

Immune spatial organization predicts metastasis risk in aggressive localized prostate cancer

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Background: Computational pathology has emerged as an attractive option for improving risk stratification in prostate cancer (PCa), but most current approaches either lack interpretability or focus solely on tumor morphology, potentially limiting their utility. We aimed to identify an interpretable, immune microenvironment-derived computational pathology biomarker for PCa.

Methods: We retrospectively identified two independent cohorts (Discovery and Validation) with localized PCa who underwent radical prostatectomy (RP) and had digitized H&E-stained whole-slides images (WSIs) and longitudinal outcomes data. We identified a third cohort from The Cancer Genome Atlas (TCGA) with localized PCa which was treated with RP and had WSIs, bulk RNA sequencing, and whole-exome sequencing. Immune cells were identified from WSIs using a publicly available deep learning model (CellViT), and spatially dense immune clusters were quantified using density-based spatial clustering of applications with noise (DBSCAN). CIBERSORTx was utilized for immune cell deconvolution and TRUST4 for immune receptor repertoire reconstruction from bulk RNA sequencing. Cox proportional hazard regression was used to examine associations between clinicopathologic features and the primary outcome of time to distant metastasis (DM), as well as secondary outcomes of biochemical recurrence (BCR) and overall survival (OS).

Results: Median follow-up periods for the Discovery (n=272) and Validation (n=218) Cohorts were 12.6 and 8.1 years, respectively. In the Discovery Cohort, median age was 63, 14% had Gleason 8-10 disease, 94% had pT2-T3a disease, and median prostate-specific antigen level at diagnosis was 6.2 ng/mL. Median immune cell proportion was 4.3% (interquartile range 3.0-5.9%), and median immune cluster density was 2.4 per 400 mm² of tissue (interquartile range 0-7.1). Similar values were observed in the Validation Cohort. In both cohorts, immune cell proportion was not associated with BCR, DM, or OS ($P \geq 0.09$). In the Discovery Cohort, while increasing immune cluster was not associated with BCR ($P \geq 0.10$), it was independently associated with a decreased risk of DM for Gleason 8-10 (adjusted hazard ratio [AHR] 0.42, 95% confidence interval [CI] 0.19-0.93) but not Gleason 6-7 patients (AHR 1.26, 95% CI 0.77-2.05; $P_{\text{int}}=0.020$). Similar results were observed in the Validation Cohort, where increasing immune cluster was not associated with BCR ($P \geq 0.10$) but was associated with a lower risk of DM in Gleason 8-10 disease (AHR 0.60, 95% CI 0.37-0.98), though not Gleason 6-7 (AHR 1.19, 95% CI 0.74-1.91; $P_{\text{int}}=0.043$). In TCGA Cohort (n=326), immune cluster was not associated with somatic alterations. For Gleason 8-10 but not Gleason 6-7 disease, high-cluster samples were enriched for CD8+ T cells, activated memory CD4+ T cells, and Tregs ($P \leq 0.037$); higher *CXCL13* expression ($P < 1 \times 10^{-5}$); and greater T cell clonality ($P \leq 0.039$).

Conclusions: Our findings nominate immune spatial clustering as a novel, interpretable computational pathology biomarker and provide insights into the unique immune features of high-grade PCa.

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Conflicts of Interest

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JDB has served on advisory boards and received fees from many companies including Abbvie, Acai Therapeutics, Amgen, Amunix, Astellas, Bayer, Bionxe Therapeutics, Boehringer Ingelheim, Celcuity, Daiichi, Dark Blue Therapeutics, Duke Street Bio Limited, Dunad Therapeutics, Eikon Therapeutics, Endeavor Biomedicines INC, Genentech/Roche, GSK, MacroGenics, Merck Serono, MetaCurUm, Moma, Morphosys, Myricx, Novartis, Nurix Therapeutics, Nuvation Bio, Oncopia Therapeutics, Inc. d/b/a SK Life Science Labs, One-Carbon Therapeutics Inc, Oncternal, Orion, Page Therapeutics, Peptone, Pfizer, Takeda, Tango Therapeutics, Tubulis GmbH, VIR Biotechnology.

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