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:
GI 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)

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>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>
<td>10</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>T3b</td>
<td>T4a</td>
<td>T4b</td>
<td>T4c</td>
<td></td>
</tr>
<tr>
<td>Biopsy Gleason Grade</td>
<td>2+2</td>
<td>2+3</td>
<td>2+4</td>
<td>3+2</td>
<td>3+3</td>
<td>3+4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Points</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
<td>160</td>
<td>180</td>
<td>200</td>
</tr>
</tbody>
</table>

Instructions for Physician:
Locate the patient's PSA on the PSA axis. Draw a line straight upwards to the Points axis to determine how many points the patient receives for his PSA. Repeat this process for the Clinical Stage and Biopsy Gleason Sum axes, each time drawing a straight line upwards to the Points axis. Then add up the points and have this sum on the Total Points axis. Draw a line straight down 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 patient who is not otherwise a candidate for radical prostatectomy. You can use this only on a patient who has already selected radical prostatectomy as treatment for his prostate cancer.

Instructions to Patient:
"Mr. X, if we had 100 men exactly like you, we would expect between (predicted percentage from nomogram - 10%) and (predicted percentage from nomogram + 10%) to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare."

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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


McNeal JE. The prostate gland: morphology and pathology. 1998:30-34


**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**

**Mucinous metaplasia**

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**IMMUNOHISTOCHEMISTRY**

- **Basal cells:**
  - 34BE12 (K903)
  - 4A4 (p63)
- **Acinar cells:**
  - PSA
  - AMACR (racemase)
- **Cocktail stains:**
  - PIN-4, Tri-view

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- **34BE12**
- **AMACR**

- small cluster
- Adj to bg glands
- silent cytoplasm
- nuclei
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

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

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Cases</th>
<th>2nd biopsy 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 → Distortion of acini
  - Lack of convincing malignant features → Clustered growth
  - Loss of focus in deeper sections (immuno) → Negative HMWCK
  - Presence of associated PIN → 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: Schlesinger et al. - AJSP 2005;29:1201-1207

Pathognomonic features of prostatic adenocarcinoma

Mucinous fibroplasia
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
- Verumtonum 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

Atrophic cancer
- Silent stroma
- Rigid glands
- Compressed cells
- Occasional nucleoli
### 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>=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</td>
<td>&lt;0.001</td>
<td>2.44</td>
</tr>
<tr>
<td>(Negative/Treatment Effect vs. Positive)</td>
<td></td>
<td></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</td>
<td>0.002</td>
<td>2.61</td>
</tr>
<tr>
<td>(Negative/Treatment Effect vs. Positive)</td>
<td></td>
<td></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