Approach to the Diagnosis of Small Glandular Lesions in Prostate Biopsies

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Incidence of T1c disease

Lifetime Risk of Developing or Dying of Prostate Cancer for a 50-Year-Old Man in the United States

<table>
<thead>
<tr>
<th>Lifetime Risk of</th>
<th>Risk</th>
<th>Risk Ratio</th>
<th>Proportional Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing histologic cancer</td>
<td>42%</td>
<td>11.7</td>
<td>100</td>
</tr>
<tr>
<td>Developing clinical cancer</td>
<td>16%</td>
<td>4.4</td>
<td>38</td>
</tr>
<tr>
<td>Dying of prostate cancer</td>
<td>3.6%</td>
<td>1.0</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Increasing incidence of minimal residual cancer in radical prostatectomy specimens  

3,038 radical prostatectomy specimens reviewed from 1988-1995  
Excluded:  
Gl 4,5 - Pos. Surg. Marg  
hx TURP - Capsular Penetration  
Androgen block  
Volumes <0.5cc: “Insignificant” tumors (26%)  
84 (2.8%) specimens identified with “minimal” residual cancer  
Volume 0.05 – 0.1cc: “Minute” tumors (n=20)  
Volume < 0.05cc: “Difficult to find” tumors (n=60)  
Volumes 0.00cc: “Absent” tumors (n=4)  

1300 RPs  
No pre-ope Tx  
No TURP  
TTV <0.5cc  
430 (33%)  
315 (24%)  
113 w/ Gleason 4/5  
7 w/ ECE  

Indolent cancer*  
TTV <0.5cc  
No Gleason 4/5  
Organ Confined  
113 w/ Gleason 4/5  
7 w/ ECE

Minimal cancer*  
No pre-ope Tx  
No TURP  
TTV <0.5cc  
430 (33%)  
No Gleason 4/5  
Organ Confined  
315 (24%)  
8 (0.6%)

'Minute' cancer  
64 (5%)

'Difficult to find' cancer  
79 (6%)

'No residual cancer'  
(No misread/mislabeled)  
8 (0.6%)

Total 148 (11%)


Clinically Localized Prostate Cancer

Now the questions are:
• Who should be treated? Is there still a role for “watchful waiting”?  
• How should they be treated – surgery, radiation, brachytherapy, hormones, combinations?  
• How can we make sure that treatment is maximally effective with lowest risk of side effects?

PROSTATIC ADENOCARCINOMA  
Routine Diagnostic/Prognostic Armament
- Digital rectal examination (DRE)  
- Transrectal ultrasound (TRUS)  
- Magnetic Resonance Imaging/Spectroscopy  
- Serum prostatic specific antigen (PSA)  
- Pathology  
- transrectal biopsy  
- prostatectomy
Preoperative Nomogram for Prostate Cancer Recurrence

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td></td>
<td>0.1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T1c</td>
<td>T1ab</td>
<td>T2a</td>
<td>T2b</td>
<td>T2c</td>
<td>T3a</td>
<td>T4a</td>
<td>T4b</td>
<td>T4c</td>
<td>T4d</td>
<td>T5a</td>
</tr>
<tr>
<td>Biopsy Gleason Grade</td>
<td>2+1</td>
<td>2+2</td>
<td>2+3</td>
<td>3+2</td>
<td>3+3</td>
<td>3+4</td>
<td>≥4</td>
<td>≥4</td>
<td>≥4</td>
<td>≥4</td>
<td>≥4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Points</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Month Rec. Free Prob.</td>
<td>.96</td>
<td>.93</td>
<td>.90</td>
<td>.85</td>
<td>.80</td>
<td>.75</td>
<td>.70</td>
<td>.65</td>
<td>.60</td>
<td>.55</td>
<td>.50</td>
</tr>
</tbody>
</table>

Instructions for Physician:
Locate the patient’s PSA on the PSA axis. Draw a line straight upward to the Points axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the Clinical Stage and Biopsy Gleason Sum axes, each time drawing a straight line to the Points axis. Then, draw a line straight downward to find the patient’s probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for radical prostatectomy. You can use this only on a man who has already selected radical prostatectomy as treatment for his prostate cancer.

Instruction to Patient:
“Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram – 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare.”

OUTLINE

- Immunohistochemistry as a diagnostic adjunct
- Morphology of precursor lesions
- Mimics of precursor lesions
- Morphology of prostate cancer
- The diagnosis of minimal cancer in biopsies
- Mimics of prostate cancer in biopsies

Prostate anatomy


**Architecture**

- Cluster of small glands
- Infiltrative appearance
  - Between benign glands
  - On both sides of benign glands
- “Silent” stroma
  - Beware of inflammatory/reactive changes

**Cytology**

- Nuclear enlargement
  - Compare with benign
- Prominent nucleoli
  - Watch out for mimics
- Cytoplasm:
  - Benign: usually pale
  - Cancer: ampho-, eosino-, basophilic

**Intraluminal Secretions**

- Dense pink secretions
- Blue-tinged mucin
- Crystalloids
Extravasated mucin

IMMUNOHISTOCHEMISTRY

Basal cells:
34BE12 (K903)
4A4 (p63)

Acinar cells:
PSA
AMACR (racemase)

Cocktail stains:
PIN-4, Tri-view

Mucinous metaplasia
Foamy Gland Carcinoma

Foamy Glands:
- Infiltrative
- Foamy cytoplasm
- Basally located nuclei
- Small hyperchromatic nuclei
- Nuclei difficult to see

Glomeruloid features
- Intraluminal tufting
- Glomeruloid structures
Pseudohyperplastic carcinoma

- Larger neoplastic glands with papillary infoldings and branching.
- Nuclei commonly basally located

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**HIGH GRADE PIN AND ASAP: Repeat Biopsy Results in a Contemporary Series**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Cases</th>
<th>Cancer (%)</th>
<th>Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Normal”</td>
<td>227</td>
<td>40 (17.6)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HG-PIN</td>
<td>71</td>
<td>13 (18.3)</td>
<td>1.05</td>
<td>0.52-2.09</td>
<td>0.895</td>
</tr>
<tr>
<td>ASAP</td>
<td>45</td>
<td>14 (31)</td>
<td>2.11</td>
<td>1.03-4.32</td>
<td>0.038</td>
</tr>
<tr>
<td>Total</td>
<td>343</td>
<td>67 (19.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MSKCC
Prostate Pathology
Factors resulting in an ASAP diagnosis

- **Size:**
  - Small number of acini in the focus
  - Small focus size
  - Lesion on edge of core

- **Histology:**
  - Lack of clear histologic detail
  - Lack of convincing malignant features
  - Loss of focus in deeper sections (immuno)
  - Presence of associated PIN
    - Distortion of acini
    - Clustered growth
    - Negative IHC
    - Atrophic w/o basal cells

- **Inflammation:**
  - Prominent inflammation in which adjacent benign acini show distortion
  - Inflammatory cellular reactive atypia with nuclear/nucleolar enlargement

Modified from: Scherer et al. - AJSP 2005;29:1201-1207

Mucinous fibroplasia

Pathognomonic features of prostatic adenocarcinoma
PERINEURAL INVASION

- Circumferential
- Importance in predicting extracapsular extension (NB) or biochemical recurrence is controversial
- Importance of the diameter of the nerve involved in predicting failure has not been confirmed
- We still mention it!

MIMICKERS OF PROSTATIC ADENOCARCINOMA

- Adenosis (atypical adenomatous hyperplasia)
- Atrophy/partial atrophy
- Post-radiation atrophy and atypia
- Basal cell hyperplasia
- Verumontanum mucosal glands
- Mesonephric remnants
- Seminal vesicle / ejaculatory duct epithelium
- Entrapped colonic glands
- Inflammatory cells (lymphocytes)
### MORPHOLOGIC DISTINCTION BETWEEN ADENOSIS AND PROSTATIC ADENOCARCINOMA

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ADENOSIS</th>
<th>ADENOCARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Pattern</td>
<td>Lobular, circumscribed</td>
<td>Infiltrative</td>
</tr>
<tr>
<td>Glandular Pattern</td>
<td>Mixture of small and large glands</td>
<td>Usually small crowded glands</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Pale-clear, similar to adjacent benign glands</td>
<td>Amphophilic, darker than adjacent benign glands</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Large (&gt;3µ) nucleoli are absent</td>
<td>Occasional large (&gt;3µ) nucleoli</td>
</tr>
<tr>
<td>Blue mucin</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Corpora amylacea</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Basal cells</td>
<td>Occasional, attenuated</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Partial atrophy

Basal cell hyperplasia/adenoma
Verumontanum mucosal gland hyperplasia

Seminal vesicles and ejaculatory ducts
MESONEPHRIC RESTS

- Glands with an atrophic appearance
- Occasional papillations
- Silent stroma
- Dense colloid-like secretions
- PSA negative / basal cell markers positive
MIMICKERS OF “BENIGN” DISEASE

- Atrophic cancer
- Treated cancer (radiation, hormones)
- Pseudohyperplastic carcinoma
- Inflamed cancer
### Predictors of Biochemical Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason (&lt;7 vs. ≥7)</td>
<td>&lt;0.001</td>
<td>1.60</td>
</tr>
<tr>
<td>Pre-Tx PSA (&lt;10 vs. ≥10)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>T-Stage (T1,T2 vs. T3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Post-RT Biopsy Result (Negative/Treatment Effect vs. Positive)</td>
<td>&lt;0.001</td>
<td>2.44</td>
</tr>
<tr>
<td>Dose (≥7560 vs. &lt; 7560)</td>
<td>=0.042</td>
<td>1.43</td>
</tr>
</tbody>
</table>

### Predictors of Distant Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason (&lt;7 vs. ≥7)</td>
<td>&lt;0.001</td>
<td>3.49</td>
</tr>
<tr>
<td>Pre-Tx PSA (&lt;10 vs. ≥10)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>T-Stage (T1,T2 vs. T3)</td>
<td>0.031</td>
<td>2.08</td>
</tr>
<tr>
<td>Post-RT Biopsy Result (Negative/Treatment Effect vs. Positive)</td>
<td>0.002</td>
<td>2.61</td>
</tr>
<tr>
<td>Dose (≥7560 vs. &lt;7560)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
ANDROGEN DEPRIVATION THERAPY

- May produce profound architectural and cytologic changes benign and malignant prostatic tissue
- Artificial high grade appearance
- Pathologic downstaging of prostatectomy specimens
- No effect on PSA recurrence or survival
APPROACH TO THE DIAGNOSIS OF SMALL GLANDULAR LESIONS IN PROSTATE BIOPSIES

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Key References:


