

Spatial Mapping of Metabolic Escape: The AR–LAT1 Axis Defines an ¹⁸F-Fluciclovine–Avid State Across CRPC and NEPC

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Background

Imaging and targeting of prostate-specific membrane antigen (PSMA) are central for the management of patients with advanced prostate cancer. However, PSMA is suppressed in androgen receptor (AR)-low castration-resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC). These disease states frequently exhibit increased expression of amino-acid transporters, including L-type amino acid transporter 1 (LAT1/SLC7A5). We hypothesized that suppression of AR activity promotes an LAT1-high metabolic state that can be detected using ¹⁸F-fluciclovine PET and contribute to PSMA heterogeneity.

Methods

We established the Spatial Heterogeneity Atlas of Prostate Cancer Evolution (SHAPE), a multimodal resource integrating PET imaging, clinical treatment history, histopathology, immunohistochemistry, spatial transcriptomics, and genomic profiling across 46 patient tumor samples spanning adenocarcinoma, CRPC, and NEPC, together with eight xenograft models. Twenty-five samples, comprising 195,905 spatial transcriptomic spots, were profiled using the 10x Genomics Visium platform, and 36 samples underwent targeted genomic profiling.

Transcript expression was compared across benign prostate, primary prostate cancer, CRPC, double-negative prostate cancer, and NEPC. AR signaling was suppressed in PSMA-positive LNCaP cells using androgen-depleted conditions or enzalutamide, and AR chromatin occupancy near the SLC7A5 locus was evaluated. Longitudinal clinical specimens and paired PET imaging were analyzed during progression from adenocarcinoma to NEPC. In prospective trial (NCT06099093), 18 patients with PSMA-low CRPC (n=5) or NEPC (n=13) underwent paired ⁶⁸Ga-PSMA-11 and ¹⁸F-fluciclovine PET/CT, with 279 metastatic lesions evaluated.

Results

When examining the spatial relationships among FOLH1/PSMA, SLC7A5/LAT1, SLC2A1/GLUT1, and lineage-associated programs. SHAPE revealed marked spatial and molecular heterogeneity. PSMA-low tumors had greater copy-number loss burden ($P < 0.05$) and contained unique spatial transcriptomic clusters enriched for glucose uptake and utilization. Within a CRPC liver metastasis, FOLH1/PSMA, SLC7A5/LAT1, and SLC2A1/GLUT1 mapped to spatially distinct regions, demonstrating intratumoral metabolic heterogeneity.

Across prostate cancer disease states, luminal associated markers such as KLK3 and FOLH1 expression declined in double-negative prostate cancer and NEPC, whereas SLC7A5 expression increased. In LNCaP cells, androgen deprivation and enzalutamide each reduced KLK3 (both $P < 0.0001$) and increased SLC7A5 ($P < 0.0001$ and $P < 0.01$, respectively). AR chromatin occupancy near SLC7A5 was evaluated across normal prostate ($n=6$), localized prostate cancer ($n=13$), and CRPC ($n=15$), with the strongest signal observed in CRPC. Progression from AR-positive, PSMA-positive adenocarcinoma to NEPC was accompanied by loss of AR and PSMA expression, increased LAT1 expression, and the emergence of ^{68}Ga -PSMA-11-negative, ^{18}F -fluciclovine-positive metastases.

In a comparative lesion-status analysis, 61 CRPC lesions (40 PSMA-positive and 21 PSMA-negative) showed no preferential ^{18}F -fluciclovine positivity by PSMA status (Fisher $P=0.26$; odds ratio [OR], 0.51; $P=0.49$). In contrast, among 203 NEPC lesions (141 PSMA-positive and 62 PSMA-negative), PSMA-negative lesions were significantly more likely to be ^{18}F -fluciclovine-positive (Fisher $P=0.0004$; OR, 3.02; $P=0.044$). Substantial inter- and inpatient heterogeneity remained, including spatially discordant PSMA and fluciclovine uptake across nodal, osseous, and visceral metastases.

Conclusions

SHAPE identifies spatially heterogeneous metabolic programs within advanced and treatment-resistant prostate cancer. Integrated spatial, mechanistic, and clinical imaging analyses link reduced AR activity with LAT1 upregulation and an ^{18}F -fluciclovine-avid phenotype. These findings support ^{18}F -fluciclovine as a complementary imaging strategy for biologically active PSMA-low disease, with the strongest clinical enrichment observed in PSMA-negative NEPC lesions. The AR–LAT1 axis may provide a framework for noninvasive characterization and treatment stratification of advanced prostate cancer.

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Conflicts of Interest Disclosure Statement

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