

PSCA Complements PSMA Across Primary, Metastatic, and Post-Pluvicto Prostate Cancer

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Background: PSMA is widely used for prostate cancer (PCa) imaging and radioligand therapy (e.g., ¹⁷⁷Lu-PSMA-617), but heterogeneous expression and resistance to PSMA-directed therapy may limit its effectiveness. Prostate stem cell antigen (PSCA) expression increases with tumor grade, stage, and progression to androgen independence, supporting its relevance in aggressive primary and metastatic PCa (metPCa), including intraductal carcinoma (IDC) and cribriform pattern (CR). We evaluated PSCA as a complementary target to PSMA across expanded primary and metastatic cohorts and examined PSCA/PSMA expression in metastases from patients with progression after PSMA-targeted radioligand therapy (Pluvicto).

Methods: Single and multiplex immunohistochemistry for PSCA, PSMA, androgen receptor, and selected microenvironment markers was performed in three cohorts: University of Washington metastatic PCa tissue microarrays (58 patients and 181 metastatic sites); 100 UCLA hormone-naïve radical prostatectomy tumors; and 49 metastatic lymph-node cases, of which 47 had current staining records. Staining was assessed by tumor-cell percentage, intensity, and/or H-score. IDC and CR were confirmed morphologically, with PIN4 support when needed. A preliminary UW TMA111A analysis included 10 patients: 5 with Pluvicto failure (22 metastatic sites) and 5 controls without prior Pluvicto exposure (19 metastatic sites). For a subset of UW cohort 1, PSCA and FOLH1 transcript levels from bulk RNA-seq were correlated with corresponding PSCA and PSMA IHC H-scores.

Results: Among 100 primary PCa, PSCA and PSMA were detected in 67% and 84%, respectively, with marked inter- and intratumoral heterogeneity. In the dedicated recount of 67 PSCA-positive primary tumors, PSCA was expressed in IDC in 32 (47.8%), CR in 43 (64.2%), both in 31 (46.3%), and IDC and/or CR in 44 (65.7%); the remaining 23 (34.3%) showed PSCA-positive acinar adenocarcinoma without IDC or CR patterns, as confirmed by PIN4. Among morphology-evaluable tumors, PSCA was expressed in the relevant component in 31/52 (59.6%) tumors with IDC and 39/72 (54.2%) with CR. In the metastatic lymph-node cohort, 20/39 (51.3%) analyzable cases were PSCA-positive by multiplex scoring. In UW TMA111A, PSCA positivity was higher after Pluvicto failure than in controls (14/22, 64% vs 7/19, 37%), whereas PSMA positivity was lower (12/22, 55% vs 14/19, 74%). PSCA-positive/PSMA-negative sites were more frequent after Pluvicto failure (9/22, 41%) than in controls (3/19, 16%). Regions with high PSCA/PSMA co-expression were associated with increased intratumoral CD3+ T-cell infiltration. In metPCa, PSCA and FOLH1 transcript levels correlated with their respective PSCA and PSMA IHC H-scores.

Conclusions: PSCA provides nonredundant coverage across primary and metastatic PCa, including clinically adverse IDC/CR morphologies. Its retention in a substantial subset of post-Pluvicto, PSMA-negative metastases supports further evaluation of PSCA-directed imaging or therapy as a complementary or sequential strategy. These treatment-associated findings are preliminary and require validation in larger cohorts. (438 words)

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Conflicts of Interest Disclosure Statement: The authors declare no conflicts of interest.

Table 1. Preliminary PSCA/PSMA positivity by treatment cohort.

Marker	Cohort	Evaluable Sites	Positive Sites	Positive (%)	Mean % Positive Cells*	Median % Positive Cells*
PSCA	Control	19	7	37%	19.7	0.0
PSCA	Pluvicto-failure	22	14	64%	26.1	5.0
PSMA	Control	19	14	74%	30.0	10.0
PSMA	Pluvicto-failure	22	12	55%	24.8	5.0

*Includes 0% for marker-negative sites.

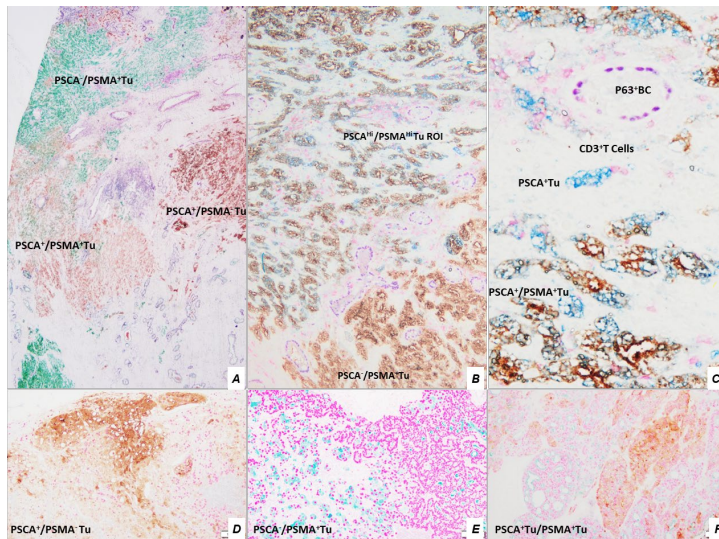


Figure 1: Quad IHC demonstrates heterogeneous PSCA and PSMA expression in primary PCa (A–C). Regions with high PSCA/PSMA co-expression show increased intratumoral CD3⁺ T-cell infiltration (C). PSCA, PSMA, and AR triple IHC demonstrates representative expression patterns in metastatic lymph nodes (D–F).

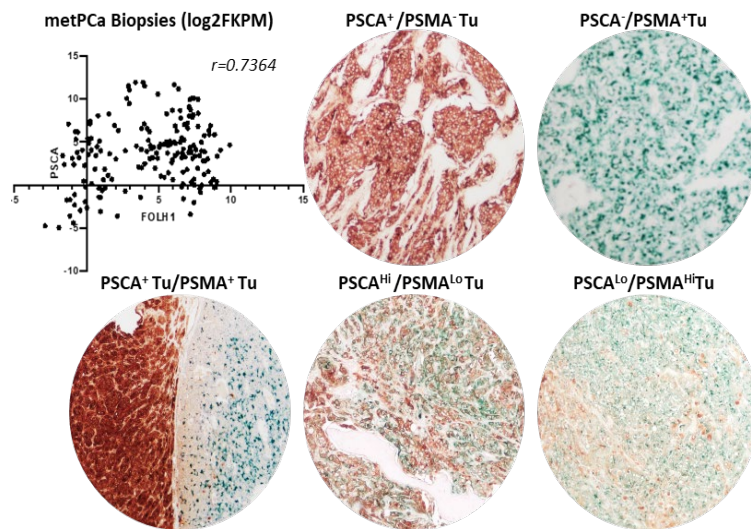


Figure 2. Correlation of PSCA and FOLH1 transcript expression in metastatic PCa and representative dual IHC for PSCA (brown) and PSMA (green) in UW cohort 1. Transcript expression is shown as log₂(FPKM).