Peer Review File

Article Information: https://dx.doi.org/10.21037/tcr-21-1507

Reviewer A

In this study, a nomogram to predict the OS of NSCLC patients with bone metastasis was made using SEER data base. They elucidate receiving chemotherapy and absence of liver metastasis as better prognostic factors. There are some issues showing below.

Response

We are thankful to the reviewer for reviewing this manuscript and giving his deep insights for further improvements. We have considered all the comments and have acted according. The revised manuscript now seems much improved after these incorporating the suggested changes.

Comment 1：A development cohort and a validation cohort were generated by splitting one SEER data. Generally, a cohort that is completely separate from the SEER data should be used to validate the developed nomogram. There are doubts about this methodology itself.

Reply 1: Thank you for your comments and feedback, developed prediction model need to be validated for generalizability using validation dataset. Many a times model developed using train dataset does not perform well on test dataset. After downloading from the SEER database, an important step is to randomly divide the database into modeling groups and validation groups. Generally, 70% of the data is modeled and 30% of the data is validated. Since it is difficult to find data similar to the SEER database for external validation, we have to split the data for validation. So our prediction model was validated for generalizability using validation datase. We add some content. All NSCLC patients with bone metast were randomly divided into the training (n=340) and validation (n=144) cohorts with a ratio of 7:3

by R (version 3.2.3) software. According to the results of the multivariate Cox analysis, the independent prognostic factors were incorporated to develop a nomogram to predict OS of NSCLC patients with bone metastasis. Receiver operating characteristic (ROC) was used to estimate the discrimination of the clinical predictive model. Meanwhile, the calibration curves and decision curve analyses (DCA) of 1, 3, and 5 years were constructed to estimate the nomogram. Generally, a cohort that is completely separate from the SEER data should be used to validate the developed nomogram. Hence, further detailed investigations are needed in the future.

Comment 2：The author focused on NSCLC patients with bone metastases, but the reason is unclear. Bone metastases should be treated same as liver metastases, lung metastasis and brain metastases as prognostic factors.

Reply 2: We have added some missing text to the revised manuscript in the respective section. (page 2, line 25). The reason of focusing on NSCLC patients with bone metastases are included and highlighted in the introduction section of the revised manuscript on page 3, line 69-78. The patient population of our study may pay more attention to NSCLC patients with bone metastasis. We identify prognostic factors and establish a prognostic nomogram of NSCLC patients with bone metastasis. So we didn't treated bone metastases as prognostic factors. However, bone metastases should be treated same as liver metastases, lung metastasis and brain metastases as prognostic factors for NSCLC (see page 8, line 192-195，page 11, line 229-231，page 11, line 249-254). Hence, further detailed investigations are needed in the future.

Changes in the text: We have added some missing text to the revised manuscript in the respective section. (page 2, line 25). The reason of focusing on NSCLC patients with bone metastases are included and highlighted in the introduction section of the revised manuscript on page 3, line 69-78.

Comment 3：Malignant pleurisy and pleural dissemination are frequent metastases as Ma in the TNM classification. There is no information on these factors.

Reply 3: Thank you for your comments and feedback. A total of 484 patients were enrolled in this study, 112(23.1) patients showed lung metastasis (page 6, line 38). In our study, the results of the univariate Cox analysis showed that absence of liver and lung metastasis could lead to higher OS of NSCLC patients with bone metastasis (page 10, line232-234). Lung metastasis **appears to be an important prognostic.** However, the details of malignant pleurisy and pleural dissemination was not provided by the SEER data center. However，we have added some missing text to the revised manuscript in the respective section to discuss malignant pleurisy and pleural dissemination of NSCLC patients. (page 10, line 223-243).

Changes in the text: We have added some missing text to the revised manuscript in the respective section to discuss malignant pleurisy and pleural dissemination of NSCLC patients. (page 10, line 223-243).

Reviewer B

General comment

Authors described prognositic factors I patients with NSCLC with bone metastasis. This study was done by SEER database and I think that the results might provide the clinical importance.

Response

We are thankful to the reviewer for reviewing and appreciating this manuscript and giving his deep insights for further improvements. We have considered all the comments and have acted according. The revised manuscript now seems much improved after these incorporating the suggested changes.

Major comments;

Comment 1：How many patients did you exclude in insufficient data such as race, location, grade et al (page 4 line 90-92) or how many patients with bone metastasis were died from other causes ?. Author should show the selection flow from initial number (60409) to enrolled patients with NSCLC (484).

Reply 1: Thank you for your comments and feedback. We added fig 1 of the subject selection algorithm. We have shown the selection flow from initial number (60409) to enrolled patients with NSCLC in the fig.1 (see Page 22, line 448-449).

Changes in the text: We have shown the selection flow from initial number (60409) to enrolled patients with NSCLC in the fig.1 (see Page 22, line 448-449). As indicated in Fig. 1, finally, 484 NSCLC patients with bone metastasis were included in this research (see Page 5, line 106-108).

Comment 2： total number 484 in table but you described 488 in manuscript.

Total numbers of 484 NSCLC with bone metastasis

Reply 2: The reviewer pointed out a good mistake.

Thank you for your comments and feedback. 484

NSCLC patients with bone metastasis were included in this research. We corrected our mis take throughout the manuscript(see Page 2,line 32, Page 6, line 132, Page 6, line 147, Page 8, line 185, Page 11, line 271).

Changes in the text: We corrected our mistake throughout the manuscript (see Page 2, lin e 32, Page 6, line 132, Page 6, line 147, Page 8, line 185, Page 11, line 271).

Comment 3 ： page 4 line 85, Code number 8046, is it correct ?

There were many code numbers in NSCLC. Authors should describe these correct numbers in NSCLC.

Reply 3: Thank you for your comments and feedback. There were many code numbers in NSCLC, such as 8140, 8141,8144, 8244, 8250–8255 and so on. However, in our study, our study studied patients with histological NSCLC (histological type code: 8046/3: Non-small cell carcinoma). There were many histological code numbers in NSCLC, further detailed investigations are needed in the future. We add some text (see Page 12, line 287-288).

Changes in the text: There were many histological code numbers in NSCLC, further detailed investigations are needed in the future. Our study focused more on patients with the histological type of non-small cell lung cancer. We add some text (see Page 12, line 287-288).