Multifocal primary prostate cancer exhibits high degree of genomic heterogeneity

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Background: Most primary prostate cancers are multifocal with individual tumors harboring different aggressiveness, but the genomic heterogeneity among these tumors is poorly understood. To better understand the biological basis for clinical variability among different lesions, we sought to comprehensively characterize the heterogeneity of somatic gene mutations in multifocal prostate cancer.

Methods: From a radical prostatectomy cohort of 571 patients operated from 2010 to 2012 with extensive clinical follow up, we selected cases with clearly distinct tumor foci. Here we have performed high-coverage whole-exome sequencing of 153 frozen tissue samples, taken from 2-3 distinct tumor foci and one non-cancerous area from each of 41 patients, covering a total of 89 tumor foci. State-of-the-art bioinformatics tools for mutation calling and copy number determination from whole-exome sequencing data.

Results: We found a very high degree of interfocal heterogeneity among tumors. That is, 76 % of pairwise compared tumor foci from the same prostatectomy specimen had no point mutations in common and DNA copy number changes were rarely shared across cancer foci. The few point mutations shared across tumor foci were seldom in cancer-critical genes.

Conclusions: In this first large genomic heterogeneity study of primary prostate cancer we observe that different tumor foci within the same patient are genetically distinct, only rarely sharing any somatic gene mutations, including those in cancer driver genes. This heterogeneity affects how genomics-based management of prostate cancer can be implemented, as information from all tumor foci is necessary to draw valid conclusions about the cancer's genomic alterations. This will influence treatment decisions in the future as each tumor's mutations will render it unique and have to be considered to gain the best treatment results. These results are now in press in European Urology (Løvf *et al.*). In ongoing studies, we have interesting results on fusion genes, both on novel fusion partner to *ERG* and other fusion partner constellations. With regards to subtyping like done in by The Cancer Genome Atlas (Cell 2015) from the same cohort as here demonstrated that half of the patients have more than one molecular subtype, when testing 2-3 foci per patient.

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