TRANSLATIONAL LUNG CANCER RESEARCH

Peer Review File

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Replies to reviewers' critiques

We sincerely thank the reviewers for their constructive critiques, which have helped us to greatly improve our study.

Reviewer A

1. This study aimed to develop and validate a nomogram model for accurately predicting the prognosis of large cell lung cancer patients, which may be useful in assisting clinicians in predicting the oncological prognosis and making decisions for appropriate adjuvant treatment. This is a meaningful and innovative work. However, the dissertation of the conclusion part – "The nomogram performs better than the AJCC TNM staging system" is not precise, please think again.
Reply: Thank you for your suggestion.
Change in the text: I have modified the sentences in the conclusion part in a more precise manner (see Page14, line 5-6).

2. The statistical method of the article is correct.
Reply: Thank you for your approval.
Change in the text: No change.

3. Images are standard.
Reply: Thank you for your approval.
Change in the text: No change.

4. The sentences in the abstract and conclusions are the same, and this is to be avoided as much as possible.
Reply: Thank you for your suggestion.
Change in the text: I have modified the sentences in the abstract and conclusions with different wording (see Page 3, line 1-3; Page 14, line2-8).

5. The authors compared their model with the AJCC 7th TNM stage. In truth, this is a meaningless comparison. The author should use the latest edition (8th) of the TNM staging system for analysis.

Reply: The reviewer's suggestion is reasonable. Predicting prognosis and treatment planning in non-small cell lung cancer (NSCLC) patients depends on the reliable staging system. Although the 6th and 7th edition of the TNM staging systems are widely used in the SEER database, the latest edition (8th) TNM staging system may be more accurate in determining the extent of tumor invasion.

Changes in the text: I have re-evaluated the cases obtained from the SEER database using the 8th edition TNM staging criteria to determine the T category (T1/T2/T3/T4), N category (N0/N1/N2) and M category (M0/M1) (see Page 6, line 15-17; Page18, table 1; Page 20, table 2; Page 22, table 3).

6. I am confused about the guiding role of this study in the selection of clinical treatment strategies of LCLC patients. So, how do we choose treatment for patients with different prognosis? Surgery? or radiotherapy/chemotherapy ? Please explain this further in the discussion section.

Reply: I regret that this article cannot answer the question of how to choose a treatment for patients with LCLC. The purpose of this study is to establish a simple and easy-to-use nomogram model to help clinicians determine the prognosis of LCLC patients after different treatment strategies. As for how to choose a treatment for LCLC patients, I think that major lung cancer guidelines (ASCO, ESMO, and NCCN) should be followed. In summary, before choosing treatment for a patient, clinicians should comprehensively consider many clinicopathological factors, such as the size and location of the tumor, clinical staging, the results of preoperative evaluation for patients, and the ability of the hospital to provide a high level of comprehensive treatment for a patient. The optimal treatment plan for a patient should be determined only after the comprehensive evaluation.

Changes in the text: No change

Reviewer B

Thank you for the privilege of reviewing this work. The authors attempt to determine a prognostic nomogram model for LCLC. Authors report an interesting retrospective study of a topic of clinical importance.

1. Decision curve analysis (DCA) is used. DCA can be a powerful tool and useful

adjunct to ROC analysis. However, its usefulness is fundamentally linked to context and explicit assumptions. Authors have made a few general statements about context and explicit assumptions as well as target range of threshold probabilities.

Reply: In 2006, Andrew Vickers and her colleagues(1) developed decision curve analysis (DCA) as a simple method for evaluating clinical predictive models, diagnostic tests, and molecular markers. I'm not particularly familiar with DCA, and I can only interpret the results to the best of my ability.

Change in the text: An interpretation of the DCA analysis results has been added to the legend of Figure 7 in the main text (see Page 29, figure 7).

2. SEER database included number of LCLC patients. But the clinical information is heterogenious. TNM stage is changed from 2007 to 2016. Authors should collect recent cases from 2010.

Reply: The reviewer's suggestion makes sense. However, I could not adopt it for the following reasons: (1) due to the suggestions raised by the reviewer, I have excluded large cell neuroendocrine carcinoma (LCNEC) patients. If only cases after 2010 were collected, the total number of LCLC patients enrolled in this study would be relatively small, which would affect the statistical effectiveness; (2) I have re-evaluated the cases obtained from the SEER database using the 8th edition of the staging criteria(2) to determine the T category (T1/T2/T3/T4), N category (N0/N1/N2) and M category (M0/M1), which will make the clinical information of the cases as consistent as possible.

Change in the text: No change

3. The pathology diagnosis of LCLC should be confirmed. Neoroendocrine LCLC should be excluded.

Reply: I would adopt your suggestion. In the 2004 WHO Lung Lancer Classification, LCNEC was a subtype of LCLC. In the 2015 WHO Classification, however, LCNEC was grouped with the other neuroendocrine tumors(3).

Change in the text: I have re-established the inclusion and exclusion criteria, the patients with LCNEC were excluded from this study (see Page 5, line 19-22; Page 11, line 14-17).

4. Authors should build lung cancer-specific survival nomogram.

Reply: Compare with overall survival (OS), lung cancer-specific survival (LCSS) is better to reflect variation in the effect of treatment. I agree with the opinion raised by the reviewer that LCSS is a better prognostic indicator than OS in this study.

Change in the text: We have changed the long-term prognostic indicator from OS to LCSS, and build 3- and 5-year LCSS nomogram models (see Page 7, line 4; Page 9, line 3; Page 25, figure 3).

5. Authors should clarify the difference and significance of neoadjuvant and adjuvent chemo- or radio-therapy.

Reply: **Effect of neoadjuvant and adjuvant chemotherapy on prognosis in LCLC patients**

The influence of neoadjuvant and adjuvant chemotherapy on the prognosis for cancer patients has been the focus of research. However, in the SEER database, no distinction was made between neoadjuvant and adjuvant chemotherapy, so this question could not be answered. After reviewing the literature, no article that comparing neoadjuvant therapy with adjuvant treatment for LCLC patients had been found.

LCLC was one of the pathological types of non-small cell lung cancer (NSCLC) and having similar biological characteristics as other NSCLCs. In 2010, Felip and his colleagues(4) published a paper related to this issue, 624 patients with stage I-IIIA NSCLC were randomly assigned to one of three arms, including preoperative chemotherapy group (n = 201), surgery arm (n=212), and adjuvant group (n = 211). They found that there were no statistical differences in the prognosis between these three groups.

Effect of the sequence of radiotherapy on prognosis in LCLC patients

After reviewing the literature, I did not find any article reporting the effect of the radiotherapy sequence on LCLC prognosis. Using the SEER database in this study, I plotted LCSS under different radiotherapy sequences and found that neoadjuvant radiotherapy (NART) could improve the prognosis (P = 0.004), but adjuvant radiotherapy (ART) could not (Figure1).

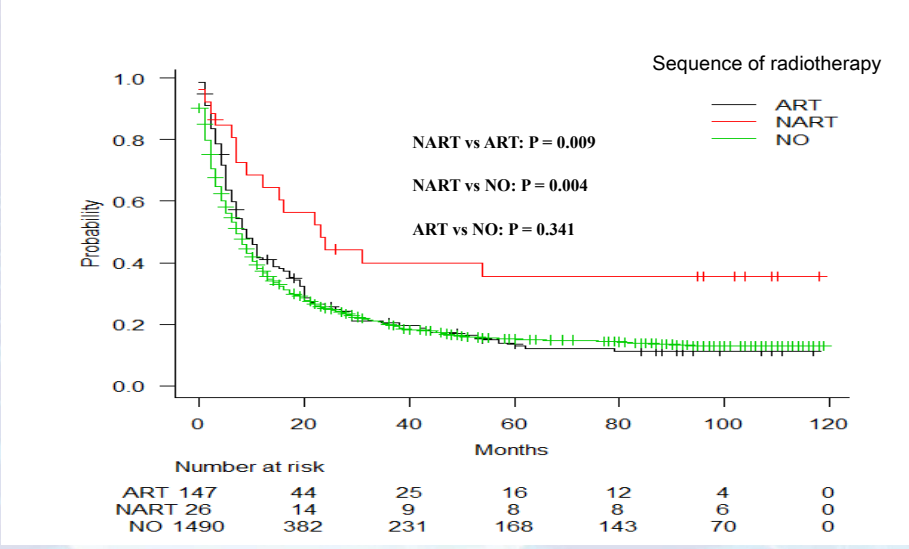

Figure 1. Lung cancer-specific survival according to the sequence of radiotherapy

Abbreviation: ART: adjuvant radiotherapy; NART: neo-adjuvant radiotherapy; NO:

no radiotherapy

Change in the text: No change

Reviewer C

In the present study, the authors establish a prognostic nomogram for prediction survival of LCNC patients. As author discussed, this study included treatment regimen in this prognostic nomogram than previous one (Hu et al). Indeed, this is a better prognostic nomogram for LCNC patients. However, there are many concerns.

1. In the establishment of prognostic nomogram, only independent prognostic factors identified by multivariate Cox analysis could be included in the prognostic nomogram. I think it not correct that including TNM stage, not T stage, N stage and M stage. TNM stage is correlated with several factors, it is not an independent prognostic factor. So, I recommend to choose T category (T1/T2/T3/T4), N category (N0/N1/N2), M category (M0/M1) instead of TNM stage (I/II/III/IV). Besides, tumor size is available for lung cancer patients in SEER database. T stage and tumor size could be choosen either.

Reply: Thank you for your suggestion

Change in the text：I have re-evaluated the cases obtained from the SEER database using the 8th edition TNM staging criteria(2) to determine T category (T1/T2/T3/T4), N category (N0/N1/N2) and M category (M0/M1). T, N, and M categories, instead of the TNM stage, were included in the final nomogram model. Tumor size is not included in the nomogram model, because there is a high correlation between tumor size and T category, and only one variable can be selected (see Page 6, line10; Page 6, line 16; Page 8, line 12; Page 18, table 1; Page 20, table 2; Page 25, figure 3).

2. Almost all previous studies based on SEER database identified age as a prognostic factor, especially for OS survival. In the establishment of prognostic nomogram, more detailed classification could better differentiate the prognosis of LCNC patients. In the present study, the authors used the average age as cutoff, but only two groups. I recommend the author could divide into several group based age. The optimal cut-off levels of age could be determined by X-tile software.

Reply: As the reviewers said, age is a prognostic factor for lung cancer(5,6). The statistical results in this article also show that age has a significant effect on OS and LCSS (all P<0.05). We adopted the reviewer's suggestion and used X-tile software to determine the best cut-off values for age variables at 54- and 81-year, respectively.

Change in the text: In the Method Section of the paper, we add the following text “Age is a continuous variable, which was converted to a categorical variable in this study. The optimal cutoff values determined by X-tile (version 3.6.1, Yale University)

software were 54- and 81-year, respectively" (see Page 5, line 11-13).

3. In SEER database, there are several marital statuses including married, divorced, etc. But the author only classified into two groups. How do you define "married" and "unmarried"?

Reply: Yes, in the SEER database, marital status can be divided into the following categories, including "married", "divorced", "separated", "single", "unmarried", "widowed" and "unknown". For the sake of simplicity in this study, all conditions except "married" are classified as "unmarried".

Change in the text: No change

4.The authors found primary site is also a prognostic factor such as lower vs upper, lower vs unknown, lower vs trachea. However, in clinical practice, primary site maybe not an important prognostic factor, especially lower vs upper. Lung cancer is not colorectal cancer, no light-side vs left-side difference. In my view, this could be a statistical matter. Maybe, in the present cohort, lower lobe patients have more metastases than upper lobe. This emphasizes again that T category (T1/T2/T3/T4), N category (N0/N1/N2), M category (M0/M1) should be included in the multivariate cox analysis.

Reply: Multivariate analysis of the LCLC patients using SPSS software showed that tumor location affects OS and LCSS. However, in this study, we found that only patients with tumors located in the main trachea had the worst prognosis, while other locations had no significant difference in prognosis. In the R software, Akaike information criterion (AIC) was used to develop multivariate models by removing predictors that were less statistically significant starting from a full model containing all predictive variables(7). We found that the AIC was the smallest, after removing the site of the primary tumor, laterality, and grade. Therefore, in the lasted nomogram model, the site of the primary tumor and laterality are no longer included.

Change in the text: No change

5. Overall, I should again emphasize only "independent" factors could be included in nomogram. The author did not consider all potential factors when they identify independent factors using multivariate cox survival analysis, including tumor size, T, N, M category.

Reply: Thank for your suggestion

Change in the text: I have re-evaluated the cases obtained from the SEER database using the 8th edition TNM staging criteria(2) to determine the T category (T1/T2/T3/T4), N category (N0/N1/N2) and M category (M0/M1). We developed the nomogram model using the following variables: age, sex, race, marital status, T, N, M, and treatment

strategy. Tumor size is not included in the nomogram model, because there is a high correlation between tumor size and T category, and only one variable can be selected (see Page 6, line10; Page 6, line 16; Page 8, line 12; Page 18, table 1; Page 20, table 2; Page 25, figure 3).

Minor concerns:

1. SEER database has a SEER historic stage classification including localized stage, regional stage, as well as distant stage. The authors also could compare your model with this model.

Reply: Thank for your suggestion. The following table shows that the predictive ability of the current nomogram model is significantly better than the historic staging system.

Change in the text: No change

Comparison of predictive ability for Lung cancer-specific survival between the historic stage and the nomogram in the training dataset

Measures	Historic stage	Present nomogram	P-value
C-index	0.661	0.767	<0.001

2. In line 227: In the past, the preferred treatment for LCLC of all stages was surgical resection, but the prognosis after surgery was always poor. I do not think this statement is correct. Is it right for IV stage, metastatic patients?

Reply: The sentences "In the past, the preferred treatment for LCLC of all stages was surgical resection, but the prognosis after surgery was always poor" comes from an article reported by Rieber *et al*(8). The original text is "*LCNEC used to be only treated by resection in all tumor stages and therefore showed poor survival rates [1, 35, 36]. Adjuvant therapy, mainly chemotherapy, led to a subsequent improvement in survival in patients with higher tumor stages [5, 37, 38]*". I think what the author wants to express is that the initial treatment for large cell carcinoma historically was surgery, but the effect was very poor, indicating that surgery alone was not enough to treat LCNEC.

Change in the text: No change

Reference

1. Vickers AJ, Cronin AM, Elkin EB, et al. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. BMC Med Inform Decis Mak 2008;8:53.

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3. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization

Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
4. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-45.
5. Lara MS, Brunson A, Wun T, et al. Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): a California Cancer Registry analysis. Lung Cancer 2014;85:264-9.
6. Wu CY, Fu JY, Wu CF, et al. Survival Prediction Model Using Clinico-Pathologic Characteristics for Nonsmall Cell Lung Cancer Patients After Curative Resection. Medicine (Baltimore) 2015;94:e2013.
7. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
8. Rieber J, Schmitt J, Warth A, et al. Outcome and prognostic factors of multimodal therapy for pulmonary large-cell neuroendocrine carcinomas. Eur J Med Res 2015;20:64.