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Tissue-based genomics to augment post-prostatectomy risk stratification in a natural history cohort.

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Abstract Disclosures

Abstract

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Background: Genomics has provided insight into the underpinnings of lethal prostate cancer and led to the development and clinical use of RNA expression based gene signatures. We performed genome wide expression profiling on tissue from a large natural history cohort of at risk men undergoing radical prostatectomy (RP). **Methods:** In an IRB approved study, we utilized a case-cohort design to identify 356 intermediate and high risk men who underwent RP and had no further treatment until the time of metastasis. RP specimens were regraded by 2005 ISUP criteria and index lesions were sampled. RNA was prepared, labelled and hybridized to Human Exon 1.0 ST microarrays from which expression signatures were analyzed. The study followed REMARK guidelines for prospective blinded evaluation and analysis of prognostic biomarkers. **Results:** Microarray quality RNA was obtained from 260 men (99 of whom metastasized) with a median follow up of 9 years (IQR 6-12). 34 gene signatures were evaluated, including 3 based on commercially available assays (genomic classifier [GC, Decipher], microarray derived [md]-CCP, and md-GPS). GC provided the highest c-index to predict metastasis free survival at 10 years post-RP (0.76). Cumulative incidence of metastasis among men with low (< 0.45), intermediate (0.45-0.6) and high (> 0.6) GC scores was 12, 31 and 47% respectively at 5 years post-RP ($p < 0.001$). GC was independently prognostic of metastasis on multivariable analysis. Stratification by GC was most notable among nomogram predicted intermediate risk men. For instance, among men with CAPRA-S score of 3-5, 10% with low GC scores would develop metastasis compared to 27% among those with high scores. Addition of expression signatures from other CLIA certified tests (md-CCP or md-GPS) or from the next best performing expression signature (md-Penney, c-index 0.74) did not improve the performance of the GC. **Conclusions:** Genomic expression signatures stratify metastatic outcomes and provide additional prognostic information in a natural history cohort of men undergoing RP. Of 34 expression signatures analyzed, GC had optimal performance and captured prognostic information provided via analysis of other signatures.