Revision Note, Manuscript ID 68284, World Journal of Gastrointestinal Oncology

Cover Letter

Dear Editors

Please find attached the revised version of the article entitled “CT-based Radiomic to Predict Resectability in Locally Advanced Pancreatic Cancer Treated with Intensive Chemotherapy and Ablative Radiation Therapy”, that we submit to World Journal of Gastrointestinal Oncology for possible publication. We would like to thank the Reviewers for their insightful comments that improved the quality of our paper. We hope that our revisions will resolve their concerns and questions. A detailed point-to-point response is appended below. The revised version of the manuscript was seen and approved by all coauthors.
The English language of the manuscript has been revised by a native speaker.

Kind regards,

Nicola Simoni, MD

Reviewer 1

In this study, CT Radiomics was used to predict whether pancreatic cancer could be resected after neoadjuvant therapy, and a significant AUC value was obtained. This paper is novel and has important clinical value. However, there are still some problems.

1.Title: "Treated with Risk Adapted Ablative Radiation Therapy" or "Neoadjuvant chemoradiotherapy"?

Thank you so much for this suggestion. The title has been modified in "CT-based Radiomic to Predict Resectability in Locally Advanced Pancreatic Cancer Treated with Intensive Chemotherapy and Ablative Radiation Therapy".

2. A total of 71 cases were included in this study, of which 32 underwent exploratory laparotomy and 19 underwent surgical resection. So, there were 19 cases in the resectable group and 62 cases in the unresectable group? Please clarify.

Thank you for this observation. In the final analysis there were 19 patients in the resected group and 52 in the non-resected group. This point has been clarified in the manuscript in the abstract and in the Statistical analysis section (L242 "For the analysis, patients surgically explored (*e.g.* exploratory laparotomy after RT) but not resected were integrated into the non-resected group").

3. Does this study only include pancreatic ductal adenocarcinoma?

The study only includes pancreatic ductal adenocarcinoma. This point has been highlighted in Matherials and Methods – Study design section, where we report "inclusion criteria for Risk Adapted Ablative Radiation Therapy (RAdAR) were: histologically-proven pancreatic ductal adenocarcinoma,…".

4. What clinical data were included? What is the predictive power of clinical data? Whether combine clinical data with radiomics feature can lead to an improved predictive power?

The authors thank the reviewer for pointing out that the description of the clinical data included in the model was not satisfactorily described in the Material and Method and Results sections. The following changes have been applied:

L240:

Removed: Statistical analysis of radiomic and clinical data was implemented in R (v3.6.3).

Added: Statistical analysis of radiomic and clinical (tumor location and size, CA19-9 value at diagnosis and after chemotherapy, clinical stage, chemotherapy regimen and radiation approach) data was implemented in R (v3.6.3).

Clinical data were rarely selected by LASSO and do not compare in the final model. In order to answer your question and quantify the predictive power of clinical data, we have run the training process 100 times and, for each repetition, LASSO selected 3.38 variables, on average. Among 100 repetitions, clinical variables were selected only 6 times, corresponding to 2% of the total variables selected. This indicate that, in these specific subsets, some clinical information might present a relevant predictive power but, since it occurs only few times, this is not statistically significant for the whole dataset. It is important to validate all the analysis step using cross-validation and repetitions because, especially dealing with limited database, it is often possible to find a model that well explained a particular combination of training-test subsets but that is not generalizable.

L284:

Added: Among the 100 repetitions of the Training process, the clinical variables were rarely selected from LASSO. On average, 98% of the selected variables were radiomic features, indicating a higher predictive power of radiomic data with respect to clinical data.

5. The abstract method part mentioned "The discriminating performance of each model". How many models have been built in this study? Isn't there just one model?

Thank you for the comment, we agree that, given the context, the mentioned sentence is not clear in the present form. The model performance was investigated through a repeated training and test, but the final model was built on the whole dataset. This detail was not included in the abstract for the sake of brevity, but now we clarified the fact that many similar models were built on different data subsets during the performance assessment.

We added the word repeatedly on L87:

Removed: Patients were divided into training and validation set.

Added: Patients were repeatedly divided into training and validation set.

6. The results of the summary are too lengthy and need to be condensed.

Thank you for the observation. The suggested correction has been made in the manuscript.

7. After applying the validated model to the entire dataset, the effectiveness of the model in the entire dataset should be obtained. How did the authors get the last four features?

LASSO procedure automatically selects an optimal set of features defined according to a scoring rule. This means that for each repetition of training-test subsets we obtained several variables (from 1 to 5 variables). We did not report these variables for brevity, but we have reported only those variables selected in the final assess of the model when we train the validated model on the entire database to have more statistical power. Indeed, differently from the models based on the different training sets, the complete model (*i.e.* based on the whole dataset) exploits all the information available at present. Furthermore, since two strongly correlated variables contain about the same information, the choice of which one to remove is somehow arbitrary; for this reason, we reported all the variables strongly correlated with at least one of the four selected variables in Figure 4 (*i.e.* the correlation map) that might be identified in future studies.

8.“Entire dataset” refers to the dataset containing the training set and the validation set. Why the AUC value bigger than the training set and the validation set?

The number of patients included in the LASSO selection is different basing on whether it is performed during the performance assessment (training has 70% of the cases) or with the whole dataset (100% of the cases). For this reason, the model trained on the whole dataset can benefit of a larger amount of data and the corresponding AUC will be higher.

Reviewer 2

The authors described that new radiomic model based on CT- radiomics could help predict resectability in LAPC treated with neoadjuvant therapy, suggesting a promising role in the context of a complex long-course downstaging, challenging the indication to surgery. This article is very interesting and valuable for pancreatic cancer treatment.

Thank you for your positive comment.

Major limitation

1. radiomic feature extraction should be more precisely explained by using figures.

Thank you for this observation. A new figure (Figure 1) describing radiomic feature extraction has been included in the manuscript.

2. The pathological findings of surgical resected specimens should be evaluated by comparing with radiomic model based on CT.

We understand your point. The correlation between tumor pathological response and radiomic features is undoubtedly intriguing. We have indeed explored this correlation in previous paper (e.g. DOI: 10.3389/fonc.2020.599907). However, the limited number (19 patients) of resected cases in the present series does not allow, in our opinion, a robust and adequate correlation between radiomic features and TRG.

Based on your input, we have added a comment about this remarkable topic in the discussion section (see L372).