JULY 12–16
2020 VIRTUAL
JOINT AAPM | COMP MEETING
EASTERN TIME [GMT-4]

# Machine learning of MAA SPECT lung perfusion radiomics to predict radiation and immune-mediated pneumonitis in patients with locally advanced non-small cell lung cancer

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## INTRODUCTION

- Pneumonitis is an adverse event following chemoradiation for locally advanced lung cancer and has been increasingly reported in patients who receive consolidated immunotherapy [1,2,3].
- For improving treatment outcomes early detection of pneumonitis is critical. Hence, it is imperative to identify biomarkers that predict patients at risk for pneumonitis.
- In this study, we use functional lung radiomics for pneumonitis risk stratification in the setting of chemoradiation and consolidation immunotherapy.

## AIMS

- **To develop machine learning models to predict incidence of combined radiation and immune-mediated pneumonitis from lung perfusion radiomics**
- **To test the stability of the model under robust perturbation of feature extraction and feature selection methods.**
- **To compare lung perfusion imaging biomarkers against lung dosimetry for pneumonitis risk stratification**

## KEY FINDINGS

- Identified SPECT lung perfusion radiomic feature (GLSZM-GLN) that predicted for combined incidence of radiation and immune-mediated pneumonitis (AUC = 0.74, OR = 2.3, p = 0.025)
- GLSZM-GLN risk stratified patients for pneumonitis risk in subgroup receiving consolidative durvalumab anti-PDL1 immune checkpoint inhibitor therapy (AUC = 0.85, p = 0.038)
- GLSZM-GLN fixed bin width discretization outperformed fixed bin size / number

## METHODS

- 30 patients with locally advanced non-small cell lung cancer (NSCLC) enrolled on the FLARE-RT trial (NCT02773238) were included in this study (**Figure 1**).
- All patients received chemoradiotherapy with functional lung avoidance planning and half (15/30) received consolidative durvalumab anti-PDL1 immune checkpoint inhibitor therapy.
- 20/30 patients had 3-month post-treatment SPECT/CT to assess longitudinal stability of radiomic features. Prediction models were built using pre-treatment information only.

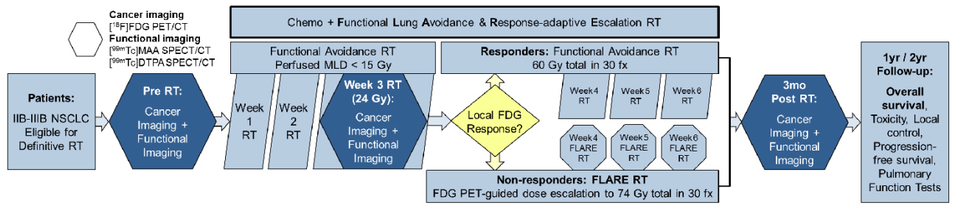


**Figure 1.** FLARE-RT phase II trial schema. Response-adaptive escalation is based on individualized assessment of local FDG PET response to overcome treatment resistance. In this work, pre-treatment FDG PET-based tumor cluster features are defined to predict week 3 mid-treatment FDG PET tumor response.

- PyRadiomics features (110 shape/intensity/texture) were extracted on pre-treatment and post-treatment SPECT within tumor-subtracted lung regions (**Figure 2**).
- Two discretization methods tested
  - Fixed bin size (FBS=64bins)
  - Fixed bin width (FBW=25CNTS)

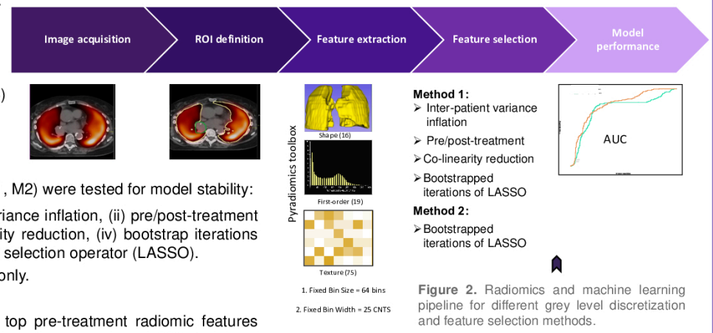


**Figure 2.** Radiomics and machine learning pipeline for different grey level discretization and feature selection methods.

- Two feature selection methods (M1, M2) were tested for model stability:
  - M1 included (i) inter-patient variance inflation, (ii) pre/post-treatment variance inflation, (iii) co-linearity reduction, (iv) bootstrap iterations of least absolute shrinkage and selection operator (LASSO).
  - M2 applied LASSO bootstraps only.
- LASSO logistic regression of the top pre-treatment radiomic features was conducted over 100 stratified random samples of 80% training / 20% testing datasets.
- Ensemble performance of testing datasets for predicting combined radiation and immune-mediated CTCAEv4 Grade 2+ pneumonitis (40% incidence rate) was quantified by the area-under-ROC-curve (AUC).
- Dosimetric parameters identified in our prior work[4] were compared to radiomic features for predicting risk of radiation and immune-mediated pneumonitis.

## RESULTS

- FBW-M1 model with GLSZM-GLN achieved the highest testing performance (AUC=0.74, OR=2.3, p=0.03), followed by FBW-M2 with GLSZM-GLN (AUC=0.72, OR=2.3, p=0.03) (**Table 1, Figure 4**)
- FBW generated single-feature parsimonious models that outperformed multivariate FBS models (AUC=0.59-0.63, OR=1.3-1.8, p<0.37). (**Table 1, Figure 4**)
- GLSZM-GLN significantly stratified pneumonitis status in the group that received consolidated immunotherapy (AUC= 0.85, p= 0.04).
- GLSZM-GLN did not discriminate pneumonitis status in patients receiving chemoradiation only (AUC = 0.396, p= 0.67) (**Figure 5**).
- Dosimetric features identified previously[4] to predict risk of radiation pneumonitis could not risk stratify patients (AUC = 0.48-0.59, p >0.05) in the setting of chemoradiation and immunotherapy. (**Table 2**)
- Age and pre-existing emphysema were the only two clinical features that trended towards significance (AUC = 0.71, p=0.053 and AUC = 0.69, p=0.063) for predicting combined risk of radiation and immune-mediated pneumonitis.

**Table 1**. Odds ratios (per standard deviation increase) and AUCs with different gray level discretization (FBS, FBW) and feature selection techniques (M1, M2) for predicting incidence of combined radiation and immune-mediated pneumonitis.

| GrayLevel Discretization technique | FBS (64 bins) | | FBW (25 CNTS) | |
|---|---|---|---|---|
| **Feature selection method** | **M1** | **M2** | **M1** | **M2** |
| GrayLevelNonUniformity (GLZSM) | 1.3 | 1.8 | 2.3 | 2.3 |
| GrayLevelNonUniformity (GLRLM) | 1.7 | | | |
| GrayLevel NonUniformityNormalized (GLZSM) | | 1.4 | | |
| **Area-under-ROC-curve** | 0.59 | 0.63 | 0.74 | 0.72 |

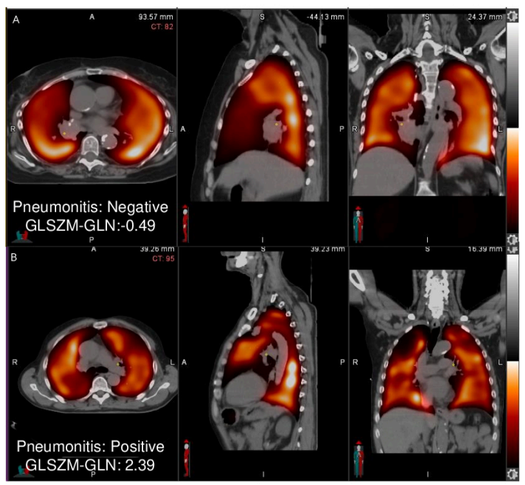


**Figure 3.** (A) Example patient without pneumonitis shows GLSZM-GLN intensity value of -0.49. (B) Example patient who developed pneumonitis showed a higher GLSZM-GLN intensity value (2.39). GLSZM-GLN values are represented as standardized z-scores. FLARE-RT patients fused to radiation planning CT. SPECT window/level display were normalized to out-of-field integral uptake.

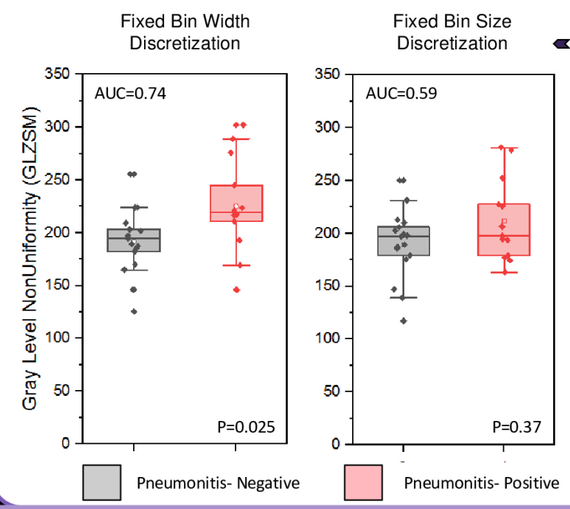


**Figure 4.** Box-whisker plots show inter-patient variability in GLSZM-GLN intensity feature values for patients without (gray) and with pneumonitis (red) cohorts. Mean (marker), median (line), quartiles (box), and range (whiskers) are displayed. AUC is reported for FBW-M1 (left) and FBS-M1 (right).

**Table 2 .** Univariate analysis of dosimetric parameters in the setting of functional lung avoidance therapy. P value (Mann-Whitney). MLD (mean lung dose), pMLD (perfused MLD), V20 (lung volume receiving at least 20 Gy), pV20 (perfused lung V20).

| Dosimetric parameters | AUC | p value |
|---|---|---|
| MLD | 0.52 | 0.87 |
| V20 | 0.59 | 0.40 |
| pMLD | 0.56 | 0.62 |
| pV20 | 0.54 | 0.74 |
| pF20 | 0.48 | 0.87 |

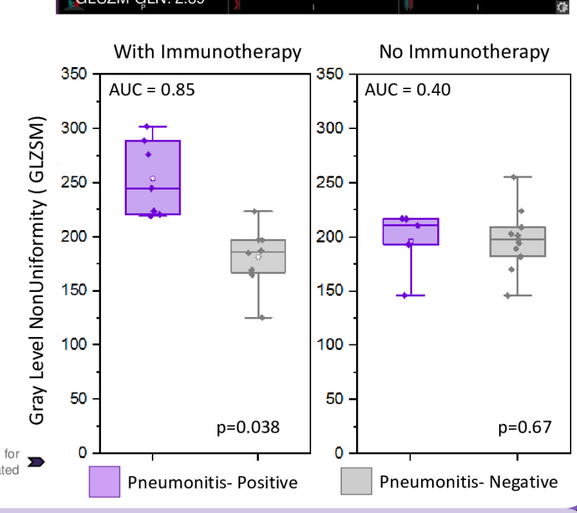


**Figure 5.** Comparison of model (FBW-M1) performance for predicting pneumonitis in patients who received consolidated immunotherapy (left) or did not receive immunotherapy (right).

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## CONCLUSIONS

- The GLSZM-GLN texture feature of lung perfusion heterogeneity was identified as a potential imaging biomarker of combined radiation and immune-mediated pneumonitis risk.
- The dosimetric parameters that could predict for radiation pneumonitis risk[4] did not predict well for combined risk of radiation and immune-mediated pneumonitis.
- Prediction model performance was more sensitive to gray-level discretization than feature selection method.
- This functional lung imaging biomarker will be tested in larger patient populations as a complement to other known risk factors of pneumonitis.
- Radiomics based pneumonitis prediction models may help improve risk stratification and personalization of therapy for locally advanced lung cancers.

## ACKNOWLEDGEMENTS

- Investigation financially supported by NIH / NCI R01CA204301
- We acknowledge Nuclear Medicine, Radiation Oncology, and Proton Center staff
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