Integrative Profiling of Tumor-Immune Dynamics and Evolution in Response to Radiotherapy for Oligometastatic Prostate Cancer

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Background Radiation therapy (RT) can confer survival advantage in oligometastatic prostate cancer (OMPC). Reports implicate immune system contribution to both local tumor control and systemic regression of metastases. However, the impact of RT, including dose and field size, on tumor-immune dynamics in shaping clinical responses in irradiated OMPC patients remains an active area of investigation. Multi-modal profiling of patients receiving RT may reveal signatures of tumor-immune dynamics that highlight potential mechanisms of RT-driven antitumor immune activity and can inform treatment optimization.

Methods Prospective samples from consented patients with OMPC (de novo/oligorecurrent) receiving RT included baseline (pre-RT) and 3 post-RT blood samples (RT end, 3-, 6-months). Olink Proteomics analysis of serum proteins, PBMC profiling by cytometry by time of flight (CyTOF), and TCR sequencing (Adaptive Biotechnology) was performed. Data analysis included standard gating/clustering algorithms and statistical analyses of through edgeR and logisitic regression to identify immune changes linked to clinical data (e.g RT dose and recurrence).

Results 14 patients met inclusion criteria (2020-2022). Two patients had de novo OMPC, 12 patients were oligorecurrent. All patients received androgen deprivation therapy. De novo OMPC patients received simultaneous RT to the prostate, lymph nodes, and OM lesions, while 6/12 oligorecurrent patients received simultaneous RT to a pelvic field along with OM lesions. Remaining patients received RT to the OM lesions alone. Median follow-up was 25.5 months (r, 13-35). Among 14 patients, 6 patients (42.9%) experienced recurrence (R, defined by PSA progression). Median time to recurrence post-RT was 20 months.

Serum analysis quantified 92 proteins. Logistic regression models accurately classified patients by radiation dose (100%) and field size (88.9%), as well as recurrence (77.8%). We identified IL-4, IL-12, and soluble CD70 as important markers with utility in distinguishing patients across predictive models. Additionally, IL-6, TNFa, and Fas-L were important in individual models.

PBMC immunophenotyping by CyTOF identified immune subsets used for differential abundance analyses that investigated baseline and post-RT changes linked to clinical information. CD4 effector memory T cells were increased post-RT in patients that experienced recurrence, while increased CD4 central memory and NKT cells were linked to non-recurrence. Logistic regression models predicted recurrence with high accuracy (88% pre-RT/RT-end, or 90% 3 months post-RT).

TCR sequencing of blood sample timepoints revealed significant difference in Morisita index of baseline versus immediate post-RT R (0.9) vs NR (0.75) samples (p=0.043), indicating that a more diverse immune repertoire is associated with NR.

Conclusions Profiling of a patient cohort receiving RT for OMPC identified longitudinal immune dynamics, particularly immediately post-RT, which may predict risk of recurrence. Further multi-modal blood and tissue analysis integrating baseline genomic status, immune repertoire and profiling assays, may refine our understanding of RT on immune system activation and clinical outcomes.

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Conflicts of Interest None