Cell-free Circulating Tumor DNA is a Reliable Specimen for Mutation Profiling in Prostate Cancer Patients with High-Burden Disease

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Background: In order to develop targeted prostate cancer (PC) therapies, it is essential that we understand the genomic events driving response and resistance to current treatments. Traditionally, a metastatic biopsy has been necessary to obtain sufficient tumor DNA for next-generation sequencing (NGS) studies; however, these procedures are costly, may yield inadequate material for testing, and are associated with side effects. The sequencing of cell-free circulating tumor DNA (ctDNA) from plasma provides an attractive alternative.

Methods: Following informed consent, patients with advanced prostate cancer provided a blood sample, and plasma-derived DNA was eluted following a two-step centrifugation process. A targeted NGS panel, UW-OncoPlex, was optimized for use with low-input DNA samples (e.g. ctDNA), and plasma-derived DNA was sequenced. Contemporaneous tumor tissue was also sequenced for comparative analyses. Associations between clinical characteristics and successful ctDNA sequencing (defined as detecting at least one mutation that was clearly somatic) were assessed by non-parametric or exact tests.

Results: Blood was obtained for plasma ctDNA sequencing from 88 patients with matched tumor and germline controls. All germline variants were detected (N=20 with deleterious germline homologous recombination alterations). Thirty-six patients had a successful ctDNA study, with key somatic mutations detected, including copy number changes. Higher PSA (>40 ng/ml) was significantly associated with a successful ctDNA sequencing study. Germline hematopoietic clones could be distinguished from ctDNA fragments based on size using a novel bioinformatics approach.

Conclusions: Disease burden, as reflected by a higher PSA, is associated with successful ctDNA sequencing. We have validated UW-OncoPlex for use with plasma DNA samples and are currently offering this in a CLIA/CAP lab environment for PC patients with PSA >40 ng/ml.

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