Update on Reporting Prostate Cancer Pathology

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Disclosures

• None
Learning Objectives

• Identify sources of data sets for reporting prostate specimens containing cancer
• Review recommended and optional items to be reported in prostate biopsies and prostatectomy specimens
• Discuss practical issues concerning recent changes to reporting guidelines, Gleason scoring and the application of Grade Groups in contemporary practice
• Review emerging topics of prognostic significance in prostate pathology.
CANCER PROTOCOL TEMPLATES

www.cap.org/

Protocol for the Examination of Specimens From Patients With Carcinoma of the Prostate Gland

Version: Prostate 4.0.0.0

Protocol Posting Date: June 2017

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

Revised Cancer Protocols and Electronic Cancer Checklists now available

The revised protocols now incorporate changes to tumor stage classification from the AJCC 8th edition Cancer Staging Manual and updated WHO classifications.

READ MORE
Protocol for the Examination of Specimens From Patients With Carcinoma of the Prostate Gland

Version: Prostate 4.0.0.0
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CAP Prostate Protocol Revision History

Summary of Changes
The following changes have been made since the June 2012 release.

This is a major revision to the protocol. Extensive changes have been made throughout the document.

Note: The Needle Biopsy case summary has been divided into 2 case summaries: specimen level and case level.

- Gleason score – Grade Group (ISUP Grade)
  - case level (composite) or specimen level for biopsies
  - % pattern 4 and/or 5
- intraductal carcinoma
- no more sub-staging of pT2 for radical prostatectomy specimens
PATHOLOGY provides the essential information for a patient’s cancer journey

www.iccr-cancer.org/

Prostate Cancer Histopathology Reporting Guide
Radical Prostatectomy Specimen

Prostate Core Needle Biopsy Histopathology Reporting Guide
Part 1 - Clinical Information/Specimen Receipt

Prostate Core Needle Biopsy Histopathology Reporting Guide
Part 2 - Specimen Level Reporting
Performance of Needle Biopsy of the Prostate for Men with Suspected or Established Prostate Cancer

Report Date: September 2017

Recommendation Report

A special report developed by the Surgical Oncology Program at Cancer Care Ontario in conjunction with the Prostate Biopsy Expert Panel

- Ordering of Prostate Biopsy
- Pre- and Peri-Biopsy Management
- Biopsy Technique
- Pathology
- Human Resources and Training
- Facility Requirements

This report was developed by Dr. Rajiv Singal (Chair), MD; Dr. Joseph Chin, MD; Dr. Christopher Morash, MD; Dr. Roland Sing, MD; Dr. John Srigley, MD; Dr. Andrew Evans, MD; Dr. Ants Toi, MD; Leigh McKnight, HBMSc; Dr. Alice Wei, MD; and Dr. Robin McLeod, MD.
Prostate Biopsies: Recommended Elements

• **Histologic type** - acinar-type adenocarcinoma (99.5%)

• **Histologic grade** - Gleason Score
  ✓ Gleason primary (predominant)
  ✓ Gleason worst remaining
  ✓ Grade Group
  ✓ % pattern 4 for Gleason score 7/10 (3+4)

• **Tumour quantitation**
  ✓ Number positive cores/total number of cores
  ✓ % core involvement for each positive core
  ✓ total mm cancer/total mm prostate tissue

• **Periprostatic fat invasion** - (yes/no)

• **Seminal vesicle/ejaculatory duct invasion** - (yes/no/not applicable)
Extent Involvement in Active Surveillance: The Devil is in the Details!

90% or 20%??

www.how-to-draw-funny-cartoons.com
Active Surveillance

• Observation **with curative intent**

• Regular follow-up:
  • PSA
  • DRE
  • serial biopsies
  • imaging (prostate MRI)

• Treatment as soon as low-risk cancers become higher risk/progress

• Avoid negative impacts of overtreatment for disease that remains low-risk
The Critical Role of the Pathologist in Determining Eligibility for Active Surveillance as a Management Option in Patients With Prostate Cancer

Consensus Statement With Recommendations Supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation

Mahul B. Amin, MD; Daniel W. Lin, MD; John L. Gore, MD, MS; John R. Srigley, MD, FRCPA, FRCPPath; Hema Samaratunga, MBBS, FRCPA; Lars Egevad, MD; Mark Rubin, MD; John Nacey, MD; H. Ballentine Carter, MD; Laurence Klotz, MD; Howard Sandler, MD; Anthony L. Zietman, MD; Stuart Holden, MD; Rodolfo Montironi, MD, FRCPA, IFCAFS; Peter A. Humphrey, MD, PhD; Andrew J. Evans, MD; Jonathan I. Epstein, MD; Brett Delahunt, MD; Jesse K. McKenney, MD; Dan Berney, MD; Thomas M. Wheeler, MD; Arul M. Chinnaiyan, MD, PhD; Lawrence True, MD; Beatrice Knudsen, MD, PhD; M. Elizabeth H. Hammond, MD

Arch Pathol Lab Med. 2014;138:1387-1405
Total core length = 8.2 mm  
Adenocarcinoma = 1.8 mm  
Intervening benign tissue = 5.6 mm

% Cancer Option 1 = 20%  
➢ 0.7 + 1.1 mm  
➢ subtracting intervening benign tissue

% Cancer Option 2 = 90% (discontinuous involvement)  
➢ 0.7 + 3.0 + 2.6 + 1.1 mm  
➢ including intervening benign tissue

% Cancer Option 3  
➢ descriptive reporting  
➢ the “compromise” option
Bottom Line on Reporting Discontinuous Core Involvement

• Be consistent in how you handle benign intervening stroma

• Make sure your clinical colleagues are aware of how you do this

• Descriptive reporting option:
  ✓ 2 discontinuous foci measuring 1.8 mm in total
  ✓ involvement of 20% of the core and spanning 90% of the core
Should Intervening Benign Tissue Be Included in the Measurement of Discontinuous Foci of Cancer on Prostate Needle Biopsy? Correlation With Radical Prostatectomy Findings

Sarah Karram, MD,* Bruce J. Trock, PhD,† George J. Netto, MD,*†‡ and Jonathan I. Epstein, MD*†‡


FIGURE 1. A, Several small foci of adenocarcinoma (arrows) discontinuously involve 80% of the length of the core (measured at Johns Hopkins), compared with 7% core involvement (excluding benign tissue) recorded at the outside institution. B, Different case from Figure 1A with triple stain consisting of p63 and high-molecular weight cytokeratin (brown chromogen) and racemase (red chromogen) showing 3 discontinuous foci of adenocarcinoma with lack of basal cells and positivity for racemase (arrows). The tumor discontinuously involved 50% of the core length (measured at Johns Hopkins), compared with 15% when intervening benign tissue was discounted (measured at outside institution).

<table>
<thead>
<tr>
<th>TABLE 1. Maximum Percentage of Cancer per Core per Case</th>
<th>Hopkins (%)</th>
<th>Outside Institutions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>64.2</td>
<td>28.8</td>
</tr>
<tr>
<td>Median</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td>Range</td>
<td>20-100</td>
<td>1-80</td>
</tr>
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</table>
**TABLE 2. Association of Preoperative Parameters With Organ-Confined Disease**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Organ Confined</th>
<th>Nonorgan Confined</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PSA (ng/mL)</td>
<td>4.7</td>
<td>6.7</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean JHH max %</td>
<td>59.7%</td>
<td>75.2%</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean outside max %</td>
<td>25.7%</td>
<td>36.4%</td>
<td>0.027</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td>0.851</td>
</tr>
<tr>
<td>T1c</td>
<td>41 (76%)</td>
<td>17 (74%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>13 (24%)</td>
<td>6 (26%)</td>
<td></td>
</tr>
</tbody>
</table>

JHH indicates the Johns Hopkins Hospital; Max %, maximum percentage of cancer per core per case.

**FIGURE 2.** A case by case comparison between the maximum percentage of cancer per core per case reported at Johns Hopkins (JHH %) (upper curve) compared with that of the outside institutions (outside %) (lower curve).

**TABLE 3. Association of Preoperative Parameters With Surgical Margins**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Positive Surgical Margins</th>
<th>Negative Surgical Margins</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PSA (ng/mL)</td>
<td>7.3</td>
<td>4.8</td>
<td>0.013</td>
</tr>
<tr>
<td>Mean JHH max %</td>
<td>79.3</td>
<td>61.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean outside max %</td>
<td>34.5</td>
<td>27.6</td>
<td>0.238</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td>0.755</td>
</tr>
<tr>
<td>T1c</td>
<td>11 (79%)</td>
<td>47 (75%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>3 (21%)</td>
<td>16 (25%)</td>
<td></td>
</tr>
</tbody>
</table>

JHH indicates the Johns Hopkins Hospital; Max %, maximum percentage of cancer per core per case.

**JHH Experience:** Including intervening benign tissue better predicted pT and surgical margin status.
One Tumour or Two?

FIGURE 1. Diagrammatic representation of hypothesized tumor configurations in the prostate gland that could yield a discontinuously positive core needle biopsy. A, Two small (potentially clinically insignificant) tumor foci located in the right posterior peripheral zone are sampled by a single core biopsy with benign intervening tissue. B, A large, crescent-shaped tumor focus is present in the same region of the prostate gland and intersects the core biopsy path at 2 different points, separated by benign intervening tissue.
• 40 biopsy-radical prostatectomy pairs
• biopsy core with highest % involvement showing discontinuous involvement (≥ 2 mm gap of intervening benign tissue)
• 31/40 (78%) cases were associated with a single large focus at radical prostatectomy (often irregularly shaped)
Clonal evaluation of prostate cancer foci in biopsies with discontinuous tumor involvement by dual ERG/SPINK1 immunohistochemistry

Jacqueline Fontugne¹,²,⁶, Kristina Davis³,⁶, Nallasivam Palanisamy³,⁷, Aaron Udager³, Rohit Mehra³,⁴, Andrew S McDaniel³, Javed Siddiqui³,⁴, Mark A Rubin¹,², Juan Miguel Mosquera¹,²,⁸ and Scott A Tomlins³,⁴,⁵,⁸
- Dual ERG/SPINK1 immunohistochemistry (IHC)
- Discrepant staining between foci = different clones/tumours

- 97 biopsies (80 patients) with at least 2.5 mm intervening benign prostate between foci
- Gleason scores 6-9/10
- 20-100% core involvement (including intervening benign prostate)

- 25% of cores with discontinuous involvement harbour distinct cancer clones - exclude intervening benign prostate in these cases when reporting % core involvement.
Prostate Biopsies: Optional Elements

• % Gleason pattern 4 and 5 for Gleason score ≥ 7/10 (4+3)

• Intraductal carcinoma - (yes/no)

• Lymphovascular invasion - (yes/no)

• Perineural invasion - (yes/no)

• Additional findings
  ✓ None identified
  ✓ HG PIN
  ✓ Adenosis
  ✓ Inflammation - specify type
  ✓ Other
Prostate Biopsies: Specimen vs Case Level

- **Specimen level** - individual diagnostic line for each part
- **Case level** - summary (synoptic) for all parts

In situations where a case level summary is used and specimen level summaries are not used, the Gleason patterns, score, grade group and tumor extent should be documented for each positive specimen (container) in the line diagnosis. The essential information could be conveyed with a simple diagnostic line such as, “Adenocarcinoma, Gleason grade 3 + 4 = score of 7 (Grade group 2), in 1 of 2 cores, involving 20% of needle core tissue, and measuring 4 mm in length.” (Note A.)
Prostatectomy: Recommended Elements

• **Histologic type** - acinar-type adenocarcinoma (99.5%)

• **Histologic grade - Gleason score**
  ✔ Gleason primary (predominant)
  ✔ Gleason secondary
  ✔ Gleason tertiary - $\leq 5\%$ not incorporated into Gleason score
  ✔ Grade Group

• **Tumour quantitation**
  ✔ Estimated % involvement
  ✔ Size of “dominant” nodule (if present)

• **Extraprostatic extension** - (no/yes)
  ✔ Focal or non-focal
Prostatectomy: Recommended Elements

- **Urinary bladder neck invasion** - (no/yes)
- **Seminal vesicle invasion** - (no/yes/no seminal vesicle present)
- **Surgical margins**
  - Uninvolved
  - Involved
    - Limited ($\leq 3$ mm) or non-limited ($> 3$ mm)
- **Treatment effect**
  - Hormone therapy - no Gleason score
- **Regional lymph nodes**
  - No lymph nodes submitted/found
  - Number involved/number examined
  - *Size of lymph nodes/metastatic deposits* – optional
  - *Extranodal extension* - optional
Prostatectomy: Optional Elements

- % pattern 4 and/or 5 - for Gleason score > 7/10
- Intraductal carcinoma - (no/yes)
- Extraprostatic extension - location(s)
- Surgical margins
  - Linear extent(s) in mm
  - Unifocal or multifocal
  - Gleason pattern at a positive margin
- Margin positivity at a site of extraprostatic extension
- Lymphovascular invasion
- Perineural invasion
Prostatectomy: Pathologic Staging (pT)

Primary Tumor (pT)*

___ pT2: Organ confined
___ pT3: Extraprostatic extension
___ pT3a: Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
___ pT3b: Tumor invades seminal vesicle(s)
___ pT4: Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

* Note: There is no pathologic T1 classification.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*
* Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.
2014 ISUP Consensus Conference: Are More Revisions to the Gleason System Really Necessary?
Recognized need for further modifications
  - lack of consensus on specific grading issues
  - some grading issues not covered in 2005
  - changes in prostate cancer management

67 urological pathologists (17 countries)

17 clinical leaders

Presentations/discussions on key issues
  - voting on evidence-based recommendations
The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD,* Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srivigley, MD,∥ Peter A. Humphrey, MD, PhD,¶ and the Grading Committee

Am J Surg Pathol • Volume 00, Number 00, 2015

TABLE 4. Morphologies Within Gleason Patterns

1. Gleason pattern 4 includes cribriform, fused, and poorly formed glands.
   VOTE: 100% Yes
2. The term hypernephromatoid cancer should not be used.
   VOTE: 78% Yes
3. For a diagnosis of Gleason pattern 4, it needs to be seen at ×10 lens magnification.
   VOTE: 78% Yes
4. Occasional/seemingly poorly formed or fused glands between well-formed glands is insufficient for a diagnosis of pattern 4.
   VOTE: 85% Yes
5. All glomeruloid glands should be graded as Gleason pattern 4 regardless of morphology.
   VOTE: 100% Yes
6. In cases with borderline morphology between Gleason pattern 3 and pattern 4 and crush artifacts, the lower grade should be favored.
   VOTE: 98% Yes
7. Branched glands are allowed in Gleason pattern 3.
   VOTE: 94% Yes
8. Small solid cylinders represent Gleason pattern 5.
   VOTE: 87% Yes
9. Solid medium to large nests with rosette-like spaces should be considered to represent Gleason pattern 5.
   VOTE: 88% Yes
10. Presence of unequivocal comedonecrosis, even if focal is indicative of Gleason pattern 5.
   VOTE: 94% Yes
11. Rarely, discrete glands (otherwise pattern 3) with necrotic debris within the lumens represents Gleason pattern 5.
   VOTE: 49% Yes

*Department of Pathology, University of Pennsylvania, Philadelphia, Pennsylvania
†Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York
‡Department of Pathology, University of Washington, Seattle, Washington
§Department of Anatomic Pathology, Mount Sinai School of Medicine, New York, New York
∥Department of Pathology, University of Michigan, Ann Arbor, Michigan
¶Department of Pathology, Harvard Medical School, Boston, Massachusetts

FIGURE 1. A. Gleason pattern 4 consisting of small round cribriform glands. Before the 2014 consensus conference there was variability grading as either Gleason pattern 3 or 4. B. Small glomeruloid glands graded as Gleason pattern 6; there was no consensus as to how to grade in the 2005 consensus. C. Molecular carcinoma, composed of discrete well-formed glands of Gleason pattern 3 (left). Before the 2014 consensus conference there was variability grading as either Gleason pattern 3 or 4. D. MD with dense cribriform glands, which is not assigned a grade as it was not discussed in the 2013 conference. E. Site case in 4) with psammomatoid basal cells (brownish chromatin) verifying carcinoma is immunostained. F. Prostatic apex poorly formed glands of Gleason pattern 4.
### Voting Summary

#### TABLE 4. Morphologies Within Gleason Patterns

1. Gleason pattern 4 includes cribriform, fused, and poorly formed glands.  
   VOTE: 100% Yes  
2. The term hypernephromatoid cancer should not be used.  
   VOTE: 78% Yes  
3. For a diagnosis of Gleason pattern 4, it needs to be seen at $\times 10$ lens magnification.  
   VOTE: 78% Yes  
4. Occasional/seemingly poorly formed or fused glands between well-formed glands is insufficient for a diagnosis of pattern 4.  
   VOTE: 85% Yes  
5. All glomeruloid glands should be graded as Gleason pattern 4 regardless of morphology.  
   VOTE: 100% Yes  
7. In cases with borderline morphology between Gleason pattern 3 and pattern 4 and crush artifacts, the lower grade should be favored.  
   VOTE: 98% Yes  
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   VOTE: 87% Yes  
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   VOTE: 94% Yes  
12. Rarely, discrete glands (otherwise pattern 3) with necrotic debris within the lumens represents Gleason pattern 5.  
   VOTE: 49% Yes
All Cribriform Glands = Pattern 4

- Original and 2005 modified Gleason allowed cribriform pattern 3
- 2008 - poor reproducibility for small cribriform glands
- 2011-2014 - cribriform glands (large and small) in prostatectomy specimens associated with biochemical failure

Sieve-like architecture (glands within glands)
Glomeruloid Glands = Pattern 4

- No consensus in 2005
- 2009 - glomeruloid glands associated with higher grade cancer (> 80% of cases on biopsy)
Borderline Pattern 3 vs 4?

• Tangential sectioning, crush artifact, occasional poorly-formed glands
• Choose the lower pattern
• Main Problem Area

- threshold for minute components of pattern 4
- especially challenging with small poorly-formed glands
- assumption that “experts” always go with higher grades
Intraductal Carcinoma (IDC)

**TABLE 2. Criteria for IDC**

Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells and:
- Solid or dense cribriform pattern

Or
- Loose cribriform or micropapillary pattern with either:
  - Marked nuclear atypia: nuclear size $6 \times$ normal
  - Necrosis
Intraductal Carcinoma is **NOT** Graded

- Issue not addressed in 2005
- IDC (not ductal variant carcinoma)

- Adverse prognostic indicator across all risk groups regardless of treatment modality
Mucinous Carcinoma

- 2005 no consensus on how to grade - default pattern 4 regardless of architecture???
- Biochemical free and overall survival same or better than conventional acinar carcinoma
- 2014
  - pattern 4 if cribriform
  - pattern 3 if discrete well-formed glands
Pattern 4

Fused Glands

Cribiform

Glomeruloid

Poorly-Formed Glands
Homogenization of Pattern 3

- Individual, discrete, well-formed glands
Evolution of the Gleason Diagram

Original Gleason

PROSTATIC ADENOCARCINOMA
(Histologic Patterns)

Hum Pathol 23;273-79, 1992

ISUP 2005 Gleason

Am J Surg Pathol 29;1228-42, 2005

Proposed modification of ISUP 2005 Gleason

J Urol 183;433-40, 2010
Question from Clinicians: Is Gleason 6 Still a “Cancer”?

- “Indolent lesion of epithelial origin” (IDLE)
- “Prostatic epithelial neoplasm of insignificant significance”

- Metastatic potential for pure Gleason 6 is negligible (but NOT zero)
  - 0.48% of 21920 prostatectomies have lymph node metastases (Liu et al, Pathology 2014:306-10)

- Still meets clinical, morphologic, immunohistochemical and molecular criteria for “cancer”.
Concept of Grade Grouping

• Rationale:
  - Gleason \( \leq 5/10 \) has all but disappeared
  - Gleason 6/10 is “low risk” - tough for patients
  - Gleason 7/10 can be (3+4) or (4+3)
  - Gleason 8-10 is “high-risk” and split into (4+4), (4+5), (5+4) and (5+5)
Grade Groups: Chicago 2014

• 5 groups
  - **Group 1** – Gleason 6/10 (3+3) or less
  - **Group 2** – Gleason 7/10 (3+4)
  - **Group 3** – Gleason 7/10 (4+3)
  - **Group 4** – Gleason 8/10 (4+4), (3+5)*, (5+3)*
  - **Group 5** – Gleason 9-10/10 (any combination of pattern 4 and 5)

• Still Gleason grading (as per modifications from Chicago 2014)
5 centres
20,845 radical prostatectomies (2005-2014)
16,172 pre-prostatectomy biopsies*
5,501 treated by radiotherapy* (2005-2014)
## CHAPTER 3

**Tumours of the prostate**

- Acinar adenocarcinoma
- Prostatic intraepithelial neoplasia
- Intraductal carcinoma
- Ductal adenocarcinoma
- Urothelial carcinoma
- Squamous neoplasms
- Basal cell carcinoma
- Neuroendocrine tumours
- Mesenchymal tumours
- Haematolymphoid tumours
- Miscellaneous tumours
- Metastatic tumours
- Tumours of the seminal vesicles

### Grade groups

<table>
<thead>
<tr>
<th>Grade group</th>
<th>Gleason score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤6</td>
<td>Only individual discrete well-formed glands</td>
</tr>
<tr>
<td>2</td>
<td>3+4=7</td>
<td>Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands</td>
</tr>
<tr>
<td>3</td>
<td>4+3=7</td>
<td>Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands*</td>
</tr>
<tr>
<td>4</td>
<td>4+4=8; 3+5=8; 5+3=8</td>
<td>Only poorly-formed/fused/cribriform glands or predominately well-formed glands and lesser component lacking glands** or predominately lacking glands and lesser component of well-formed glands**</td>
</tr>
<tr>
<td>5</td>
<td>9–10</td>
<td>Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands*</td>
</tr>
</tbody>
</table>

* For cases with >95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of <5% well-formed glands is not factored into the grade.

** Poorly-formed/fused/cribriform glands can be a more minor component.

From Epstein JI et al. (807B), with permission.
Grade Group 1

- Lowest grade possible - reassuring to patients
- Metastatic potential negligible (but not zero)
- Potential to reduce over-treatment of indolent disease
- But, follow-up required re: possibility of un-sampled higher grade cancer
Grade Groups in Practice

<table>
<thead>
<tr>
<th>1. Needle biopsy of prostate (right lateral):</th>
<th>Grade Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adenocarcinoma, Gleason score 6/10 (3+3), involving 1 of 1 core and 30% of the core.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Needle biopsy of prostate (right medial):</th>
<th>Grade Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adenocarcinoma, Gleason score 6/10 (3+3), involving 1 of 1 core and 50% of the core.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Needle biopsy of prostate (left medial):</th>
<th>Grade Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Negative for malignancy.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Needle biopsy of prostate (left lateral):</th>
<th>Grade Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adenocarcinoma, Gleason score 7/10 (3+4), involving 1 of 1 core and 20% of the core.</td>
<td></td>
</tr>
</tbody>
</table>

**Synoptic:**

Histologic type – usual acinar

**Overall Gleason Score – 7/10 (3+4)**

**Grade group – 2**

% Gleason pattern 4 – 10%

Distribution – bilateral

Number of positive cores – 3

Number of cores total – 4

% tissue involvement – 25%

% involvement for most involved core – 50%

Perineural invasion – not identified
Contemporary Gleason Grading of Prostatic Carcinoma

An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD,* Mahul B. Amin, MD,† Victor E. Reuter, MD,‡ and Peter A. Humphrey, MD, PhD§

(Am J Surg Pathol 2017;41:e1–e7)

- Reporting percent pattern 4 in biopsies and radical prostatectomies
- Reporting minor high-grade patterns in biopsies and radical prostatectomies
- Grading “core vs jar vs case” level
- Grading separate tumour nodules in radical prostatectomies
- Main goal of consensus conferences - uniformity in reporting of prostate cancer grade
Reporting % Pattern 4

• **Uniform reporting** of grade regardless of specimen type – avoids confusion created by different rules for biopsy vs RP

• **Active surveillance** patient selection - < 10% pattern 4 may be suitable (CCO PEBC, ASCO guidelines)

• **Radiation therapy** approaches can differ for (3+4) vs (4+3) - “(3+4) with pattern 4 approaching 50%”

• **Quality assurance** - < 5% pattern 4 should stimulate intradepartmental QA review
Clinical Utility of Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens

- Measure linear extent of cancer in biopsies
- Estimate % pattern 4 and/or 5
- Subdivide Gleason 7 cancers by % pattern 4:
  - 1-24% (low)
  - 25-49%
  - 50-74%
  - 75-95% (high)
Implications for Active Surveillance

- Low % pattern 4 Gleason 7/10 (3+4) on biopsy
  - 5-10% pattern 4 cases have the same risk of unfavourable Gleason score as Gleason 6/10 (3+3) at prostatectomy
- Negate effect of interobserver variability for small amounts of pattern 4, allowing low % pattern 4 cases to enter active surveillance.
Active surveillance for the management of localized prostate cancer: Guideline recommendations

Chris Morash, MD, FRCSC;† Rovena Tey;‡ Chika Agbassi, MBBS, MSc, CCRA;‡ Laurence Klotz, MD, FRCSC;* Tom McGowan, MD, FRCPC;‡ John Srigley, MD, FRCPC;§ Andrew Evans, MD, PhD, FRCPC§

*Division of Urology, University of Ottawa, Ottawa, ON; †Program in Evidence-based Care, Cancer Care Ontario, McMaster University, Hamilton, ON; ‡Division of Urology, Sunnybrook Health Sciences Centre, Toronto, ON; ‡The Cancer Centre Bahamas & The Cancer Centre Eastern Caribbean; §Credit Valley Hospital, Mississauga, ON; §Department of Pathology and Laboratory, Faculty of Medicine, University of Toronto, Toronto, ON

Fig. 1. Schematic diagram showing results from the primary literature search.
Recommendation 2

RECOMMENDATION 2: Active treatment (RP or RT) is appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume Gleason 3+4=7 localized prostate cancer, AS can be considered.

➢ Need to report estimate of % pattern 4
Reporting Minor High-Grade Patterns in Prostatectomies

• (3+3) with < 5% pattern 4 = (3+4) not (3+3) with “tertiary pattern 4”.

• (4+4) with < 5% pattern 5 = (4+5) not (4+4) with “tertiary pattern 5”.

• Use “minor” high-grade pattern - not tertiary

• Is there an upper limit to % pattern 5 as a minor pattern?
  ➢ all evidence is based on minor high-grade ≤ 5%
  ➢ 50% -3 + 30%-4 + 20%-5 will have worse behaviour
1 core per container - only 1 score
2-3 cores per container from the same site - global score for all cores
Multiple cores from different sites per container - to be avoided

Different cores can have different scores/grade groups
Some clinicians use the core with the highest score for treatment planning - others consider where the cores came from
- ipsilateral sites
- contralateral sites

**TABLE 2. Vote at the 2014 Consensus Meeting on Should We Provide a Grade for: (Multiple Choice)**

<table>
<thead>
<tr>
<th></th>
<th>Responses [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each positive core</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>Each positive specimen jar</td>
<td>11 (17.7)</td>
</tr>
<tr>
<td>Whole case overall (global grade)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>1 + 2</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>1 + 3</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>2 + 3</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>1 + 2 + 3</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>62 (100)</strong></td>
</tr>
</tbody>
</table>
Sampling Issues on Prostate Biopsy: Interpreting Gleason Scores – Highest vs Composite?
8 x 7 mm left posterior nodule
3 cores – 1) mid, 2) left medial, 3) left lateral
Mid
6/10 (3+3)
1 of 1 core
15% involvement
(% pattern 4 - 0)

Left Medial
7/10 (3+4)
1 of 1 core
80% involvement
(% pattern 4 - 10)

Left Lateral
8/10 (4+4)
1 of 1 core
5% involvement
(% pattern 4 - 100)
Sytoptic Report: Composite

Gleason Score: Case 1

- Histologic type – adenocarcinoma, usual acinar type
- **Overall Gleason Score** – 7/10 (3+4) (**not** 8/10 (4+4))
- Grade group – 2 (**not** Group 4)
- % Gleason pattern 4 – 10%
- Distribution – unilateral, left
- Number of positive cores – 3
- Number of cores total – 12
- % tissue involvement – 8%
- % involvement for most involved core – 80%
- Perineural invasion – not identified
- Intraductal carcinoma – not identified
Sampling Issues: Case 2

- 12 x 7 mm left posterolateral nodule
- 2 cores – 1) left medial, 2) left lateral
Left Medial

7/10 (3+4)
1 of 1 core
80% involvement
(% pattern 4 - 30)

Left Lateral

8/10 (4+4)
1 of 1 core
60% involvement
(% pattern 4 - 100)

Right medial - 6/10 (3+3), 1 of 1 core, 30%
Right transition zone - 6/10 (3+3), 1 of 1 core, 20%
Right lateral - 6/10 (3+3), 1 of 1 core, 10%
Synoptic Report: Composite
Gleason Score: Case 2

- Histologic type – adenocarcinoma, usual acinar type
- **Overall Gleason Score** – 7/10 (4+3) *(not 8/10 (4+4))*
- Grade group – 3 *(not Group 4)*
- % Gleason pattern 4 – 70%
- Distribution – bilateral
- Number of positive cores – 5
- Number of cores total – 10
- % tissue involvement – 20%
- % involvement for most involved core – 80%
- Perineural invasion – present
- Intraductal carcinoma – not identified
Prostate Biopsy and Radical Prostatectomy Gleason Score Correlation in Heterogenous Tumors
Proposal for a Composite Gleason Score

Javier A. Arias-Stella, III, MD,* Alpa B. Shah, MD, MPH,* Diego Montoya-Cerrillo,*† Sean R. Williamson, MD,* and Nilesh S. Gupta, MD*


Am J Surg Pathol • Volume 39, Number 9, September 2015
Gleason Score Correlation in Heterogenous Tumors

FIGURE 1. Comparison between HGS and CGS. Diagram showing a 12-core prostate biopsy with 6 total positive biopsy cores, of which 4 contiguous positive biopsy cores with highest tumor volume and grade represent the presumed dominant nodule. A CGS is assigned by measuring all Gleason patterns and estimating the percentage using the sum of all positive cores from the presumed the dominant nodule.
Cases

• 197 patients with biopsies showing:
  - > 2 Gleason scores (3+3, 3+4, 4+3)
  - > 1-step difference in Gleason score (3+4, 4+4, no 4+3)

• 100 underwent radical prostatectomy

• Radical prostatectomy Gleason score (higher, same or lower) was compared to biopsies using:
  - composite biopsy Gleason score
  - highest biopsy Gleason score
Composite Biopsy Gleason Score

- 59% had the same score at RP
- 41% had a different score at RP
  - 10% downgraded
  - 90% upgraded (typically 1-step)

FIGURE 3. A, Using the proposed CGS method, the RPGS was predicted accurately in the majority of patients, although upgrading was more common when compared with HGS. B, Most patients had the same grade group when comparing CGS with RPGS. A smaller number of patients were upgraded to a higher-grade group category, usually by 1 step.
FIGURE 2. A, Using the HGS as representative of the tumor overall, most patients were downgraded to a lower GS at RP. B, Most patients had a 1-step downgrade in grade group when comparing the highest biopsy GS with RP GS.
Take Home Points

• There will always be assumptions/risks when interpreting biopsies with different Gleason scores.
  ❖ not to mention sampling issues and pathologist factors

• Using the highest biopsy Gleason score to assess risk category will tend to overestimate the true grade (ie: downgrading at RP)

• Using composite Gleason score will be more accurate, but has a risk of underestimating the true grade (ie: upgrading at RP)
Emerging Topic: Types of Pattern 4

Fused Glands

Cribriform

Glomeruloid

Poorly-Formed Glands
Which Pattern 4 Morphologies Predict Aggressive Behaviour? Are They All the Same?
Not all Gleason Pattern 4 Prostate Cancers Are Created Equal: A Study of Latent Prostatic Carcinomas in a Cystoprostatectomy and Autopsy Series

Farshid Siadat, Jenna Sykes, Alexandre R. Zlotta, Najla Aldaoud, Shin Egawa, Dmitry Pushkar, Cynthia Kuk, Robert G. Bristow, Rodolfo Montironi, and Theodorus van der Kwast

**TABLE IV. Univariable Association of Architectural Pattern With EPE in the Autopsy Series**

<table>
<thead>
<tr>
<th>Autopsy (n = 37)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small fused glands</td>
<td>0.15 (0.03, 0.75)</td>
<td>0.02</td>
</tr>
<tr>
<td>Poorly formed glands</td>
<td>0.91 (0.21, 3.94)</td>
<td>0.9</td>
</tr>
<tr>
<td>Small cribriform</td>
<td>4.38 (0.78, 24.45)</td>
<td>0.092</td>
</tr>
<tr>
<td>Large cribriform</td>
<td>20.83 (2.04, 212.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td>10 (1.54, 64.75)</td>
<td>0.016</td>
</tr>
<tr>
<td>Cribriform architecture</td>
<td>9.62 (1.89, 48.93)</td>
<td>0.0063</td>
</tr>
</tbody>
</table>

Fig. 1. Selected architectural patterns in Gleason grade 4 cancer and intraductal carcinoma. (A) small fused glands, (B) small cribriform, (C) large cribriform, and (D) intraductal carcinoma.
Large Expansile Cribriform Pattern 4
Cribiform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer

Charlotte F Kweldam\textsuperscript{1}, Mark F Wildhagen\textsuperscript{2,3}, Ewout W Steyerberg\textsuperscript{4}, Chris H Bangma\textsuperscript{3}, Theodorus H van der Kwast\textsuperscript{5} and Geert J LH van Leenders\textsuperscript{1}

Figure 1: Gleason grade 4 patterns and intraductal carcinoma. (a) Fused glands; (b) ill-defined glands; (c) cribiform glands; (d) glomeroid glands; (e) intraductal carcinoma; and (f) 34BE12 immunohistochemistry, demonstrating the presence of basal cell supportive for intraductal carcinoma.
Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy

Charlotte F Kweldam1, Intan P Kümmerlin1, Daan Nieboer2, Esther I Verhoef1, Ewout W Steyerberg2, Theodorus H van der Kwast3, Monique J Roobol4 and Geert J van Leenders4

1Department of Pathology, Erasmus Medical Centre, Rotterdam, The Netherlands; 2Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands; 3Laboratory Medicine Program, University Health Network, Toronto, ON, Canada and 4Department of Urology, Erasmus Medical Centre, Rotterdam, The Netherlands

Table 1 Patient and tumor characteristics (N=1031)

<table>
<thead>
<tr>
<th></th>
<th>Mean (median, IQR) or n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSAs level at diagnosis (mg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of positive cores (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor percentage (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score 6 (n=486)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score 3+4 = 7 (n=310)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score 4+3 = 7 (n=104)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score 8 (n=64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score 9–10 (n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test. **Pearson's chi-square (χ²) test.
Figure 1 Kaplan-Meier disease-specific survival (DSS) according to Gleason score and CR/IDC status. (a) Gleason score 6. (b) Gleason score 3+4 = 7. (c) Gleason score 4+3 = 7. (d) Gleason score 8. (e) Gleason score 9-10. (f) DSS probabilities according to percentage of CR/IDC glands.
Distinct DNA methylation alterations are associated with cribriform architecture and intraductal carcinoma in Gleason pattern 4 prostate tumors

EKATERINA OLKHOV-MITSEL\(^1,2\), FARSHID SIADAT\(^3\), KEN KRON\(^4\), LIYANG LIU\(^1,2\), ANDREA J. SAVIO\(^1,2\), JOHN TRACHTENBERG\(^5\), NEIL FLESHNER\(^5\), THEODORUS VAN DER KWAST\(^2,6\) and BHARATI BAPAT\(^1,2,6\)

- 91 Gleason 7 prostatectomies
  - cribriform - 61/91 (67%)
  - IDC - 21/91 (23%)
- gene-specific methylation assay
- APC, RASSF1A, TBX15 significantly higher % methylation ratio with cribriform and IDC
PTEN loss and p27 loss differ among morphologic patterns of prostate cancer, including cribriform

Shira Ronen MD\textsuperscript{a}, Daniel W. Abbott MD\textsuperscript{a}, Oleksandr Kravtsov MD\textsuperscript{a}, Amrou Abdelkader MD\textsuperscript{a}, Yayun Xu MS\textsuperscript{b}, Anjishnu Banerjee PhD\textsuperscript{b}, Kenneth A. Iczkowski MD\textsuperscript{a,*}

Fig. 3 This cribriform cancer shows predominant PTEN loss centrally (A) and p27 loss peripherally (B).
New Synoptic Reporting Items at UHN

- **Grade group** - 1 to 5
- **% pattern 4 or 5** (as a global % of all carcinoma)
- **Cribriform morphology**
  - Present
  - Absent
  - Indeterminate
- **Intraductal carcinoma**
  - Present
  - Absent
  - Indeterminate
Issues With Poorly-Formed Glands

• Moved to pattern 4 by ISUP consensus 2005
  ✓ clinical outcome evidence to support the move???

• Frequently encountered in biopsies

• Suffer from high interobserver variability

• Frequent cause of grief for pathologists re: active surveillance patient selection (is it 6 or 7?)

• Not predictive of upgrading/upstaging

• Ki67 labelling index closer to pattern 3
Diagnosis of “Poorly Formed Glands” Gleason Pattern 4 Prostatic Adenocarcinoma on Needle Biopsy

An Interobserver Reproducibility Study Among Urologic Pathologists With Recommendations

Ming Zhou, MD, PhD,* Jianbo Li, PhD,† Liang Cheng, MD, PhD,‡ Lars Egevad, MD,§
Fang-Ming Deng, MD,* Lakshmi Priya Kunju, MD,∥ Cristina Magi-Galluzzi, MD, PhD,†
Jonathan Melamed, MD,* Rohit Mehra, MD,∥ Savvas Mendrinos, MD,¶
Adeboye O. Osunkoya, MD,∥ Gladell Paner, MD,,** Steve S. Shen, MD, PhD,††
Toyonori Tsuchuki, MD,‡‡ Kiril Trpkov, MD, §§ Wei Tian, MD,¶¶
Ximing Yang, MD, PhD,∥∥ and Rajal B. Shah, MD,¶¶


➢ Tangentially sectioned pattern 3?
➢ Poorly formed glands pattern 4?
➢ K = 0.34 (fair agreement)
Poorly-Formed Glands: Do They Belong in Gleason Pattern 4?

- **Outcomes** for Gleason 7 patients on active surveillance
  - types/amount of pattern 4 at initial biopsy
  - types/amount of pattern 4 after risk re-classification on follow-up biopsies after initial Gleason 6/10 (3+3).
    - *my experience that poorly formed glands are the most common reason for risk re-classification when pattern 4 = 5-10% of total carcinoma.*

- **Molecular characterization** vs pattern 3 and other forms of pattern 4
Active Surveillance for Gleason 7 Patients < 10% Pattern 4: My Predictions

- Definitely not suitable
- Most likely not suitable
- Suitable - like pattern 3 (especially cases < 10% pattern 4)
2014 ISUP Consensus Conference: Are More Revisions to the Gleason System Really Necessary?

Stay tuned for more!