A054 · Integrative Radiogenomic Analysis Identifies Imaging-Linked Molecular Subtypes and Biomarkers in Pancreatic Ductal Adenocarcinoma

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Session: Day 1 · Thu Oct 1, 2026 · 2:15–4:15 PM

Pancreatic ductal adenocarcinoma (PDAC) exhibits substantial molecular heterogeneity associated with differences in tumor biology and clinical outcomes. Integrating multi-omics and imaging datasets holds promise for refining subtype identification and therapeutic stratification. Non-Negative Matrix Factorization (NMF) of the TCGA pancreatic adenocarcinoma cohort (TCGA-PAAD) identified six transcriptomic clusters, which were characterized against established Bailey molecular subtypes. Clusters 2, 4, and 6 were enriched for ADEX, Immunogenic, and Squamous subtypes, respectively. A Random Forest classifier with iterative SHAP-guided feature selection identified a 35-marker-gene panel. The classifier was then applied to an independent rapid-autopsy cohort (RAP) from the University of Nebraska Medical Center (UNMC) with matched transcriptomic and contrast-enhanced CT imaging. The RF model assigned RAP patients to molecular subtypes with distinct survival patterns. Notably, patients assigned to Cluster 2 (ADEX-like) experienced longer survival, whereas patients in Cluster 6 (Squamous) had the shortest survival. Exploratory radiogenomic analysis revealed significant associations between the 35 marker genes and 944 CT radiomic features. Specifically, the squamous-like marker genes EPHA2 and NTF4 showed a negative correlation with texture complexity metrics wavelet-HLH_glszm_SizeZoneNonUniformityNormalized and wavelet-HHL_ngtdm_Contrast, respectively. Ultimately, integrating molecular and radiomic markers suggests that non-invasive CT imaging can act as a surrogate for underlying tumor biology. High expression of squamous markers (EPHA2/NTF4) coupled with a low size-zone uniformity or low neighboring contrast on CT reflects a shift toward coarse, poorly perfused, or necrotic tissue. This distinct radiogenomic profile serves as a non-invasive indicator of a highly aggressive squamous-like phenotype and poor patient prognosis.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by high molecular and structural heterogeneity, which underlies significant variation in tumor biology and patient outcomes. Integrating multi-omics and imaging datasets holds promise for refining subtype identification and therapeutic stratification.
Methods: Using Non-Negative Matrix Factorization (NMF) on the TCGA pancreatic adenocarcinoma cohort (TCGA-PAAD), we identified six transcriptomic clusters. These were characterized against established Bailey molecular subtypes: Cluster 2 demonstrated enrichment for the Aberrantly Differentiated Endocrine Exocrine (ADEX) subtype, Cluster 4 for the Immunogenic subtype, and Cluster 6 for the highly aggressive Squamous subtype. To construct a robust molecular classifier, we trained a Random Forest (RF) model using an initial set of 4,075 non-redundant genes. Iterative SHAP-guided recursive feature elimination (RFE) successfully reduced this signature to a highly discriminative 35-marker-gene panel, yielding multi-class cross-validation AUC values above 0.949. The final classifier was validated on an independent rapid-autopsy cohort (RAP) from the University of Nebraska Medical Center (UNMC) with matched transcriptomic and contrast-enhanced CT imaging.

Results: In the RAP cohort, the RF model successfully assigned patients to molecular subtypes, demonstrating differences in overall survival. Notably, patients assigned to Cluster 2 (ADEX-like) experienced longer survival, whereas patients in Cluster 6 (Squamous) had the shortest survival. Exploratory radiogenomic analysis revealed significant associations between the 35 marker genes and 944 CT radiomic features. Specifically, the squamous-like marker genes *EPHA2* and *NTF4* showed a negative correlation with texture complexity metrics wavelet-HLH_glszm_SizeZoneNonUniformityNormalized and wavelet-HHL_ngtdm_Contrast, respectively.

Conclusions: Ultimately, integrating molecular and radiomic markers suggests that non-invasive CT imaging can act as a surrogate for underlying tumor biology. High expression of squamous markers (*EPHA2*/*NTF4*) coupled with a low size-zone uniformity or low neighboring contrast on CT reflects a shift toward coarse, poorly perfused, or necrotic tissue. This distinct radiogenomic profile serves as a non-invasive, high-confidence indicator of a highly aggressive squamous-like phenotype and poor patient prognosis