Radiogenomic Analysis to Predict Response to Immunotherapy in Patients with NSCLC

John Boom,[1,2] Muhammad Aminu,[2] Pingjun Chen,[2] Natalie Vokes,[3] Mehmet Altan,[3] John Heymach,[3] Jia Wu[2,3]

1. Duke University; 2. Department of Imaging Physics, UTMDACC; 3. Department of Thoracic/Head & Neck Medical Oncology, UTMDACC

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Background

Profiling the gene expression of solid tumors can assist in predicting patients' responses to immunotherapy. However, extracting gene expression traditionally requires invasive biopsies or surgeries, which is impracticable for late-stage patients with multiple lesions. Additionally, biopsies are time-consuming, expensive, and invasive nature, they are usually taken only once before treatment. However, gene expression is expected to change in response to treatment, and this longitudinal information could improve physicians' decision making.[1] Novel techniques for monitoring gene expression in solid tumors have the potential to improve personalized cancer treatment.

Radiogenomics is an emerging field that principally aims to correlate features from imaging to gene expression.[2] In this way, it is non-invasive and easily integrates into the current clinical workflow. However, progress into

Motivation

Patients with late-stage non-small cell lung cancer (NSCLC) often cannot get a biopsy at every lesion. Moreover, most NSCLC patients worldwide lack access to gene expression testing, but can receive CT scans. Therefore, we sought to develop a model capable of predicting gene expression exclusively from CT scans of each lesion. Such a model could improve choice of treatment for late-stage patients, could provide a longitudinal view of gene expression, and would serve as a proof-of-concept for future radiogenomic models.

Methods

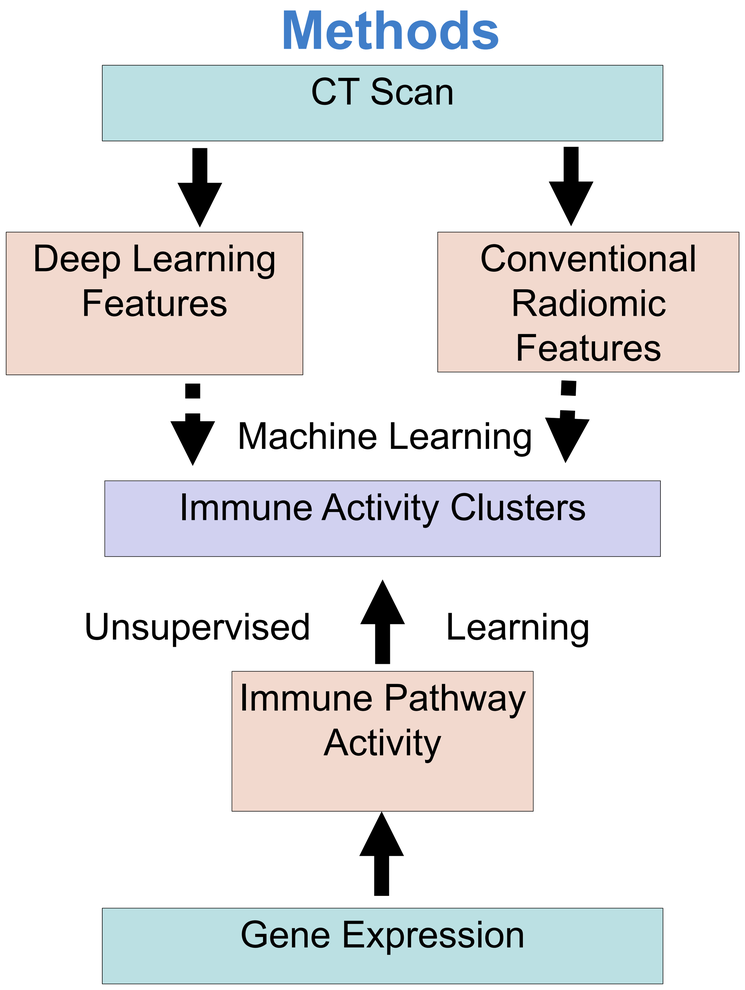

Fig 1. Overview of the proposed approach using unsupervised learning to find immune activity clusters, and the corresponding radiomics pipeline to classify clusters from imaging.

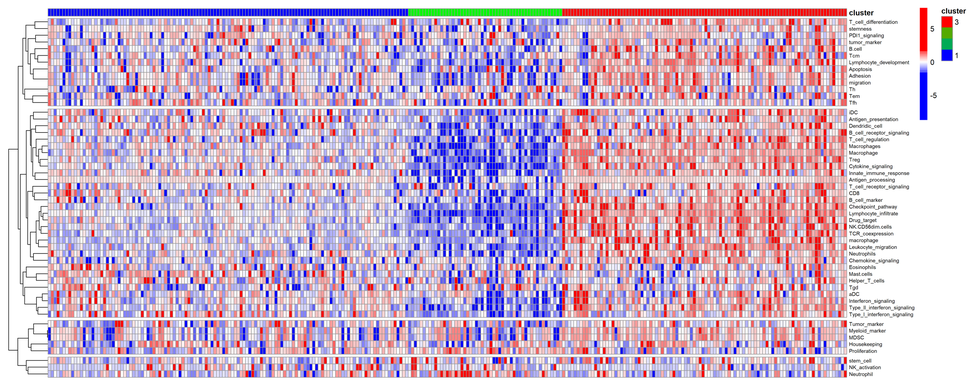

Fig 2. Heatmap of the genetic pathways, clustered by patient. The colored bars at the top denote each of the different clusters. Red indicates larger values, and blue indicates smaller. From left to right, the clusters were interpreted as immune "neutral," "cold," and "hot". The labels on the right list the immune pathways, and the rows (pathways) are grouped by correlation.

As shown in Figure 1, the overall approach relies on both unsupervised and supervised machine learning. First, unsupervised learning is used to cluster patients with similar immune profiles. Then, supervised machine learning is performed to predict clusters from the imaging features.

Before performing the unsupervised clustering, first the genomic data needed to be processed. Genomic data and pre-treatment CT scans were identified from multiple institutions for 274 patients with early-stage NSCLC.[3] Gene expression data was log2 normalized across each cohort, and then each pathway of each cohort was normalized using Z-Score normalizing. This approach assumed that the distribution of gene expression were identical in each cohort but was necessary in order to normalize between cohorts. Then, using gene set enrichment analysis, the normalized gene expression was converted into common pathways associated with immune response. The patients were then clustered using a variety of algorithms, including partition around medoid (PAM), k-means, hierarchical clustering, and spectral clustering. Ultimately, consensus clustering with the k-means algorithm using Euclidean distance was found to provide the most robust and distinct clusters. The heatmap of immune pathways, and the clusters, is shown in Figure 2.

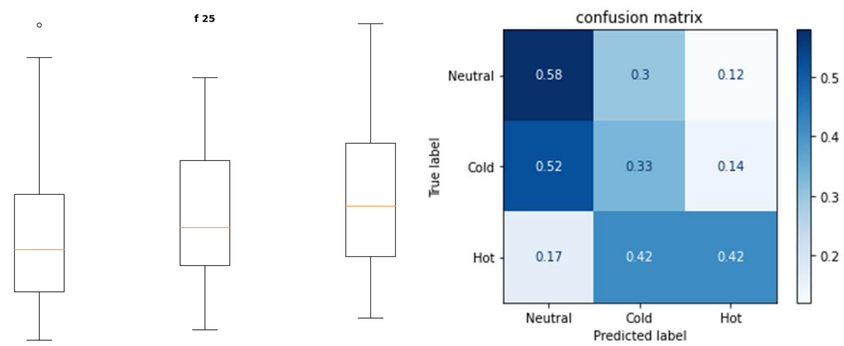

Fig 3. a) Box plots of the feature with the highest differences between classes. The classes are immune "neutral", "cold," and "hot" from left to right. p=0.08 **b)** Confusion Matrix of a Random Forest model trained to predict three classes.

Each lesion was segmented by an experienced radiologist, after which they were processed through the conventional and deep learning pipelines. Conventional radiomics features were extracted using the pyradiomics package,[4] an in-house program to extract regional variation, and an in-house program that describes the tumor structure using spherical harmonics. Deep learning features will be extracted using an 3D autoencoder to compress the tumor into a low-dimension latent space that provides rich tumor features. Ultimately, 412 conventional radiomic features were found.

Univariate testing correlated each radiomic feature with the gene expression clusters. Additionally, machine learning (ML) models, including Support Vector Machine (SVM), and Random Forest (RF) was used to predict the gene expression cluster from the radiomic features.

Results

Model	Accuracy	Precision	Recall	F1	AUC_ROC
Logistic Regression	0.52	0.49	0.51	0.46	**0.53**
Support Vector Machine	0.54	0.27	0.50	0.38	0.47
Random Forest	**0.53**	**0.52**	**0.52**	**0.52**	**0.53**

Table 1. Results of various machine learning models in attempting to classify immune hot or immune cold from the imaging features. The top results are bolded.

The heatmap in Figure 2 demonstrates that 3 clear classes were found. Three classes were found in most clustering methods; however, many samples were clustered differently depending on the algorithm used.

While the genomic results yielded distinct clusters, it was much harder to correlate the radiomic features to the gene expression. Figure 3 shows the box plots of the feature with the most interclass variation. The large amount of overlap suggests that the features do not strongly correlate to the different gene clusters.

The lack of correlation between the conventional radiomic features and the gene expression clusters was confirmed by the results of the ML models, shown in table 1. Since these models are scarcely predicting better than a random guess, either better features or better models must be developed in order to develop a robust radiogenomics model.

Conclusion

This study aimed to build a radiogenomic model in order to predict whether a patient would respond to immunotherapy. No meaningful correlation was found between the radiomic features and the gene expression clusters; however, the study is currently not complete. Notably, deep learning features have not yet been extracted from the CT scans, and they have significantly more potential to enable an accurate radiogenomic model.

After the model is built, it will be validated by applying it to a cohort of 182 patients with late-stage NSCLC from the LONESTAR clinical trial that do not have gene expression data, and hopefully showing that the predicted clusters predict changes in tumor volume.

References

1. Lu, Y. *et al.* A Gene Expression Signature Predicts Survival of Patients with Stage I Non-Small Cell Lung Cancer. *PLoS Med* **3**, e467 (2006).
2. Mazurowski, M. A. Radiogenomics: What It Is and Why It Is Important. *Journal of the American College of Radiology* **12**, 862–866 (2015).
3. Hoadley, K.A. et al. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. Cell 173, 291-304 e296 (2018).
4. van Griethuysen, J. J. M., Fedorov, A., Parmar, C., Hosny, A., Aucoin, N., Narayan, V., Beets-Tan, R. G. H., Fillon-Robin, J. C., Pieper, S., Aerts, H. J. W. L. (2017). Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Research, 77(21), e104–e107. `https://doi.org/10.1158/0008-5472.CAN-17-0339 <https://doi.org/10.1158/0008-5472.CAN-17-0339>