Progress in Understanding the Pathology of Prostate Cancer

M. Scott Lucia, MD
Professor and Vice Chair of Anatomic Pathology
Chief of Genitourinary and Renal Pathology
Director, Prostate Diagnostic Laboratory
Dept. of Pathology
University of Colorado SOM

Disclosure: Genomic Health - consultant
Metastatic Potential = $p \times T$

$p$ = phenotype (biologic aggressiveness)
- Assessed by Gleason grade, biomarkers

$T$ = time
- Reflected by volume, stage
- Currently difficult to assess
# Role of Pathology

## Prostate Biopsy
- Establish a diagnosis
  - Cancer
  - BPH, inflammation
- Determine “aggressiveness”
  - Grade
  - Perineural invasion
  - Biomarkers
- Predict extent
  - Percent cores positive
  - Linear extent

## Prostatectomy
- Confirm diagnosis
- Determine “aggressiveness”
  - Grade
  - Perineural invasion
  - Vascular invasion
  - Biomarkers
- Determine extent
  - Stage
  - Volume
  - Margin status
Assessing the Aggressiveness of Prostate Cancer on Biopsy

- Histologic grade
- Perineural invasion
- Extraprostatic disease
- Biomarkers/molecular determinants
Assessing the Aggressiveness of Prostate Cancer on Biopsy

- Histologic grade
- Perineural invasion
- Extraprostatic disease
- Biomarkers/molecular determinants
Prostatic Adenocarcinoma

Gleason Grading

• Morphologic resemblance to normal prostate

• Degree of invasiveness

• Score = most + 2nd most

• 2005 ISUP: Grading biopsies:
  — Most + highest remaining grade present
  — Grades 1&2 should not be used (most upgraded or found to be benign on RP)

Significance of Tertiary (<5%) HG Gleason Pattern*

HG = high-grade
*Tertiary pattern is defined as a third Gleason pattern in a tumor that occupies less than 5% of the tumor.

Failure Rates as a Function of Percent Gleason Pattern 4/5 Cancer

Predicting 15-year prostate cancer specific mortality after radical prostatectomy


N=23,910 across 5 institutions
Impact of grade stratification on biochemical recurrence

<table>
<thead>
<tr>
<th>N=7869</th>
<th>Multivariate regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P</td>
</tr>
<tr>
<td><strong>Preoperative variables</strong></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>0.77 (0.54-1.08)</td>
</tr>
<tr>
<td>PSA</td>
<td>1.06 (1.04-1.07)</td>
</tr>
<tr>
<td>cT2b</td>
<td>2.70 (1.79-4.06)</td>
</tr>
<tr>
<td>cT2c-cT3</td>
<td>3.36 (1.55-7.31)</td>
</tr>
<tr>
<td><strong>Biopsy Gleason score</strong></td>
<td></td>
</tr>
<tr>
<td>3 + 4</td>
<td>2.19 (1.35-3.56)</td>
</tr>
<tr>
<td>4 + 3</td>
<td>5.38 (3.33-8.68)</td>
</tr>
<tr>
<td>8</td>
<td>6.92 (3.99-11.98)</td>
</tr>
<tr>
<td>9-10</td>
<td>10.27 (5.29-19.92)</td>
</tr>
<tr>
<td>&gt;3 cores</td>
<td>0.96 (0.65-1.42)</td>
</tr>
<tr>
<td>&gt;50% positive</td>
<td>1.99 (1.31-3.00)</td>
</tr>
</tbody>
</table>

Prostate Cancer in the Contemporary Era: Does it make sense to continue to use a 2-10 scaled grading system?

- Gleason score 6 has favorable outcomes
- Gleason score 6 (low grade) is halfway between Gleason score 2 and 10
  - Contributes to reluctance to choose active surveillance
- Gleason scores 2-5 rarely used and not prognostically different from GS6
- Amount of pattern 4/5 most important for prognosis
The overall Gleason score is based on the core with the highest Gleason score. Gleason scores can be grouped and range from Prognostic Grade Group I (most favorable) to Prognostic Grade Group V (least favorable).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Prognostic Grade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6</td>
<td>I</td>
</tr>
<tr>
<td>3 + 4 = 7</td>
<td>II</td>
</tr>
<tr>
<td>4 + 3 = 7</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
</tr>
<tr>
<td>9-10</td>
<td>V</td>
</tr>
</tbody>
</table>

- 2014 ISUP (Nov. 2014, Chicago)
  - 85 GU pathologists from 17 countries with input from urologists
  - Voted to adopt 5-teired system (90% consensus)
  - Recommended that percent high grade patterns be specified for groups II and III
  - Manuscript pending - stay tuned!
Gleason Grading on Needle Biopsy: Limitations

- Cancer sampling is a function of tumor volume: prostate volume
  - Similarly, sampling of high-grade tumor is a function of high-grade component: prostate volume
- Biopsy may not sample highest grade
3-Dimensional Reconstruction of Prostatectomy: Tumor Multifocality and Heterogeneity
Gleason Grading on Needle Biopsy: Limitations

- Cancer sampling is a function of tumor volume: prostate volume
  - Similarly, sampling of high-grade tumor is a function of high-grade component: prostate volume
- Biopsy may not sample highest grade

*Have consequences for choice and potential effectiveness of expectant management*

Can we improve our prognostic ability through the addition of molecular biomarkers?
Prognostic Biomarkers for Prostate Cancer

• Identifying molecular markers associated with potentially aggressive cancer to aid in therapeutic decision making
  – Risk of progression
  – Monitoring for expectant management or targeted focal therapy

• Independent of Gleason grade and biopsy sampling

• Readily available
# Prognostic value of a cell cycle progression signature* for prostate cancer death in a conservatively managed needle biopsy cohort


*Prolaris®, Myriad Genetics, Inc.

© 2012 Cancer Research UK.

## N=349

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=349</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td>PCA specific death</td>
</tr>
<tr>
<td>Events</td>
<td>90 (26%)</td>
</tr>
<tr>
<td>Med years follow-up</td>
<td>11.8 (10.8, 12.7)</td>
</tr>
<tr>
<td>Median age</td>
<td>71 (66, 73)</td>
</tr>
<tr>
<td>Gleason</td>
<td>106 (30%)</td>
</tr>
<tr>
<td>Median PSA</td>
<td>21.4 (11.9, 42)</td>
</tr>
</tbody>
</table>

## Variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolaris Score</td>
<td>1.65 (1.31, 2.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gleason &lt;7</td>
<td>0.61 (0.32, 1.16)</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>1.90 (1.18, 3.07)</td>
<td>---</td>
</tr>
<tr>
<td>&gt;7</td>
<td>1.37 (1.05, 1.79)</td>
<td>0.017</td>
</tr>
</tbody>
</table>
Prognostic utility of the cell cycle progression score generated from needle biopsy in men treated with prostatectomy

N=582

A. Biochemical recurrence: Multivariate analysis: HR=4.83 (CI 95%); \( p<10^{-5} \)

B. Metastasis-free survival: Multivariate analysis: HR=1.53 (CI 95%); \( p<10^{-4} \)

Genomic Prostate Score (GPS)*

Genes Associated with Worse Outcome
- Stromal Response
  - BGN
  - COL1A1
  - SFRP4
- Proliferation
  - TPX2

Genes Associated with Better Outcome
- Androgen Signaling
  - FAM13C
  - KLK2
  - AZGP1
  - SRD5A2
- Cellular Organization
  - FLNC
  - GSN
  - TPM2
  - GSTM2

Reference Genes
- ARF1
- ATP5E
- CLTC
- GPS1
- PGK1
- PGK1

- PCR-based expression assay
- 17 gene panel
  - 5 reference genes
  - 12 genes covering multiple pathways predictive of:

1. Metastasis & Death when measured in RP specimens
2. Dominant grade pattern 4 & EPE/SV/LN+ when measured in biopsy specimens

*Oncotype DX®, Genomic Health, Inc
UCSF Validation Study of GPS

Improved Risk Discrimination with Addition of GPS to NCCN in 395 Men with Very Low-Intermediate Risk Prostate Cancer on Biopsy


Multivariate Analysis
NCCN p-value = 0.002
GPS p-value = 0.001
Genomic prostate score predicts adverse pathology\(^1\) at radical prostatectomy with adjustment for the clinical/pathology covariates (n=382)

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GPS/20 units</td>
<td>3.23</td>
<td>2.14–4.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Biopsy Gleason score 3 + 4 vs ≤3 + 3</td>
<td>1.89</td>
<td>1.12–3.18</td>
<td>0.016</td>
</tr>
<tr>
<td>2*</td>
<td>GPS/20 units</td>
<td>3.25</td>
<td>2.12–5.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>NCCN risk group: low vs very low</td>
<td>3.17</td>
<td>1.33–8.81</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs very low</td>
<td>4.52</td>
<td>1.81–13.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3*</td>
<td>GPS/20 units</td>
<td>2.74</td>
<td>1.77–4.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age at diagnosis, yr</td>
<td>1.06</td>
<td>1.02–1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>NCCN risk group: low vs very low</td>
<td>3.44</td>
<td>1.43–9.65</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs very low</td>
<td>5.20</td>
<td>2.05–15.18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; GPS = Genomic Prostate Score; OR = odds ratio; *\(n=372\) (NCCN risk category could not be assigned for 10 patients).

1. Adverse pathology=GS\(\geq 4+3\), any pattern 5; or \(\geq pT3\)

Univariable odds ratios for GPS in predicting adverse pathology at radical prostatectomy within different clinical subgroups

Risk of Progression

Choice of Management

Clinical Factors:
PSA
Stage

Pathologic Factors:
Grade
Extent
(# pos cores, etc)

Primary Data

Secondary Data

Current

Future?

Mutational Analysis

Molecular Profiling

Other?

Risk of Progression
Choice of Management