Peer Review File
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Reviewer A

The writing is clear, and the analysis is thorough.
My only and major concern is that the study uses AJCC 7th edition rather than the current AJCC 8th edition for staging. From the AJCC 7th edition to the 8th edition, there is major change on how adenocarcinoma is staged, with only the non-lepidic component considered as the tumor size for staging. Since this study used only the 7th ed AJCC, it was unclear how the findings can be applied to our current practice. I suggest the authors re-analysis their data using the 8th ed AJCC.

Reply: Thank you for your recognition of our work. Actually, the eighth edition of the TNM classification for lung Cancer (the AJCC 8th edition) not the AJCC 7th edition was used in our study. All patients had tumors >3 cm but ≤4 cm in greatest dimension with no regional lymph node metastasis and no distant metastasis (T2aN0M0) which were staged as IB based on the AJCC 8th edition. Sorry for the wrong information we provided in the previous manuscript.
Changes in the text: We have revised our text accordingly (see Page 5, line 136).

Reviewer B

The authors investigated the prognostic impact of the histological subtype, the molecular risk stratification by DETERMARxT, and the mutational profile in stage IB lung adenocarcinomas measuring 3-4cm. They showed that the solid and micropapillary histological subtypes and the molecular high-risk category were associated with worse DFS.
The manuscript is well written, and the results are interesting, although exploratory.

Major comments
I recommend that the authors validate their findings in an independent cohort.
Reply: Thank you for your comment. In the present study, we aimed to explore the potential prognostic factors for stage IB NSCLC patients and we used multivariable Cox regression to test whether the identified prognostic factors were independent prognostic factors. Indeed, an independent cohort to further validate the findings would be appreciated, but not mandatory for studies to explore potential prognostic factors, and we have listed this as a limitation in Discussion.

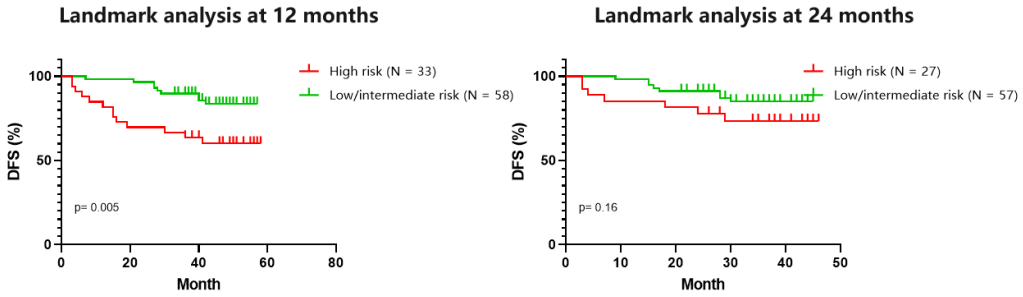
Changes in the text: We have listed this as a limitation in Discussion in the revised manuscript (see Page 11, line 344-345)

It draws the attention of the relatively small number of smokers in the cohort. Could the authors comment on that?

Reply: Thank you for your comment. In China, lung adenocarcinoma is predominantly found in female patients who are non-smokers with EGFR mutations, which may explain the relatively small number of smokers in the cohort.

Since the follow-up is relatively short, I suggest the authors perform landmark analysis at 12 and 24 months when comparing survival in subgroups.

Reply: Thank you for your comment. We would like to emphasize that the median follow-up time was 59 months (almost 5 years). Landmark analysis is commonly used when the Kaplan-Meier curves cross, which was not observed in the present study. When landmark analysis at 12 or 24 months was performed, more patients with DFS < 12 or 24 months in high-risk group would be removed from analysis, impairing the difference of DFS between high-risk and low/intermediate risk groups (Results see below).



Instead of using the history of smoking in the multivariable analysis, the authors should use smoking load (pack-years).

Reply: Thank you for your comment. We totally understand the reviewer's concern. However, in the multivariable analysis, history of smoking was usually used instead of smoking load (*1*), since smoking load is not always linearly associated with disease severity.

When analyzing the impact of EGFR mutation status in DFS, I suggest the authors compare the del19 mutation versus others (it seems there is some difference between del19 and the others when looking at the curves).

Reply: Thank you for your comment. The difference of DFS between patients with del19 mutation and others was also not significant (p = 0.21)

Changes in the text: We have provided the description comparing del19 and the others in the revised manuscript (see Page 7, line 223-225).

Is there any difference in poor risk factors (vascular invasion, pleural invasion, and so on) between patients who received or did not receive adjuvant chemotherapy?

Reply: Thank you for your comment. No difference was observed in poor risk factors including vascular invasion, pleural invasion between patients who received or did not receive adjuvant chemotherapy.

I suggest the authors collapse high and moderate molecular risk groups into one since the survival curves are very similar.

Reply: Thank you for your comment.

Changes in the text: We have provided the comparison between high-risk and low/intermediate risk groups in the revised manuscript (see Page 8, line 234-235).

Reviewer C

Your manuscript presents important findings that could significantly impact the management of stage IB LUAD patients. Addressing the above points will further strengthen your manuscript and its contribution to the field.

Introduction:

Emphasize the need for better prognostic markers specifically for stage IB patients.

Reply: Thank you for your comment.

Changes in the text: We have provided more introduction of the need for better prognostic markers for stage IB patients (see Page 4, line 93-104)

Results:

Use clearer subheadings to guide the reader through the key findings.

Reply: Thank you for your comment.

Changes in the text: We have provided clearer subheadings in the revised manuscript

(see Page 6-9)

Line 163: 'The majority of patients were female (54.4%) and had no smoking history (56.3%)', is not entirely accurate, as these percentages do not constitute a clear majority. Consider rephrasing for precision.

Reply: Thank you for your comment.

Changes in the text: We have rephrased this sentence into "Among these patients, 117 of 215 patients (54.4%) were female and 121 of 215 patients (56.3%) had no smoking history" (see Page 7, line 188-189).

Line 200: 'In line with previous reports, the patients who were stratified as high risk by the 201 14-gene assay had shorter DFS than those etc.' should be used in the discussion section, not in the results section, to maintain proper scientific reporting.

Reply: Thank you for your comment.

Changes in the text: We have revised this sentence into "The patients who were stratified as high risk by the 14-gene assay had shorter DFS than those who were stratified as low (HR =2.929, P=0.0117) and intermediate risk (HR =2.349, P=0.0627) (Figure 4A)" (see Page 8, line 232-234).

Limitations: Discuss potential biases, such as selection bias due to the retrospective design, and other confounding factors more comprehensively.

Reply: Thank you for your comment.

Changes in the text: We have provided more discussion regarding the potential biases in the Discussion (see Page 11, line 349-351)

Reference

1. Z. Wang *et al.*, Assessment of Blood Tumor Mutational Burden as a Potential Biomarker for Immunotherapy in Patients With Non-Small Cell Lung Cancer With Use of a Next-Generation Sequencing Cancer Gene Panel. *JAMA Oncol* **5**, 696-702 (2019).