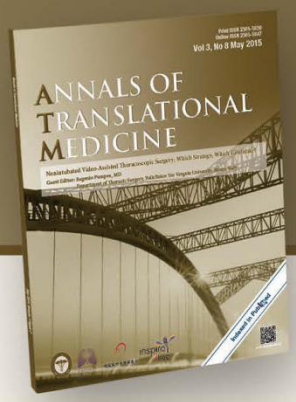
ANNALS OF TRANSLATIONAL MEDICINE



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Comment 1: **********
Reply 1: **********
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Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-6555

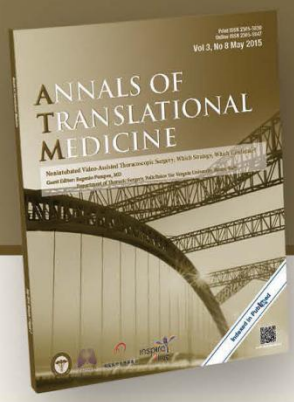
Reviewer Comments

Lin G et al. used a US national database SEER to build a nomogram to predict overall survival and cancer specific survival in patients with pulmonary mucoepidermoid carcinoma. Cases matching their selection criteria were randomly assigned into training or test cohort. According to the authors, their novel nomogram can predict patient's survival better than TNM staging system.

Comments

Comments 1: Grammar needs to be reviewed. There are many errors throughout the manuscript.
Reply 1: Thanks for your advice. We improve the grammar carefully.
Changes in the text: Revised portions are marked in red in this manuscript.

Comment 2: Authors did not present in detail about the use of nomogram as prediction model in general oncology. I wonder why they focused on this relatively rare disease rather than common disease such as non-small cell lung cancer.
Reply 2: Thank you for your suggestion on the use of nomograms and we have added this statement in the **Introduction** and **Results**.
And compared with common lung cancer, pulmonary mucoepidermoid carcinoma is a rare lung cancer with a low incidence, and its pathological staging still depends on the traditional TNM system based on general lung cancer. We hypothesized that one of the reasons for poor prognosis was the lack of a specific model specifically for PMEC patients. To provide new ideas for the treatment of PMEC, we performed this study. We also added these in **Discussion**, please refer.
Changes in the text: We have modified our text as advised (see Page 6, Line 114 to 119; Page 12, Line 260 to 267 and Page 13, Line 274 to 278).
Introduction:



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As general oncology, the nomogram as the prediction model has a wide range of applications owing to its advantages, as mentioned above. The nomogram model based on specific samples can more effectively estimate patients' survival rate with individualized baseline characteristics, applied in the prognosis estimation of malignant tumors, such as breast cancer, bladder cancer, and lung cancer.

Results:

Clinical Use

Points of each variable were obtained by drawing a vertical line to the top points row; then, the sum of the points of each variable is located on the total points row, and a vertical line is drawn from total point row to 3-, 5-, 10-year OS or CSS row to acquire the survival probability of patients (Figure 1). For example, one patient was a 47-year-old, undifferentiated PMEC with 1.8 cm and N+M0 regional stage, and received surgical and radiation therapy, the total score is 200 points with corresponding 3-, 5-, 10-year OS of 0.50-0.60, 0.40-0.50, and 0.40-0.50, respectively.

Discussion: Moreover, its pathological staging still depends on the traditional TNM system based on general lung cancer. We hypothesized that one of the reasons for poor prognosis was the lack of a specific model specifically for PMEC patients. To provide new ideas for the treatment of PMEC, we established the nomograms and the risk classifications to predict individual PMEC patients' survival probabilities.

Comment 3: In methods, authors state they use customized TNM system such as N+ - , M + - . However, in Table 1, they used Limited/regional/distant as tumor stage. I believe the latter was provided by SEER as "Stage A" system throughout the study period.

I assume "distant" stage is equal to M1, and "regional" is equivalent of N+. Why are N and M still significant in the multivariate analysis despite use of the limited/regional/distant staging?

Reply 3: Because there was no significant survival difference among N1, N2, and N3 (P=0.067), we redefined the positive lymph node metastasis (N1, N2 or N3) as one group named N+. As we know, both lymph node and distant metastasis would significantly affect the long-term survival outcomes, thus the statistically significance was observed in the two groups.

Changes in the text: We renamed N and M in manuscript, tables and figures. And we reinterpreted our customized system in the text (see Page 8, Line 155 to 158).

Methods:

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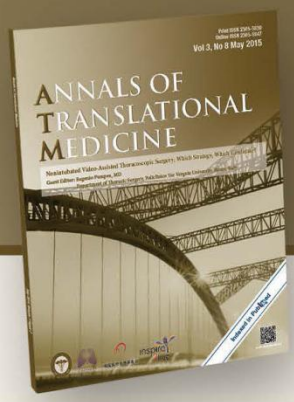

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Survival analysis indicated no survival difference among N1, N2, and N3 survival of the N stage in the original data (P = 0.067). Hence, we redefined the positive lymph node metastasis (N1, N2 or N3) as one group named N+.

Comment 4: In Table 2, primary site is significant (p=0.002) overall, but each one was negative.
Reply 4: Thank you for your question. The overall P value (0.002) represents “Primary site” as a statistically significant predictive factor in Univariate analysis. The following P value showed no significant difference in survival from pairwise comparisons with the reference group (Main Bronchus).

Comment 5: Use of chemotherapy or radiation showed poor survival as compared to no chemo/XRT. It needs explanation. I assume people with high risk features in surgery ended up getting adjuvant treatment, and these treatments may not be necessarily detrimental.
Reply 5: The reasonable explanation is adjuvant therapy after surgery inhibits immune function more than tumor growth or metastasis. Moreover, the physical and mental pain caused by adjuvant therapy significantly, and economic pressure may reduce the survival rate. Besides, some patients received chemo/XRT instead of surgical in our study samples. In the final analysis, PMEC is a rare pulmonary carcinoma with a small sample, which may affect the stability of our study.
Changes in the text: We have modified our text as advised (see Page 15, Line 329 to 334 and Page 16, Line 348 to 349).
Discussion:
We noticed that patients with adjuvant therapy had poor prognosis than without chemotherapy and (or) radiation. The reasonable explanation is that traditional adjuvant therapy is not conducive to reconstructing immune function, and the painful physical and mental also reduces the survival time. Besides, some patients can not tolerate surgery or other reasons; they received chemotherapy and (or) radiation instead of surgical in our study samples.
(5) The small sample size may still affect the stability of this data analysis, though we as far as possible to improve the analysis process.

Comment 6: There are many statements like “See Figure/Table X for detail”. It does not seem appropriate.

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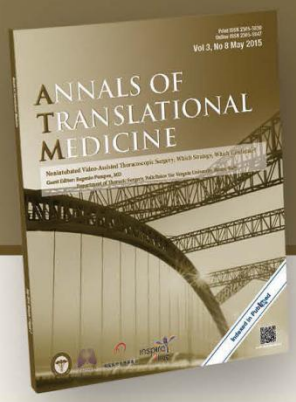

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Reply 6: It is accurate as the reviewer suggested that.
Changes in the text: We have modified our text as advised (see Page 12, Line 247 to 248).
Results: The IDI (Table 3) of our nomogram compare with the TNM system is 0.167 for 3-year OS ($P < 0.001$).

Comment 7: There are some cells smaller than 10 in Table 1. I am not sure if SEER prohibits it from publishing, but NCDB does. It is to avoid identification of individuals by chance.
Reply 7: This is inevitable because this is a small sample study. Besides, none of these variables smaller than 10 were incorporated into the model construction.