Peer Review File
Article information: https://dx.doi.org/10.21037/tlcr-23-5

Round1

Reviewer A, Comment 1: Abstract, page 1, and Table 2, page 19, Although intratumor and peritumoral radiomic signals were mentioned as important factors, they have only been mentioned in 5 of the 13 articles in Table 2. The authors should describe the essential factors from the other articles in the abstract and the conclusion.

Reply 1: We thank the reviewer for this comment. We have updated Table 2 to include another column "High Level Radiomic Features" which provides information regarding what major components of radiomic features were found to be important for outcomes. See page 12, line 6 page in the main report and changes to table 2.

Changes in the Text: Although most authors have identified tumor shape, and 1st and 2nd order elements as being important determinants of outcomes (Table 2), one surprising finding in recent studies, which was ignored in earlier reports, demonstrates the importance of including the peritumoral space (i.e., tissue surrounding the primary tumor) in radiomic analysis (22)."

Reviewer A, Comment 2: Table 2, page 19 Features Associated with Endpoints in Table 2 were not summarized, which was difficult to understand. The authors should summarize them more precisely.

Reply 2: Please see comment above which states that we have also included an additional column to table 2 which summarized the high level radiomic features. As the reviewer is aware, each publication had a slightly different list of shape, 1st, 2nd order features in their publication due to variability in the type of radiomic program and population studied in their reports which makes it impractical to provide more than a high level summary.

Change in the text: We have added an additional column to Table 2 "High Level Radiomic Features"

Reviewer A, Comment 3: The authors describe "non-small cell carcinoma" in Table 1. However, "non-small cell lung cancer" is suitable because the authors use non-small cell lung cancer (NSCLC) in the manuscript.

Reply 3: We have addressed this comment to include "Non-Small Cell Lung Cancer" in the table heading

Change in the text: Table 1: Application of Radiomics in Non-Small Cell Lung Cancer

Reviewer B, Comment 1: Step 1: Image Acquisition and Calibration. I would recommend the authors to briefly touch upon the use of ComBat harmonization methods to mitigate the heterogeneity in image parameters and obtain more reproducible prognostic signatures. In this regard, they can reference the work of Singh et al. "Resampling and harmonization for mitigation of heterogeneity in image parameters of baseline scans". This study extensively investigates the effects of heterogeneity in image parameters on the reproducibility of prognostic performance of models built using radiomic biomarkers.

Reply 1: We thank the reviewer for this suggestion. We have incorporated this article in section Step 5: Application and Validation, page 11, line 14-18 and added Singh et al reference 20. With this insertion of language, we adjusted the first sentence of the next paragraph.

Change in text: One of the key consideration to incorporate a radiomic signature in a clinical trial or for clinical decision-making purposes is to understand how the different aspects of features selection methods, classification models, and the number of top-rated features will impact the results. One critical component for developing a radiomic signature is to determine which radiomic feature(s) are reflecting measurements related to technical factors (e.g., patient preparation and image acquisition/reconstruction) rather than physiology, biology, and pathology. Recently, Singh et al (20) applied techniques typically used to remove effects of machinery and protocol on gene expression date, so-called ComBat (Combining Batches (ComBat) harmonization methods to address this issue. Using two publically available image data sets from The Cancer Imaging Archive (Breast I-SPY1 and NSCLC IO), they found that heterogeneity-mitigation using ComBat techniques that addressed voxel resampling, voxel spacing, high kernel resolution, pixel spacing and slice thickness provided more stable radiomic features compared to raw data without harmonization-mitigation.

Furthermore, Parmar et al. (17) examined the performance and stability of 14 radiomic feature selection methods and 12 classification schemes and the number of features (ranging from 5-50) in predicting the two-year survival of NSCLC in subjects undergoing radiation therapy from two independent institutional cohorts.

Reviewer B, Comment 2: Step 2: Segmentation. I would recommend the authors to include some publicly available semi-automated segmentation tools. For instance, they could cite the work by Yushkevich et al., "ITK-SNAP: An interactive tool for semi-automatic segmentation of multi-modality biomedical images".

Reply 2: We have added language that references the use of this tool on Section 2:

Segmentation, page 7 and included the reference to Yushkevich et al

Change in Text: The use of several general purpose open source tools (e.g., ITK-SNAP: http://itksnap.org) to provide easy-to-use lesion segmentation are readily available for deriving accurate ROIs/VOIs from different data sets and image modalities (9)"

Reviewer B, Comment 3: Step 3: Feature extraction. I would recommend the authors to include some publicly available radiomic toolkits. For instance, they could cite the work by Rathore et al., "Brain cancer imaging phenomics toolkit (brain-CaPTk): an interactive platform for quantitative analysis of glioblastoma".

Reply 3: We have included the brain-CaPTk platform in section 4. Conclusion section, page 16, lines 15-16 of our manuscript.

Change in Text: The democratization and public access to both a growing number of databases and open-source software platforms for radiomics analysis (e.g., PyRadiomcs:[www.python.org]and brain-CaPTk: [www.med.upenn.edu/sbia/captk.html]) is advancing this field."

Reviewer B, Comment 4: CT based radiomic studies. The authors can briefly discuss the study by Singh et al., "Development of a robust radiomic biomarker of progression-free survival in advanced non-small cell lung cancer patients treated with first-line immunotherapy"

Reply 4: We thank the reviewer for this recommendation and the excellent article by Singh et al. However, since our manuscript focuses on early-stage NSCLC, we have not included any reference to this paper which provides radiomic analysis in stage IV NSCLC front-line setting treated with IOT.

Change in Text: None

Round 2

Review Comments

I would like to praise the efforts of the authors in addressing all the comments, that has resulted in a more comprehensive review paper. I would like to point out a spelling error in line 293 of the revised manuscript text- expression data (as opposed to date). Other than that, I feel all the comments have been addressed satisfactorily by the authors.

You can refer to the review version (attached) for a better location.

Reply:Thank you for this comment and close attention to detail. The spelling error on line 293 has been corrected.