Peer Review File

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Reviewer A:

Comment 1: The authors should clearly state the inclusion and exclusion criteria for gene testing. Their inclusion and exclusion appeared inconsistent.

Reply 1: Thank you very much for your valuable suggestion. As you pointed out, we only described the inclusion and exclusion criteria in the general information, but did not explicitly put forward, and some inappropriate descriptions may indeed cause confusion to readers and are not rigorous enough.

Changes in the text: We added the words of "Inclusion and exclusion criteria" to indicate the content of the paragraph (see Page 3, line 71), and the exclusion criteria and corresponding instructions (see Page 3, line 79-81). We deleted some lengthy words and sentences (see Page 3, line 71,72,75,76-78), and modified descriptive terms that may cause misunderstanding (see Page 3, line 73) as advised

Comment 2: What is the definition of histologically invasive subtype? The authors should refer to several previous studies for the criteria.

Reply 2: Thank you for pointing out the oversight in our article. Although we explained it in the Discussion section, we did not define the histologically invasive subtype in the Methods section, which really caused confusion for the readers.

Changes in the text: We added the definition of histologically invasive subtype in Method section. (see Page 3, line 75). The definition was further explained in the Discussion section (see Page 8, line 180).

Comment 3: Paragraphs that should be included in the result section were included in the method section.

Reply 3: Thank you very much for pointing out that we miswrite the paragraph of partial results in the Method section, which really made readers feel confused.

Changes in the text: We have removed the paragraph of partial results from the Methods section, mainly the data of the number of research objects (see Page 3, line 71,82-83, 86-87). and added them to the Results section (see Page 5, line 122). At the same time, we have optimized some words to make the text read more smoothly (see Page 3, line 83).

Comment 4: There are multiple grammatical errors that should be corrected.

Reply 4: Thank you very much for your precious advice. There were many grammatical errors in our original text indeed that make it difficult to read. We have checked all the text carefully as far as possible to make sure that all the errors found are corrected. We have also checked the wordings of the main text and figures/tables by using medical writing service (AME Editing Service, http://editing.amegroups.cn/#editing; order ID: **AESE20230114**, In progress). We will resubmit a language-edited version of our manuscript to the editorial office when the order is done.

Changes in the text: We made these corrections to grammatical errors (see Page 2, line 57，61；Page 4，line 91；Page 6，line 109，111，119；Page 8，line 138，142；Page 16, line 275).

Comment 5: Funding information is missing.

Reply 5: Thank you for your careful review. Sorry, we missed the funding information. This study was not funded.
Changes in the text: We have added the funding information to the article (see Page 5, line 115).

Reviewer B:
Comment 1: Introduction:
No clear objectives for this study have been stated.
Reply 1: Thank you very much for your valuable review. It was our omission that the purpose of the study was not clearly stated in the introduction section.
Changes in the text: We added the objective of this study to the Introduction section (see Page 2, line 68).

Comment 2: Methods:
- Line 82-83: This content should be written within the Results section.
- Please specify what clinicopathological characteristics were investigated for the subject cases.
Reply 2: Thank you very much for pointing out that we miswrite the paragraph of partial results in the Method section and did not specify the histologically invasive subtype, this was likely to cause confusion for the readers. According to the WHO new pathological classification of lung adenocarcinoma, the Lepidic growth subtype is considered as a non-invasive growth pattern，Therefore non-Lepidic growth component can be defined as histologically invasive subtype, including Acinar，Papillary, Micropapillary, solid predominant and etc.
Changes in the text: We revised the Method section again, moved the paragraph of partial results from the Methods section to Result section, mainly the data of the number of research objects (see Page 3, line 71,82-83, 86-87). We also added the definition of histologically invasive subtype in Method section (see Page 3, line 75).

Comment 3: Results:
- Table 1: In this study, I believe that it is essential to describe the total tumor size and the solid tumor size on CT, and the pathologic tumor and invasion size.
- Table 2: Please state the histological subtypes in both groups.
Reply 3: Thank you for your advice, indeed, as you said, the total tumor size and the solid part size on CT, and the pathologic tumor and invasion size of the two types of LUAD are important, which is helpful for us to correctly interpret the results of the mutation comparison, so that we can draw a more cautious conclusion. We added this content in the Result section.
Some of the GGO on CT scan were finally confirmed as pathologic invasive subtype, as previously reported, imaging GGO and histological Lepidic growth do not always correspond. In our study, the enrolled patients were mainly GGO-LUAD patients with more pathologic invasive components who were willing to undergo NGS detection, while some GGO-LUAD patients similar to this study did not choose tumor NGS due to high cost and uncertain prognostic value，especially those whose histological subtype was predominantly lepidic growth pattern, their genetic mutation status was unclear. This limitation was also explained at the end of the original article.
At the same time, we also added the specific pathological features of the two types of lung adenocarcinomas as advised.

Changes in the text: We have removed this part of the original text and added a supplement about the size (see Page 8, line 123-128). We also added the pathological subtype characteristics (see Page 8, line 134).

Comment 4: Discussion:

- How can the results of this study be applied in clinical practice? Please discuss.

Reply 4: Thank you for your valuable suggestion. Our study was a retrospective study aim to decipher genetic mutation heterogeneity behind two types of lung adenocarcinomas with very different oncological behavior. We found that even if, with similar size of histological invasive components, GGO-LUAD of clinical early stage has lower mutation frequency than Solid-LUAD in suppressor genes TP53 and CDKN2A, and the mutant gene is less enriched in the cell cycle and TP53 signaling pathway, which may be the related genetic mechanism of fewer recurrence risk factors, relatively inactive cell growth, and less migration/invasion for GGO-LUAD. Of course, in the future, genetic testing with larger samples is needed to explore the key genes and signaling pathways involved, thereby explaining the genetic characteristics and molecular mechanisms of tumor heterogeneity. Next generation sequencing (NGS) technology can achieve high-throughput and high sensitivity multi-gene sequencing. Nowadays it plays an increasingly important role in early lung cancer，such as MRD（Minimal Residual Disease）test，used for tumor prognosis stratification or even replacing traditional pathological examinations to guide adjuvant treatment. Whether and when GGO-LUAD will eventually progress to Solid-LUAD remains a major clinical challenge that cannot be well predicted. For those patients with GGO-LUAD after resection, if the patient has the above genetic mutation, we can increase our attention and carry out wild type and mutant prognostic analysis. In future, we can design panel protocol designed based on these genes and use liquid biopsy technology to dynamically monitor GGO-LUAD patients who do not want to undergo repeated radiography, or who cannot tell whether the tumor is no longer indolent, even after radiography follow-up, to predict whether the tumor has turned to a more aggressive degree, or already had the ability to metastasize.

Changes in the text: We have added some ideas about how this research could be applied to clinical practice (see Page 14, line 278).

Reviewer C:

Comment 1: The most critical point of the study is its sample size. It seems difficult to conclude their clam based on such a small number of cases.

Reply 1: Thank you very much for your valuable review and you are quite right that the sample size of our study was indeed small. The main reason is that our research is retrospective, at this stage very few patients with early-stage lung cancer volunteer for NGS, especially GGO-LUAD whose histological subtype was predominantly lepidic growth pattern, because of the high cost and uncertain prognostic predictive value. We also mentioned this limitation at the end of the article. Given this limitation, as you pointed out, we should indeed be more cautious about the conclusions we draw. In the conclusion, we avoid using a deterministic tone and only make conservative and cautious speculations. Of course, in the future, genetic testing with larger samples is needed to explore the key genes and signaling pathways involved, thereby explaining the genetic characteristics and molecular mechanisms of tumor heterogeneity.

Changes in the text: We added the supplementary expound about this limitation (see Page 16, line 281).

Comment 2: The paper is not in good style. The figure must be separated from the manuscript. The first paragraph should be titled as "Introduction".

Reply 2: Thank you very much for your thoughtful comments, which help us a lot. We've refined the manuscript based on your suggestions,

Changes in the text: We have separated the figure from the manuscript (see Page 10, line 144-146), and placed it at the end of the text (see Page 22). We added "Introduction" as title for the first paragraph (see Page 2, line 56).

Comment 3:"Discussion" is too redundant and long. Too many general contents are mentioned. It should be shortened to an appropriate size.

Reply 3: Thank you for your suggestions. The discussion section is really too long, and a lot of common sense has occupied a large space. We have deleted these tedious and lengthy contents according to your suggestions.

Changes in the text: We have deleted the redundant contents in the "Discussion" section (see Page 11, line 165-168, 173-175, 184-187; Page 12, line 193-195, 198-199, 202-206; Page 13, line 229-230, 241-245; Page 14, line 256-258).