PD52-03: Multi-parametric magnetic resonance imaging (mpMRI) of multifocal prostate cancer unmasks intra-prostatic genomic heterogeneity and novel radio-genomic correlates

Results of the Smarter Prostate Interventions and Therapeutics (SPIRIT) study

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Disclosures

• No conflicts of interest
Introduction

• Multi-focal prostate cancer (PCa) exhibits genomic heterogeneity\textsuperscript{1,2}
  – Can confound selection of most appropriate management
• mpMRI interrogates whole gland, can improve diagnostic yields\textsuperscript{3}
• Radiomic features linked with specific genetic aberrations\textsuperscript{4}

**Objective:** To evaluate radio-genomic correlations between genome-wide copy-number aberration (CNA) and mpMRI in multi-focal PCa
Overview

Multi-focal Prostate Ca

High-Fidelity Co-Registration

Genomic Analysis

Radiomic Analysis

Novel Radio-Genomic Correlations
Methodology

1. Eligible men (n=35) underwent pre-operative mpMRI
2. Post-prostatectomy *ex vivo* mpMRI with fiducials
3. Axial, whole-mount tissue sections through whole gland
4. Fiducial-guided co-registration of mpMRI & histology
Methodology

5. Subset (n=8) with multi-focal PCa for genomic analysis

6. High-resolution segmentation of disease foci (pathologist)

7. Macro-dissection of foci for DNA extraction
Methodology

8. Multi-region genomic copy-number profiling
9. Bioinformatic and radiomic analysis
10. Radio-genomic correlative studies

## Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>TNM Pathologic Stage</th>
<th>Gleason Grade</th>
<th>Margin Status</th>
<th>BCR</th>
<th>Additional Treatment</th>
<th>Follow-Up Duration (months)</th>
<th>Status at Last Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pT2cN0</td>
<td>3+4</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>62</td>
<td>NED: PSA undetectable</td>
</tr>
<tr>
<td>2</td>
<td>pT3bN1</td>
<td>5+4+3</td>
<td>+</td>
<td>-</td>
<td>Adj. RT + ADT</td>
<td>29</td>
<td>Lost to FLUP: PSA undetectable on ADT</td>
</tr>
<tr>
<td>3</td>
<td>pT3bN0</td>
<td>3+4+5</td>
<td>-</td>
<td>+</td>
<td>Salvage RT</td>
<td>66</td>
<td>Well: BCR @ 29 months, rising PSA (0.55)</td>
</tr>
<tr>
<td>4</td>
<td>pT3aN0</td>
<td>3+4</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>66</td>
<td>NED: PSA undetectable</td>
</tr>
<tr>
<td>5</td>
<td>pT2cN0</td>
<td>3+4</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>62</td>
<td>NED: PSA undetectable</td>
</tr>
<tr>
<td>6</td>
<td>pT3bN0</td>
<td>3+4+5</td>
<td>+</td>
<td>-</td>
<td>Adj. RT</td>
<td>58</td>
<td>NED: PSA undetectable</td>
</tr>
<tr>
<td>7</td>
<td>pT3aN0</td>
<td>4+3</td>
<td>-</td>
<td>+</td>
<td>ADT → Apalutamide</td>
<td>48</td>
<td>Alive with disease, PSA rise immediately post-op → ADT, CRPC @ 38 mo.</td>
</tr>
<tr>
<td>8</td>
<td>pT3bN0</td>
<td>4+3+5</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>46</td>
<td>Well, slowly-rising PSA since 18 mo. (0.12)</td>
</tr>
</tbody>
</table>

**TNM** – Tumour, node, metastasis staging system; **PSA**, prostate-specific antigen; **NED**, no evidence of disease; **FLUP**, follow-up; **BCR**, biochemical recurrence; **CRPC**, castrate-resistant prostate cancer.
Results: Recurrent (>1 patient) CNAs

- Broad range of loci affected
- Most common AMP/DEL on chr. 1p, 6q, 7p, 7q, 8p, and 18q
  - EGFR, BRAF, CHD1, and STC1
- Highly-recurrent (≥4 patients): DEL of cytobands 8p21 and 18q21
  - NKX3-1 and PPP2R2A
- Findings consistent with prior multi-region genomic studies\(^1,2\)

6-point scale: 0=benign, 1=3+3, 2=3+4, 3=4+3, 4=4+4, 5=4+5, 6=5+4

Results: Burden of CNAs

- CNA burden = loci length x copy number $\Delta$
- CNA burden correlates with median ADC
- CNA burden & ADC also correlate with Gleason Score
Results: Clustering Analysis

- Foci cluster by ADC & CNA:
  - Low-grade/Benign: CNA low, ADC high
  - Higher-grade: CNA high, ADC low

- Gleason 3+4 & 4+3:
  - Some intermediate
  - Some cluster with low- or higher-grade

Gleason <3+4, PIN, N

Gleason ≥4+3

CNA Burden
CNA Length
CNA Number
CNA Gene Rate
High-Frequency CNA Count
Mean ADC
Median ADC
10th Percentile ADC
1st Percentile ADC
Minimum ADC

Gleason:
3+3
3+4
4+3
4+5
5+4
Benign

Low
High
Row Z-Score
Discussion

Limitations:
- Small sample size, exploratory study
- Potential of overfitting with multiple comparisons

Strengths:
- Whole-mount with high-fidelity, fiducial-guided co-registration
- Both central/transition & peripheral zone lesions sampled
Conclusions

• Novel correlation of low ADC with high genome-wide CNA burden
  – Assoc. with genomic instability & worse prognosis\textsuperscript{1,2}

• Proof-of-principle of our radio-genomic analysis platform

Future Work

• Expansion cohort to increase sample size
  – Additional radio-genomic correlations: PSMA-PET & whole-genome DNA methylation

• ADC radiomics to supplement mpMRI interpretation criteria

\textsuperscript{1.} Hieronymus H. Proc Natl Acad Sci U S A. 2014;111(30):11139-44
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