Clinical and Pathologic Characteristics of Prostate Cancer
(including new markers such as PCA3)

~ M. Scott Lucia, MD

Prostatic Carcinoma - 2009¹

- >192,000 new cases expected
- 27,360 deaths expected
- Lifetime risk of prostate cancer in U.S.:
  - Diagnosis: ~17%
  - Death: ~3%
- More men die with prostate cancer than of it

Prostate Cancer: The Landscape has Changed

- Shift in pathological characteristics
- Shift in clinical presentation
- Shift in treatment paradigms
  - Recognition that not all cancers need treatment
  - New approaches for low-risk cancer
    - Active surveillance
    - Targeted focal therapy
- Need for improved diagnostic tools and approaches
  - Differentiate "significant" vs "insignificant" tumors
  - Earlier diagnosis of aggressive cancers

Whole-mount prostatectomy
Clinical and Pathologic Characteristics of Prostate Cancer (including new markers such as PCA3) ~ M. Scott Lucia, MD

3-Dimensional Reconstruction of Whole-Mounted Prostatectomy Specimens

3-Dimensional Reconstruction of Prostatectomy: Tumor Multifocality and Heterogeneity

Multifocality of 293 carcinomas from 151 prostates (< 1994)

<table>
<thead>
<tr>
<th>Tumors/Pt.</th>
<th>No. Pts. (%)</th>
<th>No. Tumors</th>
<th>Mean Tumor Vol. (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66 (43.7)</td>
<td>66</td>
<td>6.52</td>
</tr>
<tr>
<td>2</td>
<td>47 (31.1)</td>
<td>94</td>
<td>1.48</td>
</tr>
<tr>
<td>3</td>
<td>25 (16.6)</td>
<td>75</td>
<td>1.01</td>
</tr>
<tr>
<td>4</td>
<td>8 (5.3)</td>
<td>32</td>
<td>0.59</td>
</tr>
<tr>
<td>5</td>
<td>4 (2.6)</td>
<td>20</td>
<td>0.40</td>
</tr>
<tr>
<td>6</td>
<td>1 (0.7)</td>
<td>6</td>
<td>0.22</td>
</tr>
<tr>
<td>Totals</td>
<td>151 (100)</td>
<td>293</td>
<td></td>
</tr>
</tbody>
</table>

- Prostatectomies 1997-2006:
  - Solitary = 20% (Mean vol = 2.14 cc)
  - Multifocal = 80% (range 2-17 tumors)

Lucia MS, Unpub

Representative Diagrams of Prostate Cancer and HGPIN in Early 1990s (A) and Present (B)

A. Tumors were larger, more confluent and more advanced
B. Tumors now smaller, more multifocal and more localized
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**PSA as a Marker for Prostate Cancer**

<table>
<thead>
<tr>
<th>PSA (ng/ml)</th>
<th>Sensitivity</th>
<th>False positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>82.0</td>
<td>59.4</td>
</tr>
<tr>
<td>1.6</td>
<td>67.4</td>
<td>41.2</td>
</tr>
<tr>
<td>2.1</td>
<td>54.4</td>
<td>29.2</td>
</tr>
<tr>
<td>2.6</td>
<td>43.6</td>
<td>20.4</td>
</tr>
<tr>
<td>3.1</td>
<td>35.8</td>
<td>14.9</td>
</tr>
<tr>
<td>4.1</td>
<td>24.5</td>
<td>7.7</td>
</tr>
<tr>
<td>6.1</td>
<td>5.4</td>
<td>2.0</td>
</tr>
<tr>
<td>8.1</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>10.1</td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Thompson et al. JAMA 2005; 294: 66–70

**PCPT: PSA and Insignificant Cancer***

<table>
<thead>
<tr>
<th>PSA (ng/ml)</th>
<th>Insignificant cancer</th>
<th>Potentially incurable (pT3 or N1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1.0</td>
<td>1.1 - 2.5</td>
<td>2.6 - 4.0</td>
</tr>
<tr>
<td>4.1 - 10</td>
<td>&gt; 10</td>
<td></td>
</tr>
</tbody>
</table>


**Prostatic Carcinoma: Issues for Screening and Detection**

- Serum prostate specific antigen (PSA)
  - A continuum of risk over all values
- Digital rectal exam
  - Poor sensitivity
- Random biopsy schema
  - Sampling issues
  - Significant vs “Insignificant” tumors
Prostate Cancer: Diagnostic Considerations

- Prostate in pelvic “blind spot”
- Limited imaging available
- Access to prostate through rectum
- Difficult to access anterior prostate
- Biopsies random
  - ~50-70% sensitive
  - Many cancers aren’t life threatening


Prostate Cancer Detection by Needle Biopsy: Implications

- Cancer sampling is a function of tumor volume: prostate volume
- Negative biopsy ≠ no cancer
- Biopsy grade may be inaccurate
- Biopsy is a poor staging tool
  - Has consequences for choice and effectiveness of therapy
    - Expectant management
    - Targeted focal therapy

Comparison of needle biopsy with prostatectomy grades in PCPT (placebo group)

<table>
<thead>
<tr>
<th>Gleason Score on Biopsy</th>
<th>Gleason Score at Radical Prostatectomy (RP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8-10</td>
</tr>
<tr>
<td>2-5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>160</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>8-10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

Proportion of high grade cancer at RP initially detected at biopsy = 53/105 (50.5%)

Lucia MS, et al. JNCI 2007; 99:1375-83

Prostatic Carcinoma: Issues for Screening and Detection

- Serum prostate specific antigen (PSA)
  - A continuum of risk over all values
- Digital rectal exam
  - Poor sensitivity
- Random biopsy schema
  - Sampling issues
  - Significant vs “insignificant” tumors
- Need new approaches to assess tumor aggressiveness
**Ideal Biomarker for Prostate Cancer**

- Sensitive and specific for aggressive cancer
- When modulated, correlates with disease outcome
- Reproducible
- Quick and easy to assay
- Low cost
- Minimal invasiveness

**New Biomarkers for Prostate Cancer Detection: PCA3**

- First described in 1999 as DD3*
- Non-coding RNA
- Unknown function
- Prostate specific, highly overexpressed in more than 95% of prostate cancers
- Not detected in any other tissue or cancer

*Bussemakers et al., Cancer Res 1999;59:5975-5979

**RNA Analysis of PCA3 Gene in Urinary Sediments**

- Ratio PCA3:PSA is used as a quantitative measure
- Ratio PCA3:PSA is consistently higher in samples from cancer patients

**Validation Studies - PCA3**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hessels et al., 2003</td>
<td>158</td>
<td>67%</td>
<td>63%</td>
<td>90%</td>
</tr>
<tr>
<td>Tinzl et al., 2004</td>
<td>158</td>
<td>92%</td>
<td>70%</td>
<td>87%</td>
</tr>
<tr>
<td>Fradet et al., 2004</td>
<td>443</td>
<td>85%</td>
<td>89%</td>
<td>84%</td>
</tr>
<tr>
<td>Groskopf et al, 2006</td>
<td>122</td>
<td>99%</td>
<td>79%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Hessels et al., Eur Urol 2003;44:8-16
Tinzl et al., Eur Urol 2004;46:182-186
Fradet et al., Urology 2004;64:311-315
Groskopf et al, Clin Chem 2006;52: 1089-1095
PCA3 score as a function of tumor volume and Gleason score

Pathology of Prostate Cancer: Assessing Aggressiveness

- Histologic type and grade
- Pathologic stage
- Margin status
- Tumor volume
- Biomarkers/molecular determinants?
  - Systems pathology – can we improve on traditional pathology?

Failure Rates as a Function of Percent GS 4/5 Cancer

Actuarial 15-year Estimates of Biochemical Progression Rates Segregated by Percent Tumor Involvement

A. Organ-confined, margin negative
B. ECE and/or margin positive

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Improved tumor sampling with saturation biopsies leads to improved detection and grading – implications for targeted therapy

- Saturation grid-biopsy data (left)
- Reverse-reconstruction model (center)
- Actual RRP specimen (right)
- Model error: -15% for Gleason 3+4 tumor (right, 5.1cc)
  +15% for Gleason 3+3 tumor (left, 0.035cc)

Kaplan-Meier curve demonstrating the classification of patients from the (A) training cohort and (B) validation cohort as being at low risk or high risk for experiencing clinical failure (CF)

Analysis of AR and AMACR

Systems Pathology

Definitions: Analyzing the interrelationships of multiple elements (molecular and pathologically) in a system rather than each one at a time

Paraffin block → Sections from block
  Mutational analysis: PCR, Sequencing, FL-FISH
  Quantitative immunofluorescence → Image Analysis

Primary Data

Pathologic Factors: Grade, Stage, Margins

Clinical Factors: PSA Stage

Secondary Data

Mutational Analysis
Quantitative IF

Risk of Progression

Systems Analysis Approach for the Prediction of Prostate Cancer Progression After Radical Prostatectomy*

- Clinicopathologic: Grade, LN mets
- Image analysis: Psa gland lumen architecture, cytoplasm color/texture
- IF: AR, AMACR

CI=0.84


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Crawford et al., BJU Int 96:996-1004, 2005
Metastatic Potential = $p \times T$

- $p$ = phenotype (biologic aggressiveness)
  - Assessed by grade (other?)
- $T$ = time
  - Reflected by volume, stage
  - Assessed by ? – to be determined

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