Evaluation of Prostate Cancer and “Atypical” on Needle Biopsy

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Difficulty in Underdiagnosing Prostate Cancer

- Limited tissue on needle biopsy (1 cm. x <1mm.)
- Limited cancer on needle biopsy
- Histologic findings often subtle

Diagnosis of Prostate Cancer

- Use a systematic approach to the diagnosis of prostate cancer based on specific architectural, cytological, and ancillary features.

*Diagnostic criteria of limited adenocarcinoma of the prostate on needle biopsy (Epstein: Hum Pathol 1995)*

- With the exception of three findings that by themselves are specific for cancer, the diagnosis of prostate cancer is based on a constellation of features.

Features Favoring The Diagnosis of Adenocarcinoma

- Abnormal architectural pattern
- Nuclear enlargement
- Nuclear hyperchromasia
- Prominent nucleoli
- Mitotic/apoptotic figures
- Amphophilic cytoplasm
- Blue mucinous secretions
- Pink amorphous secretions
- Crystalloids
Submitting Separate Jars/Each Sextant Site

- Distribution of cancer for planning RT (e.g., brachytherapy)
- Location of cancer helps target additional tissue or block sampling in cases with no apparent cancer in radical prostatectomy
- Biopsy site helps recognize potential diagnostic pitfalls (e.g., SV or CZ, seen at base & Cowper's glands at apex)
- In “atypical” cases, directs more focused repeat biopsies
- 1-2 cores per slide helps block/slide preparation with complete visualization of cores and detection of small foci of cancer
- 1-2 cores reduces fragmentation to determine number of cores involved

Other Processing Issues

- Intervening unstained sections
- Fixative
Apoptosis & Nucleoli

- Mitotic figures (13%) and apoptotic bodies (34%) more common in cancer and HGPIN.
- Number and position of nucleoli do not distinguish between cancer and benign mimickers.

*Number & location of nucleoli and presence of apoptotic bodies in diagnostically challenging cases of prostate adenocarcinoma on prostate needle biopsy. Aydin, Zhou, Herawi, & Epstein (Hum Path 2005)*
Features Diagnostic of Adenocarcinoma

- Perineural invasion
- Glomerulations
- Mucinous fibroplasia (collagenous micronodules)

Perineural invasion, mucinous fibroplasia, and glomerulations: diagnostic features of limited cancer on prostate needle biopsy. Baisden, Kahane, & Epstein (AJSP 1999)
Perineural and Intraneurral Involvement by Benign Glands

*Perineural involvement by benign prostatic glands on needle biopsy. Ali & Epstein (AJSP 2005)*
Cancers Mimicking Benign Glandular Proliferations

- Pseudohyperplastic prostate cancer
- Foamy gland prostate cancer
- Atrophic prostate cancer

Pseudohyperplastic Adenocarcinoma

Unusual variant of prostate adenocarcinoma with architecturally benign-appearing glands first reported by Hopkins.

- Patterns include:
  - Glands with papillary infolding
  - Branching glands
  - Large dilated glands
Prognosis

- When carcinomas with pseudohyperplastic features are diagnosed on biopsy, they represent tumors arising in either the TZ or PZ. They are not low-grade, have considerable tumor volume, and in some cases extend out of the prostate.

*Pseudohyperplastic prostatic adenocarcinoma on needle biopsy and simple prostatectomy. Levi & Epstein (AJSP 2000).*

Foamy Gland Carcinoma

- Despite bland cytologic appearance, corresponding RP’s showed:
  - Gleason score 5-7 in 93%
  - EPE in >50%
  - Positive margins in 27%
  - Metastases to pelvic nodes in 13%

Adenocarcinoma with Atrophic Features

- Can be seen de novo or in prostates treated with hormonal therapy
- In biopsy or TURP material, most have no history of anti-androgen therapy

*Adenocarcinoma of the prostate with atrophic features. Cina & Epstein (AJSP 1997)*

**Diagnostic Criteria**

1) Infiltrative growth pattern
2) Macronucleoli
3) Presence of adjacent non-atrophic cancer
Features Against The Diagnosis of Adenocarcinoma

- Atrophic cytoplasm
- Merging in with benign glands (r/o adenosis)
- Corpora amylacea
- Inflammation
- Adjacent PIN (r/o PINATYP)

Most Common Mimickers of Cancer on Needle Biopsy
• Partial Atrophy: The most common mimicker of prostate cancer on needle biopsy

*Partial Atrophy in Prostate Needle Cores: Another diagnostic pitfall for the surgical pathologist. Oppenheimer & Epstein (AJSP 1998)*
**Adenosis – Needle Biopsy**

- 16% with more than 1 focus
- One of the more difficult diagnoses on biopsy
- Difficult to appreciate lobular architecture

- *Gaudin PB, Epstein JJ. Adenosis of the Prostate: Histologic features in needle biopsy specimens. (AJSP 1995).*
Nonspecific Granulomatous Prostatitis

Pitfalls

- Mimics cancer clinically
- Most histological patterns do not resemble cancer
- Rare epithelioid variant easily confused with high grade cancer

Diagnosis – Special Techniques

• Benign prostate glands – Contain basal cells beneath secretory cells, thought to be stem cells.

• Prostate cancers – Lack basal cells.

• Markers that stain basal cells
  – High molecular weight cytokeratin
  – p63
Pitfalls with Basal Cell Markers

- Entirely benign glands may not stain for basal cell markers
- More commonly negative staining non-cancerous glands include: adenosis, partial atrophy, and high grade PIN.
- Cancer cells may occasionally stain nonspecifically (not in a basal cell distribution).
- Very rarely, cancers can demonstrate basal cells

Use of Basal Cell Markers

- Atypical favor cancer - negative staining, confirm diagnosis of cancer
- Atypical favor benign - negative staining, call atypical
- Benign - negative staining, call benign

Diagnosis – Special Techniques

- Marker that selectively stains adenocarcinoma of the prostate and is negative in benign prostate glands
- Alpha-methylacyl-CoA-racemase (AMACR) which is an enzyme involved in β-oxidation of branched-chain fatty acids
- Antibody to racemase (P504s)

**Pitfalls with Racemase**

**FALSE POSITIVES:**
- Labels high grade PIN
- Occasionally stains entirely benign glands
- Occasionally partial atrophy and adenosis

**FALSE NEGATIVES:**
- Up to 20% of small foci of adenocarcinoma may be negative

*Magi-Galluzzi C., Luo J, Isaacs WB, Hicks JL, DeMarzo AM, Epstein JI. AMACR: A variably sensitive immunohistochemical marker for the diagnosis of small prostate cancer foci on needle biopsy. (AJSP 2003).*

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**Atypical Needle Biopsies**

- Not use term “atypical hyperplasia”
- Problem with the term “atypical small acinar proliferation” (ASAP)
- Sign out descriptively

*Farinola MA, Epstein JJ. Utility of immunohistochemistry for alpha-methylacyl-coa racemase (AMACR) in distinguishing atrophic prostate cancer from benign atrophy. (Hum Pathol 2004).*

Atypical Signout

Prostate with small focus of atypical glands. See note:

Note: Although the findings are atypical and suspicious for adenocarcinoma, there is insufficient cytologic and/or architectural atypia to establish a definitive diagnosis. Repeat biopsy is recommended.

Incidence of Atypical on Biopsy
24 Studies

- Mean 5.0%
- Median 4.1%

Reasons for Atypia

- Atypia NOS 31.6%
- R\O adenosis 13.9%
- Atrophic glands 11.4%
- Crush artifact 11.4%
- Inflammation 10.1%
- R\O PIN 5.1%

Atypical on Biopsy: Subsequent Risk of Cancer
(21 Studies)

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<tbody>
<tr>
<td>Mean</td>
<td>40.2</td>
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<td>Mean ≥50 patients</td>
<td>41.1</td>
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<td>Median</td>
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Following Needle of a Benign Diagnosis (21 studies) Risk for Cancer (Mean & Median): 19%
Clinical Factors to Predict Cancer

• Of 10 studies, 9 found that serum PSA levels were not predictive of cancer on re-biopsy.

• Digital rectal exam or transrectal ultrasound not influential in predicting which men with atypical on needle biopsy will have carcinoma on re-biopsy.

*Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: Implications for patient care. (J Urol 2006).*

Atypical Follow-up Biopsy Strategy

• Cancer on repeat biopsy often at or adjacent to initial atypical site.

• Initial biopsies should be submitted to preserve location of each biopsy.

• Recommend repeat biopsy:
  - 3 cores at site of initial atypical
  - 2 cores at adjacent sites
  - 1 core elsewhere

*Allen EA, Kahane H, Epstein JI. Repeat biopsy strategies for men with atypical diagnoses on initial prostate needle biopsy. (Urology 1998).*

Summary

• With the exception of a few findings, the diagnosis of adenocarcinoma of the prostate is based not on any single feature, but on a constellation of features.

• One should weigh features for and against the diagnosis of cancer.

• Even in the setting of a few atypical glands, if there are several features in favor of cancer and nothing against cancer, a definitive diagnosis of cancer can be made.