Using Radiogenomics to Characterize MRI-Guided Prostate Cancer Biopsy Heterogeneity

Radka Stoyanova[1], Alan Pollack[1], Nicholas Erho[2], Charles Lynne[3], Lucia Lam[2], Christine Buerki[2], Sakhi Abraham[1], Merce Jorda[4], Olexandr Kryvenko[4], Matthew Abramowitz[1], Elai Davicioni[2], and Adrian Ishkanian[1]

[1]Radiation Oncology, University of Miami, Miami, Florida, United States, [2]GenomeDx Biosciences, Vancouver, British Columbia, Canada, [3]Urology, University of Miami, Miami, Florida, United States, [4]Pathology, University of Miami, Miami, Florida, United States

Target Audience: Physicians and scientists interested in prostate imaging research.

Purpose: Current clinicopathological factors explain just a fraction of the observed heterogeneity in prostate cancer patient outcome. There are no tests that differentiate patients who will be cured by local therapy alone vs patients who need combined modality treatments due to predicted local or systematic resistance, or identify patients with indolent cancers who can be triaged to active surveillance. Prostate cancer tumor multi-focality and genetic heterogeneity can lead to diagnostic prostate biopsy sampling bias. In this study we address the question whether quantitative imaging data from multiparametric (MP)-MRI are associated with gene expression characteristics (radiogenomics) and how these in turn relate to Gleason score (GS) and intra-patient versus inter-patient genomic heterogeneity.

Methods: MP-MRI is acquired on Siemens (Erlangen Germany) 3T Trio System (n=3) and GE (Waukesha, WI) 3T Discovery MR750 System (n=3). Images included: (i) Axial T2w-MRI of the pelvis: resolution 1.25×1.25×2.5 mm; Field of View (FOV): 320×320 mm; slice thickness=2.5mm (no gap); 72 slices; (ii) Dynamic Contrast Enhanced MRI (DCE-MRI)–12 series of T1w at 30-34s temporal resolution; and (iii) DWI - Single-shot echo-planar imaging was performed utilizing the diffusion-module and fat-suppression pulses. Water diffusion in three directions was measured by using *b* values of 50, 500, and 1000 s/mm^2. Apparent Diffusion Coefficient (ADC) maps were automatically calculated utilizing imaging console software. Custom software was used to define regionally distinct habitats based on MP-MRI in the prostate using spatially explicit quantitative image analysis. This information was used to direct MP-MRI-ultrasound fusion biopsies (Artemis system^{TM}, Eigen, Sun Valley, CA). Images were loaded in ProFuse (Eigen) and regions of interest were annotated (**Figure 1**). The MRI data, together with prostate and target contours were loaded in the Artemis^{TM} system. During each biopsy, the operator could visualize the ultrasound volume in real time on screen. Image refresh rates on the order of 100 milliseconds allow real time motion correction capability after the acquisition of the 3-D volume. RNA from habitat-directed prostate biopsies was extracted and analyzed using a high density transcriptome-wide microarray that assesses the expression of over 1.4 RNA probes (Affymetrix HuEx ST 1.0 arrays), including ~22,000 known protein-coding genes as well as many thousands of non-coding RNAs. Each habitat was further characterized with multiple quantitative imaging on MP-MRI.

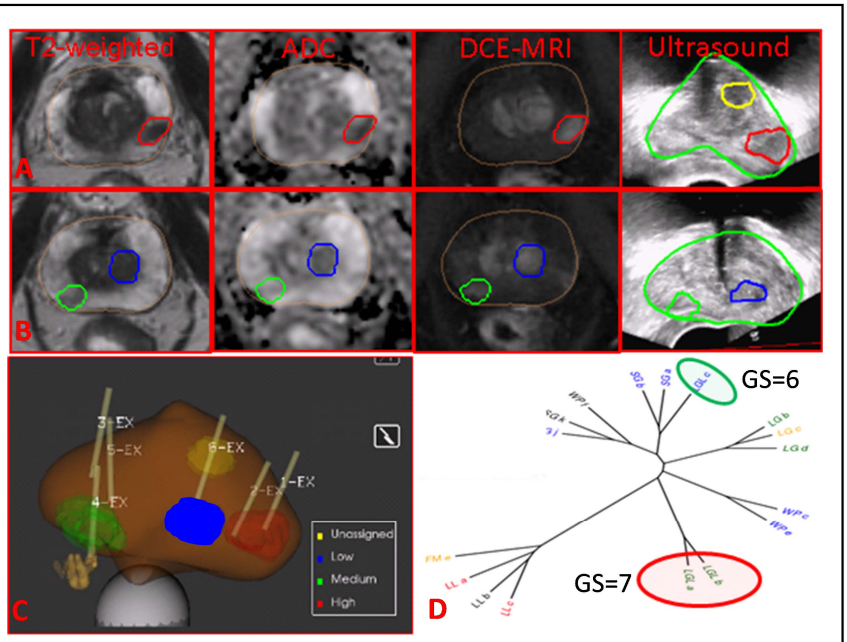

Figure 1: **(A, B)** Using custom software the joined probability for cancer is identified in T2-weighted MRI, Apparent Diffusion Coefficient (ADC) and Dynamic Contrast Enhanced MRI of the patients prostate. Three distinct habitats are identified with high (red), medium (green) and low (blue) probability of cancer. The targets are transferred to real-time ultrasound biopsy system after non-rigid fusion of the prostate boundaries on MRI and ultrasound; (**C**) Schematic representation of the prostate and target volumes. Yellow lines indicate biopsy needle tracks (1 needle in green, 2 in red and 1 in blue); and (**D**) Genomic cluster analysis of the three biopsies, containing tumor from the patient shows Gleason Score (GS) 7 in 2/2 biopsies from the high-risk region and GS6 in 1/1 biopsies in the medium risk region.

Results: Directed biopsies were performed on 17 habitats from 6 patients using MRI-ultrasound fusion. Each biopsy location was characterized with 51 radiographic features (intensity, volume, perfusion, and diffusion parameters). High quality genomic data was derived from 17 (100%) biopsies and clustered by patient origin. Genomics features with insignificant expression values (<0.25) and interquartile range <0.5 were filtered. The remaining ~2K features clustered by patient origin. Using only prostate cancer related genomic features for hierarchical clustering, samples clustered by Gleason score (GS), indicating these biopsies contain prognostic signal. Similarly, when Principal Component Analysis was performed on 51 imaging features, the primary source of variance segregated the samples into high (≥7) and low (6) GS (**Figure 2**). Pearson's correlation analysis identified 152 genomic features that were highly associated with the imaging features ($|r| > 0.7$). Furthermore, genomic features were found to be significantly enriched for prostate cancer related pathways ($p < 0.05$), representing a potential biologically meaningful link between imaging and genomic data.

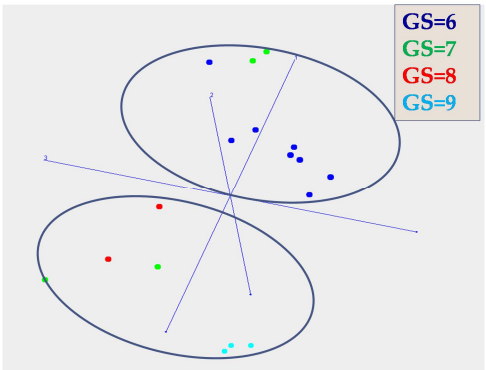

Figure 2: Display of biopsy samples after Principal Component Analysis of quantitative imaging features, associated with the location of targeted biopsies. Samples cluster into high (≥7) and low (6) Gleason Score.

Conclusions: Quantitative MP-MRI-targeted diagnostic biopsies can potentially improve risk classification by directing pathological and genomic analysis to highest risk index lesions. This is the first demonstration of a link between quantitative imaging features (radiomics) with genomic features in MRI-directed prostate biopsies.