220 DIFFERENTIAL PATTERNS OF IMMUNE INFILTRATION IN THE TUMOR IMMUNE MICROENVIRONMENT ASSOCIATE WITH THERAPEUTIC RESPONSE IN PRIMARY PROSTATE CANCER FOLLOWING CHEMOHORMONAL THERAPY

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Background There is a critical need to develop novel therapeutic strategies and diagnostic tools to precisely deliver treatments to improve survival for men with prostate cancer prostate cancer. To support this development, improved diagnostic approaches are needed to better understand heterogenous tumor microenvironments and tumor biology that associate with variable treatment response patterns. We have hypothesized that the tumor-immune microenvironment (TIME) plays a critical role in treatment resistance. In this study we evaluated TIME signatures of treatment response and resistance utilizing novel, integrated technological tools to identify response patterns and enable precision sampling for comparative cellular and molecular analysis.

Methods Thirty patients with newly diagnosed, locally advanced, high-risk, primary prostate cancer underwent ^{18}F-DCFPyL-PSMA PET/MRI with multiparametric MRI scans followed by 3 cycles of chemohormonal therapy (NCT03358563). Patients then underwent repeat PSMA PET/MRI prior to prostatectomy and the scans were used to categorize lesions as complete response(CR), partial response(PR), no response(NR) or normal tissue, respectively. MRI scans were used to print a 3D-mold of the prostate to allow microdissection of regions of interest from the resected prostate. For each patient, cellular infiltrates were analyzed by flow cytometry in 3 to 5 prostate tissue specimens including a normal area and matched bone marrow and blood specimens collected at the time of prostatectomy. Statistical analysis was performed with One-way ANOVA with Tukey-correction.

Results The frequency of tissue-infiltrating $CD8^+$ T cells in the total $CD45^+$ infiltrate was highest in both normal and CR areas and was significantly reduced in PR area vs CR ($p<0.05$). Similarly, significant reduction was found in $CXCR3^+CD8^+$, $CD4^+FoxP3^+$ and $CD103^+CD8^+$T cell frequencies in PR versus normal tissue areas ($p<0.05$, $p<0.05$, and $p=0.05$, respectively). Meanwhile, the frequency of $CXCR3^+CD8^+$ T cells was highest and significantly elevated in CR vs normal tissue. Furthermore, we have observed tendencies of reduced $CCR6^+$, $CXCR5^+$, $CCR4^+$ $CD8^+$T cells in PR vs CR lesions, meanwhile those frequencies remained higher in normal and CR areas. Next, we are integrating analysis of myeloid TIME subsets and transcriptomic analysis of sorted $CD4^+$, $CD8^+$ and $CD11b/CD14^+$ cells to further dissect patterns of therapeutic response in our study cohort.

Conclusions In conclusion, PSMA/PET MRI and 3D molds enables precision sampling of tumor tissue associated with differential therapeutic response patterns. Comparison of distinct lesions in the prostate identified differences in the TIME infiltrates that associate with complete radiologic responses. These observations identify targetable biological mechanisms to improve tumor response and potentially cure in high-risk prostate cancer.

Trial Registration NCT03358563; NCI-2017–02428 (Registry Identifier) (REGISTRY: NCI Trial ID)
Ethics Approval University of Wisconsin Institutional Review Board UW17009 #2017–0606

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