Longitudinal Profiling of Circulating Tumor DNA Reveals the Evolutionary Dynamics of Metastatic Prostate Cancer during Serial Therapy

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Background:
Metastatic castration resistant prostate cancer (mCRPC) is highly heterogeneous and evolves under therapeutic pressure. Serial tissue biopsies, especially from bone metastases, are invasive and often impractical, limiting real time molecular monitoring. Plasma circulating tumor DNA (ctDNA) offers a minimally invasive alternative that can capture tumor genomic alterations and their clonal dynamics over time. We posited that longitudinal, genome wide ctDNA profiling could resolve treatment specific evolutionary trajectories and reveal resistance associated subclones across commonly used therapies, including androgen signaling inhibitors (ASI) and taxane chemotherapy.

Methods:
We enrolled 60 mCRPC patients receiving serial systemic therapy. For each patient, we analyzed 2 to 7 longitudinal plasma ctDNA samples collected pre-treatment, on-treatment, and at progression across ASI and/or taxanes. We performed genome-wide copy number profiling and exome sequencing, reconstructed clonal substructure, and tracked subclone frequencies over time. To quantify temporal changes, we devised an Evolutionary Dynamic Index (EDI) summarizing the magnitude and direction of subclonal shifts across treatment intervals.

Results:
Longitudinal ctDNA profiling resolved patient specific evolutionary histories and identified therapy linked selection. Overall, treatment with ASI produced greater subclonal selection than taxanes by EDI. At progression, emergent subclones after ASI frequently harbored alterations in PTEN, FANCA, and RB1, whereas CTCF aberrations were enriched following chemotherapy. Genome wide ctDNA measurements captured known drivers (e.g., AR/MYC amplification, TP53 mutation, PTEN loss) and enabled detection of both resistant subclones that expanded on therapy and sensitive subclones that diminished. The EDI provided a compact, quantitative readout of clonal remodeling, differentiating stable disease from rapid evolutionary change during treatment.

Conclusions:
Serial genome wide profiling of ctDNA can noninvasively delineate clonal architecture and evolutionary dynamics in mCRPC across multiple lines of therapy. Our findings highlight therapy specific resistance mechanisms (PTEN/FANCA/RB1 after ASI; CTCF after taxanes) and support the use of ctDNA-based dynamics, including the EDI, as a framework for treatment monitoring and for optimizing sequencing of ASI and chemotherapy in advanced prostate cancer.

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Conflicts of Interest Disclosure Statement:
The authors declare no potential conflicts of interest.