellenberg, D and Okumato, K, nor does it stress a very similar study by Choi, M (reference 26) that used a 50% decrease in SUV post chemotherapy as a cutoff to evaluate prognosis.

**Response 5.** All recommended studies except for the study by Okumato, K were referred in specified paragraph of current revised manuscript. Our Pubmed search for Okumato, K revealed no result for referred author. However, if necessary and provided, we will refer this study as well with great pleasure.

6. **Comment 6:** The stated conclusions were not the focus of this study. For example, other studies have noted extremely low rates of regional failures in pancreas cancer. To conclude that FDG-PET-CT reduces geographical misses versus CT alone without any direct comparison of the two in the current study is misleading.

**Response 6.** Our second conclusion was just an anticipation which needs to be addressed in a randomized trial, rather than being solid evidence based conclusion. Nevertheless, reviewer’s comment is current and more relevant, therefore specified remark was removed from this current version, as recommended.

**Minor Revisions**
1. **Comment:** In the results section of the abstract it is unclear how the groups of greater versus lesser SUV\textsubscript{max} change are defined (this is stated only later in the manuscript)

**Response:** We redefined the criterion that we used for comparison between two groups according to the median difference (%) between pre- and post-treatment SUV\textsubscript{max} values (Lower vs. greater than median change). Therefore, “Methods” section of the abstract has been replaced by:

“Thirty-two unresectable LAPC patients received 50.4 Gy (1.8 Gy/fr) of RT and concurrent 5-FU followed by 4 to 6 cycles of gemcitabine consolidation. Response was evaluated by FDG-PET-CT at post-C-CRT 12-week. Patients were stratified into two groups according to the median difference (%) between pre- and post-treatment maximum standard uptake values (SUV\textsubscript{max}) as an indicator of response for comparative analysis.”

2. **Comment:** Background, 1st paragraph, end of second sentence reads “chemotherapeutics and/or sufficient doses…” perhaps specifying that they are referring to radiation doses versus chemotherapy doses with “chemotherapeutics and/or sufficient RADIATION doses…”

**Response:** The stated sentence was revised as recommended and replaced by; “However, local/regional relapse rates (42-68%) are still unacceptably high [1,2], and may be related to the limited radiosensitizing efficacy of available chemotherapeutics and/or insufficiency of conventionally used radiation doses of 45-50.4 Gy [3].”

3. **Comment:** Background, 2nd paragraph, end of 1st sentence…”and systemic extend of disease in tumor sites…” I think it should read “and systemic extend of disease in MANY tumor sites” or “SEVERAL tumor sites”…

**Response:** Stated sentence was revised as recommended and replaced by;

“Studies investigating FDG-PET have demonstrated significantly better sensitivity, specificity, and accuracy rates for FDG-PET over CT, in defining local, regional, and systemic extent of disease in several tumor sites, including the pancreas [6-8, 10, 12-17].”

4. **Comment:** Results, 1st paragraph, ~7th sentence “Sixteen patients developed in field recurrences, 3 of which were isolated and 13 were distant relapses” should be changed to “Sixteen patients developed in field recurrences, 3 of which were isolated and 13 were CONCOMITANT WITH distant relapses”
Response: Stated sentence was revised as recommended;
“Sixteen patients (50.0%) developed infield recurrences, 3 (9.4%) of which were isolated and 13 (40.6%) were concomitant with distant relapses.”

5. Comment: Discussion, 4th paragraph. I disagree with the sentence “Gemcitabine, with its strong radiosensitizing properties, is promising, but its utility remains to be investigated.” Studies by Brade, Murphy and others have combined gemcitabine with radiation effectively.

Response: Our knowledge and feelings about the superiority of gemcitabine in management of pancreatic carcinoma is exactly similar with the Reviewer, and what we meant was not that there exists no evidence about use of gemcitabine, rather we aimed to mean that there exists no direct evidence about its superior efficacy in terms of metabolic response in setting of LAPC. We believe that, a randomized comparison between 5-FU and Gemcitabine by utilizing FDG-PET based SUV$_{\text{max}}$ change, (or other metabolic factors) may provide beneficial evidence about their radiosensitizing potentials Therefore, to clarify the sentence it was revised and replaced by;
“Gemcitabine, with its strong radiosensitizing properties is promising [38, 42, 43], but impact of its concurrent use on treatment outcomes remains to be investigated in the era of metabolic response assessment.”

6. Comment: In figures 1 and 2 the Y axis is “Survival (%)” but the demarcations of the Y axis are 0,2 to 1,0 (the 0,8 demarcation is missing the comma). These should be changed to 20-100 to be concordant with the (%) symbol.

Response: Recommended changes have been made in all figures of this current version.

Discretionary revisions

1. Comment: Emphasizing how SUV$_{\text{max}}$ changes effect prognosis could be accomplished by reporting the differences in overall survival between “responders and non-responders” groups differentiated by the median SUV$_{\text{max}}$ change or a strict 50% reduction in SUV$_{\text{max}}$ as Choi et al. report. This might at strength to the authors’ conclusions.

Response: Our mean SUV$_{\text{max}}$ change was -49.7% for the whole group which is almost the same Choi’s 50%. However, considering the unbalanced patient distribution between two groups (11 non- or less responders vs. 21 greater responders) at this cut-off point, as the Reviewer rightfully stated in “Major Revision 1”, this may lead to unintended over or
under-estimation of the outcomes of one group against the other one. Therefore, we reanalyzed our data according to the Reviewer’s recommendation and used median SUV\textsubscript{max} change to obtain a balanced patient distribution between the groups for trustable statistical outcomes. Changes were made all over the manuscript as needed. Additionally, as specified in our response to “Major Revision 1”, results of analysis of treatment groups based on their response and progression status was added to this revised version of the manuscript.

2. **Comment:** The median SUV\textsubscript{max} seems high versus previous pancreas studies. I’m not sure this needs to be addressed but could be compared with other studies.

   **Response:** In an effort to prevent the possibility of incorrect SUV measurements or data records, we revised the data of each patient but we could not find any miss record or incorrect measurement in any of the 32 patients. Therefore, with the available data it is not possible to assign such relatively higher SUV values to a reasonable cause.

3. **Comment:** Why was the 12 weeks post CRT chosen as the time to evaluate response?

   **Response:** As the metabolic response assessment with serial FDG-PET is a new approach in pancreatic carcinoma, there is no consensus on the optimal timing of first and consequent follow-up FDG-PET imaging. Our current 12 weeks choice is just related with the “national health insurance politics” which does not allow repeated PET imaging in less than an interim of 120 days. This was the shortest and most reasonable time in its condition, reflecting our effort to assess response in shortest post-treatment period without dealing with bureaucratic problems. However, like many other tumor sites, we believe that a study addressing serial metabolic response assessments such as mid-C-CRT and post-C-CRT 0, 4, 8, and may be 12\textsuperscript{th} week as utilized here may be more beneficial in determining the optimal timing of FDG-PET based response assessment in pancreatic cancer patients. In short, although not arbitrarily, 12 weeks period was chosen as the shortest possible time as a result of our national health politics. This issue was enlightened in the methods section of this revised manuscript.