The SHAPE Cohort: Integrated Genomic and Spatial Profiling of Advanced Prostate Cancer With and Without Lu-PSMA Treatment

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Background

PSMA expression is heterogeneous across advanced prostate cancer, limiting the durability of PSMA-radioligand therapy (RLT). To investigate tumor heterogeneity and determinants of Lu-PSMA resistance, we established the SHAPE cohort (Spatial Heterogeneity Atlas of Prostate Cancer Evolution), a multimodal resource integrating PET imaging, clinical treatment history, histopathology, PSMA IHC, spatial transcriptomics, and genomic profiling across castration-resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC).

Methods

The SHAPE cohort comprises 43 patient tumor samples collected through rapid autopsy, biopsy, and surgical resection, spanning adenocarcinoma, mixed CRPC/NEPC, and NEPC states and 8 xenograft tissues. Twenty-five Visium spatial transcriptomic samples (195,905 spots) were analyzed. Targeted genomic profiling was performed using the Dana-Farber OncoPanel platform on 37 samples derived from 7 patients and 3 animal models. Four cases (21 samples) had prior Lu-PSMA exposure, and seven cases (17 samples) were untreated. Eleven clinical and preclinical samples had PSMA PET/CT, including six with both pre- and post-treatment imaging. Data integration connected structural genomic events with spatial lineage programs and imaging features.

Results

Lu-PSMA–treated tumors exhibited a copy-number–dominant profile compared with untreated tumors. Recurrent alterations enriched in treated tumors included PTEN deletion (17/21 vs 1/17, Fisher $p=3.0\times10^{-6}$), KLLN deletion (10/21 vs 1/17, $p=0.0099$), AURKA gain (10/21 vs 0/17, $p=7.9\times10^{-4}$), and ZNF217 gain (9/21 vs 0/17, $p=0.0020$). Treated tumors also showed higher

per-sample copy-number loss (47.7 vs 24.4) and amplification burden (4.22 vs 1.14). In contrast, untreated tumors displayed more single nucleotide variants (16.1 vs 6.0) and indels (7.36 vs 1.35). Tumor mutational burden was lower in treated tumors (mean 4.36, SD 1.73; range 2.28–8.37) relative to untreated tumors (mean 15.53, SD 22.96; range 4.56–69.96).

Spatial transcriptomics provided complementary insights. Treated samples with PSMA SUVmean below the liver reference demonstrated higher copy-number loss burden ($p=0.03$) and contained unique transcriptomic clusters enriched for glucose metabolism. These clusters displayed variable expression of classical neuroendocrine markers but consistently showed upregulation of genes involved in glucose uptake and utilization. In preclinical studies, head-to-head FDG and Ga-PSMA imaging of WCM12 xenografts demonstrated that FDG, as a surrogate marker of glucose uptake, was significantly increased following relapse after PSMA-RLT ($p=0.01$).

Conclusions

The SHAPE cohort integrates genomic, spatial, and imaging data to characterize tumor heterogeneity in advanced prostate cancer. Genomic profiling identified PTEN/KLLN loss and AURKA/ZNF217 gain as recurrent alterations enriched in Lu-PSMA–exposed tumors, while spatial transcriptomics revealed PSMA-low metastases with distinct clusters enriched for glucose metabolic programs. In preclinical models, FDG PET imaging functioned as a complementary marker of glucose metabolism and was increased following relapse after PSMA-RLT, highlighting its potential utility in identifying PSMA-low tumors in the post-treatment setting. Together, these findings link structural genomic alterations with spatial lineage programs and provide a resource for understanding resistance after Lu-PSMA therapy.

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Conflicts of Interest Disclosure Statement

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