Treatment-naïve, locally advanced prostate cancer contains numerous subclonal clinically significant alterations

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Abstract

Background Primary prostate cancer is genetically heterogeneous with few recurrent alterations, whereas advanced, therapy-resistant disease has recurrent alterations in clinically significant pathways. The timing of the accumulation of these alterations is unknown.

Methods We performed multiregion genomic analysis on 74 regions from ten cases of treatment-naïve, localized or locally advanced node positive prostate cancer.

Results Exome sequencing and copy number analysis demonstrated branched evolution with >90% of point mutations being subclonal and broad spatial occupancy by comingled subclones. Compared to localized disease, locally advanced disease contained higher number of mutations in cancer genes (0.6 vs 2), higher fraction of genome altered by amplifications and deletions (0.05 vs 0.19), and more co-occurring subclonal alterations in CRPC pathways (3 vs 20, $p<0.05$ for all comparisons). Locally advanced cases demonstrated predicted susceptibility to up to 20 targeted therapies, but within biomarker-positive cases, 60% of regions were biomarker-negative.

Conclusions Our data are consistent with a model whereby progression to locally advanced disease is coincident with the accumulation of numerous subclonal clinically significant alterations; advanced, therapy-resistant disease emerges from enrichment of these subclones.

Conflict of Interest

None

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