Update on Prostate Cancer: New Developments in Diagnosis, Grading, Staging and Reporting

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Diagnosis

• Cribriform HGPIN
• Intraductal carcinoma (IDC-P)
• Atypical intraductal proliferation (AIP)
• Prostate adenocarcinoma, Gleason score 4+4, GG 4
Diagnosis

• Prostate adenocarcinoma, Gleason score 3+3=6, GG 1 with HGPIN
• Prostate adenocarcinoma, Gleason score 3+4=7, GG 2
• Prostate adenocarcinoma, Gleason score 4+3=7, GG 3
• Prostate adenocarcinoma, Gleason score 3+3, GG 1 with intraductal carcinoma (IDC-P)
Diagnosis

- Prostate adenocarcinoma, Gleason score 3+3=6, GG 1
- Prostate adenocarcinoma, Gleason score 3+4=7, GG 2
- Prostate adenocarcinoma, Gleason score 4+3=7, GG 3
- Prostate adenocarcinoma, Gleason score 4+4=8, GG 4
Diagnosis

• Prostate adenocarcinoma, Gleason score 3+3=6, GG 1
• Prostate adenocarcinoma, Gleason score 4+3=7, GG 3
• Prostate adenocarcinoma, Gleason score 4+5=9, GG 5
• Prostate adenocarcinoma, Gleason score 5+4=9, GG 5
Important Changes in Prostate Cancer Classification, Grading, Staging and Reporting

• New entities
  Intraductal carcinoma of the prostate (IDC-P)

• Grading
  Modifications of grading and Grade groups
  Cribriform architecture

• Reporting
  Tertiary pattern, % pattern 4, Multifocal tumors

• Staging
  pT2 no longer substaged into pT2a-c
Intraductal Carcinoma of the Prostate (IDC-P)
Histological Features

**Hallmarks**

1. Expansile proliferation of PCa cells
   - Cribriform or solid architecture
2. Within native prostate glands
   - Basal cell layer at least partially preserved
Many atypical cribiform/solid glands
Partially involves native benign glands
Diagnostic Criteria for IDC-P

(Guo CC and Epstein JI, Mod Pathol. 2006)

- Large glands with lumen-spanning atypical cells and preserved basal cells
- Solid architecture
  - or
  - Dense cribriform
    - or
    - Marked atypical nuclei >6X adjacent benign nuclei
      - or
      - Non-focal comedonecrosis

YES  NO

IDC-P  Atypical intraductal proliferation
Dense cribriform: Irregular lumina

Dense cribriform: Punched out lumina
Dense cribriform with comedonecrosis
Histopathologic criteria for IDC-P:

- Expansile growth of malignant cells filling prostatic ducts/large acini
- Preservation of basal cells

Morphologic Architecture:
- Solid
- Dense Cribriform
- Loose Cribriform
- Micropapillary

+ Non-focal comedonecrosis (≥ two glands) or
  Marked nuclear atypia (nuclear size ≥ 6 times that of adjacent benign nuclei)

IDC-P
You require nuclear criteria or comedonecrosis when there is no dense or solid architecture!

Marked variation in nuclear size

Pleomorphic nuclei >6X adjacent nuclei
Intraductal Carcinoma of the Prostate (IDC-P)
Diagnostic Criteria

➢ Use a constellation of morphological features (architecture and cytology)
➢ Use stringent diagnostic criteria to ensure its unique clinical implication, ie, association with adverse outcomes
➢ Any atypical expansile, lumen-spanning lesion warrants further work-up
Significance of IDC-P in Prostate Biopsy
INTRADUCTAL CARCINOMA OF THE PROSTATE: OUTCOME

- Independent predictor of various adverse outcomes
- Contemporary studies focusing on outcomes lump cribriform Gleason pattern 4 and IDC-P as “cribriform architecture”
- Isolated intraductal carcinoma in prostate biopsy: Definitive therapy may be indicated although 10% of patients will have intraductal carcinoma only at radical prostatectomy, so repeat biopsy is an option
Differential Diagnosis of Intraductal Carcinoma of the Prostate
(DDX for Atypical Cribriform/Solid Lesions)

- High grade PIN
- Atypical Intraductal Proliferation (AIP)
- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Urothelial carcinoma involving the prostate
- Metastatic (colorectal) adenocarcinoma
IDC-P vs Cribriform HGPIN

- Atypical cribriform lesion with basal cells intermixed with or within 3 mm from the border of PCa
- Atypical cribriform lesion with basal cells > 3 mm from the border of PCa

Shah et al AJSP 2010; Han et al AJSP 2010
### Morphological Difference b/w of IDC-P and Cribriform HGPIN

*(Shah, Magi-Galluzzi, Han, Zhou, AJSP 2010)*

<table>
<thead>
<tr>
<th></th>
<th>IDC-P</th>
<th>Cribriform HGPIN</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
<td>43</td>
<td>23</td>
<td>N.A.</td>
</tr>
<tr>
<td># atypical cribriform lesion /prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>23.8</td>
<td>2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Range</td>
<td>1-143</td>
<td>1-6</td>
<td></td>
</tr>
<tr>
<td>Smallest size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean± S.D.</td>
<td>0.34 ± 0.19</td>
<td>0.33 ± 0.13</td>
<td>0.848</td>
</tr>
<tr>
<td>Range</td>
<td>0.2-1.1</td>
<td>0.2-0.6</td>
<td></td>
</tr>
<tr>
<td>Largest size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean± S.D.</td>
<td>1.5 ± 1.3</td>
<td>0.43 ± 0.15</td>
<td>0.002</td>
</tr>
<tr>
<td>Range</td>
<td>0.4-2.5</td>
<td>0.2-1.0</td>
<td></td>
</tr>
<tr>
<td>Glandular contour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>29 (67.4%)</td>
<td>19 (82.6%)</td>
<td>0.187</td>
</tr>
<tr>
<td>Irregular</td>
<td>34 (79.1%)</td>
<td>12 (52.2%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Branching</td>
<td>36 (83.7%)</td>
<td>1 (4.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Architecture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular cribriform</td>
<td>41 (95.3%)</td>
<td>23 (100%)</td>
<td>0.293</td>
</tr>
<tr>
<td>Dense cribriform or solid</td>
<td>10 (23.3%)</td>
<td>0 (0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Comedo necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uniform</td>
<td>15 (34.9%)</td>
<td>14 (60.9%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Variable</td>
<td>22 (51.2%)</td>
<td>9 (29.1%)</td>
<td>0.35</td>
</tr>
<tr>
<td>&gt; 6X or pleomorphic</td>
<td>12 (27.9%)</td>
<td>0 (0%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Morphological comparison between IDC-P and HGPIN

- Morphologic criteria for IDC-P has high specificity but poor sensitivity
- There is significant overlap at “lower grade” morphological spectrum (HGPIN and AIP)
IDC-P vs Cribriform HGPIN

✓ ERG gene fusion: 75%
✓ ERG fusion status concordant between IDC-P and adjacent PCa in 100% cases

➢ IDC-P and cribriform HGPIN are genetically distinct
➢ ERG gene status identical between IDC-P and PCa
✓ IDC-P: resulting from intraductal spread of PCa

Shah et al AJSP 2010; Han et al AJSP 2010
## MOLECULAR FEATURES OF INTRADUCTAL CARCINOMA

PTEN loss can be utilized as a surrogate marker of IDC-P

<table>
<thead>
<tr>
<th>Study</th>
<th>ERG expression</th>
<th>PTEN loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HGPIN</td>
<td>IDC-P</td>
</tr>
<tr>
<td>Han B et al, AJSP, 2010</td>
<td>0 %</td>
<td>75 %</td>
</tr>
<tr>
<td>Lotan TL et al, Mod Pathol, 2013</td>
<td>13 %</td>
<td>58 %</td>
</tr>
<tr>
<td>Morais CL et al, AJSP, 2015</td>
<td>0 %</td>
<td>58 %</td>
</tr>
<tr>
<td>Morais CL et al, Hum Pathol, 2016</td>
<td>7 %</td>
<td></td>
</tr>
<tr>
<td>Hickman RA et al, AJSP, 2017</td>
<td>7 %</td>
<td>61 %</td>
</tr>
<tr>
<td>Shah RB et al, Histopathol, 2017</td>
<td>15 %</td>
<td>55 %</td>
</tr>
</tbody>
</table>
Case 1: Atypical intraductal proliferation
Pathology outcomes of AIP detected in prostate biopsy without an associated IDC-P and cribriform pattern 4

Table 2: Breakdown of adverse pathology at follow up in 40 patients who were potential candidates for no therapy (AIP alone) or active surveillance (AIP with Grade Group 1 or Grade Group 2 prostate cancer without cribriform Gleason pattern 4)

<table>
<thead>
<tr>
<th>Category [n (%)]</th>
<th>Available Follow-Up [n]</th>
<th>Follow-Up Biopsy [n (%)]</th>
<th>Radical Prostatectomy [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>≥ GG 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDC-P</td>
<td>IDC-P + PCa</td>
</tr>
<tr>
<td>AIP alone 12 (30)</td>
<td>6</td>
<td>1 (17)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>GG 1 without cribriform pattern 10 (25)</td>
<td>3 (1 Bx, 2 RP)</td>
<td>0 (0)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>GG 2 without cribriform pattern 18 (45)</td>
<td>11 (all RP)</td>
<td>2 (18)</td>
<td>9 (81)</td>
</tr>
</tbody>
</table>

AIP is a marker of unsampled IDC-P and other adverse pathological features at radical prostatectomy
Case 2: PCA, Gleason score 3+3=6 with extensive intraductal spread
WHEN TO PERFORM BASAL CELL STAINING?

- Lack of definitive infiltrative carcinoma with a suggestion of intraductal carcinoma
- In setting of low grade infiltrative carcinoma where documentation of intraductal carcinoma is necessary to correctly assign Gleason score to case
- Not recommended in the setting of already high-grade PCa
Case 2: PCA, Gleason score 4+4=8 with intraductal features
Ductal Adenocarcinoma of the Prostate
Ductal Adenocarcinoma of the Prostate with residual basal cells: Intraductal spread
Reporting Recommendations for Prostate Biopsy with IDC-P

IDC-P in Prostate Biopsy
(Do not grade IDC-P)

Associated with PCa

Grade >8 PCa

✓ Recommend to report IDC-P (may provide an additional prognostic value)

Grade 6/7 PCa

✓ Grade PCa and document IDC-P and its poor prognostic significance in the report

Without PCa

✓ Diagnose IDC-P and document its poor prognostic significance in the report
✓ Advise immediate rebiopsy or recommend definitive therapy

Atypical Intraductal Proliferation

✓ Recommend immediate repeat biopsy

Hickman RA et al, AJSP, 2016; 41:550-556
Shah RB et al, Histopathol, 2017 Epub ahead of print
Ideal Grading System

• Prognostic ability exceeding clinical parameters
• Reproducibility among pathologists
• Grading on biopsy representative of entire cancer
Key Changes: Definitional and Operational
Similarity: Gleason grading remains a mid to low power (not high power) exercise!
2005 Modifications of Gleason Grading

• **Definition**
  ✓ Gleason pattern 1 and 2 should not be assigned to needle biopsy
  ✓ Poorly formed glands included as pattern 4
  ✓ Large cribriform cancer glands separated from pattern 3 and included as pattern 4
  ✓ Grading new entities/variants: small glomeruloid glands included as pattern 3 while large glomeruloid glands included as pattern 4
2005 Modifications of Gleason Grading

• **Operational**
  ✓ Secondary pattern of lower grade when of limited extent
  ✓ Secondary pattern of higher grade when of limited extent
  ✓ Tertiary pattern
  ✓ Percent pattern 4/5
  ✓ Multifocal tumors
  ✓ Needle biopsy with different cores showing different grades
Key Changes: Definitional and Operational
Similarity: Gleason grading remains a mid to low power (not high power) exercise!
2014 Modifications of Gleason Grading

- **Definition**
  - All cribriform cancer regardless of size included as Pattern 4
  - Glomerulations regardless of size included as pattern 4
  - Intraductal carcinoma (IDC-P) should be reported but not graded
PROBLEMS WITH CURRENT GLEASON GRADING SYSTEM

• 6 is the middle of the 2-10 numerical scale but is the lowest score reported
• Patients incorrectly may think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer
• Gleason score often grouped into 3 tiers (6, 7, 8-10) for prognostic and therapeutic purposes despite the fact that GS 3+4 vs. 4+3 and 8 vs. 9-10 have significantly different prognosis
NEW GRADING SYSTEM: GRADE GROUPS

| Grade group 1 | GS $\leq 6$ | Only individual discrete well-formed glands |
| Grade group 2 | GS $3+4=7$ | Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands |
| Grade group 3 | GS $4+3=7$ | Predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands |
| Grade group 4 | GS $4+4=8$ | Only poorly-formed/fused/cribriform glands |
|              | GS $3+5=8$ | Predominantly well-formed glands with a lesser component lacking glands |
|              | GS $5+3=8$ | Predominantly lacking glands or with a lesser component of well-formed glands |
| Grade group 5 | GS $9/10$ | Lacks gland formation (or with necrosis) with or w/o poorly-formed/fused/cribriform glands |

- Proposed by J Epstein (Johns Hopkins)
- Grade grouping NOT A NEW grading method; based on Gleason system; a novel way to group Gleason grades
OUTCOME OF 20,845 MEN BASED ON BIOPSY GRADE GROUPS

NEW GRADING SYSTEM: GRADE GROUPS

• **Advantages**
  ✓ More accurate stratification than the current system
  ✓ Lower number of categories (5 vs 10 with Gleason)
  ✓ Lowest grade is 1 and not 6

• **Used in conjunction with the Gleason system**
  ✓ Prostate adenocarcinoma, Gleason score 3+5=8 (Grade group 4)
Accepted by 2016 WHO and AJCC.....

Also referred to as ISUP grade in some publications
Disease-specific death and metastasis do not occur in patients with Gleason score ≤6 at radical prostatectomy

Charlotte F. Kweldam, Mark F. Wildhagen*, †, Chris H. Bangma* and Geert J.L.H. van Leenders

Departments of Pathology, *Urology, and †Research Office Sophia, Erasmus Medical Center, Rotterdam, The Netherlands
GLEASON PATTERN 4 IN CONTEMPORARY BIOPSY PRACTICE

• Morphologic subpatterns:
  – Poorly formed/Ill-formed
    Abortive glands
  – Fused glands
  – Glomeruloid (small and large)
  – Cribriform (small and large)
    Ductal
  – Papillary
    Ductal
    Non-ductal
Ill-defined glands cluster with poorly formed lumina where tangential sectioning is ruled out is Gleason pattern 4
How to differentiate “Poorly formed” glands from tangential sectioning?
• Consensus definition for “poorly formed glands”: Cancer glands with no or rare lumens, elongated compressed glands, and elongated nests
• Kappa=0.34
• Reproducibility improved when quantitative criteria applied
Use high threshold! Default to grade 3 if in doubt, especially dealing with small focus.
Case 3: Prostate adenocarcinoma, Gleason score 3+3=6
(Poorly formed glands adjacent to well-formed glands, >10, Consensus not pattern 4)
All cribriform cancers (large and small) are pattern 4
The presence of cribriform cancer conferred highest odds ratio for PSA failure, 5.9, among five high-grade patterns.
### TABLE 1. Biochemical Recurrence* of Prostate Cancer Containing Gleason 4

<table>
<thead>
<tr>
<th>Studies</th>
<th>Median Follow-up (y)</th>
<th>BCR or Cancer-specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatectomy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iczkowski et al\textsuperscript{7}</td>
<td>5.9</td>
<td>BCR: cribriform had the highest odds ratio among 5 high-grade prostate cancer patterns for PSA failure, OR = 5.89, ( P &lt; 0.0001 )</td>
</tr>
<tr>
<td>Dong et al\textsuperscript{10}</td>
<td>5</td>
<td>BCR in 32% of cribriform and 21% of noncribriform (( P = 0.009 )); cribriform predicts recurrence, OR = 2.4, ( P = 0.003 )</td>
</tr>
<tr>
<td>Trudel et al\textsuperscript{11}</td>
<td>10.8</td>
<td>BCR: presence of cribriform or IDC confers OR = 3.0, ( P = 0.0002 ). Independent predictor of BCR, along with Gleason ( \geq 8 ) and positive margin</td>
</tr>
<tr>
<td>Kir et al\textsuperscript{13}</td>
<td>3.5</td>
<td>96% of BCR-positive cases had cribriform pattern, vs. 57% of BCR-negative. Cribriform pattern is independent BCR predictor, OR = 11.9, ( P = 0.02 )</td>
</tr>
<tr>
<td>Choy et al\textsuperscript{23}</td>
<td>6.3</td>
<td>BCR: cribriform 30%; poorly formed 22%; fused 19%</td>
</tr>
<tr>
<td>Choy et al\textsuperscript{24}</td>
<td>5</td>
<td>In prostatectomy 3+4 cancer with low volume, BCR: If tumor volume &lt;5%: 5% no cribriform; 18% cribriform. If tumor volume &lt;10%: 15% no cribriform; 18% cribriform</td>
</tr>
<tr>
<td>Kweldam et al\textsuperscript{17}</td>
<td>15</td>
<td>Cancer-specific survival, 94% in cribriform/IDC\textsuperscript{−}, and 67% in cribriform/IDC\textsuperscript{+}, OR = 2.8</td>
</tr>
<tr>
<td>Choy et al\textsuperscript{25}</td>
<td>1.5</td>
<td>Cribriform or IDC associated with BCR, OR = 2.2</td>
</tr>
<tr>
<td>Biopsy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harding et al\textsuperscript{8}</td>
<td>2.7</td>
<td>Among Gleason 8 biopsy cases, cribriform pattern predicted BCR, OR = 6.1, ( P = 0.018 ). It is more important than 4+4 vs. 3+5</td>
</tr>
<tr>
<td>Billis et al\textsuperscript{26}</td>
<td>Not given</td>
<td>Time to BCR was less (( P = 0.49 )) in biopsy specimens with mixture of patterns than in those with exclusively a fused pattern</td>
</tr>
</tbody>
</table>

*Generally defined as a postoperative rise in serum PSA to \( \geq 0.2 \) ng/mL.

BCR indicates biochemical recurrence; IDC, intraductal carcinoma; OR, odds ratio; PSA, prostate-specific antigen.
## Table 2. Systemic Metastasis and Cancer-specific Death From Prostate Cancer

<table>
<thead>
<tr>
<th>Studies</th>
<th>Median Follow-up (y)</th>
<th>Metastasis</th>
<th>Cancer-specific Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostatectomy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dong et al(^{10})</td>
<td>10</td>
<td>Grade 4 cribriform 13.3% vs. without cribriform 2.6%, OR = 5.6, (P = 0.02)</td>
<td>Other than Gleason score, cribriform pattern was only independent predictor for metastasis, OR = 5.4, (P &lt; 0.001)</td>
</tr>
<tr>
<td>Kweldam et al(^{16})</td>
<td>10</td>
<td>Cribriform pattern was the only independent predictor for metastasis, OR = 8.0, (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Choy et al(^{25})</td>
<td>10</td>
<td>Cribriform or IDC associated with BCR, OR = 3.3, (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>Biopsy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kweldam et al(^{17})</td>
<td>15</td>
<td></td>
<td>If cribriform absent 94%; if present 67%, OR = 2.6, (P = 0.002). A 3+4 = 7 cancer without cribriform was not significantly different from 3+3 = 6</td>
</tr>
</tbody>
</table>
Cribiform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer

Charlotte F Kwemd1, Mark F Wildhagen2,3, Ewout W Steyerberg4, Chris H Bangma3, Theodorus H van der Kwast5 and Geert J LH van Leenders3

Figure 2 Kaplan-Meier estimates on impact of cribriform growth pattern in (a) biochemical recurrence-free survival; (b) distant metastasis-free survival; (c) disease-specific survival; and (d) overall survival.
A. Left base x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 3+4=7, grade group 2, involving one of two cores (25%, 2.5 mm; 15% of sampled tissue).

B. Left mid x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 3+4=7, grade group 2, involving one of two cores (60%, 7 mm; 45% of sampled tissue).

C. Left apex x 2 prostate, biopsy - Benign prostatic tissue.

D. Right base x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 4+3=7, grade group 3, involving two cores (90%, 6 mm, 15%, 2 mm; 45% of sampled tissue).
   - Gleason pattern 4 accounts for 80% of the tumor.

E. Right mid x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 3+4=7, grade group 2, involving one of two cores (35%, 4 mm; 20% of sampled tissue).

F. Right apex x 2 prostate, biopsy - Minute focus of adenocarcinoma of prostate, Gleason score 3+3=6, grade group 1, involving one of two cores (2%, less than 0.5 mm).

G. Target 1 prostate, biopsy - Benign prostatic tissue.

H. Target 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 4+3=7, grade group 3, involving four cores (100%, 6 mm, 100%, 5 mm, 95%, 7 mm, 75%, 6 mm; 85% of sampled tissue).
   - Gleason pattern 4 accounts for 50% of the tumor.
   - Perineural invasion present.

Prostate Cancer Biopsy Summary

Number of cores examined: 18
Number of cores positive: 10
Highest Grade Group: 3
Highest % of core involvement: 100%
Cribriform pattern 4: Absent
Intraductal carcinoma: Absent
Size of the cribriform glands likely matters!

Various definition of large cribriform gland:
1) > 12 lumens
2) Two times benign gland
3) > 0.5 mm
Ductal Adenocarcinoma of the Prostate
Glomeruloid structures – Now uniformly Gleason pattern 4
Common pitfalls that may result in over grading of Pattern 3 as 4
Tangentially sectioned glands mimicking “poorly formed” pattern 4
Branching of glands mimicking “fused” pattern 4
Mucinous fibroplasia mimicking cribriform pattern 4
Mucinous extravasation with collapsed stroma mimicking cribriform pattern 4
Crowded small well formed glands mimicking cribriform pattern 4
Telescoping (Gleason 3) mimicking Glomerulation pattern 4
Pseudopapillary pattern in Pseudohyperplastic PCA mimic pattern 4
Adenocarcinoma with mucinous differentiation – Grade based on architecture, Default grade is NOT Gleason pattern 4
PIN-like ductal without papillary or cribriform architecture is NOT Gleason pattern 4
GLEASON PATTERN 5 IN CONTEMPORARY BIOPSY PRACTICE

• Morphologic subpatterns:
  – Infiltrating cords
  – Single cells
  – Solid Sheets
  – Comedocarcinoma
  – Linear arrays and solid nests
• Infiltrating cords and single cells most common; frequently co-exist
• Tertiary distribution most common presentation
• Pattern 5 under recognized in practice (Al-Hussain TO et al, Urology 2012;79:178-181)

Shah RB and Tadros Y. Hum Pathol 2014; 45:2263-2269
ISSUES WITH GLEASON PATTERN 5

- Solid nests: Size
- Single cells/cords:
  - Quantity
  - Topographic location (relationship with other pattern 4)
- Comedocarcinoma
  - True necrosis versus secretions
- Variant histology
  - Signet ring cell-like
  - Neuroendocrine differentiation
• Overall Kappa=0.376

• Among sub patterns, comedocarcinoma had highest reproducibility (k=0.499), followed by variant morphology (k=0.443), single cells/cords (k=0.369), and nests (k=0.347)

• Reproducibility improved when restrictive morphologic and quantitative criteria applied
Prostate adenocarcinoma, Gleason score 5+4=9
(Single cells/cords >10; clustered or intermixed with glands; Consensus for pattern 5)
Case 4: Prostate adenocarcinoma, Gleason score 4+3=7
(Single cells/cords ≤5; Consensus against pattern 5)
Large nests with or without glandular differentiation (Consensus for 5)
Comedonecrosis with or without karyorrhectic debris (Consensus for 5)
Signet ring cell-like cells in single cells or in nests (Consensus for 5)
Paneth cell change within nests (consensus against 5)
REPORTING
WHO 2016 RECOMMENDATION: REPORT % GLEASON PATTERN 4

- Percentage of high-grade pattern 4/5 proposed as significant prognosticator (JAMA 281;1395, 1999)
- Mainly tested in RP setting but recent studies show similar impact at biopsy
- May have implications for active surveillance and radiation therapy
- Can improve risk stratification even in 3+4 vs. 4+3 subsets of Gleason score 7
- Not established: increments to use
IMPACT OF LOW (< 10%) GLEASON 4 IN 3+4 PROSTATE CANCER IN BIOPSY

• No/minimal impact of < 5% or 10% Gleason pattern 4 in 7s.

• Lack of significant risk of adverse pathology among Gleason 7 patients when G4% is 5% or 10%; however is markedly different when G4% reaches 20% (J Urol Feb 2016)

• 3+3=6 vs. 3+4=7 with ≤ 5% Gleason grade 4: No difference in pathologic findings in RP (AJSP 38:1096, 2014) and biochemical recurrence (Ann Diagn Pathol 20:48, 2016)
Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4 = 7 prostate cancer

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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

\[
4 \rightarrow 3 \leftarrow (\leq5\%)
\]

\[
4 + 4 = 8
\]

\[
3 \rightarrow 4
\]

\[
3 + 4 = 7
\]

\[
3 \rightarrow 4 \rightarrow 5
\]

\[
3 + 5 = 8
\]
Multifocal cancer with different Gleason score is common

Dominant nodule (Index tumor) is reported.

Not necessary to report small, organ-confined GS 3+3 foci

4+4=8 NOT 4+3=7
MULTIPLE DOMINANT NODULES

PZ

TZ

2+2

4+4

4+2 = 6
2+4 = 6
NON-DOMINANT NODULE OF HIGHER GRADE

Multiple nodule with non-concurrent path parameters:

Each major tumor nodule should be graded separately

Two foci of cancer, 4+4=8 and 3+3=6. NOT 3+4=7
REPORTING TERTIARY GRADE/PATTERN IN RP

- Reporting approach different than biopsy
- Reported as tertiary pattern as long as higher than primary or secondary pattern
- Some experts consider tertiary pattern only <5% of tumor
- Some would assign it as tertiary pattern even if it is >5% as long as the highest pattern is tertiary in quantity
- Both approaches are OK as long as understood by your urologists.
STAGING
- Clinical stage T2 is considered as T2a-c based on DRE
- Pathological stage T2 is no longer substaged due to lack of prognostic significance
Microscopic bladder neck involvement
(Zhou M et al, Mod Pathol, 2009)

✓ Presence of cancer glands within smooth muscle bundles of coned bladder neck without benign prostate glands
✓ Staged as pT3a, not pT4

Gross bladder neck involvement: T4
TABLE 4. American Joint Committee on Cancer Prognostic Stage Grouping

<table>
<thead>
<tr>
<th>WHEN T IS...</th>
<th>AND N IS...</th>
<th>AND M IS...</th>
<th>AND PSA IS...</th>
<th>AND GRADE GROUP IS...</th>
<th>THEN THE STAGE GROUP IS...</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1a-c, cT2a</td>
<td>NO</td>
<td>MO</td>
<td>&lt;10 ng/mL</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>pT2</td>
<td>NO</td>
<td>MO</td>
<td>&lt;10 ng/mL</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>cT1a-c, cT2a</td>
<td>NO</td>
<td>MO</td>
<td>≥10, &lt;20 ng/mL</td>
<td>1</td>
<td>IIA</td>
</tr>
<tr>
<td>pT2</td>
<td>NO</td>
<td>MO</td>
<td>≥10, &lt;20 ng/mL</td>
<td>1</td>
<td>IIA</td>
</tr>
<tr>
<td>cT2b-c</td>
<td>NO</td>
<td>MO</td>
<td>&lt;20 ng/mL</td>
<td>1</td>
<td>IIA</td>
</tr>
<tr>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>&lt;20 ng/mL</td>
<td>2</td>
<td>II B</td>
</tr>
<tr>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>&lt;20 ng/mL</td>
<td>3</td>
<td>II C</td>
</tr>
<tr>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>&lt;20 ng/mL</td>
<td>4</td>
<td>II C</td>
</tr>
<tr>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>≥20 ng/mL</td>
<td>1-4</td>
<td>III A</td>
</tr>
<tr>
<td>T3-4</td>
<td>NO</td>
<td>MO</td>
<td>Any</td>
<td>1-4</td>
<td>III B</td>
</tr>
<tr>
<td>Any T</td>
<td>NO</td>
<td>MO</td>
<td>Any</td>
<td>5</td>
<td>III C</td>
</tr>
<tr>
<td>Any T</td>
<td>N1</td>
<td>MO</td>
<td>Any</td>
<td>Any</td>
<td>IVA</td>
</tr>
<tr>
<td>Any T</td>
<td>Any</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
<td>IV B</td>
</tr>
</tbody>
</table>

Abbreviation: PSA indicates prostate-specific antigen. *Note that, when either PSA or grade group is not available, grouping should be determined by T category and/or either PSA or grade group, as available.
TAKE HOME MESSAGES

• Report intraductal carcinoma; do not grade
• Report the presence or absence of cribriform Gleason pattern 4
• Gleason grade and Grade groups are both required for reporting
• % pattern 4 should be reported for Gleason 7 carcinoma
• Further optimization of grade groups is expected
TAKE HOME MESSAGES

• In needle biopsy when tertiary pattern is higher than primary or secondary, it should be included in final GS as secondary pattern; No specific recommendation for radical prostatectomy

• Radical prostatectomy with multiple tumors: dominant tumor is reported; for non-dominant nodule of higher grade, each major tumor graded separately

• pT2 is no longer substaged into T2a-c
Diagnosis of Limited Prostate Cancer and Atypical Glands Suspicious for Cancer (ATYP)