Peer Review File

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Reviewer A

The authors verify the correlation between radiomic features (RFs) and the biological behavior of clinical stage IA adenocarcinomas. They grouped patients based on the RFs using consensus clustering, enabling comparison of tumor biological characteristics among the clusters. They found that Differences in tumor biological behavior were detected among consensus clusters based on the RFs of clinical stage IA adenocarcinoma.

This paper presents a unique analysis of imaging features using recent technology. However, I think that the characteristics of cluster 2 are consistent with risk factors already mentioned by past reports, and no new findings were obtained.
I have the following concerns.

Comment 1
Tumor diameter is analyzed as one of the imaging findings. However, there are two types of tumor diameters: whole tumor diameter and tumor invasion diameter. It is necessary to specify which is the tumor diameter evaluated in this paper.
Furthermore, it is a well-known fact that tumor invasion diameter is more related to prognosis than whole tumor diameter.

Reply 1: Thank you for your insightful comment. In our study, we initially measured the whole tumor diameter. Based on your suggestion, we have now included the measurement of the solid component of the tumor. This addition specified in the Methods and the Results section have been updated.

Comment 2
Patients with fewer than 6 lymph nodes removed have been excluded. Please add the rationale for this.

Reply 2: We are very sorry for the misunderstanding. What we mean is at least 3 hilar/peripheral and 3 mediastinal stations should be assessed during resection (see Page 6, line 93-94).

Reference:
1. Rami-Porta R, IASLC Staging Handbook in Thoracic Oncology, 2nd edn. North Fort Myers, FL: Editorial Rx Press; 2016.

Comment 3
In their introduction, the authors raise the following issues.
(Line 81-86)
The conventional RFs study process emphasizes statistical concepts for feature selection, prioritizing predictive power over the biological significance of RFs. This approach, coupled with the susceptibility of various machine learning models to overfitting, has sparked a controversy in RF studies. These shortcomings contribute to a growing disparity between decision-making in routine clinical practice and the interpretation of images by RFs.
The authors should discuss in the Discussion section how the results of their study may affect future treatment strategies in clinical practice. For example, they should add a discussion of whether thorough lymph node dissection or intensified postoperative chemotherapy should be used in high-risk clusters.

Reply 3: Thank you for your valuable feedback. Our study has identified a high-risk cluster characterized by an increased likelihood of having bigger median nodule diameter, pleural metastasis, occulted lymph node metastasis, EGFR mutation positivity, and poor prognosis. Based on our findings, we propose that thorough lymph node dissection and adjuvant preoperative or postoperative therapy may be considered in high-risk

patients. This approach aligns with the principles of personalized medicine, where treatment is tailored to an individual's risk profile (see Page 14-15, line 281-291).

Comment 4
More than half of the stage IA lung adenocarcinomas were excluded in this study.
The authors note as a limitation that a large number of excluded cases may have affected the results of the analysis.

Reply 4: Thank you for your comment. The flowchart in our manuscript details the reasons for excluding more than half of the stage IA lung adenocarcinoma cases. To clarify, our limitation section did not imply that the results were affected by the large number of excluded cases during the screening process. Instead, we highlighted that the results might be impacted by the inability to review some pathological sections due to long storage times and the limited number of genetic testing cases due to high costs. These factors would affect the results of certain clusters but were not due to subjective intervention or artificial screening. We acknowledge that a larger sample size is needed to verify the stability of our results.

Comment 5
The introduction is long.
Authors need to change to a more concise introduction.

Reply 5: Thank you for your suggestion. I intend to revise the introduction to make it more concise. The revised structure will be:

- Heterogeneity in early lung cancer is important for treatment and prognosis.
- Potentials and challenges of implementing radiomics features in clinical practice for Lung Adenocarcinoma
- The purpose of this study.

This addition specified in the Introduction section have been updated.

Comment 6
Line 34 histologic → histological

Reply 6: Thanks for your suggestion. We have revised it (see Page 2, line 24, 27).

Reviewer B

The authors emphasized a usefulness of radiomics features (RF) in clinical stage IA lung adenocarcinoma. RFs are potential non-invasive biomarkers for predicting a spectrum of heterogeneous biological behaviors, however, the relationship between RFs and the biological behavior of early-stage lung adenocarcinoma, particularly clinical stage IA adenocarcinoma, remains unclear. Patients were clustered into groups based on RFs using consensus cluster analysis. Three distinct clusters with distinct tumor biological behavior were identified, which indicates that RFs can reflect the biological behavior of tumors.
This manuscript was well written. I have some question about this research.
1) The representative CT image allows readers to understand the feature of each cluster.

Reply 1: Thank you for your suggestion. We have included representative CT images and corresponding pathological images for each cluster in the revised manuscript to help readers better understand the features of each cluster (Figure 5).

2) Is there any relationship between Consolidation Tumor ration (CTR) and each cluster?
What is the priority of RF to CTR or other preoperative factors?

Reply 2: Thank you for your carefully review. We measured the solid component of the nodules and calculated the CTR. We found that nodules with CTR=1(solid nodules) were more prevalent in the Cluster 2. Nodules with CTR=0 (pure ground glass nodule) were more common in the Cluster 1. However, we did not

observe a statistically significant difference in the distribution of part solid nodules based on CTR (≤0.5 vs. >0.5) within the cluster. We acknowledge the importance of further investigating the potential impact or relevance of these findings in future studies (see Table 2 and Table S1).

The purpose of the study is to verify whether RFs can reflect biological behavior of clinical stage IA adenocarcinomas. Through consensus cluster analysis, this study demonstrated significant variations in the biological behavior of early lung adenocarcinoma among groups based on radiomics feature differences, with Cluster 2 showing poorer biological behavior. We did not compare the predictive power of RF and CTR or other preoperative factors in this study. While previous studies have suggested that preoperative factors like CTR and lobulation have been shown to predict biological behavior and prognosis, some studies suggested that radiomics feature -based models outperformed other factors. However, combining RF with other factors generally enhances predictive ability.

Reference:

1. Ye T, Deng L, Wang S, et al. Lung Adenocarcinomas Manifesting as Radiological Part-Solid Nodules Define a Special Clinical Subtype. J Thorac Oncol. 2019;14(4):617-627. doi:10.1016/j.jtho.2018.12.030
2. Nakao M, Oikado K, Sato Y, et al. Prognostic Stratification According to Size and Dominance of Radiologic Solid Component in Clinical Stage IA Lung Adenocarcinoma. JTO Clin Res Rep. 2022;3(2):100279. Published 2022 Jan 21. doi:10.1016/j.jtocrr.2022.100279
3. Chen B, Li Q, Hao Q, et al. Malignancy risk stratification for solitary pulmonary nodule: A clinical practice guideline. J Evid Based Med. 2022;15(2):142-151. doi:10.1111/jebm.12476
4. Wu G, Woodruff HC, Shen J, et al. Diagnosis of Invasive Lung Adenocarcinoma Based on Chest CT Radiomic Features of Part-Solid Pulmonary Nodules: A Multicenter Study [published correction appears in Radiology. 2020 Nov;297(2):E282]. Radiology. 2020;297(2):451-458. doi:10.1148/radiol.2020192431
5. Liu MW, Zhang X, Wang YM, et al. A comparison of machine learning methods for radiomics modeling in prediction of occult lymph node metastasis in clinical stage IA lung adenocarcinoma patients. J Thorac Dis. 2024;16(3):1765-1776. doi:10.21037/jtd-23-1578
6. Wang T, She Y, Yang Y, et al. Radiomics for Survival Risk Stratification of Clinical and Pathologic Stage IA Pure-Solid Non-Small Cell Lung Cancer. Radiology. 2022;302(2):425-434. doi:10.1148/radiol.2021210109

3) In this cohort, 82 patients (12.3%) and 53 patients (7.9%) had hilar and mediastinal lymph node metastases, respectively. Preoperative lymph node metastases were evaluated by PET-CT or EBUS-TBNA? Are there any associations between up-staging and RF or other clinicopathological factors?

Reply 3: Thank you for your inquiry. In our study, preoperative lymph node metastases were primarily evaluated using enhanced CT, supplemented by PET-CT in some cases due to cost considerations. Our manuscript did discuss the relationship between stages and different clusters. Specifically, we observed that patients initially classified as clinical stage IA had advanced pathological stages, attributed to lymph node metastasis and pleural invasion. Although we did not directly correlate specific clusters with stage rise in the paper, our analysis did reveal associations between certain clusters and lymph node metastasis as well as pleural invasion. For further clarity, we have detailed these findings in our supplementary materials, including a table that provides details of the reasons for up-staging (see Table S2).

4) How do you use the RF obtained from preoperative CT images to the perioperative therapeutic strategy, for example, the range of lymph node dissection, adjuvant chemotherapy?

Reply 4: Thank you for your carefully review. Lymph node dissection and postoperative adjuvant therapy are directly associated with lymph node metastasis and prognosis. When radiomics features can predict lymph node metastasis and prognosis, they help physicians identify patients who are suitable for lymph node dissection and adjuvant therapy. It is important to note that our study does not aim to identify the best radiomics features for guiding treatment. Instead, our goal is to demonstrate that radiomics features can be used for prediction. The next step will be to develop a model for more accurate treatment guidance.

5) Table2. There is a mistake of spelling “smoking status”.

Reply 5: Thanks for your suggestion. We have revised it (see Table 2).