patients had a continued cCR at last follow up. Among non-operative patients, 18 (49%) had no late GI toxicities and 0 had late G3/4 GI toxicities. In the 42 patients with a partial CR, 60% underwent low anterior resection, 29% underwent abdominoperineal resection, and 9.5% underwent transanal excision or proctectomy. Seven of 85 patients had local regrowth at a median of 8.5 mos (range 2.3-12 mos) after SCR-CH. Six cases occurred in non-operative patients requiring salvage surgery at a median of 6.0 (range 4.8-15) mos after completion of SCR-CH. Four (4/90, 4.4%) patients developed metastatic disease, all of whom had an initial partial CR and had undergone surgery.

Conclusion: Our preliminary data show that SCR-CH can result in cCR and organ preservation in patients with locally advanced and/or low-lying rectal cancer with acceptable GI toxicity. Further follow-up is required to evaluate the durability of response and toxicity.

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Comparative Transcriptomics of Prostate Tumor Show Enrichment of Biologically Distinct Pathways Among Men of African Origin

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Purpose/Objective(s): Native African men (NAM) experience disproportionate burden of prostate cancer (PCa) and have higher mortality rates compared to European American men (EAM). While socioeconomic status has been implicated as a driver of this disparity, little is known about the genomic mechanisms that predisposes men of African origin to higher PCa incidence and mortality. To understand biological factors that contribute to this disparity, we performed a comparative genomic analysis across race groups.

Materials/Methods: Tumor samples were identified from men with PCa who presented for radiotherapy between 2003 and 2017. Formalin-fixed paraffin-embedded specimens (FFPE) were obtained from two institutions (US and Ghana) and were centrally reviewed for Gleason score grading. Samples were run on an HTG EdgeSeq Processor using the HTG EdgeSeq customized probe sets. Median gene expressions were compared using Kruskal Wallis test, and p values were adjusted using false discovery rate (FDR). Gene set enrichment analysis (GSEA) using molecular signatures database (MSigDB), was used to evaluate pathway differences based on race using HALLMARK gene sets.

Results: The entire study cohort included 1888 patients, of which ~10% had available and adequate tumor tissue, and passed the rigorous quality control metric for RNA quality and integrity; 180 (106-NAM, 46-EAM, 28-African American [AAM]) patients with localized PCa were included. As expected, 56% of EAM tumors had *TMPRSS2-ERG* fusion (ERG^{POS}), whereas 24% AAM and 17% NAM were ERG^{POS}. *SPINK1* expression ($SPKIN1^{POS}$) was four-fold higher in NAM than in EAM (22% vs 5%, p = 0.0001). The double negative molecular subtype (ERG^{NEG}/$SPKIN1^{NEG}$) was predominant in NAM and AAM compared with EAM, particularly in the higher-Grade Groups, (Grade Groups; GG 3-5: 64% vs. 77% vs. 33%; p = 0.003). A composite mean expression score (AR-activity score) of major canonical AR-target genes *was* compared across race group with NAM having lowest AR-activity score compared to both EAM and AAM, p = 0.0003. However, no race differences in AR expression were observed (p = 0.49). When compared to EAM, NAM exhibited significant differences in gene expression of several immune-regulatory, NFκB, DNA-damage repair, and Apoptosis pathways. In an unsupervised GSEA, selectively upregulated genes among NAM were also enriched for JAK-STAT, NFκB-dependent TNFα signaling, and immune-regulatory pathways.

Conclusion: Significant transcriptomic differences were observed in NAM compared to their European counterparts with enrichment of multiple immune-regulatory, DNA damage repair, TNFα signaling, and JAK-STAT pathways. Genomically distinct tumors that manifest lower AR activity in NAM can be used to understand distinct biological features that predispose men of African descent to aggressive PCa and may inform the use of combined immuno-radiotherapy and AR-targeted therapies.

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Single-nucleus RNA-seq and Spatial Transcriptomics of Archival Primary Pancreatic Ductal Adenocarcinoma Uncovers Multi-compartment Intratumoral Heterogeneity Associated with Neoadjuvant Chemoradiotherapy

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Purpose/Objective(s): Pancreatic ductal adenocarcinoma (PDAC) remains a treatment-refractory disease and existing molecular subtypes do not inform clinical decisions. Previously identified bulk transcriptomic subtypes of PDAC were often unintentionally driven by "contaminating" stroma. RNA extraction from pancreatic tissue is difficult and prior single-cell RNA-seq efforts have been limited by suboptimal dissociation/RNA quality and poor performance in the setting of neoadjuvant treatment. We developed a robust single-nucleus RNA-seq (sNuc-seq) technique compatible with frozen archival PDAC specimens.

Materials/Methods: Single nuclei suspensions were extracted from frozen archival primary PDAC specimens (n = 27) derived from patients who underwent surgical resection with or without neoadjuvant chemo-radiotherapy (CRT). Approximately 170,000 nuclei were processed with gene expression software and gene expression libraries were sequenced.

Results: Distinct nuclei clusters with gene expression profiles/inferred copy number aberrations consistent with malignant and non-malignant cell types were identified with proportions similar to corresponding multiplexed ion beam imaging. Neoplastic cells featured eight distinct transcriptional topics characterized by developmental (epithelial, mesenchymal, endoderm progenitor, neural progenitor) and environmental (anabolic, catabolic, cycling, hypoxic) programs. CAFs exhibited five different transcriptional topics (activated/desmoplastic, myofibroblast, neurogenic, osteochondral, developmental). Differential gene expression and gene set enrichment analyses demonstrated that CRT was associated with an enrichment in myogenic programs in CAFs, activation pathways in immune cells, and type I/II interferon response in malignant cells. CRT was also associated with a depletion in pancreatic developmental programs within malignant cells. Treated $CD8^+$ T cells showed an upregulation in *IL7R, TCF7, STAT4,* and *SLAMF6* associated with memory, activation, cell survival and response to checkpoint inhibitors while treatment-naïve $CD8^+$ T cells exhibited higher expression of exhaustion markers *HAVCR2* and *ENTPD1* suggesting that checkpoint inhibitors may provide benefit in the