Journal for ImmunoTherapy of Cancer

Correspondence on 'Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab' by Jazieh *et al*

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To cite: Zheng J, Zhang B. Correspondence on 'Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab' by Jazieh *et al*. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e004965. doi:10.1136/jitc-2022-004965

Accepted 16 May 2022

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Dear Editor,

We read with great interest the study by Jazieh *et al*,[1] recently published in the *Journal for ImmunoTherapy of Cancer*. Consolidation immunotherapy after chemoradiation has already become the standard of care for locally advanced, unresectable non-small cell lung cancer (NSCLC); yet, only a fraction of patients achieved a durable clinical benefit, thus it is of great importance to developing biomarkers of NSCLC to guide immunotherapy. Current biomarkers are limited by the availability of samples and fail to accurately select who will benefit from immunotherapy. This study highlighted the potential of CT-based radiomics as a new non-invasive imaging biomarker for the prediction of prognosis in stage III unresectable NSCLC treated with chemoradiation and durvalumab. The constructed radiomic risk score (RRS) is capable of identifying patients who will benefit from immunotherapy, which may effectively improve clinical decision support. Ineffective treatment with durvalumab can be avoided in patients who are unlikely to respond to this therapy and more intensive monitoring can be administrated for patients with a high risk of poor outcomes.

Despite the promising results, we are concerned about several steps of radiomic workflow. Standard and rigorous radiomic processes are crucial for reliable and reproducible radiomic biomarkers. The workflow of radiomics is complex and its robustness and reproducibility can be influenced by each step of the workflow. First, most features are dependent on imaging modality, making them susceptive to variations in scan protocol. Given that the pretreatment CT images were acquired from several machines with different parameters, image preprocessing is necessary to reduce the density variations among CT scanners, which is a crucial step prior to feature extraction. Although the authors acknowledged in the limitations that they did not evaluate the influence of scanning parameters on the extracted radiomic features. Second, given the fact that most radiomic features were redundant (ie, those that are highly correlated with one another), the current feature selection was not enough despite the authors using the least absolute shrinkage and selection operator, more sophisticated and rigorous dimensionality reduction methods (such as univariate analysis, intraclass correlation analysis, and Pearson correlation coefficient analysis) are needed to be implemented to ensure the reproducibility and independence of the selected radiomic features. Considering the methodological issues, the robustness of the identified radiomic features warrants extensive validations.

Other issues regarding methods and results should also be pointed out. First, demographics and clinical characteristics (age, sex, race, and smoking) of the D3 cohort significantly differed from that of the D1 and D2 cohorts, suggesting potential selection bias. Second, the association of RRS with progression-free survival (PFS) and overall survival (OS) was evaluated using Kaplan-Meier survival analysis and the log-rank test. However, we observed crossed survival curves in figure 1, thus, the survival differences should be assessed with landmark test rather than log-rank test. Third, this study analyzed the difference in clinical outcomes between high and low PD-L1 expression groups based on different PD-L1 cut-off criteria (threshold of 1% and 50%). The results demonstrated significant differences in PFS and OS

between patients with low and high PD-L1 using the 50% instead of 1% cut-off criteria. The authors could perform subgroup analysis by continuous PD-L1 cutoffs (such as ≤1%, >1% to≤ 10%, >10% to ≤50%, and >50%) to show the trend towards median PFS and OS with increasing PD-L1 expression. RRS was not significantly associated with OS in the high PD-L1 group may be due to the very small sample size. Fourth, the identified radiomic features strongly associated with outcomes were not reported and their relative importance was also unclear in this study. Fifth, the number of never-smoking was dramatically fewer than that of former or current smoking (2 vs 57), and there was no significant difference in smoking status between high-risk and low-risk patients (p=0.68), thus, the smoking status can be removed from the clinical and combined predictive models. The results of the nomogram also showed very little impact of smoking status on the PFS prediction (HR: 1.11, 95% CI: 0.52 to 1.82, p=0.86). Finally, this study used the single discriminative metric C-index to compare the predictive performance of various models, while additional indicators such as integrated discrimination improvement and net reclassification index are better to evaluate the risk prediction improvement of radiomic features.

Biological interpretability of radiomic features is vital but challenging. A disconnect between radiomic features and biological meaning will inherently hinder the clinical translation of radiomics analysis.[2] Efforts to introduce biological meaning into radiomics are gaining traction in this field with distinct emerging approaches available, including correlation with pathology features and biological function, radiology–pathology coregistration, and analysis of biological pathways or genomic correlations in humans or animals.[3] Nevertheless, the biological cause of patients' outcomes remains poorly understood. Treatment outcome is closely related to tumor biology and interaction with the tumor microenvironment. This study speculated that intratumoral Laws and Haralick features correlated with dysregulation of blood supply, one property of tumor hypoxic environment, resulting in suboptimal response to chemoradiotherapy in NSCLC. However, the connection between these features and biological basis remains unproven, which needs to be further investigated. The authors may detect the biomarker of hypoxia, hypoxia-inducible factor-1α (HIF-1α), by using immunohistochemistry with NSCLC samples and then explore correlations between radiomic features and the expression of HIF-1α to establish the biological meaning of these features. This study also speculated that angiogenesis may be captured by peritumoral Laws features, which can be linked to the biomarker of tumor angiogenesis, vascular endothelial growth factor. Additionally, this study supposed that textural patterns of peritumoral radiomics could capture the degree of immune response, which was in turn correlated with the effects of immunotherapy. The immune response can be investigated by detecting the percentage of cytotoxic T cell (CD3 +CD8+) or cytotoxic T cells subsets, so that the association between textural patterns and immune response can be validated. Similarly, it was postulated that the Gabor texture feature may capture the increment of PD-L1 and lymphocyte level selectively in peritumoral regions, which can be proved through the detection of PD-L1 and lymphocyte level and the analysis of their relationships with this feature. Generally, the biological meanings of the radiomic features in this study have not yet been clarified.

Notably, the identification of reliable predictive biomarkers remains one fundamental bottleneck in improving patient selection for immunotherapy, despite the confirmed role of PD-L1 expression as a predictive biomarker for immunotherapy of NSCLC. The suboptimal response to durvalumab can be attributed to resistance to immunotherapy with checkpoint inhibitors (ICIs). Hence, we should consider other predictive biomarkers affecting the resistance to ICIs and investigate their clinical characteristics and relationships with prognosis. Tumor-intrinsic mechanisms involve genetic mutations that have immune regulatory functions, including JAK1 and JAK2 mutations-mediated PI3K activation, MAPK pathway alterations.[4] Tumor-extrinsic factors are related to tumor microenvironment including increased infiltration of myeloid-derived suppressor cells, tumor-associated macrophages, M2 macrophages, and regulatory T cells.[5] These signal pathways and cell subsets may be potential biomarkers for patient selection for immunotherapy and need further investigation.

Contributors JZ and BZ drafted the manuscript. BZ critically revised and and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

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