The genomic-transcriptomic landscape of high-risk localized prostate cancer in the Genomic Umbrella Neoadjuvant Study

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Background

High-risk localized prostate cancer (HRLPC) frequently recurs after definitive therapy. Neoadjuvant androgen deprivation therapy plus androgen receptor (AR) pathway inhibition enhances pathologic response compared to monotherapy, yet complete response rates remain < 8% — poor compared to other cancers. Precision therapy guided by genomic biomarkers, e.g. homologous recombination repair defects or microsatellite instability (MSI), may improve outcomes. To deepen molecular insight into HRLPC, we analyzed genomic and transcriptomic data from the Genomic-biomarker-selected Umbrella Neoadjuvant Study (GUNS; NCT04812366), an adaptive, multi-center phase-II trial testing biomarker-targeted neoadjuvant combinations in HRLPC.

Methods

From September 2021 to March 2025, GUNS enrolled 151 patients at UBC, Vancouver, or UHN, Toronto. Diagnostic tumor biopsies underwent Tempus' 648-gene DNA sequencing (xT) and whole-transcriptome RNA-seq, plus PTEN immunohistochemistry. GUNS data were compared to publicly available MSK-IMPACT and TCGA data from prostate cancer (PC) stratified by risk/stage. PC subtype (PCS) classification, single-sample gene set enrichment analysis (ssGSEA), and unsupervised hierarchical clustering (UHC) were applied to RNA-seq data. Generalized linear modeling followed by GSEA was performed to relate gene expression to genomic alterations. Fisher's exact test, Kruskal-Wallis or Wilcoxon rank-sum test, and Pearson correlation were used to test for associations between factors/variables.

Results

GUNS comprised 76% grade group 5 and 46% prostate-specific antigen ≥ 20 ng/mL. Intraductal carcinoma (IDC), a poor prognosticator, was observed in 40% of patients. Tempus xT was successful for 129/151 and matching RNA-seq for 97/129 patients. ETS gene fusions (36%), especially *TMPRSS2-ERG* (30%), and *FOXA1* (23%), *TP53* (16%), *SPOP* (14%), and *PTEN* (13%) alterations were the most frequent reportable genomic alterations. Associations between genomics and clinical factors were identified; combination of an ETS fusion with either a *TP53* or *PTEN* alteration was strongly associated with IDC. The overall tumor mutational burden of HRLPC was more consistent with metastatic PC than with lower-risk localized PC, and HRLPC in both GUNS and TCGA was enriched for the unfavorable, metastatic-enriched luminal PCS1 transcriptomic subtype compared to low/intermediate-risk PC. UHC based on RNA-seq ssGSEA roughly aligned with PCS luminal/basal subtypes but revealed greater heterogeneity than three subtypes and demonstrated strong associations with genomics (ETS fusions, *SPOP*, and *PTEN*). Moreover, ETS fusions were associated with lower AR-signaling, E2F-target, and cell-cycle/proliferation gene expression than were *SPOP* or *FOXA1* mutations. MSI-high tumors had distinct genomic and transcriptomic profiles and were immunologically enriched, consistent with being candidates for immunotherapy.

Conclusions

HRLPC molecularly resembles metastatic PC more than it resembles low/intermediate-risk PC, emphasizing its clinical urgency. Genomic alterations in GUNS were associated with transcriptomic and clinical features, with the combination of an ETS fusion and *TP53* or *PTEN* alteration being notable for a strong association with IDC. MSI-high tumors were genomically and transcriptomically distinct and immune-enriched, warranting continued investigation of immunotherapy to target these tumors.

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