# Appendix-1

## Section 1: Radiomic Feature Extraction.

Lung nodules were annotated by an expert radiologist using 3D-slicer (3D Slicer, version 4.6: NIH-funded; https://www.slicer.org) and a freehand tool. Intratumoral and peritumoral areas were selected using these annotations. For intratumoral region, the annotated tumor is used as the area of interest. Following annotations, the peritumoral region corresponding to the lesion was defined using the following steps. Firstly, a morphological operation of dilation was performed to capture the area outside the nodule, up to a radial distance of 15mm from the lesion boundary. The choice of peri-nodular size was based on previous findings, where a resection margin >15mm did not have a prognostic effect in the context of disease recurrence. The intranodular mask was then subtracted from this dilated mask to obtain a ring of lung parenchyma immediately around the nodule. The perinodular region was subsequently divided into five equally spaced 3-mm rings.

Radiomic features were extracted from the three slices having the maximum area of the tumor using software developed in the Center of Computational Imaging and Personalized Diagnostics, Case Western Reserve University, implemented on a MATLAB release 2016a platform (MathWorks, Natick, MA, USA).

A total of 124 textural descriptors were commutated voxel-wise across the three slices from each of the annotated region. The features included 48 from Gabor feature family, 13 from Haralick, 13 from Collage, 25 from Laws, and 25 from Laplace feature families. The First-order statistics (mean, median, SD, skewness, and kurtosis) were calculated from each feature vector. Table-S1 explains all the extracted features.

## Section 2: QVT feature Extraction

The segmented nodule and the 3D segmented vasculature surrounding the nodule were used for extracting vessel tortuosity features (QVT). The vasculature surrounding the nodule was segmented using a region growing algorithm by using an initial seed point. A fast-marching algorithm was then employed to identify the center lines of the 3D segmented vasculature. A set of 74 QVT features were then measured form points, branches, and the entire vasculature centerlines. These features pertain to the tortuosity, curvature and branching statistics as well as the volume of the vasculature. In addition, we measured the angles of each three consecutive points of the vasculature and computed the distribution of these angles.

A total of 74 QVT features were extracted for each patient, representing the curvature and tortuosity of the nodule associated vessels and their branching statistics.

## Section 3: Total Extracted Radiomic Features.

**Table S.1** – Total Radiomic Features extracted from intratumoral and annular ring-shaped peritumoral regions. A total of 6 statistics- (mean, median, kurtosis, skewness, standard deviation, and range) were calculated for each feature.

| Radiomic Feature Family | Radiomic Feature Parameters | Radiomic Feature Family | Radiomic Feature Parameters |
|---|---|---|---|
| Haralick Feature Family | Entropy, Window Size = 5 | Laws Energy Feature Family | Level, Level |
| | Energy, Window Size = 5 | | Level, Edge |
| | Inertia, Window Size = 5 | | Level, Spot |
| | Inverse Difference Moment , Window Size = 5 | | Level, Wave |
| | Correlation, Window Size = 5 | | Level, Ripple |
| | Information Measure of Correlation-1, Window Size = 5 | | Edge, Level |
| | Information Measure of Correlation-2, Window Size = 5 | | Edge, Edge |
| | Sum Average, Window Size = 5 | | Edge, Spot |
| | Sum Variance, Window Size = 5 | | Edge, Wave |
| | Sum Entropy, Window Size = 5 | | Edge, Ripple |
| | Difference Average, Window Size = 5 | | Spot, Level |
| | Difference Variance, Window Size = 5 | | Spot, Edge |
| | Difference Entropy, Window Size = 5 | | Spot, Spot |

| Gabor Wavelet Feature Family | | Laplace Feature Family / CoLIAGe Feature Family | |
|---|---|---|---|
| **Gabor Wavelet Feature Family** | Orientation=0, Bandwidth=1, Frequency=0 | | Spot, Wave |
| | Orientation=0, Bandwidth=1, Frequency=2 | | Spot, Ripple |
| | Orientation=0, Bandwidth=1, Frequency=4 | | Wave, Level |
| | Orientation=0, Bandwidth=1, Frequency=6 | | Wave, Edge |
| | Orientation=0, Bandwidth=1, Frequency=8 | | Wave, Spot |
| | Orientation=0, Bandwidth=1, Frequency=10 | | Wave, Wave |
| | Orientation=$\pi/8$, Bandwidth=1, Frequency=0 | | Wave, Ripple |
| | Orientation=$\pi/8$, Bandwidth=1, Frequency=2 | | Ripple, Level |
| | Orientation=$\pi/8$, Bandwidth=1, Frequency=4 | | Ripple, Edge |
| | Orientation=$\pi/8$, Bandwidth=1, Frequency=6 | | Ripple, Spot |
| | Orientation=$\pi/8$, Bandwidth=1, Frequency=8 | | Ripple, Wave |
| | Orientation=$\pi/8$, Bandwidth=1, Frequency=10 | | Ripple, Ripple |
| | Orientation=$\pi/4$, Bandwidth=1, Frequency=0 | | Level, Level |
| | Orientation=$\pi/4$, Bandwidth=1, Frequency=2 | | Level, Edge |
| | Orientation=$\pi/4$, Bandwidth=1, Frequency=4 | | Level, Spot |
| | Orientation=$\pi/4$, Bandwidth=1, Frequency=6 | | Level, Wave |
| | Orientation=$\pi/4$, Bandwidth=1, Frequency=8 | | Level, Ripple |
| | Orientation=$\pi/4$, Bandwidth=1, Frequency=10 | | Edge, Level |
| | Orientation=$3\pi/8$, Bandwidth=1, Frequency=0 | | Edge, Edge |
| | Orientation=$3\pi/8$, Bandwidth=1, Frequency=2 | | Edge, Spot |
| | Orientation=$3\pi/8$, Bandwidth=1, Frequency=4 | | Edge, Wave |
| | Orientation=$3\pi/8$, Bandwidth=1, Frequency=6 | | Edge, Ripple |
| | Orientation=$3\pi/8$, Bandwidth=1, Frequency=8 | **Laplace Feature Family** | Spot, Level |
| | Orientation=$3\pi/8$, Bandwidth=1, Frequency=10 | | Spot, Edge |
| | Orientation=$\pi/2$, Bandwidth=1, Frequency=0 | | Spot, Spot |
| | Orientation=$\pi/2$, Bandwidth=1, Frequency=2 | | Spot, Wave |
| | Orientation=$\pi/2$, Bandwidth=1, Frequency=4 | | Spot, Ripple |
| | Orientation=$\pi/2$, Bandwidth=1, Frequency=6 | | Wave, Level |
| | Orientation=$\pi/2$, Bandwidth=1, Frequency=8 | | Wave, Edge |
| | Orientation=$\pi/2$, Bandwidth=1, Frequency=10 | | Wave, Spot |
| | Orientation=$5\pi/8$, Bandwidth=1, Frequency=0 | | Wave, Wave |
| | Orientation=$5\pi/8$, Bandwidth=1, Frequency=2 | | Wave, Ripple |
| | Orientation=$5\pi/8$, Bandwidth=1, Frequency=4 | | Ripple, Level |
| | Orientation=$5\pi/8$, Bandwidth=1, Frequency=6 | | Ripple, Edge |
| | Orientation=$5\pi/8$, Bandwidth=1, Frequency=8 | | Ripple, Spot |
| | Orientation=$5\pi/8$, Bandwidth=1, Frequency=10 | | Ripple, Wave |
| | Orientation=$3\pi/4$, Bandwidth=1, Frequency=0 | | Ripple, Ripple |
| | Orientation=$3\pi/4$, Bandwidth=1, Frequency=2 | | Entropy, Window Size = 5 |
| | Orientation=$3\pi/4$, Bandwidth=1, Frequency=4 | | Energy, Window Size = 5 |
| | Orientation=$3\pi/4$, Bandwidth=1, Frequency=6 | | Inertia, Window Size = 5 |
| | Orientation=$3\pi/4$, Bandwidth=1, Frequency=8 | | Inverse Difference Moment , Window Size = 5 |
| | Orientation=$3\pi/4$, Bandwidth=1, Frequency=10 | | Correlation, Window Size = 5 |
| | Orientation=$7\pi/8$, Bandwidth=1, Frequency=0 | **CoLIAGe Feature Family** | Information Measure of Correlation-1, Window Size = 5 |
| | Orientation=$7\pi/8$, Bandwidth=1, Frequency=2 | | Information Measure of Correlation-2, Window Size = 5 |
| | Orientation=$7\pi/8$, Bandwidth=1, Frequency=4 | | Sum Average, Window Size = 5 |
| | Orientation=$7\pi/8$, Bandwidth=1, Frequency=6 | | Sum Variance, Window Size = 5 |
| | Orientation=$7\pi/8$, Bandwidth=1, Frequency=8 | | Sum Entropy, Window Size = 5 |
| | Orientation=$7\pi/8$, Bandwidth=1, Frequency=10 | | Difference Average, Window Size = 5 |
| | | | Difference Variance, Window Size = 5 |
| | | | Difference Entropy, Window Size = 5 |

## Section 4: Radiomic Feature Stability.

Feature stability and reproducibility were evaluated using the RIDER test-retest dataset. This dataset had 31 lung cancer patients, scanned two times with 15 mins' difference apart. Two scans of every patient were used for calculating the intraclass correlation coefficient (ICC) for each feature vector. Considering the threshold of 0.85, the analysis was performed using all feature vectors having ICC values higher than the threshold limit. After completing the above experiment, a total of 757 features were retained from the intratumoral and peritumoral feature pool of 4464. These stable features were used for further analysis for feature selection and model building.

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## Section 5: Tumor Growth Kinetics.

Target lesions were identified and assessed on each interval CT scan using the RECIST version 1.1 criteria (Eisenhaur et al). A sum of diameters (SOD) of the target lesions pre- baseline (SODpre), baseline (SODbaseline) and post ICI (SODpost) was calculated. Using a previously described methodology to calculate tumor growth kinetics, the rate of change in the dimensions of target lesions pre and post-therapy was calculated (Le Tourneau at al, Saada et al). Tumor growth kinetics pre-therapy (TGKpre) was defined as SODbaseline – SODpre/ Timebaseline- Timepre. Similarly, TGK post ICI (TGKpost)= SODpost-SODbaseline/ Timepost-Timebaseline.
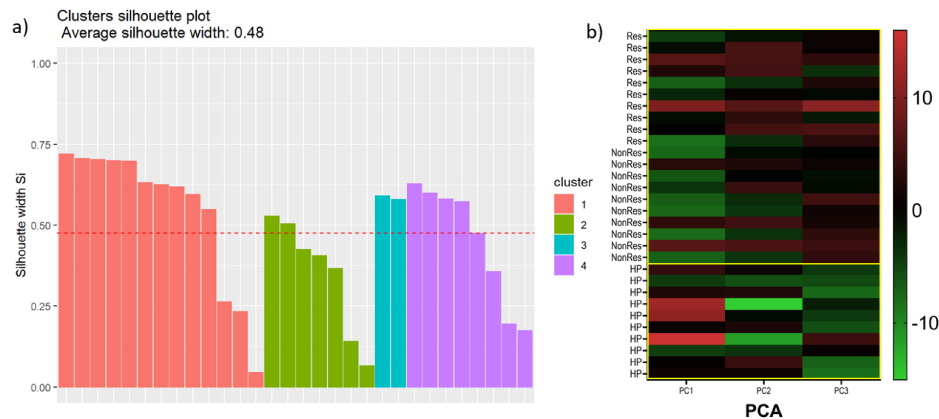
Hyperprogressive disease was defined as

1. Time to treatment failure < 9 weeks (or 3-cycles)

2. Progressive disease on first radiographic assessment after ICIs

3. Greater than two-fold increase in tumor growth kinetics after initiating immune checkpoint blockade (TGKpost: TGKpre $\geq$ 2)

## Section 6: CT Scan parameters.

**Table S.2** – CT scan parameters

| | | No. of studies = 109 | Kernal |
|---|---|---|---|
| | Siemens | 75 | B30f, B31f, B31s, B35f, B35s, B41f, B60f, B60s, B70f, I40f\2, I50f\1 |
| | Philips | 20 | B, C, D, L, YA, YB |
| | Toshiba | 1 | FC52 |
| | GE | 12 | Lung, SOFT, Standard |
| | <=1 | 9 | |
| | <1<=3 | 89 | |
| | 3< <=5 | 10 | |
| | With Contrast | 89 | |
| | W/o Contrast | 20 | |

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Supplemental material

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## Section 7: Unsupervised cluster validations



**Fig S1:** Validation of unsupervised clustering maps with a) silhouette coefficients and b) heatmaps

## Section 8: Top Features.

Top features selected using minimum redundancy maximum relevance (mRMR) feature selection method. The number of top features were restricted to 3 to avoid potential overfitting.

<div align="center">

**Table S.3** – Top selected features

</div>

| | Feature Family | | Descriptor | Location | Statistics |
|---|---|---|---|---|---|
| 1 | QVT7 | Mean Curvature of branches surrounding the tumor | Mean | Surrounding the tumor | Mean |
| 2 | QVT44 | Curvature values associated with vasculature | Entropy | Intratumoral | Mean |
| 3 | Radiomics | Gabor | Freq-π/2 theta-90 | 5-10mm | Median |

## Section 9: Correlation.

The selected top features were compared against clinical features with pearson's correlation coefficien. Further the tumor volume was computed and correlation coefficient was calculated between radiomic top features and tumor volume. The following graph shows correlation coefficients between these variables. The maximum correlation was observed between Radiomics Gabor feature and tumor volume which was 0.588.

**Fig S2:** Pearson's Correlation coefficients between Radiomics Top Features and clinical variables.

## Section 9: Distribution of Patients within Training and Testing Sets
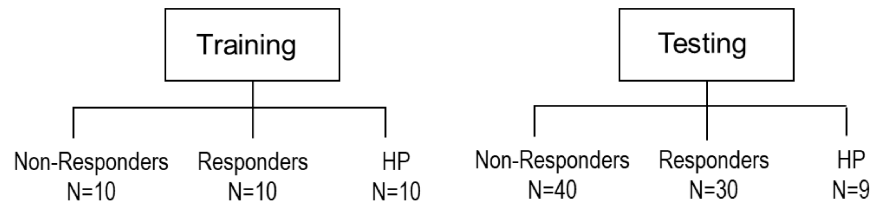


**Fig S3:** Distribution of patients into training and testing set

## Section 9: Classifier Performance on Training Set

**Feature Selection Method: mRMR**

Table S.4 – Classifier performances on training set

|  | Classifier | AUC | Accuracy | Specificity | Sensitivity |
|---|---|---|---|---|---|
| *1* | *RF* | *0.85 ± 0.06* | *0.86 ± 0.06* | *0.91 ± 0.10* | *0.78 ± 0.11* |
| 2 | LDA | 0.80 ± 0.07 | 0.82 ± 0.07 | 0.86 ± 0.11 | 0.75 ± 0.13 |
| *3* | DLDA | 0.81 ± 0.08 | 0.83 ± 0.06 | 0.88 ± 0.10 | 0.74 ± 0.13 |
| 4 | QDA | 0.75 ± 0.11 | 0.81 ± 0.06 | 0.89 ± 0.09 | 0.68 ± 0.16 |
| 5 | DQDA | 0.50 ± 0.00 | 0.63 ± 0.00 | 1.00 ± 0.00 | 0.00 ± 0.00 |
| 6 | SVM | 0.81 ± 0.06 | 0.83 ± 0.06 | 0.87 ± 0.11 | 0.76 ± 0.12 |
|  |  |  |  |  |  |

## Section 10: Classifier Performance on Test Set

**Table S.4** – Classifier performances on test set

|   |          | Accuracy | Specificity |
|---|----------|----------|-------------|
| 1 | AUC      |          | 0.96        |
| 2 | Accuracy |          | 0.83        |
| 3 | TP       |          | 9           |
| 4 | TN       |          | 57          |
| 5 | FP       |          | 13          |
| 6 | FN       |          | 0           |
| 7 | F1 Score |          | 0.58        |

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