Low-risk versus High-risk Prostate Cancer on Multiparametric MRI

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Risk Stratification

- Biological aggressiveness of prostate cancer and risk of disease progression have management implications
- Clinical classification schemes are based on a combination of:
  - PSA level (normal < 4.0 ng/mL)
  - Gleason score, and
  - T tumor stage
- Factors to select active surveillance vs. radical treatment include:
  - Serum PSA
  - PSA density
  - Gleason score
  - % biopsy core involvement
  - Results of DRE
Risk Stratification

- **T stage** (size of the tumor on digital rectal exam and/or ultrasound)
  - **T1c**  Tumor identified by needle biopsy (not palpable or seen on imaging)
  - **T2a**  Tumor involves 1/2 of one lobe or less
  - **T2b**  Tumor involves more than 1/2 of one lobe but not both lobes
  - **T2c**  Tumor involves both lobes
  - **T3**  Tumor extends outside the prostate
    - **T3a**  Extracapsular extension
    - **T3b**  Seminal vesicle invasion
  - **T4**  Invasion into nearby structures (membranous urethra, bladder, rectum, pelvic wall)

![Diagram of prostate with T1, T2, T3, T4 stages]

Cancer confined to the prostate  
Cancer extends outside of the prostate

[Primer for using PI-RADS v2.1 for Prostate MRI | American College of Radiology (acr.org)]
Prognostic Gleason Grade Grouping - GG

Gleason grade groups accurately reflect prognosis (JHU - ISUP):

- G score 3+3=6 (well-differentiated) | prognostic GG 1
- G score 3+4=7 (moderately differentiated) | prognostic GG 2
- G score 4+3=7 (mod-poorly differentiated) | prognostic GG 3
- G score 4+4=8 (poorly differentiated) | prognostic GG 4
- G score 4+5=9, 5+4=9, 5+5=10 (undifferentiated) | prognostic GG 5

5-year biochemical free survival rates:

<table>
<thead>
<tr>
<th>G Score</th>
<th>3+3</th>
<th>3+4</th>
<th>4+3</th>
<th>8</th>
<th>9-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Biopsy</td>
<td>94.6%</td>
<td>82.7%</td>
<td>65.1%</td>
<td>63.1%</td>
<td>34.5%</td>
</tr>
<tr>
<td>RP</td>
<td>96.6%</td>
<td>88.1%</td>
<td>69.7%</td>
<td>63.7%</td>
<td>34.5%</td>
</tr>
</tbody>
</table>

p < 0.001

BJU Int. 2013 May; 111(5): 753–760.
### NCCN National Comprehensive Cancer Network

<table>
<thead>
<tr>
<th>RISK</th>
<th>LOW</th>
<th>INTERMEDIATE</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ng/mL</td>
<td>≤10</td>
<td>&gt; 10 and ≤ 20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Gleason score</td>
<td>2–6</td>
<td>7</td>
<td>8–10</td>
</tr>
<tr>
<td>T Stage</td>
<td>T1-T2a not very low-risk</td>
<td>T2b or T2c not low-risk</td>
<td>T3a not very high risk</td>
</tr>
<tr>
<td></td>
<td><strong>very-low risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3 cores+ and ≤50% cancer in each core</td>
<td></td>
<td><strong>very high-risk</strong> T3b-4</td>
</tr>
</tbody>
</table>
### Biomarkers

<table>
<thead>
<tr>
<th>Serum Plasma Blood</th>
<th>1st Biopsy</th>
<th>Repeat Biopsy</th>
<th>Aggressiveness Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (PSAD) PHI 4K Score</td>
<td>PSA (PSAD) PHI 4K Score</td>
<td>PSA (PSAD) N-Glycan CTCs</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>PCA3 ExoDX</td>
<td>PCA3 TMPRSS2-ERG Mi-prostate score</td>
<td>Mi-prostate score GCNT1 gene</td>
</tr>
<tr>
<td>Tissue</td>
<td>N/A</td>
<td>N/A</td>
<td>OncotypeDX ProMark Prolaris Decipher GC</td>
</tr>
</tbody>
</table>

**PSA** -- Kallikrein-3 enzyme  
**PHI** -- ((2)proPSA/fPSA) vPSA  
**4K** -- 4 Kallikreins: fPSA, tPSA, intact PSA + kallikrein-lime peptidase 2 (hK2)  
**PCA3** -- Prostate Cancer Antigen-3 ncRNA, PCA3 Score PCA3/PSA mRNA ratio x 1000  
**Mi-Prostate** -- Plasma PSA + urinary PCA3 + T2-ERG  
**TMPRSS2:ERG** -- Transmembrane serine protease (TMPRSS2) and ETS transcription factor (ERG) gene fusion (TMPRSS2-ERG fusion gene is the most frequent, present in 40% - 80% of prostate cancers in humans)  
**ExoDx** -- Genomic-based test returns a risk score that determines a patient’s risk of clinically significant prostate cancer (Gleason Score ≥7) on prostate biopsy  
**Prolaris** -- Genetic test measures tumor cell growth with 10-year disease specific mortality risk  
**Decipher** -- 22-gene genomic classifier (GC) for prognostication after RP into disease phenotypes
Guidelines for Active Surveillance (AS)
National Comprehensive Cancer Network

- 23% to 42% of all screen-detected cancers in the US are over-treated
- PSA detection responsible for up to 6.9 years of lead-time bias
  - Range: 12.3 years in a 55-year-old to 6 years in a 75-year-old men
- Who should be recommended for active surveillance:
  - men with very low–risk prostate cancer and life expectancy < 20 years
    or those with low-risk cancer and life expectancy estimated < 10 years
- Epstein et al (JHU) introduced clinical criteria to predict pathologically “insignificant” prostate cancer:
  - clinical stage T1c, biopsy Gleason score ≤ 6, presence of disease in < 3 biopsy cores, ≤ 50% prostate cancer involvement in any core, and PSA density < 0.15 ng/mL/g (PSAD = tPSA / gland volume)
  - caveat - 8% of cancers that qualified as insignificant using the Epstein criteria were not organ-confined based on postsurgical findings
Prediction of Insignificant Disease

Among cancers predicted to be insignificant (≤ 0.5cm³, organ confined, and Gleason score ≤ 6) in Caucasian men based on biopsy:

- 29.9% cases (original Epstein criteria) and 27% cases (modified Epstein criteria unilateral +cores only) had significant cancer at RP

Among cancers predicted insignificant in AA men:

- 54.1% cases using the original and 51.6% cases using the modified Epstein criteria were misclassified
- Dominant anterior tumors were seen in 44% AA men and 28.5% Caucasian men
Role of mpMRI

- **19 - 34%** men with low-grade disease on initial biopsy have Gleason upgrading on repeat random extended biopsy, suggesting under-sampling by the initial biopsy.
- MRI has a role in ensuring that the most aggressive tumor is sampled (MR-guided biopsy).
- MRI localizes tumor in atypical locations, i.e. anterior TZ and apex, or small volume aggressive tumors in the peripheral zone.
Utility of mpMRI in the risk stratification of men with grade group 1 PCa on active surveillance

Mamawala et al, JHU 2018

Upgrading to Grade Group ≥ 2

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Follow-up since diagnosis (Years)</th>
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<tbody>
<tr>
<td>Negative mpMRI 225</td>
<td>201 131 85 55 31</td>
</tr>
<tr>
<td>Pre-mpMRI 669</td>
<td>623 442 339 277 226</td>
</tr>
<tr>
<td>PI-RADS 3-5 207</td>
<td>153 68 37 13 3</td>
</tr>
</tbody>
</table>

- Negative mpMRI
- Pre-mpMRI
- PI-RADS 3-5
Correlation of PI-RADS score of regions of interest (ROIs) on mpMRI with targeted biopsy (bx) findings (benign, Gleason score or GS 6, GS ≥7) in the AS cohort (A), confirmatory biopsy cohort (B) and targeted biopsy cohort (C).
The prevalence of PI-RADS 3 index lesion in the diagnostic work-up is significant, varying between 1 in 3 (32%) to 1 in 5 (22%) men, depending on patient cohort of first biopsies, previously negative biopsies, and active surveillance biopsies.
PI-RADS 3 Lesions in PZ

(A) axial T2-weighted image, (B) high-b-value DWI, (C) early DCE time-point, (D) ADC map

Gleason 3+4 tumor (red arrows)

No prostate cancer (blue arrows).

Schoots IG. *Transl Androl Urol* 2018;7(1):70-82
PI-RADS 3 Lesions in TZ

(A) axial T2-weighted image, (B) high-b-value DWI, (C) early DCE time-point, (D) ADC map

Gleason 3+4 tumor (red arrows)

No prostate cancer (blue arrows).
PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway

For 100 biopsy-naïve men

PI-RADS 1-2

About 33% (26-41) have PI-RADS 1-2 scans

- No cancer/benign
  74% (69-81)

<table>
<thead>
<tr>
<th>ISUP=1: 18% (14-24)</th>
<th>ISUP=2: 8% (6-12)</th>
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</table>

100 biopsy naïve men with PI-RADS 1-2 MRI undergoing systematic biopsies only

- Insignificant cancers (ISUP grade 1) detected by MRI-directed and systematic biopsy.
- Proportion of insignificant cancers (ISUP group 1) found by systematic biopsy cores.
- Significant cancers (ISUP grade ≥ 2) detected by MRI-directed and systematic biopsy.
- Proportion of significant cancers (ISUP grade ≥ 2) found by systematic biopsy; undetected by MRI-directed biopsies.

PI-RADS 3-5

About 67% (57-74) have PI-RADS 3-5 scans

- No cancer/benign
  29% (23-35)

<table>
<thead>
<tr>
<th>ISUP=1: 21% (17-27)</th>
<th>ISUP=2: 4% (2-7)</th>
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</table>

100 biopsy naïve men with PI-RADS 3-5 MRI undergoing MRI-directed and systematic biopsy

* ISUP=2: 44% (39-50)
Case 1: Active Surveillance (AS)

71M followed in AS for >10 years. Multiple + cores **G3+3 (GG1)** from the location of the tumor visualized by MRI. Although his disease was reclassified owing to the number of biopsy cores involved with cancer (3), he elected to remain on AS because of his age, comorbidities, and low grade cancer.

**PI-RADS:**
Size 12 mm
T2W score 3
DWI - ADC $0.783 \times 10^{-3}$ mm$^2$/s – score 4
DCE positive
* MRSI positive
Overall Score 4

Mullins JK et al. BJU Int. Jun 2013; 111(7): 1037–1045
Case 2: Confirmatory MRI – Not eligible for AS

60M considering AS
G3+3 TRUS-BX

MRI detected anterior TZ tumor
G3+4 (GG2) on MR-TRUS fusion biopsy

PI-RADS:
Size 21 mm
T2W score 5
DWI - ADC $0.650 \times 10^{-3} \text{ mm}^2/\text{s}$ – score 5
DCE positive
Overall Score 5
Case 3: Candidate for AS
71M with PSA 4.5 ng/mL increased from 3.0, DRE negative. TRUS BX: 1 core G3+3 (GG1) 5% right base, HPIN right apex, and atypia left apex (T1c). Patient is a candidate for AS, with very low risk prostate cancer. Patient is anxious and opts for MRI before AS.
Case 3: Candidate for AS
71M with PSA 4.5 ng/mL increased from 3.0, DRE negative. TRUS BX: 1 core G3+3 (GG1) 5% right base, HPIN right apex, and atypia left apex (T1c). Patient is a candidate for AS, with very low risk prostate cancer. Patient is anxious and opts for MRI before AS.
Case 3: (cont.)
Robotic radical prostatectomy, final pathology multifocal disease with a dominant nodule Gleason 4+3 (GG3) adenocarcinoma in the Left Mid PZ postero-lateral with extraprostatic extension, non-focal pT3a pN0 pM0.

Even cancer located in PZ, that is accessible to TRUS biopsy, may be undetected due to sampling omission.
Case 4: Missed Clinically Significant Cancer on TRUS
71M, PSA 4.83 ng/mL and multiple negative TRUS-guided biopsies

MR-targeted biopsy: Gleason score 4+4=8 (GG4) involving 2 cores (30%, 40%)
Case 5: Anterior Transition Zone Cancer
65M with slowly rising PSA over 4 years from 2.98 to 6.95 ng/mL with a negative TRUS biopsy

**PIRADS:**
- Size 16 mm
- T2W score 5
- DWI - ADC $0.900 \times 10^{-3}$ mm$^2$/s score 5
- DCE positive
- Overall Score 5

**Targeted biopsy:**
- Gleason score 3+3=6 (GG1) in 3 cores (100%, 40%, 5%)
Case 6: Upgrade on Targeted Biopsy
60M, PSA 4.5 ng/mL. Negative prior TRUS biopsy

Standard biopsy:
GLEASON SCORE 3+4=7 (GG 2)
INVOLVING 10% OF 1 of 2 CORES
(20% GLEASON PATTERN 4)

Targeted biopsy:
GLEASON SCORE 4+3=7 (GG 3)
INVOLVING 4 of 4 CORES (100%, 70%, 30%, 20%).
Extracapsular tumor extension?

Left Mid lateral gland extra-cap?
The Index Nodule

Nodule volume: 1.7 cc
DOMINANT NODULE:
Left, posterolateral, mid, Gleason 4+3=7 with ductal features
Pathology

Organ confined
Extracapsular tumor extension?

Right Mid lateral gland extra-capsular tumor T3a?
Extra-prostatic extension Gleason 3+4=7
Who cares about minimal extra-prostatic disease?

- Minimal **microscopic** extracapsular prostate cancer extension is **undetectable** on mpMRI!
- Accuracy of local staging T2 vs. T3
  - high specificity 91%
  - variable sensitivity 57%
- “Risk-tailored” approach
- **Avoid positive surgical margin** - intraoperative frozen section at index nodule
- T3 disease is directly related to the index nodule’s size and aggressiveness

*de Rooij M et al. European Urology 2015*
*Padhani AR et al. European Urology 2015*
*Petralia G et al. Radiology 2015*
Established Extraprostatic Extension T3a
MRI grade 3 was associated with a 66% positive predictive value and 82% negative predictive value for defining pathologic EPE of prostate cancer.
Seminal Vesicle Invasion T3b?

MRI SVI False +

MRI SVI False -
Case 7: Prostate Cancer in Central Zone

59M PSA < 3.0 ng/mL, RP Gleason 4 + 3 (GG3) prostate cancer in the left base with extra-prostatic extension and left seminal vesicle invasion.

Cancers originating in the CZ are uncommon < 5% but significantly more aggressive, with greater risk of ECE, seminal vesicle invasion and positive surgical margins.

Classic Seminal Vesicle Invasion
Case 8: Distal Apex Nodule
68M, PSA 13.3 ng/mL - RP positive margins at apex

Biopsy: RIGHT APEX: GLEASON SCORE 3+5=8 (GG 4) 90% OF ONE CORE, GLEASON SCORE 3+4=7 (10% GLEASON PATTERN 4) 60% OF ONE CORE.

Radical prostatectomy: GLEASON SCORE, DOMINANT NODULE: 3+4=7 (GG2) 40% PATTERN 4 (TERTIARY PATTERN 5)

**Margin:** RIGHT, ANTERIOR, APEX; FOCAL; POSITIVE IN AN AREA OF INTRAPROSTATIC INCISION
Case 9: Prostate Cancer at Distal Apex and Urethra

59 M pre-op PSA 10.1 ng/mL
RP: dominant nodule with 3+4=7 (GG 2) disease at the apex with a **positive margin** at the left anterior apex.

Initial post-op PSA 4.2 ng/mL, rising to 6.5 ng/mL 2 months later, scheduled for PSMA-targeted $^{18}$F-DCFPyL PET-CT

Pre-op MRI
Post-RP PSMA PET-CT

Pre-op MRI
Post-RP Trans-perineal US and Biopsy

Adenocarcinoma
Gleason score
3+4=7 (GG 2)
Case 10: Very High Risk Large Volume Cancer

63M presented with hematuria and PSA 56.7 ng/mL; PHI: 215
BLADDER TUMOR RESECTION
TRANSURETHRAL (TURBT)
Gleason 5+4 = 9 (GG5)
Metastatic, TX → ADT, after 2 years of ADT, he developed CRPC
SVI

Nodal Metastases
Bone metastases
Summary

- **Clinical risk**: age, race/ethnicity, family history
  - 1 in 6 men with prostate cancer has a hereditary genetic variant
  - With metastatic disease, survival of men with BRCA1 or BRCA2 variant is half of men with no genetic variant (16% more men develop metastases with BRCA at 5 years)
  - Lynch Syndrome (hereditary non-polyposis colorectal cancer, or HNPCC)

- DRE
- Histopathology - ISUP GG
- Biomarker-based risk
- **Imaging-based risk** + MR-guided biopsy

Important to incorporate imaging + clinical data

Standardization in image interpretation PI-RADS v2.1