Editorial

Are radiomic signatures ready for incorporation in the clinical pipeline?

Apurva Singh[1,2]^, Leonid Roshkovan[1], Jeffrey C. Thompson[3], Despina Kontos[1], Sharyn I. Katz[1]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Thoracic Oncology Group, University of Pennsylvania, Philadelphia, PA, USA

Correspondence to: Sharyn I. Katz, MD, MTR. Department of Radiology, University of Pennsylvania, Dulles Building, 3400 Spruce St., Philadelphia, PA 19104, USA. Email: Sharyn.Katz@pennmedicine.upenn.edu.

Comment on: Libling WA, Korn R, Weiss GJ. Review of the use of radiomics to assess the risk of recurrence in early-stage non-small cell lung cancer. Transl Lung Cancer Res 2023;12:1575-89.

Keywords: Radiomics; tumor heterogeneity; precision medicine

Submitted Aug 02, 2023. Accepted for publication Sep 01, 2023. Published online Sep 19, 2023.
doi: 10.21037/tlcr-23-502
View this article at: https://dx.doi.org/10.21037/tlcr-23-502

Lung cancer is the leading cause of cancer deaths in the United States. The growing number of available targeted therapies and immunotherapeutic options have transformed the treatment landscape of patients with non-small cell lung cancer (NSCLC). However, determining which patients will ultimately respond to these therapies remains a challenge, and there is an urgent need to identify additional biomarkers to better determine the subgroups of patients most likely to benefit from particular therapeutic strategies. Thus, efforts to improve precision medicine are a significant focus of lung cancer research. Traditionally, analysis of a biopsied region of tumor tissue is used to study the molecular and pathologic features of the tumor. These small biopsy specimens, however, may not be fully representative of the tumor heterogeneity (1), or peritumoral tissue microenvironment, the latter which has been increasingly demonstrated to have clinical significance. In addition, tumor biology and mutational expression profiles are dynamic over time, and it is not feasible to perform repeated tumor biopsies to capture this temporal evolution, in part due to patient discomfort, and exposure to procedure-related complications (2).

Medical imaging now is primarily utilized to screen for the presence of tumors, assess tumor stage and response to therapy, and surveil for disease recurrence following curative intent therapy. However, with the broader utilization of radiomic techniques, conventional medical imaging may be leveraged to non-invasively interrogate the tumor microenvironment and facilitate more personalized therapeutic strategies.

Radiomics focuses on the quantification of high-throughput data from diagnostic scans (3). Recent studies have explored the use of radiomics models built from computed tomography (CT) and positron emission tomography (PET)/CT images to prognosticate outcomes in patients with early-stage NSCLC. For instance, a multi-feature based radiomics signature built from CT images by Huang *et al.*, was identified to serve as an independent risk factor of disease-free survival in patients with early-stage NSCLC and added value when combined with other clinical risk factors, including traditional cancer staging (4). Similarly, Yu *et al.* developed a prognostic radiomic biomarker from CT scans, to predict mortality risk in patients who had undergone surgical resection for stage I NSCLC. The signature was also validated with another group of patients who had undergone stereotactic ablation radiation (SABR). The model was significantly associated with distant metastasis recurrence in the SABR

^ ORCID: 0000-0001-5600-800X.

cohort (5). In addition, a PET-based radiomics model was developed and validated by Ahn *et al.* for the purpose of risk classification in NSCLC. Combining information from the PET-based signature with tumor, node, metastasis (TNM) stage led to an improvement in outcome prediction in patients with NSCLC (6).

While these advances are exciting and suggest a potential role for radiomics in oncologic management, there are significant challenges to widespread clinical translation of these techniques. For example, currently used techniques of manual/semi-automated segmentation of tumor regions of interest (ROIs) by radiologists are time-consuming and subject to inter-reader variability. In other words, "ground truth" segmentation does not exist (7). Furthermore, for radiomic signatures to be successfully implemented as clinical biomarkers and gain acceptance by the clinical community, they must remain comparable, even if there is a variation in the image acquisition process. There is wide variation in image parameters during routine image acquisition. This includes differences in imaging protocols, scanner hardware, radiation dose reduction algorithms, voxel spacing, and reconstruction algorithms adapted by different vendors during routine CT imaging acquisition. Variables including patient factors, drugs the patient may be on, differences in scanner uptake time and washout period in case of PET imaging, due to the metabolic nature of this imaging agent, contribute to the list of differences as well. These sources of variability create significant limitations in the reproducibility of radiomics results obtained across institutions (8).

In a recent issue of *Translational Lung Cancer Research*, Libling *et al.* provide a review of the current literature for radiomics in lung cancer, focusing on the applications for radiomics to detect disease recurrence in early-stage NSCLC, following curative intent therapy (9). The authors have targeted this population, as it is optimal for exploring the added benefit of radiomics in surveillance over the course of treatment and assess response to therapy. The authors have outlined the five essential steps involved in radiomic-signature development, while also listing the shortcomings and potential areas of improvement in each of them. For instance, in the "image acquisition and calibration" step, they discuss the need to apply pre-processing methods to correct for acquisition differences between patients, including pixel re-sizing, grey level normalization, re-sampling, histogram equalization, and so on. In the segmentation step, they discuss the strengths and drawbacks of the various techniques adopted in radiomics analyses. As mentioned above, the commonly used manual or semi-automated segmentation approaches are time-intensive and suffer from inter-reader variability. Alternatively, fully automated methods offer the advantage of speed and reproducibility but are dependent on large image sets for effective training and large curated aggregated imaging datasets are not widely available in part due to restrictions on the use of patient medical data. Thus, selection of the appropriate segmentation approach is done based on the specifications of the dataset.

In their article, the four main categories of radiomic features are described in the "feature extraction" step: (I) lesion shape; (II) first order; (III) second order and (IV) high order. Similarly, the "model building" step talks about supervised random forest (RF) and support vector machine (SVM), unsupervised k-means clustering, consensus clustering and so on, and semi-supervised large datasets trained using unsupervised learning to minimize feature space dimensionality, that are then tested using a supervised model to determine the relationship of features with the clinical categories learning techniques. In the "application and validation" step, the authors underscore how the training and validation steps are essential to understand the model's diagnostic performance. The authors also discuss the use of harmonization techniques to mitigate heterogeneity at the feature level, and the variability observed in the predictive performance of radiomic studies based upon selection of features and classifiers. Harmonization techniques hold the promise of making it possible to aggregate imaging data across institutions using differing scanner types and imaging protocols.

In addition, the authors provide a range of potential applications for radiomics in the management of lung cancer, such as in the detection of lung cancer recurrence after curative intent using CT-based radiomics in early-stage NSCLC and predicting treatment outcomes using radiomic signatures derived from intra-tumor regions. The role of tumor histology in driving the radiomic signature is discussed, underscoring the importance of accounting for histological subtypes when evaluating the strengths and limitations of a radiomic signature. Beyond the tumor itself, there is ample evidence that activity within peri-tumoral tissues is of clinical importance, and the implications of analysis of the peri-tumoral area for radiomic signature development are discussed. Interestingly, one of the studies observed that peri-tumoral areas exhibited less variation resulting from CT acquisition parameters compared to intra-tumoral regions resulting in more stability of the

extracted radiomic features (10). The discussion section notes that radiomic studies typically focus on CT-derived radiomic features rather than fluorodeoxyglucose (FDG)-PET. While this is reasonable since CT is the imaging workhorse of oncologic management, FDG-PET does offer data on metabolic activity within the tumor, which offers another aspect of tumor biology to leverage with radiomics. However, ^{18}F-FDG PET is most often acquired as a staging modality, rather than longitudinal imaging assessment, and PET images suffer from comparatively poor spatial resolution, as well as variability introduced from patient factors and acquisition parameters. However, despite this, some studies have demonstrated that PET signal produced from different scanner and reconstruction algorithms has more consistency compared to CT-derived signals. Thus, multi-modality models, that combine strengths from each modality, may be of merit. To highlight this idea, the authors discuss a study that combines anatomic signals from CT and metabolic signals from ^{18}F-FDG PET to build a time to event prediction model (11). To conclude, the authors discuss the need for making additional databases publicly available for discovery, testing, training and validation purposes. Further, they stress the need to focus efforts on robustness and generalizability of radiomic features, to make the clinical translation of these strategies possible.

Radiomics is a high-dimensional analysis technique that is rapidly advancing in the pre-clinical space and holds the promise of gaining new layers of insight into tumor biology derived from conventional medical imaging and enabling an increase in precision oncologic management. A major barrier to the success of radiomics is the current lack of large, curated datasets of aggregated medical imaging. The statistical power of radiomic analyses improves with an increase in sample size, and big data is needed to discern the radiomic signal through the many sources of variability present in medical imaging data. There are several collaborative efforts currently underway to develop radiomics-based biomarkers, which have resulted in the establishment of several imaging repositories with a large volume of medical images and correlated clinical information. An example of such a repository is the National Lung Cancer Screening Trial American College of Radiomic Imaging Network Biomarker Repository (12). Such large dataset is critical to the development of generalizable radiomic signatures that can serve as clinically relevant biomarkers.

Previous studies have studied the reproducibility of radiomic features in a limited setting, such as test-retest and phantom experiments (13). While these studies have explored the sensitivity of individual radiomic features to the variation in image parameters, enough attention has not been focused on exploring the effects of these variations on the reproducibility of image signatures. In addition to striving towards harmonization of acquisition parameters, it is also important to standardize approaches to post-processing of radiomic features, especially in multi-institutional cohorts. The study by Singh *et al.* investigates the effects of variability in individual image parameters on the prognostic performance of models derived from them (14). This was done by utilizing a variety of resampling and harmonization techniques to address the heterogeneity in the radiomic features. The results indicated that irrespective of site or modality of the diagnostic images, accounting for the variation in image parameters is important to obtain more standardized and generalizable prognostic scores of the models derived from them. The study addresses the critical question of ensuring the robustness of prognostic radiomic biomarkers to the variation in image parameters. Coordination between imaging device manufacturers, academic institutions, healthcare providers and practicing physicians is important to ensure the reproducibility of the results of radiomics studies. In accordance with this idea, the National Cancer Institute (NCI) established the Quantitative Imaging Network (QIN), which consists of multidisciplinary teams of oncologists, radiologists and informatics scientists purposed with developing and testing imaging methods to measure response to cancer therapy (15). From this effort, the Quantitative Imaging Biomarker Alliance (QIBA) was initiated at the annual Radiological Society of North America (RSNA) session in 2007. This initiative aims to bring together national regulatory agencies, to collectively determine standardization techniques for imaging signatures (16). The radiomics community is steadily recognizing the importance of addressing image parameter heterogeneity, to develop reproducible radiomic biomarkers. This is crucial for ensuring consistent and accurate interpretations of patient data, and for improving the field of precision medicine.

Acknowledgments

Funding: This work was supported by the National Institutes of Health (No. R01CA264835) granted to DK and SIK.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-502/coif). AS and SIK report funding received from the NIH for the proposed research and the NCI funding for work in radiomics in lung cancer with the Kontos laboratory. SIK also reports that he has received a NIBIB grant that supports the creation of an open-source database of COVID-19 clinical and imaging data to potentiate research, development, and education, and he serves as the Chair of the CIRR, American College of Radiology. JCT has received consultancy fees from AstraZeneca and institutional research finding from Delfi Diagnostics and Incyte. DK has received institutional research grant support from iCAD Inc., GenMab and Calico, and she received the Radiology AI Deputy Editor Honorarium from RSNA, Grant Reviewer Honorarium from Breast Cancer Alliance, DOD and NIH, and the Advisory Board Honorarium from the University of Alabama at Birmingham. LR has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Marusyk A, Polyak K. Tumor heterogeneity: causes and consequences. Biochim Biophys Acta 2010;1805:105-17.
2. Vaidyanathan R, Soon RH, Zhang P, et al. Cancer diagnosis: from tumor to liquid biopsy and beyond. Lab Chip 2018;19:11-34.
3. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 2012;48:441-6.
4. Huang Y, Liu Z, He L, et al. Radiomics Signature: A Potential Biomarker for the Prediction of Disease-Free Survival in Early-Stage (I or II) Non-Small Cell Lung Cancer. Radiology 2016;281:947-57.
5. Yu W, Tang C, Hobbs BP, et al. Development and Validation of a Predictive Radiomics Model for Clinical Outcomes in Stage I Non-small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2018;102:1090-7.
6. Ahn HK, Lee H, Kim SG, et al. Pre-treatment (18)F-FDG PET-based radiomics predict survival in resected non-small cell lung cancer. Clin Radiol 2019;74:467-73.
7. Cooper JS, Mukherji SK, Toledano AY, et al. An evaluation of the variability of tumor-shape definition derived by experienced observers from CT images of supraglottic carcinomas (ACRIN protocol 6658). Int J Radiat Oncol Biol Phys 2007;67:972-5.
8. Kumar V, Gu Y, Basu S, et al. Radiomics: the process and the challenges. Magn Reson Imaging 2012;30:1234-48.
9. Libling WA, Korn R, Weiss GJ. Review of the use of radiomics to assess the risk of recurrence in early-stage non-small cell lung cancer. Transl Lung Cancer Res 2023;12:1575-89.
10. Khorrami M, Bera K, Leo P, et al. Stable and discriminating radiomic predictor of recurrence in early stage non-small cell lung cancer: Multi-site study. Lung Cancer 2020;142:90-7.
11. Amini M, Hajianfar G, Hadadi Avval A, et al. Overall Survival Prognostic Modelling of Non-small Cell Lung Cancer Patients Using Positron Emission Tomography/Computed Tomography Harmonised Radiomics Features: The Quest for the Optimal Machine Learning Algorithm. Clin Oncol (R Coll Radiol) 2022;34:114-27.
12. National Lung Screening Trial Research Team; Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243-53.
13. van Timmeren JE, Leijenaar RTH, van Elmpt W, et al. Test-Retest Data for Radiomics Feature Stability Analysis: Generalizable or Study-Specific? Tomography 2016;2:361-5.
14. Singh A, Horng H, Chitalia R, et al. Resampling and harmonization for mitigation of heterogeneity in image parameters of baseline scans. Sci Rep 2022;12:21505.
15. Clarke LP, Nordstrom RJ, Zhang H, et al. The

Quantitative Imaging Network: NCI's Historical Perspective and Planned Goals. Transl Oncol 2014;7:1-4.
16. Shukla-Dave A, Obuchowski NA, Chenevert TL, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. J Magn Reson Imaging 2019;49:e101-21.

Cite this article as: Singh A, Roshkovan L, Thompson JC, Kontos D, Katz SI. Are radiomic signatures ready for incorporation in the clinical pipeline? Transl Lung Cancer Res 2023;12(9):1845-1849. doi: 10.21037/tlcr-23-502