Targeted sequencing for molecular stratification of matched primary tumor samples and metastatic biopsies in castration-resistant prostate cancer.

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Background: Genomics of localized and metastatic castration-resistant prostate cancer (mCRPC) can be utilized to guide more precise cancer care. Biopsy of mCRPC remains challenging for implementation of genomics into clinical practice. We evaluated whether targeted next-generation sequencing (NGS) of diagnostic prostate biopsies allows accurate genomic characterization of mCRPC.
Methods FFPE prostate biopsies were collected from 91 patients who also underwent mCRPC biopsies. Targeted amplicon-based NGS was performed for patient-matched samples (Illumina MiSeq). PCR-based quality control tests (QC) were implemented. 6025 amplicons of 113 genes were evaluated.
Results All 91 mCRPC biopsies and 73/91 (80.3%) archival primary tumor samples passed QC tests. Median sequencing coverage was higher for fresh mCRPC biopsies (542x vs 399x, p=0.006). In 14/30 (46.7%) patients who initially had localized disease, and in 18/43 (41.9%) with metastatic disease at diagnosis, there was $\geq$1 new missense mutation in the mCRPC biopsy. The burden of new mutations was however low, with only 3/73 (4.1%) patients having 5 or more new missense mutations detected after castration-resistance. In 19/73 (26%) cases, the targeted NGS mutational profiles of the primary and metastases were identical. *TP53* was the gene with the higher number of intra-patient discrepancies detected (9/73, 12.3%). *TP53* mutations in primary tumors were enriched among patients with metastatic disease at diagnosis (37% vs 17%, p=0.05). All DNA repair genes aberrations in primary tumors were also later found to be present in mCRPC biopsies. Contrarily, in 5/73 (6.8%) cases a DNA repair aberration found in the mCRPC biopsy was not detected in the matched primary tumor. Due to the single-sample per time-point approach, we could not assess if these were secondary to tumor evolution or multi-focality.
Conclusions: Limited intra-patient heterogeneity was observed between primary tumors and mCRPC. However, some discrepancies could be clinically relevant; the success rate and coverage was higher in mCRPC fresh biopsies. Clinical trials including genomic biomarkers should consider acquiring biopsies.

Conflict of Interest: none

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