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Manuscript Type: REVIEW

Dear Editors and Reviewers:

Thank you very much for taking time to review our manuscript. We appreciate you comments and the opportunity to improve on our work. We have addressed your specific comments below and edited our manuscript accordingly (attached).

We thank you for your consideration, and we look forward to hearing from you soon.

Sincerely,

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RESPONSE TO REVIEWER COMMENTS

SCIENCE EDITOR:

I suggest that the manuscript should be rejected. The scientific classification of this manuscript is Grade A, Grade A and Grade E. Summary of the peer-review report: The reviewer#03270441 thinks the current imaging characteristics of NSCLC with different driving-gene mutations are not enough to be defined as "Imaging Biomarkers" according to the current literatures provided by the authors, including the author's own “Conclusion”. The background of NSCLC driving-gene mutation is introduced in detail in nearly half of the manuscript, such a large discussion has little to do with "imaging biomarkers", which will make the article deviate from the theme. (Han Zhang)

RESPONSE:

Thank you again for reviewing our manuscript and taking into account the other reviewers' comments.

In this manuscript, we define "biomarkers" are measurable or objective features that are indicative of the presence of a certain mutation in NSCLC. And while the imaging features that we discussed are by no means 100% sensitive or specific for certain mutations, these features are indicative of their presence. For instance, miliary-type metastases are strongly associated with EGFR-mutant NSCLC and sclerotic metastases (prior to treatment) are suggestive of underlying rearrangements, such as ALK and ROS1.

Testing for certain mutations have become standard of care, but there are several testing platforms that are available and each has its own advantages and shortcomings. In addition, more novel mutations that are not routinely tested for. There are also significant disparities in compliance for testing around the world. The recognition of both clinical and imaging features that are associated with driver mutations in NSCLC can improve the yield of testing and wider utilization.

There is more awareness of clinical features in terms of demographics and smoking history but the association of the imaging features and underlying driver mutations in NSCLC is under recognized. Therefore, our aim was to highlight these associations to improve the compliance with genetic testing to guide the treatment.

We hope to introduce readers to the growing evidence that there are imaging features that are indicative of underlying mutations. While these imaging features are unlikely to replace

molecular testing in diagnosing these mutations, they can play a role in selection of patients that may benefit from expedited testing or repeat testing when results are either equivocal or discordant with the clinical presentation. Given the importance of initiating targeted therapy in those with targetable mutations, it is important to use all biomarkers available—clinical, radiologic, and histopathologic—in detecting these mutations. We have clarified and emphasized the above points in our manuscript.

We agree that our background is extensive and detailed. We decided to do this as the data on mutated NSCLC continuously and rapidly evolving as we learn more about these malignancies. We also wanted to frame "imaging biomarkers" as adjuncts to clinical and histopathological biomarkers rather than standalone features. Nevertheless, we have edited our manuscript to shorten part of our background. If there are additional specific sections that you would like for us to remove or shorten, we are willing to do so.

REVIEWER 1:
Conclusion: Accept (High priority)
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
The manuscript is well designed and with a fluent style. I recommend it to be published in the World Journal of Clinical Oncology.

RESPONSE 1:

Thank you for reviewing our manuscript and for your favorable comments. We hope that readers benefit from this review article.

REVIEWER 2:
Conclusion: Rejection
Scientific Quality: Grade E (Do not publish)
Language Quality: Grade A (Priority publishing)
This is an article with massive information. The authors reviewed a large number of literatures of NSCLC with driving-gene mutations related to imaging characteristics, and summarized these imaging characteristics of different driving-gene mutations. But this article has two major flaws: First, according to the current literatures provided by the authors, including the author's own "Conclusion", the current imaging characteristics of NSCLC with different driving-gene mutations are not enough to be defined as "Imaging Biomarkers". Second, the background of NSCLC driving-gene mutation is introduced in detail in nearly half of the manuscript, which helps readers to understand the role of driving-gene mutations in NSCLC, but such a large discussion has little to do with "imaging biomarkers", which will make the article deviate from the theme.

RESPONSE 2:

Thank you for reviewing our manuscript and for your constructive comments.

As we discussed above, in this manuscript, we define "biomarkers" are measurable or objective features that are indicative of the presence of a certain mutation in NSCLC. The available data suggests that these imaging features fit this criterion. And while we agree that the imaging features that we discussed are by no means 100% sensitive or specific for certain mutations, these features are indicative of their presence can play a role in selection of patients that may benefit from expedited molecular testing or repeat testing when results are either equivocal or discordant with the clinical presentation.

There is increasing awareness of the clinical features (e.g. minimal to no smoking history, Asian descent, etc.) that point to the presence of an underlying mutation, but the association of the imaging features and underlying driver mutations in NSCLC is under recognized. Therefore, our aim was to highlight these associations to improve the compliance with genetic testing to guide the treatment. Given the importance of initiating targeted therapy in those with targetable mutations, it is important to use all biomarkers available—clinical, radiologic, and histopathologic—in detecting these mutations. We have clarified and emphasized the above points in our manuscript.

We agree that our background is extensive and detailed. We decided to do this as the data on mutated NSCLC continuously and rapidly evolving as we learn more about these malignancies. We also wanted to frame "imaging biomarkers" as adjuncts to clinical and histopathological biomarkers rather than standalone features. Nevertheless, we have edited our manuscript to shorten part of our background.

REVIEWER 3:

Conclusion: Accept (High priority)
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
We appreciate the invitation to review this manuscript which has been read carefully by our team. The authors elucidated that the different molecular mutations of NSCLC can be predicted by different imaging features. Furthermore, this review lists the common types of genetic mutations in NSCLC and the corresponding imaging features, It's a novel idea.

RESPONSE 3:

Thank you for reviewing our manuscript and for your favorable comments. We agree that the distinct imaging features of mutated NSCLC are very interesting and may play a role in patients in whom molecular testing cannot be performed or wherein the results are equivocal or non-concordant with the clinical features.