Proteomic Serum Analysis of Biomarkers in Metastatic Bone Disease (DoD Framingham-5)

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INTRODUCTION:
Mechanisms underlying metastatic bone disease (MBD) remain elusive, and early diagnosis of MBD remains constrained by the limits of conventional imaging. The purpose of this study was to identify serum proteins associated with MBD to facilitate early diagnosis and identify possible therapeutic targets.

METHODS:
Military serum repository samples in patients with MBD were assessed from draws prior to primary cancer diagnosis, after primary cancer diagnosis, at diagnosis of MBD, and after diagnoses of MBD. Patients with and without MBD were matched by age, sex, treatment, and primary diagnosis. Proximity extension assay analysis was performed using the Olink® Target 96 Inflammation and Immuno-Oncology panels. To develop a protein signature distinguishing patients who developed MBD from those who did not, we applied a random forest machine learning technique. We used feature selection using Boruta algorithm, leave-one-out cross-validation with quantifying the performance using receiver operating characteristic curve, area under the curve (AUC).

RESULTS:
540 samples from patients with subsequent MBD and 527 samples from patients without MBD were identified in breast, prostate, lung, renal, and thyroid cancer. We derived a cytokine signature that successfully identified cytokines that were differentially abundant between serum samples taken from MBD cases after primary tumor diagnosis compared to age-matched controls for each pathology subgroup. The AUC for the derived random forest classifier had good discriminatory ability (AUC= 0.77 (± 0.045)).

DISCUSSION AND CONCLUSION:
We successfully identified serum factors predictive of MBD. This may enable earlier MBD diagnosis, improve prognostic algorithms, and facilitate the development and testing of targeted therapies.