Role of Immunohistochemistry in Prostate Pathology

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Contemporary Surgical Pathology

• Foundation is the integration of clinical history, gross examination & microscopy
• Cornerstone is still the H&E with appropriate and judicious IHC support – *IHC guides and does not dictate the diagnosis*
• Made considerably more objective by ancillary techniques (IHC)
Prostate - IHC

Prostate lineage specific

- PSA, PSAP
- proPSA (*investigational*)

Basal cell associated

- HMWK (34ßE12), p63, CK 5/6, CK14
- Cystatin A, calcyclin (*investigational*)

“Prostate cancer specific”

- AMACR/p504S

Other markers in prostate

- Pancytokeratin
- Cytokeratin subset – CK7(-), CK20(-)
PSA/PSAP - IHC

**Principle:** Confirm prostatic acinar cell origin

(+) both benign and malignant prostate glands

**Indications:**
1) D.D. of prostatic vs. non-prostatic origin e.g. S.V., Cowpers gland, hyperplasia of mesonephric remnants, nephrogenic adenoma
PSA/PSAP - IHC

Indications: 2) Confirmation of prostatic cancer in a metastastic/extraprostatic setting

Caution: Not absolutely “prostate specific” Stains salivary gland and other neoplasms occasionally
HMCK(34ßE12)/p63 - IHC

**Principle:** Basal cells (+)
Cancer by definition lacks basal cells (-)

**Indication:** In the D.D. of benign vs. malignant proliferation

**Caution:** Dx of cancer is made on a negative immunoreaction
AMACR/P504S - IHC

Principle: Differential stain for malignant (+) vs. benign (-) prostate glands

Caution: Not absolutely specific/sensitive
Other Markers - IHC

Pancytokeratin

Poorly differentiated prostate cancer (+) vs. non-epithelial prostate cancer mimics (-)

CK subsets

Typical prostate cancer pattern $CK7(-)$, $CK\ 20(-)$ vs. non-prostatic origin
Role of IHC in Prostatic Needle Biopsy Specimens
Indications for IHC – Needle Biopsy

Pattern Based Approach

• Atypical small cell proliferation
• Atypical large acinar proliferation
• Post treatment setting
Indications for IHC – Needle Biopsy

Pattern Based Approach, Others

- Basal cell/Adenoid cystic-like
- Clear cell proliferation
- Small cell proliferation
- Signet ring
Indications for IHC – Needle Biopsy

Atypical Small Cell Proliferation

• To confirm focus as cancer
• Confirm benignity in ASAP felt to be benign
• Unusual patterns
  - Atrophic
  - Pseudohyperplastic
Specimen Handling – Needle Biopsy

- Save intermediate levels on gelatinized slides
- Obtain 2 levels on the “saved” slides
Basal Cell Layer Markers

• **HMCK** - “time honored”

• **p63** – more recent, nuclear, (?) better sensitivity

Recommendation: both as cocktail or whichever works better in your lab

• **Others : CK16, CK5/6** – value beyond HMCK, p63 not established
HMCK(34ßE12)/p63 - IHC

Interpretation:

• Insist on appropriate external and internal controls
• All glands in the focus considered ASAP should be negative
• Consistency of staining (2 levels on the slide with similar reaction)
HMCK(34βE12)/p63 - IHC

Pitfalls:

• Obvious benign glands may totally lack staining

• Variable negativity:
  Atrophy, AAH (adenosis), PAH

• Completely negative yet benign:
  Nephrogenic adenoma, MGH
HMCK(34βE12)/p63 - IHC

Pitfalls: (cont.)

• Stain in prostatic cancer
  - Entrapped benign gland
  - “Cancerization” and intraductal growth
  - High grade and metastatic cancer – usually focal if (+)
AMACR/P504S/Racemase - IHC

- cDNA library subtraction of human prostate tissue
- 207 cases (137 cancerous, 70 benign)
- 100% cancer positive for racemase
- 84-91% benign negative for racemase
- Strong cytoplasmic granular staining – suggestive of cancer
AMACR/P504S - IHC

(+) cumulative literature past 5 years:

- 82-100% Cancers
- 56-100% HGPIN
- 2-36% Benign
Interpretation guidelines:

- Granular cytoplasmic – luminal or entire cytoplasm
- Must be in conjunction with H&E and a basal cell layer marker
- Negative IR does not rule out cancer
- Positive IR does not automatically indicate prostate cancer (see pitfalls)
- Circumferential staining
- Staining must be stronger than adjacent benign gland
AMACR/P504S - IHC

• Pitfalls (false -)
  • 5-10% typical cancers
  • Varies on pattern of cancer
    - 30% atrophic cancer
    - 32% foamy gland
    - 23% pseudohyperplastic
  • (+) in usual, ductal, signet ring – sensitivity varies
  • (+) post Rx (related to degree of Rx effect)
AMACR/P504S - IHC

- **Pitfalls (false +)**
  - Benign
    - Rare benign glands, atrophy, PAH, SV, NA
  - Premalignant
    - AAH
    - PIN
  - Malignant
    - Urothelial Ca
    - Metastatic colonic Ca
Prostate Cocktail

- **Basal cell cocktail**
  - p63 and 34βE12

- **Triple cocktail “PIN cocktail”**
  - p63/34βE12/AMACR
Triple Cocktail

• HWCK/p63 – basal cells
• AMACR – cancer cells
• 37 – 68% of “atypical” cases were confirmed as cancer
• Overcomes problems associated with individual markers
• Foci often limited
Triple Cocktail

• Expected reactions
  • PCa: \textit{p63}(-), \textit{HMCK}(-), \textit{AMACR}(+)
  • Benign small cancer mimics: \textit{p63}, \textit{HMCK}(+), \textit{AMACR}(-)
  • HGPIN: \textit{p63}, \textit{HMCK}(+), \textit{AMACR}(-/+)
  • Ductal cancer:
    - \textit{Invasive component}: \textit{p63}, \textit{HMCK}(-), \textit{AMACR}(+)
    - \textit{Intraductal component}: \textit{p63}, \textit{HMCK}(+), \textit{AMACR}(+)
  • Urothelial cancer: \textit{p63}, \textit{HMCK}(+/-), \textit{AMACR}(+)
Post-Treatment Prostate Cancer

- **Recommended panel**
  - CK – to detect isolated PCa cells
  - PIN cocktail – to confirm malignancy
  - MIB1 (investigational)
PSA/PSAP - IHC

• Indications: *within prostate*

• Panel more effective
  - Cancer (+) vs. mimics (-)
    SV, Cowper’s gland, paraganglia, nephrogenic adenoma, hypermesonephric remnants
  - Cancer (+) vs. inflammation (-)
    Granulomatous, xanthoma
  - Variants vs. metastasis:
    Ductal, mucinous, signet ring, small cell
PSA/PSAP - IHC

• Pitfalls – false (+):
  - Seminal vesicle:
    (+) 32% with polyclonal antibody
    (-) with monoclonal antibody
  - Nephrogenic adenoma
    Rare weak (+)
PAN CYTOKERATIN - IHC

• Poorly differentiated carcinoma (+) vs.
  - granulomatous inflammation (-)
  - crushed/marked inflammation (-)
  - xanthoma (-)

• Post-treatment cancer
  - Identify individual “atrophic” cancer cells
Role of IHC in Metastatic or Regional Prostate Cancer
PSA/PSAP

Indications:

• Metastasis
  - Tumor of unknown primary
  - Confirm prostate cancer diagnosis

• Pelvic tumor
  - Prostate vs. high grade UCa (or with glandular differentiation)
  - Prostate vs. urethral adenocarcinoma, enteric type
PSA/PSAP – In Metastasis

**Pitfalls**

- Poorly differentiated prostate cancer (-)
- False (+)
  - Salivary gland
  - Breast carcinoma
  - Urothelial carcinoma
  - Periurethral gland adenocarcinoma
  - Neuroendocrine neoplasm (PSAP)
proPSA

- (+) benign/malignant prostate glands
- Stronger intensity than PSA/PSAP
  - \([-5/-7]\) proPSA antibody
- Enhanced detection for poorly differentiated prostate cancer
  - \(\text{PSA/PSAP} (-) \text{ PCa can be proPSA } (+)\)
- Maybe better for metastatic Pca

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# Unusual Situations in Prostate IHC

## D.D. of prostate vs. bladder

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Bladder</th>
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<tbody>
<tr>
<td>PSA (+)</td>
<td>PSA (-)</td>
</tr>
<tr>
<td>PSAP (+)</td>
<td>PSAP (-)</td>
</tr>
<tr>
<td>HMCK (-)</td>
<td>HMCK (+)</td>
</tr>
<tr>
<td>p63 (-)</td>
<td>p63 (+)</td>
</tr>
<tr>
<td>CD57 (+)</td>
<td>CD57 (-)</td>
</tr>
<tr>
<td><em>Thrombomodulin</em> (-)</td>
<td><em>Thrombomodulin</em> (+)</td>
</tr>
</tbody>
</table>
# Unusual Situations in Prostate IHC

**D.D. of prostate vs. carcinoid tumor**

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Carcinoid tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (+/-)</td>
<td>PSA (-)</td>
</tr>
<tr>
<td>PSAP (+/-)</td>
<td>PSAP (-)</td>
</tr>
<tr>
<td>CD57 (+)</td>
<td>CD57 (+)</td>
</tr>
<tr>
<td>Synap (+/-)</td>
<td>Synap (+)</td>
</tr>
<tr>
<td>Chromo (+/-)</td>
<td>Chromo (+)</td>
</tr>
<tr>
<td>Vimentin (-)</td>
<td>Vimentin (+/-)</td>
</tr>
<tr>
<td>Androgen R (+)</td>
<td>Androgen R (-)</td>
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Unusual Situations in Prostate IHC

D.D. of prostate ductal vs. colonic cancer

Prostate: PSA, PSAP (+)
Colonic: CDX2 (+)