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# Survival Differences of Adenocarcinoma Lung Tumors with Squamous Cell Carcinoma or Neuroendocrine Profiles by Gene Expression Subtyping

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**Background:**

Gene expression profiling can provide valuable information beyond the morphologic diagnosis. A previously validated 52-gene Lung Subtype Panel (LSP) for differentiating lung tumors into Adenocarcinoma (AD), Squamous Cell Carcinoma(SQ), and Neuroendocrine (NE) was explored in several publically available lung tumor datasets, including the TCGA RNAseq dataset.

**Methods:**

The LSP 3-class nearest centroid predictor developed in array data was applied to AD and SQ samples in TCGA (RNAseq, n=1,160), the Director's Challenge (Affy array, n=442), and Tomida et al. (Agilent array, n=117) datasets. Each sample was predicted as AD, SQ, or NE. Kaplan Meier plots and log rank tests were used to assess and compare 5-year overall survival in two gene expression groups, AD predicted AD (AD-AD) and AD predicted SQ or NE (AD-notAD). Cox models were used to assess survival differences while controlling for T stage, N stage, and proliferation (as measured by the PAM50 score). The distribution of samples among the AD subtypes (Terminal Respiratory Unit(TRU), Proximal Proliferative(PP), and Proximal Inflammatory(PI)) was investigated.

**Results:**

The predictor confirmed AD in 80% of the AD samples. AD samples were called SQ and NE by the LSP in 8% and 12% of cases, respectively. The AD-notAD group (AD by histology and SQ or NE by gene expression LSP) had worse survival than the AD-AD group (AD by both histology and LSP) in each data set (logrank p-value in TCGA, Director's Challenge, and Tomida were 1.17e-06, 0.0009, and 0.0001, respectively). Pooling the 3 data sets and using a stratified cox model that allowed for different baseline hazards in each study, the hazard ratio comparing AD-notAD to AD-AD was 2.14 (95% CI 1.70-2.70). When we fit the model adjusting for T stage, N stage, and proliferation score, the HR was 1.70 (95% CI 1.31-2.20). Adenosubtype profiling of AD-notAD samples indicated that tumors were overwhelmingly of the PP or PI gene expression subtypes (209/213).

**Conclusion:**

Gene expression tumor subtyping may provide valuable clinical information identifying a subset of AD samples with poor prognosis. Poor prognosis adenocarcinoma samples belong to the PI and PP expression subtypes, and demonstrate elevated proliferation scores. This subset of AD tumors may be less responsive to standard adenocarcinoma management.

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