Critical Role of Pathology for Active Surveillance Criteria and Definition of “Progression”

Jonathan I. Epstein
Financial and Other Disclosures

- Off-label use of drugs, devices, or other agents: None
- Data from IRB-approved human research is not presented

<table>
<thead>
<tr>
<th>I have the following financial interests or relationships to disclose:</th>
<th>Disclosure code</th>
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<td>PathAI</td>
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<td>Oncology Analytics</td>
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Outline

• Criteria for selection for AS

• Follow-up for men on AS

• Trigger for intervention on AS

• Changes in reporting grade for AS
Criteria for Selection of Men for Active Surveillance

- Age (life expectancy or follow-up time)
- Patient preference
- Cancer extent (clinical stage)
- Needle biopsy findings (grade, extent)
- PSA criteria
  - PSA
  - Density
Pathologic and Clinical Findings to Predict Tumor Extent of Nonpalpable (Stage T1c) Prostate Cancer

Jonathan I. Epstein, MD; Patrick C. Walsh, MD; Marné Carmichael; Charles B. Brendler, MD

JAMA 1994
Pre-Operative Model to Predict Insignificant Cancer

- Stage T1c (nonpalpable)
- Gleason score 6
- <3 cores involved by cancer
- No core with >50% involvement

» PSADensity (PSA/gland weight) <0.15
Pre Treatment Criteria Accurately Identify Men With “Significant” Cancers

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th># Men</th>
<th>Small volume (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al, '94</td>
<td>Retrospective</td>
<td>157</td>
<td>26</td>
<td>86</td>
<td>79</td>
</tr>
</tbody>
</table>
The NCCN definition of *favorable* risk prostate cancer?

<table>
<thead>
<tr>
<th>Low (D'Amico)</th>
<th>Very low (Epstein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T2a</td>
<td>T1c</td>
</tr>
<tr>
<td>Gleason score 6</td>
<td>Gleason score 6</td>
</tr>
<tr>
<td>PSA &lt;10ng/ml</td>
<td>PSA &lt;10ng/ml</td>
</tr>
<tr>
<td></td>
<td>PSA density &lt;0.15ng/ml/cc</td>
</tr>
<tr>
<td></td>
<td>&lt;3 biopsy cores with cancer</td>
</tr>
<tr>
<td></td>
<td>≤50% of core with cancer</td>
</tr>
</tbody>
</table>

NCCN 2016
Why Distinguish Between Very Low (factors in extent of cancer on bx) and Low Risk Disease?

1) Cancer extent on biopsy AND PSA density at diagnosis are directly associated with grade reclassification during surveillance
   (Loeb et al, Eur Urol 2015)

2) 2 fold higher risk of surgically confirmed non organ confined cancer and Gleason pattern 4 in men with low risk versus very low risk disease
   (Tosoian et al, J Urol 2013)

3) 2 fold higher risk of metastatic disease, prostate cancer death, and treatment failure with surveillance for low risk vs very low risk disease
   (Godtman et al, Eur Urol 2016)
Low risk (D’Amico) and very low risk represent 2 distinct subsets if untreated.

Grade Reclassification After 2 years

HR (Low-risk vs Very-low-risk) = 2.4 (95% CI=1.9, 3.5)

log rank-test chi-square= 0.008
Biopsy Criteria for Determining Appropriateness for Active Surveillance in the Modern Era

Oleksandr N. Kryvenko, H. Ballentine Carter, Bruce J. Trock, and Jonathan I. Epstein
Modified Epstein Criteria (Extended Core Biopsy)

- No Gleason pattern 4 or 5
- Less than 3 positive cores
- Unilateral Cancer
- PSAD<0.15
Variable Inclusion Criteria

- T1c (minority) vs. T1c-T2a vs. T1c-T2
- PSA \leq 10 \text{ (most)} vs. PSA \leq 15 vs. PSA \leq 20
- PSAD \leq 0.15 vs. PSAD \leq 0.2 vs. not criteria (most)
- Gleason score \leq 6 \text{ (almost all)} vs. \leq 3+4=7 \text{ (older men)}
- \leq 2 \text{ positive cores (most)} vs. \leq 3 \text{ cores vs. } \leq 33\% \text{ vs. } \leq 50\%
- \leq 50\% \text{ max per core (most)} vs. \leq 20\% vs. not criteria
- Unilateral vs. Bilateral
Variable Criteria for Reclassification

• Most based on subsequent worse biopsy (grade, no. cores, max. % cancer per core) criteria than original inclusion criteria

• JHH has never used PSA based criteria to determine reclassification as never been shown to be accurate

• Recent dropping of PSA based criteria in other AS centers, yet some use PSA doubling times or use to trigger MRI or more frequent biopsies
Risk prediction tool for grade re-classification in men with favourable-risk prostate cancer on active surveillance


The James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA
## Multivariable Model Results

<table>
<thead>
<tr>
<th>Covariates</th>
<th>B Coefficient</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed before 2005</td>
<td>0.385</td>
<td>2.16</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.047</td>
<td>1.05</td>
<td>0.0004</td>
</tr>
<tr>
<td>PSA Density at last biopsy (per 0.1 unit increase)</td>
<td>0.076</td>
<td>1.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Laterality as of last biopsy (Bilateral vs. Unilateral)</td>
<td>0.525</td>
<td>2.86</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Risk status as of last biopsy (Low-risk vs. Very-low-risk)</td>
<td>0.290</td>
<td>1.79</td>
<td>0.0009</td>
</tr>
<tr>
<td>Total number of biopsies (Biopsies not showing Gleason ≥ 7)</td>
<td>-0.381</td>
<td>0.68</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Practical Utility of Calculator

• 60% of our cohort had a predicted probability of grade reclassification of $\leq 20\%$ with a false negative rate of $\leq 10\%$.

• Reassure patients that they have a high probability of successfully staying on AS and can space out the repeat biopsies.
## Surveillance Outcomes Differ Depending on Selection Criteria and Triggers for Intervention

<table>
<thead>
<tr>
<th>Program</th>
<th>Gleason score 7 (%)</th>
<th>Biopsy frequency, yrs</th>
<th>10yr treated (%)</th>
<th>Metastases (%)</th>
<th>PCSM (%), 10yr</th>
<th>Overall mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins n=1298</td>
<td>0</td>
<td>1-2</td>
<td>50</td>
<td>0.4</td>
<td>0.1</td>
<td>4</td>
</tr>
<tr>
<td>Sunny-brook n=993</td>
<td>13</td>
<td>3-4</td>
<td>36</td>
<td>2.8</td>
<td>1.9</td>
<td>15</td>
</tr>
</tbody>
</table>

Tosoian JJ et al, J Clin Oncol 2015

Klotz L et al, J Clin Oncol 2015
Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience

Hima Bindu Musunuru, Toshihiro Yamamoto, Laurence Klotz, Gabriella Ghanem, Alexandre Mamedov, Peraka Sethukavalan, Vibhuti Jethava, Suneil Jain, Liying Zhang, Danny Vesprini and Andrew Loblaw*
Gleason $\leq 6$ – 15 year metastases-free survival 94%

Gleason 3+4=7 with PSA $\leq 20$ - 15 year metastases-free survival 84%

“AS for Gleason 7 disease should be offered only in the setting of a clinical trial.”
AS for Gleason Score 3+4=7 (GG2) ?

Is there a subset of men with Gleason score 3+4=7 (GG2) intermediate risk prostate cancer on biopsy with favorable characteristics to minimize the risk of adverse findings in the prostate?
Cohorts

• A prospective cohort of men (2005-July 2016) undergoing radical prostatectomy was evaluated.

• VLR – 1,264 men

• LR – 4,849 men

• FIR (1-2 cores of Gleason 3+4=7, PSA<20ng/ml) – 608 men
Primary Outcome

- At radical prostatectomy upgrading to Gleason $\geq 4+3=7$ (GG $\geq 3$), seminal vesicle invasion (pT3b), or lymph node metastasis (pN1).

- Universal acceptance that AS is inappropriate for patients harboring such features.
Rates of Adverse Pathology at RP

• VLR - 4.7%
• LR - 5.8%
• FIR - 24.7%

• 94% of FIR with adverse pathology with Gleason $\geq 4+3=7$ (GG$\geq 3$); only 9 additional patients were identified solely due to pT3b (n=8/5.3%) or pN1 (n=1/0.7%) disease.
Limited Cancer Volume FIR

- 271 men with FIR and VLR biopsy criteria (except GS 3+4=7) - 18.5% had adverse pathology at RP

- ? Percent pattern 4 (1%-approaching 50%)

- ? Cribriform vs. Poorly formed/fused pattern 4
Men with Gleason score 3+4=7 on biopsy who are otherwise eligible for curative intervention should be fully informed as to the avoidable risk associated with AS.
## Novel Markers and Imaging May be Useful in Surveillance

<table>
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<tr>
<th>Tests</th>
<th>Potential</th>
</tr>
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<tbody>
<tr>
<td>• Urinary markers (PCA3/TMPRSS2:ERG, <em>exosome gene expression assay</em>)</td>
<td>-reduce misclassification by accurate prediction of disease aggressiveness</td>
</tr>
<tr>
<td>• Serum markers (Prostate Health Index and 4K)</td>
<td>-expand the pool of surveillance candidates</td>
</tr>
<tr>
<td>• Molecular tissue based markers (Prolaris, Oncotype DX, PTEN)</td>
<td>-reduce the burden of monitoring</td>
</tr>
<tr>
<td>• Multi-parametric MRI/ image guided biopsy</td>
<td></td>
</tr>
</tbody>
</table>

Reichard CA et al, Cancer 2015  
Schoots IG et al, Eur Urol 2015
Impetus for a New Prostate Cancer Grading System
Problems with Gleason System: Scale

- 6 is the lowest grade reported although the scale goes from 2-10

- Patients are told they have a Gleason score of 6 out of 10 and logically but incorrectly think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer
• Urologists need to reassure and educate patients when told they have Gleason score 6 cancer.

• Modify how pathologists report prostate cancer grade to more accurately reflect their behavior.
Qualitative Study About Grading

• 7 focus groups with n=37 prostate cancer patients in two clinical settings from 2015-2016

• Majority of patients (84%) agreed that it would be clearer if grades were reported on a scale of 1-5 instead of 6-10

• 88% would prefer to hear they have “Group 1” rather than “Gleason 6”

• 80% would feel more comfortable choosing active surveillance with “Group 1” versus “Gleason 6”

Loeb et al. (Unpublished data)
Problems with Gleason System Grouping

• Gleason 7 is not homogeneous: 4+3=7 has a much worse prognosis than 3+4=7
Prognostic Gleason grade grouping: data based on the modified Gleason scoring system

Phillip M. Pierorazio*, Patrick C. Walsh*, Alan W. Partin* and Jonathan I. Epstein**††

BJU International 2013; 111:753-60
New 5 Grade System

• Grade Group 1 (≤6)
  Only individual discrete well-formed glands

• Grade Group 2 (3+4)
  Predominantly well-formed glands with a lesser component of poorly-formed/fused/cribriform glands

• Grade Group 3 (4+3)
  Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands
The graph shows the probability of recurrence-free progression over years since surgery for different groups (GrGp 1 to GrGp 5). The y-axis represents the probability of recurrence-free progression, ranging from 0.00 to 1.00, while the x-axis represents the years since surgery, from 0 to 10. Each group has a distinctive line color and pattern, indicating the trend and rate of recurrence-free progression over time.
The new grading system was recently accepted

2016 World Health Organization (WHO)  
Pathology & Genetics:  
Tumours of the Urinary System and Male Genital System  
College of American Pathologists (CAP)  
Summary

- Pathology plays a critical role in:
- Criteria for selection for AS
- Criteria for intervention on AS
- Reporting prostate cancer to more accurately reflect extent and grade for both urologists and patients
Problems with Gleason System: Inconsistent & Inaccurate Grouping

Various combinations have been used in the literature including some of the highest impact studies:

Prostate Cancer Outcomes Study (NEJM): 2-4; 5-7; 8-10
Scandinavian Prostate Cancer Group Study (NEJM): 2-6, 7; 8-10
Prostate Cancer Intervention vs. Observation (NEJM): 2-6; 7-10
Prostate Cancer Prevention Trial (NEJM): 2-6; 7-10
D’Amico Risk Classification
Stratification

- Low Risk: T1C/T2a & PSA $\leq 10$ & Gleason $\leq 6$
- Intermed. Risk: T2b or PSA 10-20 or Gleason 7
- High Risk: T2c or PSA $>20$ or Gleason 8-10
Problems with Gleason Grading

Too Many Grades with Similar Prognoses

- 1+1; 1+2; 1+3; 1+4; 1+5; 2+1; 2+2; 2+3; 2+4; 2+5; 3+1; 3+2; 3+3; 3+4; 3+5; 4+1; 4+2; 4+3; 4+4; 4+5; 5+1; 5+2; 5+3; 5+4; 5+5

- 25 potential grades!

- What are the least number of grades with a similar prognosis?
• **Grade Group 4** (4+4/3+5/5+3)
  Only poorly-formed/fused/cribriform glands **or**
  Predominantly mix of well-formed and lack of glands

• **Grade Group 5** (4+5/5+4/5+5)
  Lack gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands
<table>
<thead>
<tr>
<th>Hosp</th>
<th>Freq.</th>
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<tbody>
<tr>
<td>Pittsburgh</td>
<td>2,102</td>
</tr>
<tr>
<td>Karolinska</td>
<td>3,763</td>
</tr>
<tr>
<td>Hopkins</td>
<td>6,137</td>
</tr>
<tr>
<td>Memorial</td>
<td>6,673</td>
</tr>
<tr>
<td>CCF</td>
<td>2,170</td>
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<tr>
<td>------------</td>
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</tr>
<tr>
<td>Total</td>
<td>20,845</td>
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## Biopsy Grade Meta-Analysis

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<td>Hopkins</td>
<td>6,137</td>
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<tr>
<td>Memorial</td>
<td>5,791</td>
</tr>
<tr>
<td>CCF</td>
<td>2,146</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16,176</strong></td>
</tr>
</tbody>
</table>
Multiple Additional Studies Validating New Grading System

Correlating with BCR, distant metastases, mortality following RT and radical prostatectomy