

## Multi-institutional analysis shows low *PCAT-14* expression associates with poor outcome in prostate cancer

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The majority of prostate cancer patients are diagnosed at a potentially curable stage and are often treated with radical prostatectomy (RP) or other first-line treatments. However, a subset of patients with aggressive disease face the risk of prostate cancer recurrence, which can manifest as persistently elevated/increasing serum PSA or metastasis. Therefore, a critical goal in prostate cancer research is determining the molecular underpinnings of aggressive and indolent disease to improve patient management and prognosis. Recent studies demonstrated the utility of protein-coding genes as prognostic biomarkers. However, lack of tissue specificity hinders the ability to monitor their expression levels non-invasively. In contrast, long non-coding RNAs (lncRNAs) are used successfully to diagnosis and risk stratify prostate cancer. Therefore, our study focuses on exploring lncRNAs as biomarkers for risk stratification to ultimately improve patient management. To date, all of the transcriptome-based discoveries have utilized patient samples from high quality specimens (i.e., abundance of tissue, snap frozen tissue, recently collected), which made them ideal to perform transcriptome sequencing (RNA-Seq) but lacked longer-term clinical outcomes. To address this, we systematically identified lncRNAs as clinical predictors for disease progression through an integrative analysis of both microarray and transcriptome sequencing data from three independent patient cohorts. This led to the identification of *Prostate Cancer Associated Transcript-14 (PCAT-14)* as the most prevalent lncRNA that is aberrantly expressed in prostate cancer patients and significantly associated with Gleason score. Next, radical prostatectomy microarray and clinical data was obtained from 910 patients, as part of the Decipher GRID, in three published institutional cohorts: Mayo Clinic I (N=545, median follow-up 13.8 years), Mayo Clinic II (N=235, median follow-up 6.7 years), and Thomas Jefferson University (N=130, median follow-up 9.6 years). We found that down-regulation of *PCAT-14* expression significantly associated with Gleason score and a greater probability of metastatic progression, overall survival, and prostate cancer-specific mortality across multiple independent datasets and ethnicities. Gene Set Enrichment Analysis of coexpressed genes with *PCAT-14* were enriched in biological processes promoting aggressive disease. *In vitro* analysis confirmed that low *PCAT-14* expression increased migration while overexpressing *PCAT-14* reduced cellular growth, migration, and invasion. Notably, we observed that patients who received ADT appeared to have a greater distant metastasis-free survival prognostic difference between *PCAT-14* high and low expression in comparison to patients that did not receive ADT. Our multivariate interaction analysis coupled with the *in vitro* data demonstrating that *PCAT-14* is androgen responsive suggests that *PCAT-14* warrants further study as a predictive marker for ADT response. Overall, we discovered that androgen-regulated *PCAT-14* is overexpressed in prostate cancer, suppresses invasive phenotypes, and lower expression is significantly prognostic for multiple clinical endpoints supporting its significance for predicting metastatic disease that

could be used to improve patient management.

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