Concepts in Prostate Pathology

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Outline (1)

- Peculiarities of prostate cancer
- Peculiarities of prostate needle biopsy
  - Needle bx vs. TURP
  - Prostate cancer vs. breast cancer
  - Prostate needle bx vs. breast needle bx

Outline (2)

- High-grade PIN
  - Clinical significance
- Suspicious for malignancy
  - All ASAPs are not the same
- Accuracy vs. reproducibility
- Processing needle bx
  - Rationale for examining levels

Peculiarities of Prostate Cancer

Racial predilection

- African-Americans have highest incidence and mortality rate
  - ? Genetic
  - ? Diet (red meat)
  - ? Access to health care
- Followed by Caucasians, Hispanics, Asians ...... Alaska natives.

Racial predilection (contd)

- Implications for literature analysis
  - Cancer pick-up and survival rates vary depending on population studied
  - Original Partin Tables may not be applicable to African-Americans
    - only 6% in the cohort studied

High incidence of clinically insignificant cancer that “old men die with”

- Prostate cancer in up to 80% of men at age 80
- Bx protocols that pick up all cancers may do more harm than good
### Peculiarities of Prostate Cancer

Only a carefully selected proportion of pts undergo radical prostatectomy
- Accurate grade and stage data available only for this sub-group
- Data from this sub-group extrapolated to general population (eg. Partin’s table)
- Few high-grade cancers (Gleason 8-10) in radicals
  - Confidence limits for high-grade cancer in nomograms is wider

### Zonal Anatomy: McNeal’s model

- CZ: Central zone
- PZ: Peripheral zone
- TZ: Transition zone
- Fm: Anterior fibromuscular stroma
- Bn: Bladder neck

### Zonal Anatomy: Simplified

- Transition zone
- Peripheral zone

### Zonal Anatomy

**Transition zone**
- Inner gland
- Site of origin of BPH nodules
- Transition zone cancer
  - Generally low grade, low volume
  - Good prognosis
  - Sampled by TURP

**Peripheral zone**
- Outer gland
- Peripheral zone cancer
  - Clinically significant cancer
- Sampled by needle bx

<table>
<thead>
<tr>
<th>Area sampled</th>
<th>TURP</th>
<th>Needle bx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periurethral (transition zone)</td>
<td>Periurethral, posterior</td>
<td>Peripheral zone, posterior</td>
</tr>
<tr>
<td>Cancer</td>
<td>Ductal</td>
<td>Microacinar</td>
</tr>
<tr>
<td>Small volume, Gleason 2-4</td>
<td>Generally clinically insignificant</td>
<td>Often significant (so no Gleason &lt;5)</td>
</tr>
<tr>
<td>PIN</td>
<td>Rare</td>
<td>5%</td>
</tr>
<tr>
<td>Architecture</td>
<td>Easier to appreciate</td>
<td>May be difficult</td>
</tr>
<tr>
<td>Benign lesions</td>
<td>Nephrogenic adenoma, sclerosing adenosis, Clear cell cribriform hyperplasia</td>
<td>Seminal vesicle/ Ejaculatory duct</td>
</tr>
</tbody>
</table>
Peculiarities of Prostate Needle Bx

Most needle biopsies non-targeted
• Clinical/radiological/biochemical tests have low accuracy
• Bx has to carefully screened for tiny suspect foci
• Minimal cancer in bx does not equate to low volume prostate cancer

Tip of the Iceberg

• Prostate cancer often multifocal
  • Cancer in bx may not be dominant tumour
  • Implications for studies of prognostic markers

• Cancer often not apparent on macroscopic examination of radical prostatectomy specimen
  • Some cancers may still not be found even after specimen is all submitted:
    “vanishing prostate cancer”

Problems with Needle Bx Dx

Significant false negative rate
• All patients with benign biopsies must be followed up with serum PSA
• Only 2 management decisions based on histology
  • Repeat biopsy
  • Radical therapy
• Advising PSA follow-up based on biopsy findings is irrelevant

Significant sampling error
• Apparent grade or tumour volume progression on active surveillance may be due to undersampling in the previous bx
• Pattern 4 in re-bx had been missed in original 3+3=6 biopsy rather than representing disease progression
Problems with Needle Bx Dx

- “suspicious for cancer” cases cannot be easily resolved by re-biopsy or local excision

Gold Standard for Needle Biopsy Dx

- Not repeat biopsy
  - Benign repeat bx may be false negative
  - Cancer in repeat bx may be unrelated to the initial suspicious focus
- Not radical prostatectomy
  - “Vanishing prostate cancer”
- Only gold standard is THAT biopsy

Prostate Cancer vs. Breast Cancer

<table>
<thead>
<tr>
<th>Similarities</th>
<th>BREAST</th>
<th>PROSTATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender predominance</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Hormone dependence</td>
<td>Oestrogen</td>
<td>Androgen</td>
</tr>
<tr>
<td>Some clinically insignificant</td>
<td>Tubular carcinoma</td>
<td>Transitional zone</td>
</tr>
<tr>
<td>Screen detectable</td>
<td>Mammography</td>
<td>Serum PSA</td>
</tr>
<tr>
<td>Hormonal manipulation</td>
<td>Tamoxifen</td>
<td>Androgen ablation</td>
</tr>
<tr>
<td>In situ</td>
<td>DCIS</td>
<td>PIN</td>
</tr>
<tr>
<td>In situ vs. invasive</td>
<td>Myoepithelial cells (H/E and immuno)</td>
<td>Basal cells (H/E and immuno)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Differences</th>
<th>BREAST</th>
<th>PROSTATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable Tm</td>
<td>Often yes</td>
<td>Generally not</td>
</tr>
<tr>
<td>Radiol. localisatn</td>
<td>Reliable</td>
<td>Unreliable</td>
</tr>
<tr>
<td>Needle bx</td>
<td>Targeted</td>
<td>Non-targeted</td>
</tr>
<tr>
<td>Excision bx</td>
<td>Possible</td>
<td>Not possible</td>
</tr>
<tr>
<td>Serum marker</td>
<td>None</td>
<td>PSA</td>
</tr>
<tr>
<td>Final staging</td>
<td>Generally histological</td>
<td>Often only clinico-radiological</td>
</tr>
</tbody>
</table>

Prostate Cancer vs. Breast Cancer

DCIS

- Often segmental
- Treated by excision because precursor of cancer

High-grade PIN

- Generally multifocal
- Less important as precursor lesion
  - Elderly patients
  - PIN takes years to develop into cancer
  - Cancer takes years to become clinically significant
- Surrogate marker for missed cancer
  - Immediate repeat biopsy
### High-grade PIN
- Extended bx protocols have lower false negative rate
  - No need for repeat bx?
- More comparable with LCIS than DCIS
- Not necessary to report if cancer present

### Low-grade PIN
- Low risk of cancer in repeat bx
- Poor reproducibility
- Do not include in report

### Three Different ASAPs
1) Adenosis cannot exclude cancer
2) Cancer cannot exclude adenosis
3) ? Intraductal carcinoma

### Three Different Scenarios with Different Clinical Implications

#### 1) Cancer reported as suspicious
- Delay in diagnosis
- Limited clinical impact
  - Prostate cancer is indolent disease
  - 1 core 3+3 cancer may not require Rx (NICE guidelines in the UK)
  - Some centres would not re-bx (PSA F/U)

#### 2) Adenosis reported as suspicious
- Repeat biopsy, follow-up, anxiety

#### 3) ? Intraductal carcinoma
- Delay in diagnosis
- Significant clinical impact
  - Cancers with intra-ductal extension are generally aggressive tumours
  - Immediate repeat biopsy mandatory
  - ? Radical Rx: surgery/radioRx)
Reproducibility vs. Accuracy

- Reproducibility = getting the same answer every time (right or wrong)
- Accuracy = the right answer
  - Very difficult to determine
- Many of the criteria in the literature are about improving reproducibility rather than accuracy

Reproducibility Studies

Depends on
- Choice of participants
  - Intra-observer
  - Intra-departmental
  - National
  - International
- Choice of cases
  - Classic
  - Borderline

Processing Prostate biopsies

Why Process Prostate Bx Differently as Compared to Other Biopsies?

- Prostate cancers often small and not localised by clinical/TRUS examination
- Limited cancer in prostate bx ≠ minimal prostate cancer
- “suspicious for cancer” cases cannot be easily resolved by re-biopsy or local excision
- 18 gauge prostate biopsies thin and easily fold (cf. firmer thicker breast bx)

Breast vs. prostate needle bx (2x magnification)

18 Gauge Prostate Biopsies are Thin and Difficult to Embed Flat in a Single Plane

Breast

Prostate
Cutting Too Deep in First Level Could Result in Permanent Tissue Loss

Cardiff Bx Processing Protocol

- Cores processed separately
  - Easier to embed flat
  - Avoids overlapping cores
  - Avoids cores embedded in different planes
  - Permits adoption of targeted strategy for repeat biopsy
- 3 levels examined by H&E
- Unstained sections from each level saved for immunohistochemistry
  - Small foci often cut out in Deeper levels

Cardiff protocol: Advantages

- Biopsy embedded flat and examined along entire length
- Our MLSOs prefer embedding biopsies separately
- Only 1 slide/block

Advantages (contd)

Section in straight line so easier to screen
Immunostained section corresponds more closely with H&E section

Advantages (contd)

Cardiff protocol: *Drawbacks*

- More blocks to cut
- More blocks to store
  - At least 10 per case
- More unstained slides to store
  - Necessary to store indefinitely?

**Rationale for examining levels**

1. To find cancer deeper in core
2. To examine entire length of core

If cores embedded flat, 2 levels may be adequate

**Prostate Cancer and Evidence Based Medicine**

- “It is better to have no ideas than false ones; to believe nothing than to believe what is wrong”
  - Thomas Jefferson
- Bad evidence is worse than no evidence as it can result in inappropriate treatment and preclude search for better evidence