Circulating tumour DNA prior to therapy initiation in *de novo* metastatic prostate cancer

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Background: There are several therapeutic options for *de novo* metastatic castrate-sensitive prostate cancer (mCSPC). Tumour molecular subtype may influence decision-making. Circulating tumour DNA (ctDNA) can molecularly profile metastatic castration-resistant prostate cancer (mCRPC) but remains untested in mCSPC.

Methods: We collected plasma cell-free DNA from 53 *de novo* mCSPC patients at diagnosis and during treatment. Cell-free DNA and tumour DNA from diagnostic prostate tissue were subjected to deep targeted sequencing and somatic profile comparison.

Results: Mean ctDNA fraction was 23.3% (range 0-84.4) among untreated patients but significantly lower (6.7%, range 0-51.3) in patients with brief exposure (median 22 days) to androgen deprivation therapy. TP53 mutations and DNA repair defects were identified in 47% and 21% of the cohort, respectively. Concordance for mutation detection in matched samples was 80%. Combined analysis of ctDNA and tissue provided driver gene status for 94% of the cohort, whereas use of either ctDNA or biopsy alone was insufficient in 19 cases (36%). Limitations include the use of a narrow gene panel and the likely under-sampling of primary disease by prostate biopsy.

Conclusions: In *de novo* mCSPC, ctDNA provides information beyond that captured by a prostate biopsy. However, exposure to short term therapy rapidly reduces ctDNA availability. Primary tissue and ctDNA share driver gene alterations, suggesting that either are suitable for molecularly subtyping *de novo* mCSPC. However, neither captures somatic profiles in all *de novo* mCSPC patients, so the optimal approach should utilize both a tissue and liquid biopsy at diagnosis.

Conflicts of Interest: None declared

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