Molecular Dissection of Magnetic Resonance Imaging Visible and Invisible Prostate Cancer

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Background: Up to 20% of patients with negative multiparametric magnetic resonance imaging (mpMRI) harbor high grade prostate cancer. In this study, we sought to characterize and compare the molecular profiles of multiparametric magnetic resonance imaging (mpMRI) visible and invisible prostate cancer to elucidate the molecular basis of cancer visibility on mpMRI.

Methods: Patients who underwent mpMRI prior to radical prostatectomy were identified for this IRB-approved study. mpMRI for each patient was re-reviewed by a radiologist with expertise in prostate mpMRI and histopathology was re-reviewed by a genitourinary pathologist. Whole-mount histopathology was co-registered with axial mpMRI images. DNA and RNA were co-isolated from all tumor foci pre-identified on formalin-fixed paraffin-embedded specimens. High depth, targeted DNA and RNA next generation sequencing was performed to characterize the molecular profile of each tumor focus using the Oncomine Comprehensive Panel (DNA) and a custom targeted RNAseq panel assessing prostate cancer relevant genes. A multigene RNAseq model was developed and validated to predict MRI visible prostate cancer.

Results: A total of 26 primary tumor foci from 10 patients were analyzed. The median number of prostate cancer foci was 3. Of the 14 (54%) invisible lesions on mpMRI, 5 (36%) were Gleason 3+4=7. We detected high-confidence prioritized genetic mutations in 54% (14/26) of tumor foci, 43% (6/14) of which were in mpMRI-invisible lesions. Additionally, 64% (9/14) of lesions exhibiting prioritized mutations were Gleason 7. Notable point mutations were in *APC, AR, ARID1B, ATM, ATRX, BRCA2, FAT1, MAP3K1, NF1, SPEN, SPOP, TP53,* and a frameshift mutation was detected in *SOX2.* A multiplex model, composed of 9 genes **(Figure)**, majority of which are involved in cellular organization and structure, was developed to predict MRI visible tumor with an AUC of 0.89. Validation of this model in an independent data set (n = 16) yielded an AUC of 0.88.

Conclusions: Prostate cancer lesions visible on mpMRI exhibited differential expression in cellular organization and structural genes. More work is needed to discern the significance of this model and mpMRI to predict prostate cancer oncological outcomes.

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