48 Prostate Needle Biopsy Interpretation and Reporting: Contemporary Issues and Emerging Concepts

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Prostate needle biopsy is one of the most common specimen types received in surgical pathology laboratories. However, there is significant error rate in diagnosing cancer in prostate biopsy, slow adoption of the modified Gleason grading system, and considerable variation in reporting. This course will use real-life prostate biopsy cases to discuss the practical issues pathologists encounter in their daily practice. The topics will include:

1. Comprehensive review of the histological criteria for diagnosis of limited cancer in prostate needle biopsy and use of immunohistochemical markers in such setting.
2. Benign mimickers of prostate cancer and cancer that mimics benign prostate lesions.
3. New concepts and entities of important clinical significance in prostate pathology.
4. Modified Gleason grading system on prostate biopsy.
5. Reporting of prostate biopsy to include clinically relevant histological parameters.
6. Brief overview of new molecular and genetic markers that have potential to impact the prostate biopsy diagnosis.

- Provide practical guideline and tips for using the modified Gleason grading scheme
- Provide an update on new concepts and entities of important clinical significance in prostate pathology
- Identify clinically relevant histological parameters that should be included in the surgical pathology report

FACULTY:

Ming Zhou MD, PhD
Rajal Shah MD, FASCP
Practicing Pathologists
Surgical Pathology
Surgical Pathology (GI, GU, Etc.)
2.0 CME/CMLE Credits

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Prostate Needle Biopsy Interpretation and Reporting: Contemporary Issues and Emerging Concepts

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Disclosure

• No conflict of interest*

* Dr. Rajal B. Shah works for Caris Life Sciences but has no conflict of interest related to this presentation

Case 1

➢ 67 year-old male with elevated PSA (5.2 ng/ml). Digital rectal examination was normal. He underwent sextant biopsy.
Case 1

- Which of the following is the best diagnosis?
  - Low grade prostatic intraepithelial neoplasia (low grade PIN)
  - High grade PIN
  - Benign central zone glands
  - Basal cell hyperplasia

Prostatic Intraepithelial Neoplasia (PIN)

- Preferred diagnostic term for a putative pre-malignant proliferation of atypical epithelial cells within the pre-existing prostatic ducts and acini
- Can only be diagnosed by histology
- No specific clinical, radiological findings
- Does not cause PSA elevation
Prostatic Intraepithelial Neoplasia (PIN)

- Preferred diagnostic term for a putative pre-malignant proliferation of atypical epithelial cells within the pre-existing prostatic ducts and acini
- Can only be diagnosed by histology
- No specific clinical, radiological findings
- Does not cause PSA elevation

PIN: Histological Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low grade PIN</th>
<th>High grade PIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Basophilic appearance</td>
<td>Similar to LGPIN, but more pronounced</td>
</tr>
<tr>
<td></td>
<td>Normal glandular architecture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luminal cell crowding, irregular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>spacing, multilayering</td>
<td></td>
</tr>
<tr>
<td>Luminal cell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclei</td>
<td>Enlarged, marked size variation</td>
<td>Enlarged, size and shape variation</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Normal</td>
<td>Course and clumped</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Inconspicuous</td>
<td>Large and prominent, similar to PCa</td>
</tr>
<tr>
<td>Cytosolm</td>
<td>Amphophilic</td>
<td>Amphophilic</td>
</tr>
<tr>
<td>Basal cell layer</td>
<td>Intact</td>
<td>Often discontinuous, or absent</td>
</tr>
</tbody>
</table>
Low-grade PIN: A Diagnosis That Should Not Be Made

- Poor interobserver reproducibility
- Not associated with cancer risk in subsequent biopsy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade PIN</td>
<td>18%</td>
</tr>
<tr>
<td>Benign</td>
<td>20%</td>
</tr>
</tbody>
</table>

Humphrey PA: Prostate Pathology

PIN: Histological Diagnosis

- Distinct, prominent nucleoli: the best discriminator between LGPIN & HGPIN
- Mitosis, marked nuclear pleomorphism or hyperchromasia
- Diagnosis is subjective: err on conservative side

LGPIN, signed as benign prostatic tissue
High Grade PIN

Differential Diagnosis

- Benign
  - Prostatic central zone glands
  - Seminal vesicle/ejaculatory duct epithelium
  - Reactive atypia due to inflammation, infarction or radiation
  - Metaplasia (transitional cell, squamous cell)
  - Hyperplasia (clear cell cribriform hyperplasia, basal cell hyperplasia)
- Malignant
  - Prostate carcinoma with cribriform pattern
  - PIN-like prostate carcinoma
  - Intraductal carcinoma of the prostate
  - Ductal adenocarcinoma
  - Urothelial carcinoma

Significance of High Grade PIN

- Short-term cancer risk (marker for concomitant, but missed, cancer in initial biopsy, within 12 months)
- Long-term cancer risk (precursor lesion to prostate cancer, within 1-3 years?)

HGPIN: Risk of PCa in Repeat Bx

<table>
<thead>
<tr>
<th>Year</th>
<th>Cancer Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HGPIN</td>
<td>Benign</td>
</tr>
<tr>
<td>1995 and before (n=796)</td>
<td>48.4%</td>
<td>17.6%</td>
</tr>
<tr>
<td>1996-1999 (n=623)</td>
<td>32.4%</td>
<td>17.7%</td>
</tr>
<tr>
<td>2000 and later (n=10838)</td>
<td>21.9%</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

P value: <0.001 | 0.42

Analysis by M Zhou using data in Epstein & Herawi, J Urol 2006
HGPIN Cancer Risk Is Related to the Extent of Initial Bx

<table>
<thead>
<tr>
<th># Bx cores</th>
<th>Cancer Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 (n=5379)</td>
<td>24.9%</td>
<td>18.4%</td>
</tr>
<tr>
<td>≥ 8 (n=716)</td>
<td>16.1%</td>
<td>12.7%</td>
</tr>
</tbody>
</table>

P value <0.001 0.048

HGPIN diagnosed on extended bx is not associated with increase cancer risk and probably does not need repeat bx

Clinicopathological Parameters Predicting Cancer Risk Associated with HGPIN

- Clinicoradiological parameters
  - PSA (total PSA, free PSA, PSA velocity) and DRE not associated with the risk of PCa in repeat bx
  - Imaging (ultrasound or MRI) does not predict cancer risk
- Tumor markers
  - Maybe useful, but not in clinical use yet
- Pathological parameters
  - Morphology (flat vs. tufting vs. micropapillary vs. cribriform) not associated with cancer risk in repeat bx
- # cores involved by HGPIN
  - Uni-focal HGPIN not associated with increase Ca risk
  - Multi-focal (≥2) associated with a significantly increased cancer risk

Long-term Risk of Cancer Following High Grade PIN Diagnosis

- Scant data on the natural history of HGPIN
- Recommend repeat biopsy 2-3 years after initial HGPIN diagnosis
If HGPIN is multi-focal, consider rebiopsy

**Predictive value of HGPIN for PCa declined significantly in recent years due to a variety of factors**
- Use stringent diagnostic criteria
- Report extent of HGPIN

**Case 2**
- 76 year-old man with elevated PSA (6.4 ng/mL). He underwent extended 12-core biopsy.
Case 2

- Which of the following is the best diagnosis?
  - Benign
  - Atypical glands suspicious for cancer
  - Prostate carcinoma

Atypical Glands Suspicious for PCa (ATYP)

- Diagnostic term: a gland or a focus of glands suspicious for PCa, but lack sufficient architectural/cytological atypia to establish a definitive dx
- Not a biological entity, but to convey pathologist’s uncertainty regarding the diagnosis
- Many terms have been used
  - Atypia
  - Atypical hyperplasia
  - Borderline lesion
  - Uncertain biological behavior
  - Atypical small acinar proliferation (ASAP)
Histological Features Resulting in ATYP

- Limited number of glands (PCa minimally sampled in biopsy)
- Biopsy and tissue processing artifact
  - Crush artifact obscuring histology
  - Atypical glands at the tip or edge of biopsy core
- Atypical morphology not cancer specific
  - Crowded glands with minimal cytological atypia (cancer vs adenosis)
  - Atypia in atrophic glands (atrophic PCa vs benign atrophy)
  - ATYP adjacent to HGPIN (PINATYP, microinvasive cancer vs outpouching or tangential sectioning off HGPIN)
  - Atypia in the presence of inflammation (inflamed PCa vs reactive atypia)
- Confusing immunohistochemistry
  - Non-PCa glands with + AMACR

ATYP: due to limited number of glands

ATYP: due to limited atypical histological features
ATYP: due to atrophic glands

ATYP: Atypical Glands at the Edge of the Biopsy Core

ATYP: Can’t Rule Out HGPIN
ATYP: Can’t Rule Out Adenosis

ATYP: due to inflamed glands

HGPIN with Adjacent Atypical Glands (PINATYP)
Atypical Glands Suspicious for PCa (ATYP)
Incidence in Needle Biopsy

- Mean: 5.0%
- Median: 4.4% (range 0.7-23.4%)
- Trend towards lower incidence in recent studies

Schlesinger et al, AJSP 2005

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Atypical Glands Suspicious for PCa (ATYP)
Cancer Risk in Subsequent Biopsy

<table>
<thead>
<tr>
<th>Year</th>
<th>Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1996</td>
<td>45%</td>
</tr>
<tr>
<td>1997-1999</td>
<td>39%</td>
</tr>
<tr>
<td>2000-2005</td>
<td>41%</td>
</tr>
</tbody>
</table>

Schlesinger et al, AJSP 2005

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Atypical Glands Suspicious for PCa (ATYP)
Clinicopathological Predictors of Cancer in Subsequent Bx

- No correlation between PSA measurements (PSA, free PSA, PSA velocity), DRE, TRUS and subsequent PCa detection
- Pathological parameters
  - ATYP favor cancer: Cancer risk: 60%
  - ATYP indeterminate: Cancer risk: 25-55%
  - ATYP favor benign: Cancer risk: 20-33%
- Multiple repeat biopsies
  - ~ 90% PCa detected in the 1st repeat bx

Epstein and Herawi J Urol 2006
Case 3

- 72 year-old man with elevated PSA. He underwent extended 12-core biopsy.
Case 3

Which of the following is the best diagnosis?

- Prostate carcinoma, as some glands are negative for K903 and positive for AMACR (P504S)
- Definitely benign
- Atypical glands (ASAP, ATYP)

Immunohistochemistry for Differential Diagnosis of PCa

- To distinguish PCa from benign mimics
  - Basal cell markers (High molecular weight Cytokeratin [HMWCK], P63)
  - Alpha-methylacyl-CoA-Racemase (AMACR, P504S)
  - ERG rearrangement product (Park et al, Neoplasia 2010; Furusato et al, Prostate Cancer Prostatic Dis, 2010)

- To distinguish poorly differentiated PCa from TCC, colonic adenocarcinoma, etc
  - Prostate-specific markers (PSA, PSAP, PSMA, P501S)
  - Cytokeratins (CK7, CK20)
  - P63, HMWCK
  - Lineage-specific markers (CDX-2, TTF-1, etc)
Prostate Basal Cell Markers

- HMWCK
- P63
- CK5/6
- CK14

Useful in resolving atypical diagnoses
- Establish, confirm or change diagnosis in 64% Nbx (Wojno and Epstein, AJSP, 1995)
- Reduce ASAP from 8.3% to 0.4% (Kalousec, Urology, 1995)

Useful in diagnosing
- Pseudohyperplastic, foamy gland, atrophic PCa, radiation atypia

Diagnostic Pitfall: Basal Cell Markers Can Occasionally Be Absent in Non-PCa Lesions

- HMWCK sensitive to formalin fixation with progressive loss of immunoreactivity with increased fixation time (Varma, Mod Pathol, 1999)
- Centrifugal decrease of HMWCK staining in benign glands (Goldstein, AJCP, 1999)
- HGPIN, adenosis, partial atrophy: fragmented, patchy basal cell staining
- Absolutely critical to study the benign glands as internal positive control
Alpha-Methylacyl-CoA Racemase (AMACR, P504S)

- Key enzyme in metabolism of branched-chain fatty acids and bile acid intermediates
- Preferentially overexpressed in PCa (Xu 2000; Rubin 2002; Luo 2002)
- Detected with monoclonal antibody P504S
- Also overexpressed in other tumors (colon, lung, breast, papillary RCC, etc.) (Zhou 2003)
AMACR Expression May Be Detected in Morphologically Benign Glands

Benign

PCa

Heterogeneous AMACR Expression in PCa

Utility of AMACR in Diagnosis of PCa

- Staining frequently weak and heterogeneous
- Foamy and Pseudohyperplastic PCa: lower sensitivity
- Positive staining in PCa 62- 95% in needle biopsies (average 80%)
- Positive staining supports PCa diagnosis
- Negative staining in suspicious focus may not exclude PCa
Expression of AMACR in PCa and Non-PCa Lesions

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Antibody Type</th>
<th>Pca (%)</th>
<th>HGPIN</th>
<th>Benign (%)</th>
<th>NA (%)</th>
<th>AAH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al</td>
<td>2001</td>
<td>P504S</td>
<td>100%</td>
<td>+</td>
<td>12%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Jiang et al</td>
<td>2002</td>
<td>P504S</td>
<td>94.50%</td>
<td>NA</td>
<td>0%</td>
<td>0%</td>
<td>17.50%</td>
</tr>
<tr>
<td>Beath et al</td>
<td>2002</td>
<td>P504S</td>
<td>82%</td>
<td>NA</td>
<td>0%</td>
<td>9%</td>
<td>11.50%</td>
</tr>
<tr>
<td>Luo et al</td>
<td>2002</td>
<td>P-AMACR</td>
<td>88%</td>
<td>Majority</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubin et al</td>
<td>2002</td>
<td>P-AMACR</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kunju et al</td>
<td>2003</td>
<td>P504S</td>
<td>90%</td>
<td></td>
<td>20%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Skinnider et al</td>
<td>2004</td>
<td>P504S</td>
<td>90%</td>
<td></td>
<td>20%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Gupta et al</td>
<td>2004</td>
<td>P504S</td>
<td>90%</td>
<td></td>
<td>20%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Wu et al</td>
<td>2004</td>
<td>P504S</td>
<td>90%</td>
<td></td>
<td>20%</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

NA=Nephrogenic adenoma, AAH= adenosis

Antibody Cocktails in PCa Diagnosis

- AMACR + basal cell marker cocktail
  - AMACR+ basal cell markers equivalent to each antibody alone in staining pattern, sensitivity and specificity (Hameed, AJSP 2005; Trpkov, AJCP 2009)
  - Useful on biopsy with small focus of cancer

Diagnostic Utility of Antibody Cocktails in PCa Diagnosis
TMPRSS2 and ERG Gene Fusion in Prostate Cancer

- Fusion between androgen-activated TMPRSS2 and ERG genes occurs in 40-50% of prostate cancer in PSA-screened radical prostatectomy series
- Immunohistochemistry using ERG antibody highly correlates with the gene fusion status (Park et al, 2010; Furusato et al, 2010)
- Potentially useful for prostate biopsy evaluation (Yaskiv et al, 2011)

P63 + ERG Cocktail

Immunohistochemistry in DDx of PCa

Summary

- Not a screening test
  - Applied to selected cases whose ddx includes PCa based on H&E morphology
- IHC must be interpreted in the context of H&E morphology
  - Clearly define benign and atypical glands on H&E
  - Nature of atypical glands: favor PCa vs favor benign
  - Use IHC to support/verify H&E diagnosis
Disclosure

• No conflict of interest*

* Dr. Rajal B. Shah works for Caris Life Sciences but has no conflict of interest related to this presentation

Case 4
A 60-year-old male presented with an elevated PSA of 5 ng/ml. The patient underwent 12 core biopsies. Representative images are shown.
Haphazard proliferation of several large to mid size glands, frequent undulated architecture resembling benign proliferation like BPH.
Basal cell cocktail antibodies: p63+34betaE12

Adenocarcinoma of prostate with pseudohyperplastic features: 3+3=6.

Foamy gland carcinoma
Pseudohyperplastic carcinoma
Adenocarcinoma with atrophic features
Adenocarcinoma with glomeruloid features
Ductal adenocarcinoma
Mucinous (colloid) carcinoma
Small cell neuroendocrine carcinoma
Sarcomatoid carcinoma (carcinosarcoma)
Signet ring cell carcinoma
Squamous and adenosquamous carcinoma
Adenoid cystic basal cell carcinoma
Urothelial carcinoma

Histologic Variants of Prostate Carcinoma

- Histologic variants account for 5% to 10% of prostate carcinomas
- Typically associated with ordinary acinar prostate adenocarcinoma
- Morphologic spectrum range from tumors resembling benign conditions to highly aggressive forms
- Often differ from acinar carcinoma in clinical, immunophenotypic, and genetic features

<table>
<thead>
<tr>
<th>Histological pattern of cancer</th>
<th>Benign condition they may mimic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foamy gland carcinoma</td>
<td>Cowper’s glands, mucinous metaplasia, xanthomatous inflammation</td>
</tr>
<tr>
<td>Atrophic carcinoma</td>
<td>Benign atrophy</td>
</tr>
<tr>
<td>Pseudohyperplastic carcinoma</td>
<td>Benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia (PIN)</td>
</tr>
</tbody>
</table>
Crowded glands with abundant "xanthomatous" cytoplasm, low N:C ratio, eosinophilic secretions and concomitant ordinary cancer

Foamy gland carcinoma
Gleason score 3+3=6

Poorly differentiated Foamy gland carcinoma mimicking Xanthoma cells
- CD 68 negative, CK positive

Adenocarcinoma of prostate with pseudohyperplastic features, Gleason Score 3+3=6
Dx: Atypical glands, suspicious for pseudohyperplastic carcinoma. Cannot rule out HGPIN.

Prostate adenocarcinoma with atrophic features
Carcinomas mimicking benign lesions: take home points

- Be aware about these histologic variations
- Diagnosis should be made cautiously in presence of few glands only
- Concomitant conventional acinar cancer usually present
- IHC helpful – though AMACR can be negative due to low sensitivity
Ductal adenocarcinoma with solid-papillary growth patterns

Ductal Adenocarcinoma: Immunoprofile

D/D:
Urothelial carcinoma
Colonic adenocarcinoma

- PSA +
- PSMA +
- HMWCK -
- P63 -
- Thrombomodulin -
- Beta catenin -
- CDX2 -

Ductal adenocarcinoma with intraductal spread
**Case 5:**
A 70-year-old male presented with an abnormal digital rectal examination and elevated PSA of 10 ng/ml. The patient underwent 12 core biopsies. The representative images are shown.
A contemporary approach to the Gleason grading in needle biopsies/2005 ISUP Gleason grading recommendations

Natural history of prostate cancer progression

- Which localized cancers will recur biochemically, metastasize and can be lethal?
- Which localized cancers are clinically innocuous and can be conservatively managed?

| TABLE I. Clinical Stage T1c (nonpalpable, PSA elevated) |
|-------------|-------------|
| PSA Range (ng/mL) | 0–2.5 | 2.6–4.0 | 4.1–6.0 | >6.0 |
| Pathologic Stage | Organ confined | Extraprostatic extension | Seminal vesicle (+) | Lymph node (+) |
| Gleason Score 2-4 | 95 (89–99) | 8 (2–18) | — | — |
| 5-6 | 90 (88–93) | 15 (13–18) | 0 (0–1) | 0 (0–1) |
| 3+4=7 | 79 (74–85) | 27 (22–33) | 2 (1–5) | 2 (1–5) |
| 4+3=7 | 71 (62–79) | 25 (18–34) | 4 (1–5) | 4 (1–5) |
| 8-10 | 66 (54–76) | 28 (20–38) | 6 (3–12) | 6 (3–12) |

KEY: PSA = prostate-specific antigen.
NCCN Recurrence Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>T1c plus Gleason score 2–6 plus PSA &lt; 10 ng/mL</td>
</tr>
<tr>
<td>Low</td>
<td>T1-T2a plus Gleason score 2–6 plus PSA &lt; 10 ng/mL (only 1 in 14 will die from prostate cancer)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>T2b–T2c or Gleason score 7 or PSA 10–20 ng/mL (11% will die from prostate cancer within 15 y)</td>
</tr>
<tr>
<td>High</td>
<td>T3a or Gleason score 8–10 or PSA &gt; 20 ng/mL</td>
</tr>
<tr>
<td>Very high</td>
<td>T3b–T4 (locally advanced) or metastasis present</td>
</tr>
</tbody>
</table>

Significance of Gleason score

- Predicts outcome after various forms of treatments (active surveillance (watchful waiting), radical prostatectomy, radiation)
- Low GS (<=6) may be candidate for active surveillance treatment
- GS 7 often a critical decision making step – need for some type of definitive therapeutic intervention (e.g. lymph node dissection for pt. undergoing prostatectomy)
- Gleason score 8-10 often candidate for adjuvant therapy or radiation therapy

Contemporary approach to Gleason grading-Why?

- Practice change in 40 years
  - Stage migration
  - Sampling strategy
- Special techniques
  - Immunoperoxidase (CribriformPIN / Adenosis)
- Variants
- Tertiary grade issue
- Correlation between biopsy and RP is not very good – under grading of biopsy a significant problem
2005 ISUP Modified Gleason Grading of Prostate Cancer: Key Issues

• Clean Gleason pattern 3 or less group
• Clarify Gleason pattern 4
• Grading recommendations for newly described variants
• Grading approach in extended needle biopsies

Diagnosis of low grade Gleason score 2-5 carcinomas on needle biopsy should be rarely if ever utilized
Gleason Pattern 3

- Varically sized, infiltrative, individual glands, typically smaller than 1 and 2
- "Individual cells" not allowed in 3
- Only "rounded, well circumscribed cribriform glands of same size as of normal glands, resembling cribriform PIN is 3"

Gleason pattern 3

Only rare rounded, well-circumscribed glands of same size of normal glands is Cribriform pattern 3
Pitfalls in grading pattern 3: “U” and “Y” – shaped glands

Majority (>95%) of cribriform carcinomas are Gleason pattern 4
Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology.


- 30 needle biopsy cases that possibly represented cribriform Gleason pattern 3 carcinoma were shared amongst the group of experts
- Sixty seven percent cases (n=24) which reached consensus (defined as 6/10 experts agreement): 23 pattern were classified as 4 and 1 pattern as 3
- Some experts now classify all cribriform carcinomas regardless of its architecture as Gleason pattern 4 or 5 if associated with necrosis
Ill-defined glands cluster with poorly formed lumina where tangential sectioning is ruled out is Gleason pattern 4

Pitfalls in grading pattern 3: tangentially sectioned glands mimicking as pattern 4
Gleason 4 - Raggedly infiltrating fused glands

Gleason 4 - Hypernephroid pattern

Gleason Pattern 4

- Fused glands
- Ill-defined glands with poorly formed glandular lumina (tangential sectioning is ruled out)
- Large cribriform glands
- Cribriforming glands with irregular lumina
- Hypernephroid morphology
Gleason Pattern 5

- Solid sheets, cords, or raw of single cells with essentially no glandular differentiation
- Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

Pitfalls of Gleason pattern 5-
Pseudo comedonecrosis
2005 ISUP Modified Gleason Grading of Prostate Cancer: Key Issues

- Documentation of current practice
- Clean Gleason pattern 3 or less group
- Clarify Gleason pattern 4
- Newly described variants
- Extended needle biopsies

<table>
<thead>
<tr>
<th>Gleason Grading of Unusual &quot;Variant&quot; Histology Types and Patterns</th>
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</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Foamy gland pattern</td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
</tr>
<tr>
<td>Atrophic</td>
</tr>
<tr>
<td>Intracytoplasmic clear vacuoles</td>
</tr>
<tr>
<td>Distal adenocarcinoma</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma and squamous carcinoma</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
</tr>
<tr>
<td>Glomeruloid pattern</td>
</tr>
<tr>
<td>Collagenous micronodules</td>
</tr>
<tr>
<td>Mucinous (colloid) carcinoma</td>
</tr>
</tbody>
</table>

Mucinous fibroplasia

- Subtract away the mucinous fibroplasia grade based on underlying architecture
- Most Score 6
- Do not misinterpret fibrous invaginations as cribriform architecture
Glomerulation – no consensus, new data suggest 4

Small cell high grade neuroendocrine carcinoma

- Indicates an aggressive phase of prostate cancer differentiation
- Should not be graded due to different therapeutic significance
- Resistant to androgen deprivation therapy but often respond to platinum based chemotherapeutic agents

3+4=7
2005 ISUP Modified Gleason Grading of Prostate Cancer: Key Issues

- Documentation of current practice
- Clean Gleason pattern 3 or less group
- Clarify Gleason pattern 4
- Newly describes variants
- Extended needle biopsies

Grading when the different cores demonstrate different Gleason grades:

<table>
<thead>
<tr>
<th>4+4 (8)</th>
<th>3+3 (6)</th>
<th>3+4 (7)</th>
<th>4+3 (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Rt. mid | Rt. apex | Lt. mid | Lt. base

Each core should be assigned Gleason score as long as urologist has defined their location or in separate container.

Report of Global Gleason score optional

Extended sampling – Effect on Gleason score

<table>
<thead>
<tr>
<th>GS Type</th>
<th>Downgrade at RP (%)</th>
<th>No Change at RP (%)</th>
<th>Upgraded at RP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global GS</td>
<td>6</td>
<td>64</td>
<td>30</td>
</tr>
<tr>
<td>Worst GS</td>
<td>12</td>
<td>64</td>
<td>24</td>
</tr>
<tr>
<td>Highest Volume GS</td>
<td>8</td>
<td>57</td>
<td>35</td>
</tr>
</tbody>
</table>

Sextant biopsy accuracy average 42% (range 28%-68%), Significant risk of underestimation average 43% (25-57%)

GS = Gleason score, RP = Radical Prostatectomy
Rationale for not compressing into only one Global grade

- One core with 4+4 and other cores with 3+3, the pathologic stage at RRP is comparable to all cores demonstrating 4+4 (Kunz et al, Hum Pathol, 2003)
- Majority of Urologist would pick highest grade and would label the patient accordingly (Rubin et al, Am J Surg Pathol, 2004)

Should multiple cores with different grades within the same container without specific site identifiers or “right” or “left” should be assigned individual grades?

If cores are not fragmented:
- Attempt to provide information of core with worst Gleason grade
- Provides better correlation with radical prostatectomy Gleason grade

Reporting in needle biopsy
1) Limited (<5%) secondary patterns of lower grade
2) Limited higher grade
3) Tertiary pattern of higher grade in needle biopsy

Kunjy L.P, Shah RB et al, Hum Pathol, 40, 558-564, 2009
Pattern distribution: 3, 4, 5
Call 3+5=8

✓ Pathology outcomes similar to Gleason 8-10 cancer
✓ Current nomograms incorporate only primary and secondary patterns
✓ Be conservative but don’t ignore it if visible at low power examination!

**Impact of ISUP-modified Gleason grading system**

- Increased utilization of secondary Gleason pattern 4 is the most noticeable impact of ISUP grading recommendations
- Modified but not conventional Gleason score better predicts PSA failure after radical prostatectomy
  (Billis A et al, J Urol 2008, 180:548-552)
- Large scale impact of new recommendations for patient management remains to be validated

**Case 6:**
A 55-year-old male presented with an abnormal digital rectal examination and elevated PSA of 8 ng/ml. The patient underwent 12 core biopsies. Representative images are shown
Intraductal Carcinoma of the Prostate (IDC-P)

- Intraductal carcinoma of the prostate (McNeal & Yemoto, 1996)
  - Almost never seen in the absence of invasive carcinoma
  - Concomitant invasive carcinoma almost always high grade and high volume
  - Significantly worse prognosis
- Morphological criteria
  - Solid/loose cribriform, marked nuclear atypia, comedo necrosis (Guo & Epstein, 2006)
  - Large glands with cells spanning the lumen, branching contour, comedonecrosis (Cohen et al, 2007)
IDC-P or Cribriform HGPIN?

**Morphological And Molecular Differences of IDC-P & Cribriform HGPIN**

- **ACL-PCa (PCa associated cribriform lesion – IDC-P)**
  - Atypical cribriform lesions with basal cells
  - Intermixed with invasive PCs
  - Within 3 mm from the border of invasive cancer

- **Isolated ACL (Non-PCa associated cribriform lesion – Cribriform PIN)**
  - Atypical cribriform lesions with basal cells
  - Not associated with invasive PCs
  - > 3 mm distant from the border of invasive cancer

ACL = Atypical cribriform lesions with basal cells
Summary of 2 studies

- Atypical cribriform lesions without associated invasive PCa (cribriform HGPIN) are uncommon; overwhelming majority of atypical cribriform lesions are associated with PCa (IDC-P)
- Majority of IDC-P are associated with high grade and high volume PCa
- Cribriform HGPIN and IDC-P overlap at the “low grade” morphologic spectrum
- IDC-P is enriched with ERG gene fusions while isolated cribriform HGPIN lack ERG gene fusions


Approach to Atypical Cribriform Lesions in Biopsy

- High grade PCa + IDC-P
  - No need to mention IDC-P
- Gleason pattern 3 PCa + IDC-P
  - document IDC-P and its poor prognostic significance
  - or grade IDC-P as pattern 4 or 5 if associated with necrosis
- Invasive PCa not present in prostate biopsy
  - diagnose IDC-P
  - Comment: IDC-P is often associated with high grade PCa and advise immediate rebiopsy and recommend definitive therapy

Intraductal Carcinoma of the Prostate (IDC-P) (Reporting)
Promising Biomarkers for Prostate cancer:

Diagnostic and prognostic:
- GSTP1 Hypermethylation
- Urinary PCA3
- TMPRSS2: ETS gene fusions

Prognostic:
- PTEN deletions
- Reduced p27
- AR gene mutations/amplifications

Science, 2005

- 50-60% of prostate cancers harbor these gene fusions
- TMPRSS2:ERG is the most common class of gene fusions, accounting for 40-50% of prostate cancers in prostatectomy cohorts
- An early molecular event, present in a small fraction (~18%) of HGPIN intermingled with adjacent cancer demonstrating identical gene fusions
- TMPRSS2:ETS gene fusions are highly specific to prostate cancer
- Promising diagnostic and prognostic marker
PCA3 urine test: A genetic marker for prostate cancer

- Much greater degree of specificity than PSA
- Quantitated in urine using QRT-PCR method and reported as a ratio of PCA3 and PSA mRNA
- Higher the ratio (≥ 35), stronger the likelihood of detecting cancer at biopsy
- A higher PCA3 correlate with tumor volume and Gleason grade (indicative of significant disease) (Haese A et al, Eur Urol, 2008)

Men 50-70 years – DRE and Initial PSA

- Elevated PSA
- Prostate Biopsy
  - Negative
  - Positive

- Monitor
- PCA3<35
- PCA3≥35
- Treatment
- Repeat biopsy
  - Negative
  - Positive

Current Application Model of PCA3 in the management of prostate cancer
Adapted from Y. Frader et al

Reporting of Prostate Biopsy

- Correct diagnosis
- Histological information
  - Prognosis
  - Therapeutic decision-making
Reporting of Prostate Biopsy

Benign Biopsy

- Benign prostatic glands and stroma
  - Do not use “glandular/stromal hyperplasia”
  - Mention scant tissue or stroma only in biopsy

Optional:
- Benign mimickers of cancer
- Chronic and acute inflammation
  - Do not use “prostatitis”
- Granulomatous prostatitis
- Atypical adenomatous hyperplasia (adenosis)
- Severe atrophy

Amin et al, 2005

HGPIN

- Do not report LGPIN

Optional:
- Extent of HGPIN (focal vs multifocal)
- # of cores involved
- Laterality (uni- vs bilateral)

Atypical glands, suspicious for cancer

- Designating the atypical biopsy as suspicious for PCa
- Recommend not to use ASAP
- Recommend re-biopsy?

Amin et al, 2005
**Location and distribution of tumor (site of biopsy if specified)**

- Significance of knowing the location and distribution of PCa
  - Prognosis
  - Therapy planning
  - Subsequent prostate gland sampling

- How to preserve the biopsy location information
  - Submit individual biopsy core in separate container
  - Biopsy cores from left and right sides submitted separately
  - Ink cores from different sites in different color

**Histopathologic type**

- Conventional acinar type: Need not specify
- Morphological variants (atrophic, pseudo-hyperplastic, foamy gland): Need not specify
- PCa with ductal features
- PCa with signet ring cell features
- PCa with mucinous differentiation
- Small cell carcinoma
- Sarcomatoid carcinoma of prostate
- Adenosquamous carcinoma
- Urothelial carcinoma
- Basal cell carcinoma

**Gleason score, including primary and secondary patterns**

- Minute focus does not equate to low grade cancer

**Extent of involvement**

- Tumor volume in needle biopsy: an extremely important histological parameter
  - Correlates with the pathological parameters in radical prostatectomy
  - Predicts PSA recurrence, disease progression, therapy failure

- How to report tumor volume in biopsy
  - # of cores involved
  - Amount of PCa in biopsy
    - Linear length of PCa (in mm)
    - % of cores involved
Local invasion

- Extraprostatic extension
  - PCa in fat in a biopsy = extraprostatic extension
  - PCa involving skeletal muscle/ganglion cells = extraprostatic extension
- Seminal vesicle invasion
  - Seminal vesicle/ejaculatory duct not always distinguishable
  - PCa involving seminal vesicle/ejaculatory duct
  - Targeted biopsy: should mention if whether seminal vesicle is represented in the biopsy

Lymphovascular invasion (report only if identified)

- Therapy-related changes (if clinical history of radiation or hormonal therapy)
- Perineural invasion (report only if identified)
  Optional:
  - Extent (focal, multifocal)
  - Caliber of nerve bundles