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Molecular hallmarks of prostate-specific membrane antigen in treatment-naïve prostate cancer

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Abstract

Background and objective: We characterized tumor PSMA levels as a reflection of cancer biology and treatment sensitivities for treatment-naïve prostate cancer.

Methods: We first correlated PSMA PET SUVmax in primary prostate cancer with tumor *FOLH1* (PSMA RNA abundance) to establish RNA as a proxy (n=55). We then discovered and validated molecular pathways associated with PSMA RNA levels in two large primary tumor cohorts. We validated those associations in independent cohorts (18 total; 5684 tumor samples) to characterize pathways and treatment responses associated with PSMA.

Key findings and limitations: PSMA RNA abundance correlates moderately with SUVmax (ρ= 0.41). In independent cohorts, androgen receptor signaling is more active in tumors with high PSMA. Accordingly, patients with high PSMA tumors experienced longer cancer-specific survival when managed with ADT for biochemical recurrence (adjusted hazard ratio [AHR] 0.54 [0.34–0.87]; n=174). PSMA low tumors possess molecular markers of resistance to radiotherapy. Consistent with this, Patients with high PSMA tumors experience longer time to recurrence following primary radiotherapy (AHR 0.50 [0.28–0.90]; n=248). In the SAKK09/10 trial (n=224), patients managed with salvage radiotherapy with high PSMA tumors experienced longer time to progression in the 64Gy arm (Restricted mean survival time [RMST] +7.60 [0.05–15.16]) but

this effect was mitigated in the 70Gy arm (RMST 3.52 [−3.30–10.33]). Limitations include using PSMA RNA as a surrogate for PET SUVmax.

Conclusion and clinical implications: PSMA levels in treatment-naïve prostate cancer differentiates tumor biology and treatment susceptibilities. These results warrant validation using PET metrics to substantiate management decisions based on imaging.

Keywords

prostatic neoplasms / genetics; Prostatic Neoplasms / pathology; Humans; Gene Expression; Biomarkers; Tumor; Prognosis; Gene Expression Profiling

1. Introduction

Even at early stages, prostate cancer biology and clinical phenotype can vary greatly.

Consequently, treatment options for localized prostate cancer range from surveillance to multimodal therapy.[1,2] Due to variable treatment response, efforts to better characterize and stage prostate cancer have led to imaging strategies such as positron emission tomography (PET) based on the expression of the cellular membrane glycoprotein prostate-specific membrane antigen (PSMA).[3] However, PSMA abundance is highly variable in prostate cancer[4] and most studies correlating biology with tumor PSMA levels have focused on late stage disease following multiple therapies.[5–7] A recent pan-cancer genomics assessment suggests that treatment-naïve and treatment resistant metastatic prostate cancer differ more than any other tumor type.[8] Thus, it's difficult to extrapolate prior work assessing PSMA in late stage disease to treatment-naïve disease.

Given PSMA PET is used to stage most prostate cancer,[1,2] leveraging heterogeneity in intratumoral PSMA levels as a biomarker of cancer phenotypes may refine precision care for future patients. We hypothesized PSMA variation reflects underlying tumor biology which might be causally related to response to treatments. This can help augment the interpretation of PSMA PET imaging and contribute to individualizing cancer care. Here, we perform broad correlative analyses of PSMA RNA abundance in tumors from radical prostatectomies (Figure 1a). We then validate molecular pathways associated with PSMA in independent cohorts (5684 total tumor samples) to assess treatment susceptibilities associated with PSMA levels.

2. Materials and methods

2.1 Primary analysis: Discover pathways associated with PSMA

We first sought to assess *FOLH1* abundance (PSMA) as a proxy for PSMA uptake on PET. To do this we queried tumors from patients derived from a prospective trial of patients with localized prostate cancer who underwent PSMA PET-MRI prior to radical prostatectomy (NCT03392181; n=38) merged with a retrospective cohort who also underwent PSMA PET-CT prior to surgery (n=17; both using 18F-DCFPyL). RNA profiling of surgery or biopsy specimens from Northwestern University (Chicago, IL, USA) was done for both groups of patients. Maximum standardized uptake values (SUVmax) were measured within

the prostate. Primary discovery analyses were then performed in The Cancer Genome Atlas (TCGA) obtained from cBioPortal (n=491).[9–11] We correlated hallmark cell pathways (n=50) with PSMA in TCGA using multivariable linear regressions adjusting for clinical variables (Supplemental methods) and tumor purity (Supplemental figure 1b). The Decipher Genomics Resource for Intelligent Discovery database cohort (GRID; NCT02609269)[12] was used to validate all pathways significantly associated with PSMA in TCGA using multivariable linear regressions. The GRID cohort was comprised of tumors acquired at prostatectomy through the commercial use of the Decipher prostate genomic classifier test[13] December 2015-September 2017 (n=2612). Validated pathways included those associated with PSMA with the same directional relationship and False discovery rate<0.05 in both TCGA and the GRID.

2.2 Validate associations with high and low PSMA in independent cohorts

After associating molecular pathways with high and low PSMA in TCGA and GRID, we then sought to validate these findings in independent cohorts or with orthogonal methods. Using these biological associations, we queried clinical cohorts to test how tumor biology reflected by PSMA levels might translate to treatment responsiveness.

2.3 Clinicopathological variables and PSMA

It's unclear if PSMA is a marker of tumor aggressiveness outside the context of therapies whose efficacies might vary based on tumor biology. Thus, we sought to correlate PSMA with standard clinicopathologic variables in various cohorts. We also assessed PSMA and time to metastatic recurrence in a group of patients who underwent radical prostatectomy at Johns Hopkins Medical Institute (JHMI; n=498) and no additional treatments until loss to follow-up or metastatic recurrence.

All other data sources totaling 5684 tumors samples from 18 human cohorts and two cell line or mouse models are discussed in the Supplemental methods and listed in Supplemental table 1. Signatures, biomarkers, and statistical considerations are also noted in the Supplemental methods and Supplemental table 2.

3. Results

3.1 PSMA correlates with biological pathways

Among 55 patients who underwent PSMA PET with 18F-DCFPyL prior to prostatectomy (Supplemental table 1), intraprostatic PSMA RNA abundance (hereafter "PSMA") correlated moderately well with SUVmax on PET (ρ= 0.41; Supplemental figure 1a). Thirty-one hallmark molecular pathways were differentially active in TCGA based on PSMA (High, n=16; Low, n=15; Supplemental table 3). Of these, 25 pathways were also differentially activated in GRID (Figure 1c and Supplemental table 4). Pathways associated with increased PSMA in both cohorts including markers of increased metabolism, cell cycle promotion, and androgen response (Supplemental figure 1c). Twelve pathways were confirmed to be associated with decreased PSMA including those related to inflammation, the tumor microenvironment, cell cycle arrest/death, and epithelial-mesenchymal transition (EMT). Previously developed TCGA subtypes (Supplemental table 2) were not associated

with PSMA (Supplemental figure 1d and Supplemental table 5). In GRID, lower PSMA was associated with low androgen receptor (AR) activity and basal phenotypes based on RNA signatures (Supplemental figure 1e and Supplemental table 6). These analyses suggest PSMA in treatment-naïve prostate cancer does differentiate tumors by relevant biological processes.

3.2 High PSMA tumors are more susceptible to AR-targeting therapies

PSMA high tumors were associated with AR activity and luminal signatures in TCGA and GRID (Figure 1b–c and Supplemental figure 1e).[14] Accordingly, PSMA is increased in primary adenocarcinoma (n=59) compared to benign tissue (n=28), metastatic castration-resistant prostate cancer (mCRPC; n=35; GSE35988), and neuroendocrine tumors[15] (Figure 2a and Supplemental figure 2a). Together, these findings suggest high PSMA signals increased AR activity. Therefore, we assessed PSMA in response to AR-targeting therapies. Prior work has shown PSMA levels tend to change in various ways in the setting of AR-targeting therapies.[16,17] In a mouse xenograft, RNA was quantified before castration and at timepoints after castration (GSE56829; Supplemental table 1). PSMA increased somewhat immediately after castration, then declined as the tumor became resistant (Supplemental figures 2b). In human trial data (Rajan *et al.* cohort; Supplemental table 1), tumors treated with 22 weeks of androgen deprivation therapy (ADT) were associated with lower PSMA (Wilcoxon, P=0.016; Supplemental Figure 2c). Lower PSMA was also associated with intensive treatment with ADT and the AR antagonist, enzalutamide (P<0.001; Figure 2b and Supplemental table 7). Importantly, prior exposure to an AR signaling inhibitor for mCRPC was not associated with differential PSMA (Supplemental figure 2d). These results suggest PSMA is associated with increased AR activity and declines with AR-targeting therapies specifically in treatment naïve disease.

In two clinical trials testing ADT and 3–6 months enzalutamide prior to surgery (NCT01990196 & NCT02430480; Supplemental table 1), high pre-treatment PSMA was associated with a greater decrease in the hallmark androgen response pathway following treatment (P=0.002; Supplemental tables 2 and 7 and Supplemental figure 2e). This pattern suggests high PSMA reflects a susceptibility to AR-targeted therapies. Among patients with biochemical recurrence following prostatectomy managed with ADT monotherapy (Karnes *et al.* Cohort; n=178),[18] tumors in the highest quartile of PSMA were associated with longer cancer-specific survival (AHR: 0.54, 95%CI: 0.34–0.87; Figure 2c and Supplemental table 8), particularly in later years of follow-up. Similarly, the ECOG-ACRIN 3805 trial randomized patients with metastatic castration-sensitive prostate cancer to ADT with or without docetaxel chemotherapy (n=157).[19] Although we saw evidence that high PSMA tumors in the ADT alone arm (n=73) were associated with longer overall survival, this difference was not statistically significant (AHR: 0.55, 95%CI: 0.28–1.08; Figure 2d and Supplemental table 9). Additionally, only low PSMA tumors were associated with benefit from the addition of chemotherapy (n=79; AHR: 0.32, 95%CI: 0.14–0.72). However, in the limited sample from the trial, there was no interaction between PSMA and treatment arm (Supplemental table 9d). Conversely, in the mCRPC setting, PSMA showed no association with overall survival after starting abiraterone or enzalutamide (Supplemental figure 2f).

Together, these findings offer preliminary evidence that PSMA high, treatment-naïve tumors are more susceptible to AR-targeted therapies which warrants further investigation.

3.3 Stemness and resistance to radiotherapy define low PSMA tumors

EMT in prostate cancer has been linked to increased “stemness” or lineage plasticity.[20] hypoxia and angiogenesis pathways have also been shown to be associated with emergence of stemness in prostate cancer.[21,22] Therefore, we sought to validate the association between low PSMA and increased EMT and these markers of stemness (Figures 1b–c). Three methylation-based signatures for stemess and RNA-based signatures for cancer stem cells, angiogenesis, and hypoxia were all negatively associated with PSMA in TCGA (Figure 3a–b, Supplemental table 2, and Supplemental table 10). In LNCaP cells exposed to hypoxic conditions (GSE195571), FOXA1 downregulation led to upregulated hypoxia pathways and was associated with lower PSMA (P<0.001; Supplemental figure 3a). Hypoxia-inducible factor-1-α (HIF-1α) inhibition led to downregulation of hypoxia pathways and increased PSMA (P=0.025). Stemness and EMT in prostate cancer are also stimulated by pro-inflammatory pathways induced by cancer-associated fibroblasts via nuclear factor-κB (Figure 1b–c) and HIF-1α.[23,24] Accordingly, in TCGA, PSMA was negatively associated with increased numbers of tumor-infiltrating lymphocyte clusters on immunohistochemistry (Supplemental figure 3b and Supplemental table 11)[25] and increased proportions of NK cells, cytotoxic lymphocytes, and fibroblasts in the tumor microenvironment (Supplemental figure 3c, Supplemental table 2, and Supplemental table 12).

Previously, increased angiogenesis, hypoxia and reactive oxygen species (ROS; Figure 1b–c) pathways have been associated with resistance to radiotherapy.[26–29] Accordingly, in a cohort of patients who received primary radiotherapy for prostate cancer (n=248), [30] patients with the lowest quartile PSMA tumors experienced a shorter time to cancer recurrence (Interquartile and highest quartile *vs* Lowest quartile, AHR: 0.50, 95%CI: 0.28–0.90 ; Figure 3c and Supplemental table 13). Notably, these patients received a median of 72Gy in 2Gy fractions without boost, which would be less intense treatment compared to contemporary practice.[1] To assess the relation between different radiation doses, PSMA, and treatment response, we evaluated the SAKK 09/10 trial. This study randomized patients with recurrent prostate cancer after surgery to either 64Gy or 70Gy to the prostate bed without any ADT (n=233).[31] In the 64Gy arm (n=109), PSMA levels above the lowest quartile were associated with a significantly longer time to cancer progression (5-year RMST: +7.60 years, 95% CI 0.05 to 15.16; Figure 3d and Supplemental table 14). However, in the higher dose arm (70Gy; n=115), there was no significant difference based on PSMA (+3.5 years, 95% CI −3.3 to 10.3; Figure 3d and Supplemental table 14). Together, these data suggest PSMA low tumors demonstrate characteristics of stemness and are associated with shorter times to progression after radiotherapy that can be overcome with higher dosing.

3.4 Clinicopathologic associations with PSMA

Given PSMA has previously been associated with markers of tumor aggressiveness, [32,33] we next sought to correlate PSMA with standard clinicopathologic variables. In

TCGA, grade group increase was not consistently associated with PSMA (Figure 4a and Supplemental table 15) but did correlate positively with percentage of cribriform or intraductal carcinoma histology, which have been associated with aggressive phenotypes and was previously associated with increased uptake on PSMA PET (Supplemental figure 4a and Supplemental table 16).[34,35] In a cohort of patients who underwent radical prostatectomy and pelvic lymphadenectomy (n=23; Supplemental table 1), PSMA did not differ between paired primary and nodal metastatic tumors (P=0.3; Figure 4b). In multivariable regression, we also assessed PSMA by self-reported race in a merged dataset from JHMI and the National Cancer Centre Singapore (White n=318; Asian n=238; Black n=176; Supplemental table 1). We found tumors from patients of Black race were associated with lower PSMA compared to those of White patients (Supplemental figure 4b and Supplemental table 17).

Due to the non-linear relationship we noted with tumor grade in TCGA (Figure 4a), we assessed how PSMA correlates with a commercially available genomic risk score originally developed to predict metastatic recurrence after prostatectomy stratified by primary Gleason grade pattern in GRID.[13] In a multivariable linear regression, there was a significant interaction between primary Gleason grade pattern and high genomic risk (P<0.001; Supplemental table 18). As such, PSMA correlated positively with genomic risk scores only for lower grade tumors and not for high grade primary pattern 5 tumors (Figure 4c). In the JHMI cohort (Supplemental table 1), patients with high grade group tumors (4–5) accounted for 34% of all patients and 63% of all metastatic recurrences. Tumor PSMA quartile did not differentiate time to metastasis in an adjusted analysis (Highest quartile *vs* lowest quartile PSMA, AHR: 1.00, 95%CI: 0.61–1.65; Figure 4d and Supplemental table 19). To summarize, PSMA does not directly relate to many standard clinicopathologic factors for treatment-naïve PC. Patients of Black race may harbor tumors with lower PSMA compared to those from patients of White race. Among patients with high grade tumors, PSMA does not correlate with innate tumor aggressiveness based on an RNA-based genomic risk score or risk of metastatic recurrence following surgery.

4. Discussion

In this work, we leveraged molecular profiles from 5684 tumors across multiple cohorts to investigate how PSMA abundance reflects differential tumor biology and treatment susceptibilities in treatment-naïve prostate cancer (Figure 1a). This investigation is significant because: 1) Prostate cancer biology is diverse and personalizing management can optimize treatment for future patients; 2) PSMA PET is increasingly used for staging prostate cancer;[1,2] and 3) the biology underlying PSMA levels in treatment-naïve disease is less understood compared to advanced prostate cancer which is genetically distinct.[5,6,8] Findings from this work also shows that clinical correlations with PSMA differ between treatment naïve and mCRPC (Supplemental figure 2d and 2f). Thus, PSMA uptake on PET is becoming a routinely collected metric that can be exploited as a biomarker for treatment-naïve prostate cancer behavior.

Our findings suggest PSMA high tumors may respond better to AR-targeting therapies. Tumors with low PSMA possess markers of cancer stem cells and are associated with resistance to radiotherapy. Prior work positively associated PSMA with markers of tumor

aggressiveness.[32,33,36] However, we noted inconsistent correlations between PSMA and N-category, grade, and recurrence after prostatectomy. Only for lower grade tumors did PSMA differentiate aggressiveness based on genomic risk scores which can have implications for those considering surveillance as primary management.[13] Similarly, in a prior study of 71 patients who underwent PSMA PET prior to prostatectomy, uptake on PET was associated with tumor recurrence only for patients with ≤GG2 tumors on biopsy.[37] These results suggest PSMA levels from PET can risk-stratify patients with lower grade tumors and can help individualize hormone and radiotherapy.

The current study is limited by use of PSMA RNA, and thus future work should assess cohorts using metrics from PSMA PET or protein abundance (Figure 1a). The difference between correlating tumor biology with RNA abundance *vs* tumor uptake and volume on PET[38] is unclear and requires external validation prior to clinical application. It is also unclear if there are clinically relevant cutoffs for PSMA in the current work without PET correlates. Additionally, this work does not examine the mechanisms underpinning biological and clinical correlates. However, if confirmed, PSMA uptake on PET may serve as a biomarker for tumor biology and treatment susceptibilities for treatment-naïve prostate cancer. As the management options for these patients expand, biomarkers aimed at predicting treatment response for those who benefit most from them will be critical for maximizing the chance for cure while minimizing unnecessary treatment exposures.

5. Conclusion

PSMA levels in treatment-naïve prostate cancer correlate with cancer biology and treatment susceptibilities. Because PSMA PET is commonly used to stage patients with prostate cancer, validation with PET metrics can help develop PSMA as a biomarker to direct cancer care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What does the study add:

Thousands of patients with newly diagnosed prostate cancer undergo PSMA PET imaging for staging annually. However, it is currently unknown how variations in PSMA levels reflect tumor biology. Our work suggest PSMA correlates with various molecular pathways and PSMA low tumors are more resistant to hormone therapy and radiotherapy.

Patient summary:

PSMA is a protein on the cell surface of most prostate cancer. Here, we find that variations in the amounts of this marker reflect cancer biology and whether the cancer will be amenable to certain treatments.

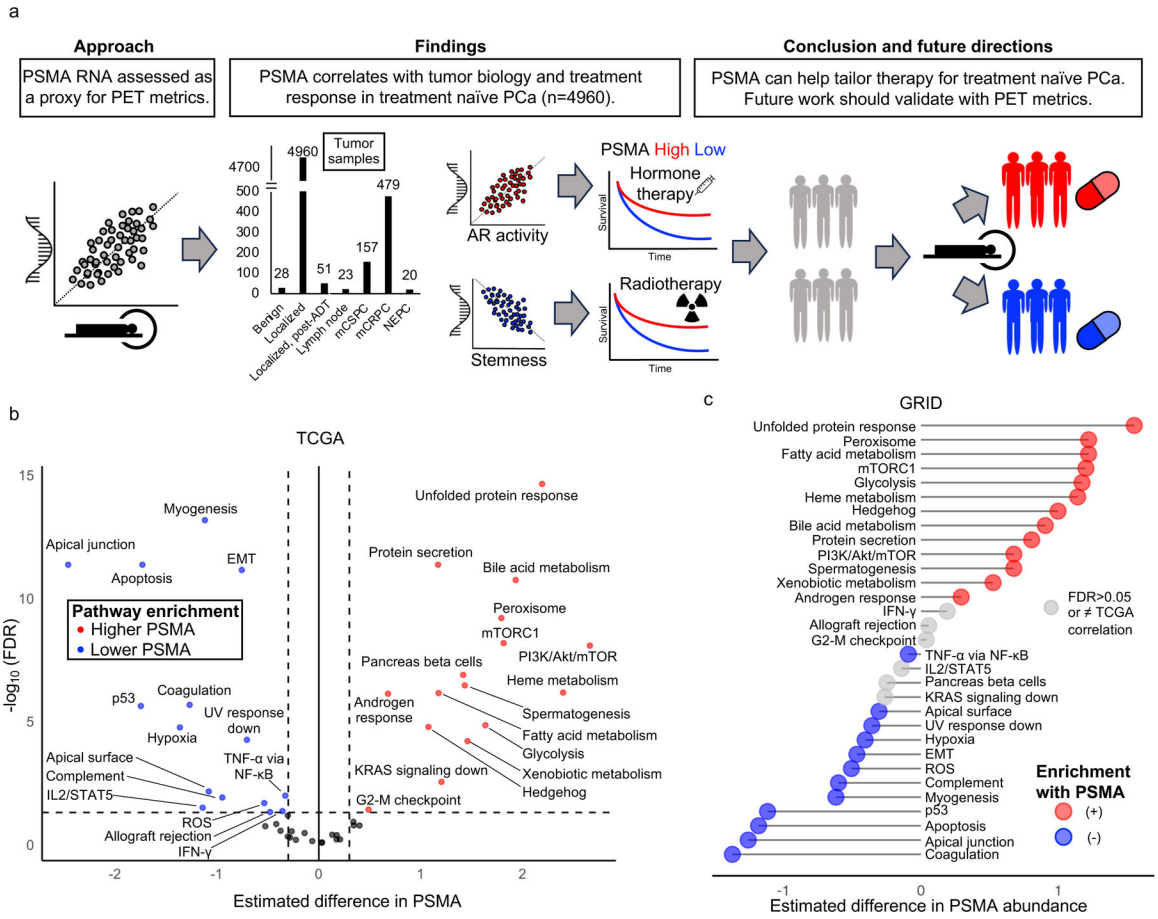

Figure 1: PSMA correlates with molecular pathways treatment naïve prostate cancer.

Graphical illustration of this study's approach, findings, conclusions, and proposed future directions (a). In a multivariable linear regressions adjusting for patient age, tumor purity, T-stage, serum PSA, and grade groups, 50 hallmark cell pathways were correlated with PSMA abundance in TCGA (b) and significantly associated pathways were validated in GRID (active in PSMA high tumors, n=13; active in PSMA low tumors, n=15; c). Abbreviations: PSMA, prostate-specific membrane antigen; PET, positron emission tomography; PCa, prostate cancer; ADT, androgen deprivation therapy; mCSPC, metastatic castration sensitive prostate cancer; mCRPC, metastatic castration resistant prostate cancer; NEPC, neuroendocrine prostate cancer; AR, androgen receptor; FDR, false discovery rate; TCGA, The Cancer Genomic Atlas; GRID, Decipher Genomics Resource for Intelligent Discovery database.

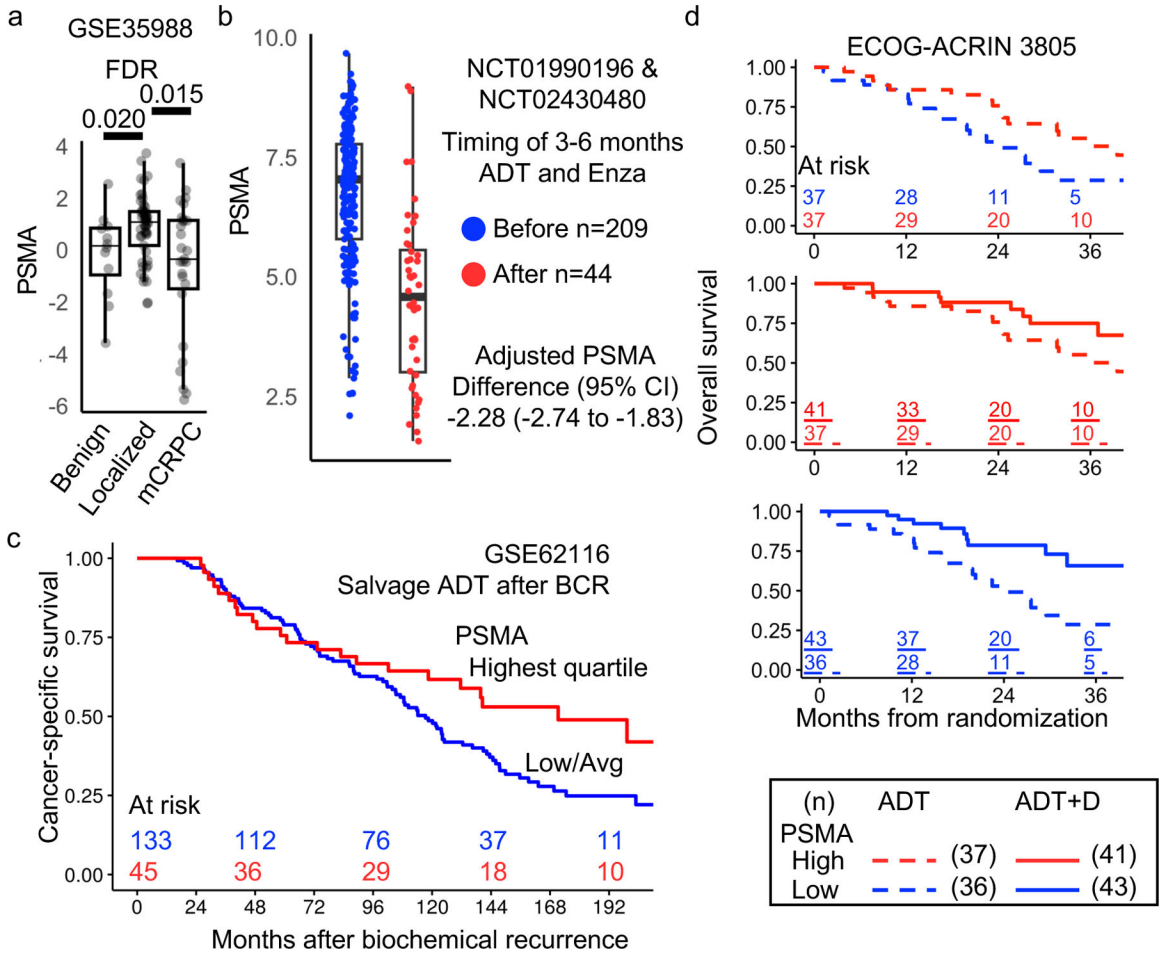

Figure 2: PSMA declines with AR-targeting treatments.

PSMA abundance was noted to be higher in primary, non-metastatic adenocarcinoma compared to benign tissue or mCRPC (a; FDR from Wilcoxon). Intense neoadjuvant hormonal therapy with ADT and enzalutamide resulted in lower PSMA (b; Multivariable linear regression). In a cohort of patients who experienced BCR after surgery for prostate cancer and received salvage ADT without radiotherapy, patients with PSMA high tumors experienced longer cancer-specific survival (c; Multivariable Cox regression). In patients with metastatic hormone sensitive prostate cancer randomized to either ADT without or with docetaxel, patients with PSMA low tumors benefited from the addition of chemotherapy due to a relative resistance to hormone therapy while those with PSMA high tumors did not benefit from chemotherapy (d; All multivariable Cox regression). Abbreviations: PSMA, prostate-specific membrane antigen; mCRPC, metastatic castration-resistant prostate cancer; FDR, false discovery rate; ADT, androgen deprivation therapy; Enza, enzalutamide; BCR, biochemical recurrence; AHR, adjusted hazard ratio; CI, confidence interval; Avg, average; ADT+D, androgen deprivation therapy and docetaxel.

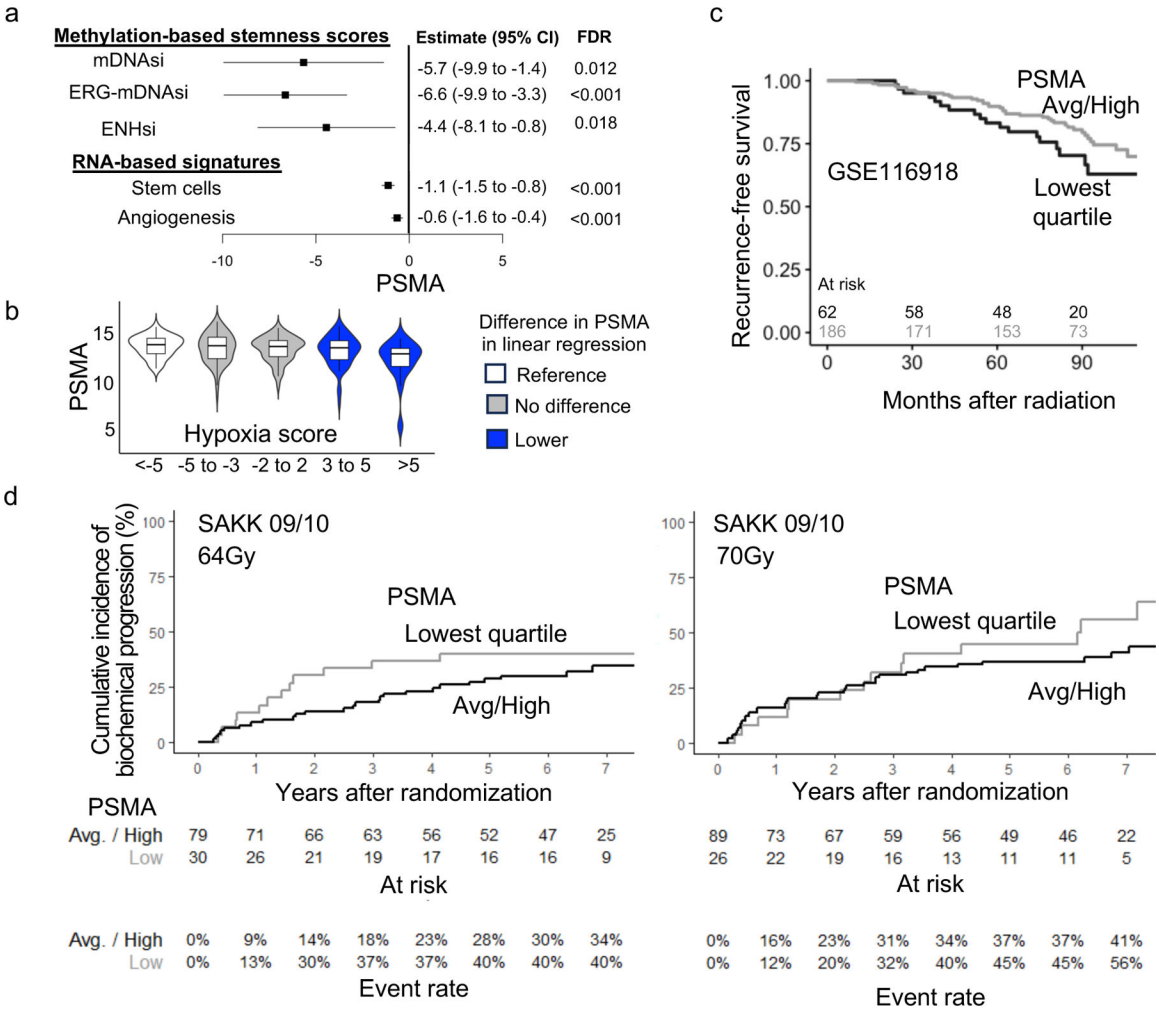

Figure 3: Stemness markers and radioresistance are associated with low PSMA.

Low PSMA tumors have increased stemness, angiogenesis, and hypoxia based on methylation RNA-based signatures in TCGA (a-b; Multivariable linear regression). Patients with low PSMA tumors at the time of primary radiotherapy experienced a shorter time to recurrence (c; Multivariable Cox regression). However, radioresistance suggested by low PSMA might be overcome by increase dosing as suggested by data from the SAKK 09/10 trial (d; Multivariable restricted mean survival time). PSMA, prostate-specific membrane antigen; FDR, false discovery rate; TCGA, The Cancer Genome Atlas; AHR, adjusted hazard ratio; CI, confidence interval; Avg, average; RMST, restricted mean survival time.

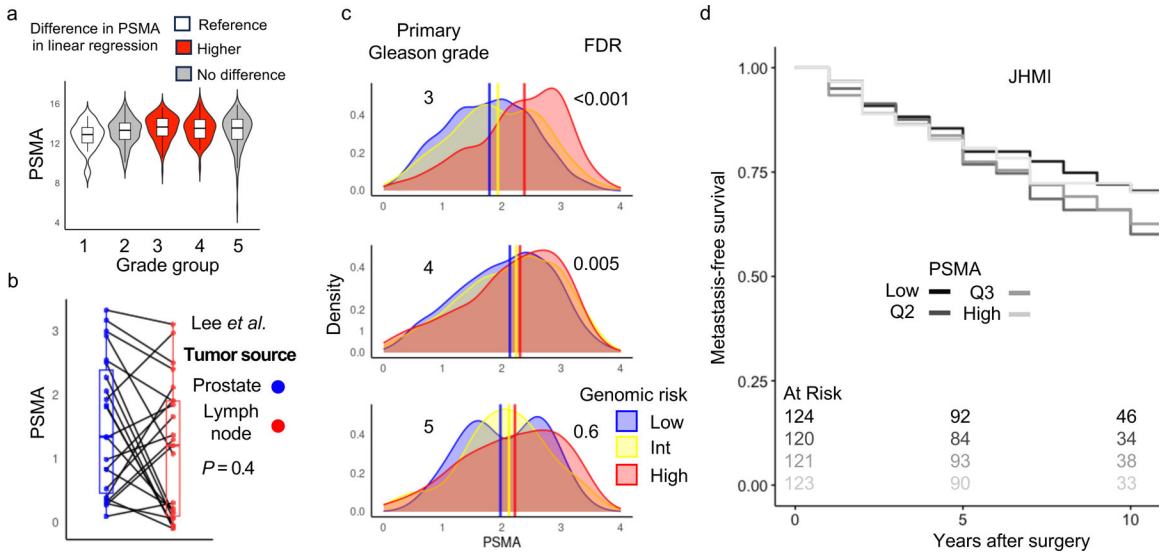

Figure 4: Clinicopathologic associates with PSMA.

In TCGA, PSMA was inconsistently increased in higher grade groups relative to grade group 1 (a; Multivariable linear regression; Supplemental table 12). In patients with metastatic pelvic nodal disease found at the time of prostatectomy, PSMA was not significantly different between primary and nodal tumors (b; Wilcoxon). In GRID, tumors with high genomic risk scores had more PSMA only in lower grade tumors (c; Kruskal-Wallis). Accordingly, in a cohort of patients who underwent prostatectomy without any adjuvant or salvage treatment, PSMA abundance did not differentiate metastasis-free survival (d; Multivariable Cox regression). In this group, 52% of patients with high grade tumors had metastatic recurrence while the same was true for only 16% of patients with intermediate and low-grade tumors. PSMA, prostate-specific membrane antigen; JHMI, Johns Hopkins Medical Institute; AHR, adjusted hazard ratio; CI, confidence interval.