Author’s response to reviews

Title: Postoperative chemoradiotherapy is superior to postoperative chemotherapy alone in squamous cell lung cancer patients with limited N2 lymph node metastasis

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you very much for your email and comments concerning our manuscript entitled “Postoperative chemoradiotherapy is superior to postoperative chemotherapy alone in squamous cell lung cancer patients with limited N2 lymph node metastasis” (ID: BCAN-D-19-00741).

We reviewed all comments carefully and revised the manuscript according to the reviewers’ comments. The followings are the responds to the reviewer’s comments.

Reviewer Lijun Xue (Reviewer 1):

1. As for the assessment of roles of postoperative adjuvant therapy in NSCLC patients, disease-free survival (DFS) is usually used as one of the most pivotal research endpoints because many factors after the stage of adjuvant therapy (especially after recurrence) will significantly influence overall survival (OS), such as genotypes and EGFR TKIs and checkpoint inhibitors and so on. But in this study, OS has been chosen as the only one standard to analyze effects of adjuvant CRT and CT in NSCLC.
Response: Thank you very much for your suggestion! It is true that the disease-free survival (DFS) is also a pivotal research endpoint and should be analyzed to evaluate the effects of POCRT and PCT alone in NSCLC. Unfortunately, we are not able to analyze the DFS time for there are not enough clinical data for DFS calculating in the current study.

2. As for the N2 issue, which is repeatedly mentioned as one of key factors indicating superior survival benefit from CRT than from CT not only in the title but in the whole text including the part of discussion. In addition, researchers have used a propensity score matching (PSM) analysis to "compensate for differences in baseline characteristics" to improve the accuracy of present study.

However, according to the related results shown in Fig.2 G and H, "...the survival differences between POCRT and pCT in the various subgroups were not statistically significant..." (Page 9, line 37-40) after PSM analysis, although with significance before matching. And, the only one significant factor indicated in the study may be the histology of squamous cell type.

Response: Thank you very much for your careful review. Yes, as you find that the squamous cell lung cancer is the only one subgroup achieved survival benefits significantly from POCRT before or after PSM in the study. Patients with pN2a or total number of MLNs ≤7 had not achieved survival benefits after PSM, however, for that: 1) patients with pN2a or total number of MLNs ≤7 can obtain very significant survival benefit from POCRT before PSM, 2) limitation to patients with pN2a or total number of MLNs ≤7 enrolled after PSM, which might cover up the fact that those patients may benefit from POCRT, and we can only make speculation that these patients may benefit from the POCRT in the current study.

3. Page 8, line 9-15, "...with the exception of surgical modality and total number of chemotherapy cycles (Table 1), which did not affect patient survival..."

However, according to the related results shown in Tables 1 and 3, operation modality and CT cycle numbers did affect...before matching but did not after matching, and did affect...by univariate analysis but did not by multivariate analysis.

Response: Thank you very much for such correction! We have corrected the results in the revised manuscript.

4. Page 8, line 51-54, ".. >7 MLNs had a significantly… with ≤7 MLNs (P=0.001)."

However, there are no related data about P=0.001 can be found in the essay (Tables or figures). As Fig2 E & F shown, both p values before or after matching are not 0.001.
Response: Thank you very much! We add the P value in the revised figure.

5. Page 9, line 9-12, "...POCRT benefited patients with squamous cell histology, without lymphovascular invasion, ≤7MLNs or N2a (Figure 2A, 2C, 2E and 2G)."

Page 10, line 37, ".. POCRT achieved a significant survival benefit in N2-NSCLC."; line 46-48, "...indicating that POCRT should be considered for patients with N2-NSCLC..."

Page 11, line 12-15, ".. patients with N2a (whether N2a1 or N2a2) treated with POCRT achieved a significantly better survival..."; line 26-29, "...>7 MLNs, gained a significant survival benefit from POCRT ..."; line 51-54, "...the conclusion that POCRT may improve the survival of N2-NSCLC patients ..."

Page 13, line 1, "...POCRT may be specifically recommended to N2 patients..."; line 23, "...particularly those with limited N involvement and T4 disease..."

However, as figures shown, these p values (vascular invasion, MLN7, N2a) are of significance only before matching but not after matching. So, how to explain the role of PSM analysis in this study, which can influence the conclusion mentioned above or not?

Response: Thank you very much for your question and suggestion. As we all known that, PSM was used to balance the bias due to the retrospective nature of this study to make the results more accurate. However, limitation to the cases enrolled, the PSM method was not perfect in the current study which leaded our conclusion unconvinced.

6. Page 12, line 18-20, ".. our results strongly suggest that POCRT should be recommended for T4N2 patients.."

However, for this subgroup of T4N2, what are the related data in this study to support it?

Response: Thank you very much for your suggestion! However, for there was only one patient with T4 disease after PSM, we cannot provide survival figure in the current study.

7. Some points such as follows associated with the language may need to be improved.

(1) page 2, line 8-11,

"..of postoperative chemoradiotherapy (POCRT) following surgery in non-small-cell lung cancer patients.."
Reviewer Fang Yang (Reviewer 2):

1. No detailed figure legends were provided for figures, especially for figure 2.
Response: Thank you very much! We revised them in the revised manuscript.

2. The paper didn't show the ROC curve of the cut-off number of MLNs.
Response: Thank you very much for such correction! We added figure according in the revised manuscript.

3. In your conclusion, you mentioned POCRT should be recommended particularly for T4 disease. I think it's not strong enough to draw that conclusion because of too small samples in this subgroup.
Response: Thank you very much for such suggestion! We correct the conclusion in the revised manuscript.

Reviewer Chong-Rui Xu (Reviewer 3):

1. This retrospective study was approved by IRB in 2018 and the data was collected between 2004 to 2014. Why the patients can sign the informed consents before the treatment?
Response: Thank you very much for your question! Yes, it is a retrospective study, but in fact, all patients enrolled in the current study provided written informed consent prior to treatment and they were anonymized prior to analysis.

2. Survival curves were produced by the Kaplan-Meier method and the result of OS comparison should list the HR instead of survival rate.

Response: Thank you for your suggestion! We added the HR in the revised manuscript.

3. In univariable analysis, how to define the impact of CTV dose in the pCT group? The univariable and multivariable analysis need to be verified by statisticians.

Response: Thank you very much your correction! We correct the CTV dose in the pCT group and verified the univariable and multivariable analysis.

4. After PSM, there was no significant difference between the POCRT and pCT groups. The difference was observed only in 29 squamous cancer patients. The sample size was too small to identify any difference in two groups.

Response: Thank you very much for your review! Yes, this is one unovercome limitation of the current study.

5. The conclusion of a retrospective study should be conservative. It only demonstrated some trend, not any evidence for recommendations.

Response: Thank you very much for such suggestion! We revised the conclusion in the revised manuscript.

Thank you very much for your comments and suggestion!