Biomarkers in Localized Prostate Cancer
Sure you can, but why would you?

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Localized Prostate Cancer
Our Perspective

- Decision Making Complexity
- Broad Spectrum of Localized Disease
- Relatively Long Natural History (Competing Risks)
- Morbidity of Treatment

Surveillance

Treatment

Prostatectomy

Surveillance

Adjuvant/Salvage Therapy
Localized Prostate Cancer

To Treat or Not to Treat

1.) From the biopsy (GS 3+3, 3+4)
   • Active Surveillance vs Active Treatment

2.) From the prostatectomy with adverse pathology (pT3 +/- R1)
   • "Active" Surveillance vs "Active" or Adjuvant Radiation
How to overcome indecisiveness in one easy step!

ThriftyGuardian.com
Testing in Prostate Cancer

Who to biopsy? → When to re-biopsy? → Who to treat? → Follow on therapy?

- PSA
- Confirm MDx
- Prostate Cancer Assay
- Decipher prostate cancer classifier
- PCA3
- 4Kscore
- phi test
- ProMark proteomic prognostic test for prostate cancer
- ProLaris
- ProLaris
Prostate Cancer Biomarkers

- No biomarkers are routinely used; <1% to date
  - Inconsistent results (methods)
  - Small retrospective studies-underpowered
  - Tissue availability
  - Single institution
  - Lack of validation sets
  - Biochemical or PSA recurrence
  - Performance in multivariate models
Prostate Cancer Biomarkers

• Optimism- molecular understanding, facility/technology, need, …

• Statistical significance ≠ Clinical significance

• Technical validation ≠ Clinical validation
  • Rules of evidence

• Caution- spectrum of disease/heterogeneity/continuum of risks
Prostate Cancer Biomarkers

• Confusion among patients and providers
  • Overlapping clinical spaces
  • Tests assess similar molecular phenotypes
  • Aggressive marketing
  • Expectations: Does not give an answer

• Patients think we are improving outcomes…
  • Which is true if anxiety is the target outcome
<table>
<thead>
<tr>
<th>Test</th>
<th>Tissue type</th>
<th># of genes/proteins</th>
<th>Main results</th>
<th>Utility assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decipher</td>
<td>Radical prostatectomy</td>
<td>22</td>
<td>Decipher scores, in addition to clinical variables, predict 10-yr distant metastasis after surgery (AUC = 0.81). GC (alone or plus CAPRA score) has a higher ability to predict the occurrence of metastases (AUC = 0.83–85).</td>
<td>Adjuvant treatment after radical prostatectomy</td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>Prostate biopsy</td>
<td>17</td>
<td>GPS combined with clinical parameters (age, PSA, clinical stage, and biopsy GS) or with the CAPRA score is a predictor of high-grade (primary GS of 4 or any pattern of 5) or high-stage disease (pT3 or higher), and BCR.</td>
<td>Active surveillance or active treatment</td>
</tr>
<tr>
<td>Prolaris</td>
<td>Prostate biopsy</td>
<td>31</td>
<td>CCP score is an independent predictor of PCa death, BCR, and metastasis after radical prostatectomy and radiation therapy.</td>
<td>Active surveillance or active treatment</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td></td>
<td>The combination of CCP and the CAPRA score achieves a higher prognostic power.</td>
<td>Adjuvant therapy in high-risk patients</td>
</tr>
</tbody>
</table>
LET ME LULL YOU INTO A FALSE SENSE OF SECURITY
**Decipher**

**Case-cohort blinded validation study**

- **Men Treated with RP at high risk of recurrence (2000-2006)**

Inclusion Criteria:
- Pre-op PSA >20 ng/mL; or
- p-Gleason score 8-10 or;
- SVI (pT3b) or; GPSM ≥ 10

**Study Design: Case-cohort**
- 20% random sample of population + all cases (n=219 Patient Expression Profiles)
- 8.1 Median years of follow-up
- 3 year BCR rate ~27%
- 5 year metastasis rate ~ 7%

Karnes et al., Journal of Urology 2013
Genomic Classifier shows better performance for predicting metastasis after RP than clinical variables

C-INDEX

<table>
<thead>
<tr>
<th>Metric</th>
<th>C-INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>0.79</td>
</tr>
<tr>
<td>ECE</td>
<td>0.65</td>
</tr>
<tr>
<td>Path GS</td>
<td>0.64</td>
</tr>
<tr>
<td>SVI</td>
<td>0.59</td>
</tr>
<tr>
<td>LNI</td>
<td>0.56</td>
</tr>
<tr>
<td>Pre-op PSA</td>
<td>0.56</td>
</tr>
<tr>
<td>Margins</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Metastasis in Cohort Stratified by GC Score Groups

<table>
<thead>
<tr>
<th>GC Score Groups</th>
<th>5-yr incidence of mets</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC &gt; 0.6</td>
<td>22.5%</td>
<td>19%</td>
</tr>
<tr>
<td>0.4 ≤ GC ≤ 0.6</td>
<td>6.0%</td>
<td>21%</td>
</tr>
<tr>
<td>GC &lt; 0.4</td>
<td>2.4%</td>
<td>60%</td>
</tr>
</tbody>
</table>

# Pts. at risk

- GC < 0.4: 478, 355, 111
- 0.4 ≤ GC ≤ 0.6: 172, 132, 45
- GC > 0.6: 153, 72, 16
Genomic Classifier harbors independent, significant prognostic information in multivariable analysis

- Genomic Classifier $0.4 \leq \text{GC} \leq 0.6$
  - p < 0.10
- Genomic Classifier $> 0.6$
  - p < 0.001
- Pathological Gleason Score $\geq 8$
  - p = 0.14
- Pre-operative Prostate Specific Antigen
  - p = 0.47
- Seminal Vesicle Invasion
  - p = 0.11
- Positive Surgical Margins
  - p = 0.84
- Extra Capsular Extension
  - p = 0.35
- Lymph Node Involvement
  - p = 0.90
- Adjuvant Hormone Therapy
  - p = 0.54
- Adjuvant Radiation Therapy
  - p = 0.75

1. Hazard ratio reported in comparison with low risk group GC<0.4
2. Hazard ratio reported for 1.0 unit increments of log-transformed level.
GC identifies significant number of clinically high risk patients who do not experience adverse outcomes.
Genomic Classifier Identifies Men With Adverse Pathology After Radical Prostatectomy Who Benefit From Adjuvant Radiation Therapy


ABSTRACT

Purpose
The optimal timing of postoperative radiotherapy (RT) after radical prostatectomy (RP) is unclear. We hypothesized that a genomic classifier (GC) would provide prognostic and predictive insight into the development of clinical metastases in men receiving post-RP RT and inform decision making.
Study Design

- A total of 188 patients with pT3 and/or SM+ PCa, who received post-RP RT in two academic centers (Thomas Jefferson University, n=137) and (Mayo Clinic, n=51), between 1990 and 2009 were identified.

- The tumor block with the index lesion was selected for specimen processing. The index lesion was identified as the prostatectomy FFPE block with the highest pathologic Gleason grade.

- After RNA extraction and microarray expression data generation, 22-marker GC scores were obtained using the locked model. CAPRA-S scores were also generated using clinicopathologic variables.
Methods

• The primary endpoint for the analysis was metastasis (regional or distant) as evidenced by positive CT and/or bone scans

• Adjuvant and salvage radiation treatment (RT) were defined by PSA levels of ≤0.2 and >0.2 ng/mL prior to initiation of RT, respectively. This study follows the REMARK guidelines for evaluation of prognostic biomarkers

• Prognostic accuracy of the models were tested using c-index and decision curve analysis. Cox regression tested the relationship between GC and metastasis after adjusting for available covariates
Patient Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (%)</td>
<td>188 (100%)</td>
</tr>
<tr>
<td><strong>Patient age, yr</strong></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>61 (42, 78)</td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>56 - 66</td>
</tr>
<tr>
<td><strong>Preoperative PSA (ng/ml)</strong></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>7.8 (0.4, 80.4)</td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>5.3 - 12.3</td>
</tr>
<tr>
<td><strong>Pathologic Gleason Score, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>28 (14.9%)</td>
</tr>
<tr>
<td>7 (3+4)</td>
<td>60 (31.9%)</td>
</tr>
<tr>
<td>7 (4+3)</td>
<td>50 (26.6%)</td>
</tr>
<tr>
<td>≥8</td>
<td>48 (25.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td><strong>Seminal Vesicle Invasion, n (%)</strong></td>
<td>65 (34.6%)</td>
</tr>
<tr>
<td><strong>Surgical Margins, n (%)</strong></td>
<td>147 (78.2%)</td>
</tr>
<tr>
<td><strong>Pre-RT PSA (ng/ml)</strong></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>0.2 (0, 39)</td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>0.1 - 0.7</td>
</tr>
<tr>
<td><strong>RT Modality, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Adjuvant RT</td>
<td>96 (51.1%)</td>
</tr>
<tr>
<td>Salvage RT</td>
<td>89 (47.3%)</td>
</tr>
<tr>
<td>Unknwnon</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td><strong>ADT, n (%)</strong></td>
<td>56 (29.8%)</td>
</tr>
<tr>
<td><strong>Time from RP to RT, months</strong></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>5 (1, 159.7)</td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>3.6 - 15.3</td>
</tr>
</tbody>
</table>

A total of 19 (10%) patients experienced metastasis
GC has the highest c-index
GC reclassifies clinical risk

- 71 (42.5%) patients with average and high-risk CAPRA-S scores were reclassified as low GC
- 96% of these patients remained metastasis-free on study follow-up
GC improves risk stratification

The 5-year cumulative incidence of metastasis:

<table>
<thead>
<tr>
<th></th>
<th>LOW</th>
<th>AVERAGE</th>
<th>HIGH</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRA-S</td>
<td>13%</td>
<td>2%</td>
<td>14%</td>
<td>0.042</td>
</tr>
<tr>
<td>GC</td>
<td>0%</td>
<td>9%</td>
<td>29%</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Limitations

• This was a retrospective study and the selection of ART as opposed to SRT varied amongst physicians and patients

• No concrete guidelines for the incorporation of androgen deprivation therapy with post prostatectomy radiation therapy

• This study included patients who received radiation therapy and thus could not identify a patient population in whom post prostatectomy radiation therapy could be withheld completely
Oncotype Clinical Utility Study

Badani Urol Pract. 2015.
Clinical Utility Oncotype DX

Percent of Patients Recommended AS/WW

Percent of Patients Receiving AS/WW

In two clinical utility studies Prolaris results lead to change in management in up to 65% of patients.

Prolaris extends active surveillance candidate population by 62% compared to clinical and pathologic features alone.

Crawford, E D, et al. 2014:30(6), 1025-1031
Summary

• The results provided by these biomarkers, mostly expressed as a percentage of risk, can lead to misinterpretations.

• These genetic scores should be considered as continuous variables and not categorized as negative or positive.

• These biological markers should ideally be evaluated together with other tumor-related features (eg, PSA, grade, Gleason score, percentage of biopsy involvement, and extension of the disease) and patient characteristics (age, comorbidities, and life expectancy).

• Larger-scale, multi-institutional, and multinational studies will still be required to prospectively validate the utility of these markers, their cost effectiveness, and how they should truly be used in clinical practice.
Conclusion

• The available Biomarkers are not proven to improve long term outcomes

• These tests focused on a pelvic organ are being used to treat Supratentorial disease