TRANSLATIONAL LUNG CANCER RESEARCH

Peer Review File

<mark>Reviewer A</mark>

You have submitted quite a fascinating manuscript and I sure would like to see it printed soon. I think that there are a few improvements that should be made before publication.

In Result part line 168
Authors described "Impact of primary tumor resection on survival outcomes in IV NSCLC patients".
I think it better to change "Impact of primary tumor resection on survival outcomes in stage IV NSCLC patients".
Response: Thank you very much and we appreciate the attention to precise language. We have changed the wording as your suggestion.
Changes: Impact of primary tumor resection on survival outcomes in stage IV NSCLC patients

In Result part line 177
I think it better to change "Primary tumor resection as an indepedent prognostic factor for survival in stage IV NSCLC patients".
Response: Thank you very much for the comment. We have changed the language as your suggestion.
Changes: Primary tumor resection as an independent prognostic factor for survival in stage IV NSCLC patients

In Disucussion part line 228
You do not need to put space before "comma"
Response: Thank you very much for the comment. We have accordingly made the change as your suggestion.
Changes: We delete the space before "comma".

<mark>Reviewer B</mark>

SUMMARY
The authors analyzed the Surveillance, Epidemiology, and End Results (SEER)

database to determine the impact on cancer-specific survival (CSS) for patients with clinical stage IV NSCLC who underwent surgery or non-surgery. After 1:1 PSM, the authors found that surgical intervention was independently correlated with longer median CSS time (19 vs. 9 months, p<0.001). And then the authors created a predictive model to identify optimal candidate for surgical resection of the stage IV NSCLC. I have some comments and questions.

Comments:
Methods:
Line 164: 1. Baseline characteristics before and after PSM should be both presented for our readership.

Response: Thank you very much for your comments. We added the baseline characteristics after PSM in Table 2, please kindly check.

Changes: After the 1:1 PSM, 4,872 stage IV NSCLC patients treated with or without primary site surgery were enrolled in the following survival analysis. Baseline characteristics, including age, gender, race, TNM stage, primary site, laterality, histology, differentiation, chemotherapy, radiation therapy and surgery to distant tumor, were all balanced (P>0.05), the detail was presented in Table 2.

Results:
Please explain the definition of differentiation of tumor and when it was obtained? If this was obtained preoperatively, the small specimen could not represented the whole tumor; if it was obtained from the primary tumor resection, the neoadjuvant also alter its' characteristics.

Response:
Thank you very much for your valuable comments. SEER database did not offer the information when and how the tumor specimen obtained, which would bring such confusing as you mentioned. We admit your point of view and constructed another model and draw a nomogram without differentiation information for reader to use. Please kindly check.

Changes: Because the preoperative small specimen could not represent the whole tumor and the neoadjuvant therapy might alter tumor characteristics, not all cases represented accurate differentiation information. As a consequence, we constructed another model without differentiation information, the nomogram is presented in Supplementary Figure 3.

Please explain tumor position definition since it was an independent factor account into

the nomogram.

Response: Thank you for your comments. We have added this into method part.

Changes: We evaluated age, gender, TNM stage, histologic type and differentiation grade and position (over lapping lesion, bronchus tumor, lobe tumor) as possible clinical candidate predictors for surgery benefit.

Line 220: The standard treatment for stage IV lung cancer is induction systemic treatment currently, and radical consolidative therapy is only applied for non-progression patients or solitary metastasis. In your nomogram, there was no assessment regarding to the systemic therapy evaluation, please explain this. Same argument also noted in Line 239. I just wonder that whether the authors advocate primary lung resection before induction systemic treatment if the model predict the patient will benefit from primary tumor resection? Or the author could tell us what critical point should we apply this model and make our decision for patients who should receive primary tumor resection?

Response: Thank you very much for your consideration and the comments. Systemic therapy information is not completed in SEER database, thus this predictive model did not include it. Based on current evidence and materials, we could not answer that whether before or after the systemic treatment would the primary tumor resection bring more survival profit. We acknowledge that this was the limitation of this study and will add in discussion. As for the clinical use, this model could be used at any time when we made decision of primary tumor resection for a stage IV patient. Because when we developed this model, all data were used without selection for time point or any other situation.

Changes: Third, data on systemic therapies were unavailable in SEER data base. The lack of information regarding target therapies and immunotherapy represents a major limitation of the current study. We are unable to answer whether before or after the systemic treatment would the primary tumor resection bring more survival profit. However, data from single center are limited and also lack of representative to evaluate such clinical question. SEER is the only comprehensive population-based database and open access to worldwide represents an ideal approach to study the survival of patients in such setting.

Reviewer C

Dear author, It has been interesting reading your paper because this is a very relevant

topic. However, I have found some issues that should be address before recommending your paper for publication.

Comments for improvement:

1. - English needs a review by an English native speaker. The language is irregular along the paper with very correct sections and other no so good.

Response: Thanks for your comments and valuable suggestion. We have asked a English-native speaker with academic background to polish and fix the wording, thank you very much.

Changes: We fixed the language and logic problem, please kindly check in text.

2.- Three-question abstract:

Key question should be written as a question. Please, amend

Key-findings: the current sentence says nothing. Please, be more specific, add details about the findings of the study

Take-home message: Again, be more specific and give details about the model or the results of its application

Response: Thank you for the valuable suggestion. According to the instruction for authors, we found the TLCR did not ask for this part. We download several published papers on official website of TLCR, finding no study reported "Key question, Key finding and Take home message". As the consequence, we delete this part. But if required, we would be happy to add these to the manuscript.

Changes: We deleted this part in manuscript.

2. - Abstract. Again, try to be more specific about the model and the variables that enter into it.

Response: Thank you for the valuable comment. We added the specific variables that were included in the predictive model in abstract.

Changes: Differentiated characters (beneficial and non-beneficial group) included age, gender, TNM stage, histologic type, tumor position and differentiation grade, which were integrated as predictors to build a nomogram.

3. - Keywords: I recommend adding the word "nomogram"

Response: Thank you so much for the suggestion. We added "nomogram" in keywords.

Changes: We added "nomogram" in keywords.

5.- Methods:

Please, specify in the text whether the group of patients selected for developing the nomogram were from the propensity score surgical group or not.

Response: Thank you for the valuable comments. Because the majority stage IV NSCLC patients did not receive surgery, the population of non-surgery group (n=27906) was much bigger than surgery group (n=2436) before PSM. After 1:1 PSM, all patients (n=2436) in surgery patients matched their counterpart, the non-surgery group patient number was also 2436. That is to say, the surgery group patients did not change before and after PSM. Then we divided the surgery group into two cohort (beneficial or non-beneficial) according to median survival time (9 month in this study) of non-surgery population (after PSM) to develop the nomogram. Patients underwent surgery lived longer than the median survival time of non-surgery population were regarded as beneficial group, while patients underwent surgery live shorter than median survival time of non-surgery population were regarded as non-beneficial group. Then we used the significant independent variable (selecting through multivariate Cox analysis) between beneficial or non-beneficial patients to developed the model.

Change: No changes in text.

Please, explain why you chose the five specified variables as the only predictive variables for developing the nomogram.

Response: Thank you for the question. The six variables were picked from multivariate Cox analysis between beneficial or non-beneficial patients as mentioned above. We added this statement into methods.

Changes: Factors that independently affect the CSS in multivariate Cox analysis and can be accessed before surgery were collected into the training set, including age, gender, TNM stage, histologic type, tumor position (over lapping lesion, bronchus tumor, lobe tumor) and differentiation grade.

Line 151, there is a typo it says "to text" when the correct form is "to test"

Response: We have corrected the typo from "text" to "test".

Changes: Kaplan-Meier analyses and log-rank test were conducted to test whether this model would distinguish patients that could benefit from primary tumor resection

6.- Results:

Please, specify the variables used for PSM developing.

Response: Thank you for your question. We have mentioned this in methods and now added in result part.

Change: Variables that could influence the outcomes of treatment were included in 1: 1 PSM, including age, gender, TNM stage, differentiation grade, primary site, laterality, histological type, radiation therapy, chemotherapy and surgery to metastasis site.

Table 2: please, specify in the text the definitions of the different positions of the tumor considered in the table (this should go into the methods section).

Response: Thank you for your comments. We have added this into method part.

Changes: We evaluated age, gender, TNM stage, histologic type and differentiation grade and position (over lapping lesion, bronchus tumor, lobe tumor) as possible clinical candidate predictors for surgery benefit.

In my opinion, there is a serious problem with the population of validation of the nomogram because it was applied to "all" the patients after PSM which means that the population used to train the model was also included. To be a real validation, the training group should be excluded, and the model only tested in the rest of the population. Please, evaluate and modify.

Response: Thank you very much for your comments, we agree with your point. We validated the distinguish ability of the model in validation set. And we re-calculated the survival analysis.

Change: We then validated the distinguish ability of the model in validation set. According to Kaplan-Meier analyses and log-rank test (Figure 4), beneficial & surgery group is significantly live longer than non-beneficial & surgery group (HR=0.57, 95% CI 0.39-0.79, P<0.001) or non-surgery group (HR=0.54, 95% CI 0.40-0.74, P<0.001), but no difference was observed between non-beneficial & surgery and non-surgery group (HR=0.97, 95% CI 0.87-1.07, P=0.694).

7.- Discussion:

Line 249 there is a typo. It says "metastasis NSCLC" I guess it is "metastatic NSCLC"

Response: Thank you for pointing this out. We fixed this typo and changed "metastasis NSCLC" into "metastatic NSCLC".

Changes: Last, we compare the pre-operative baseline characters between surgery performed patients who live longer than 9 month (beneficial group) and who not (non-beneficial group), and then logistic model was used to construct the model. After such screening process, metastatic NSCLC patients who really suitable for surgery were identified.

I would suggest including a clear description (in the conclusion paragraph) of the developed model suggesting which patients would benefit from the surgical approach being stage IV.

Response: Thank you very much for your comments and advice. We added a description in conclusion.

Changes: To be specified, in stage IV NSCLC patients, <60 years old, female,

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adenocarcinoma, well differentiation, tumor in lobe, T1-2, N0 and M1a NSCLC patients would be potentially benefit more from primary tumor resection.