Prostate Cancer Grading Over a Decade After the 2005 Modified System

Jonathan I. Epstein
Breakdown of Gleason Patterns

2,911 cases (percentages added up to approximately 150% since 50% of the tumors showed at least two different patterns).

- Pattern 1 - 3.5%
- Pattern 2 - 24.4%
- Pattern 3 - 87.7%
- Pattern 4 - 12.1%
- Pattern 5 - 22.6%.
Cribriform Pattern 3 Prior to 2005
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

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The American Journal of Surgical Pathology: Volume 40.
February 2016, p 244-52
Gleason Pattern 3

- Individual well-formed discrete glands
PROSTATIC ADENOCARCINOMA
(Histological Patterns)
All Cribriform Cancer Glands are Graded as Gleason Pattern 4
Glomeruloid Glands: Pattern 4
CONTEMPORARY PROSTATE CANCER GRADING IMAGES

Grading diagram that uses photomicrographs instead of line drawings to show the various patterns within each grade.

Sent to Pathologists in >40 Countries

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VARIANTS of ADENOCARCINOMA
Grading Variants of Prostate Adenocarcinoma

Same rule as grading usual prostate adenocarcinoma based on underlying grade pattern, except small cell carcinoma.

- Individual well-formed glands – pattern 3
- Cribriform – pattern 4
- Individual cells or necrosis – pattern 5
Foamy Gland Cancer
Pseudohyperplastic Cancer
Colloid Carcinoma
Signet Ring Cell-Like Adenocarcinoma
Ductal Adenocarcinoma
Ductal Adenocarcinoma

• Cribriform/papillary ductal adenocarcinomas should be graded as Gleason score 4+4=8

• PIN-Like ductal adenocarcinoma graded 3+3=6.

• Duct adenocarcinoma with necrosis grades as Gleason pattern 5.
Small Cell Carcinoma

Small cell carcinoma of the prostate has unique histological, immunohistochemical, and clinical features, which differ from those associated with Gleason pattern 5 prostatic acinar carcinoma, such that small cell carcinoma should not be assigned a Gleason grade.
Post-RT or HT Cancer

If histologically, ordinary prostate cancer is seen following hormone or radiation therapy, which resembles non-treated cancer – “Cancer without significant treatment affect” and Gleason grade.

Histologically cancer is seen, yet shows treatment effect – “Cancer with significant treatment affect” and do not Gleason grade.
Post Cryo or HIFU

- Following cryotherapy or HIFU, benign prostate tissue and prostate cancer undergoes infarction.

- Successful therapy eventually shows scarring, hemosiderin deposition, and maybe necrotic tumor.

- If non-necrotic tumor is seen, looks like non-treated cancer and can be graded and indicates viable active tumor that needs further treatment.
Intraductal Carcinoma

• Do not grade intraductal carcinoma (IDC)

• Consider IHC if the overall grade in the case would change depending on whether IDC or infiltrating high grade carcinoma
Reporting Rules for Gleason Grading
Cribiform Glands

• Vast majority of studies on prostate cancer with cribriform architecture, whether inclusive of IDC-P or not, demonstrate associations between these prostate cancers and both adverse clinical outcomes and molecular features typically seen in advanced disease.

• Based on these findings, recommend reporting the presence or absence of cribriform glands in biopsy and radical prostatectomy specimens with Gleason pattern 4 carcinoma.
Rationale for Reporting Percent Pattern 4 for Gleason Score 7
IMPROVED PATIENT CARE

1. The major advantage for patient care to record the percent pattern 4 on needle for Gleason 3+4=7 would be for active surveillance (AS). For the appropriate patient, Gleason 3+3=6 is accepted for men to undergo AS. However, there may be some men, depending on age, co-morbidity, extent of cancer, MRI findings, patient desire, etc, that could be a candidate for AS with 3+4=7 if the pattern 4 is limited. Currently, this information is not apparent in pathology reports.
2. The amount of pattern 4 is not only used for active surveillance but could be used for radiation therapy as well. Currently, there is different radiation therapy for 3+4 vs 4+3. In a case with borderline 3+4 vs 4+3, one pathologist could call it 3+4 and the other 4+3. Depending on whether 3+4 or 4+3 the percent pattern 4 could range from <5% to 90% and would not be evident in a report. By reporting the case as 3+4=7 (approaching 50% pattern 4) or 4+3=7 (60% pattern 4) the borderline nature of the case would be evident and clinicians could use other factors (PSA, number of cores positive, imaging, etc.) for therapy.
Personal Preferences in My Practice

• Do not record percent pattern 4 in small foci of 3+4=7 or 4+3=7 (GUPS no consensus)

• <5% or <10% with 10% intervals (GUPS recommendation)

• Do not record percent pattern 4 if any other core has Gleason score 9 or 10 (GUPS no consensus)

• If borderline between lower and higher grade cancer, I assign the lower grade and do levels to clarify.
Minor Pattern of Lower Grade

- On RP or needle do not mention if the lower grade component is <5%.

- Core or RP nodule with 98% pattern 4 and 2% pattern 3 is graded as 4+4=8.
Minor Tertiary Pattern 5 on RP

Use in RPs with 3+4=7 or 4+3=7 with <5% pattern 5

3+4=7 with 50% pattern 3, 30% pattern 4, 20% pattern 5

GUPS recommends limits to <5% pattern 5 (ie minor high grade) : 3+5=8
Gleason Pattern 5 as Minor 3rd Most Common Pattern on Biopsy

- **Not** use tertiary on needle biopsy

Needle biopsy: 3+4=7 with lesser pattern 5 is 3+5=8
4+3=7 with lesser pattern 5 is 4+5=9
NEEDLE BIOPSY WITH DIFFERENT CORES SHOWING DIFFERENT GRADES

One should assign individual Gleason scores to separate cores as long as the cores are submitted in separate containers or the cores were in the same container yet specified by the urologist as to their location (ie. by different color inks).

Same with MRI-targeted biopsy of a lesion

Assigning a global (composite) score is optional.
Reporting of Gleason Grade in RPs

• Each major tumor focus should be graded separately. For example: 2 tumor nodules – One left PZ 4+4=8 with larger right PZ 3+3=6. Give two scores and not call 3+4=7.

• Typically only the largest tumor foci are graded. Not necessary to report small multifocal lower grade cancer.

• Exception when there is a smaller tumor focus of higher grade, report this Gleason score.
Problems with Gleason System: Scale

- 6 is the lowest grade reported although the scale goes from 2-10

- Patients are told they have a Gleason score of 6 out of 10 and logically but incorrectly think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer
Problems with Gleason System Grouping

- Gleason 7 is not homogeneous: $4+3=7$ has a much worse prognosis than $3+4=7$

- Gleason 8-10 is often considered as one group - high grade disease
Problems with Gleason Grading
Too Many Grades with Similar Prognoses

• 1+1; 1+2; 1+3; 1+4; 1+5; 2+1; 2+2; 2+3; 2+4; 2+5; 3+1; 3+2; 3+3; 3+4; 3+5; 4+1; 4+2; 4+3; 4+4; 4+5; 5+1; 5+2; 5+3; 5+4; 5+5

• 25 potential grades!

• What are the least number of grades with a similar prognosis?
Prognostic Gleason grade grouping: data based on the modified Gleason scoring system

Phillip M. Pierorazio*, Patrick C. Walsh*, Alan W. Partin* and Jonathan I. Epstein*††

BJU International 2013; 111:753-60
New 5 Grade System

• **Grade Group 1 (≤6)**
  
  Only individual discrete well-formed glands

• **Grade Group 2 (3+4)**
  
  Predominantly well-formed glands with a lesser component of poorly-formed/fused/cribriform glands

• **Grade Group 3 (4+3)**
  
  Predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands
• **Grade Group 4 (4+4/3+5/5+3)**
  
  Only poorly-formed/fused/cribriform glands **or**
  
  Predominantly mix of well-formed and lack of glands

• **Grade Group 5 (4+5/5+4/5+5)**
  
  Lack gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands
2014 - RP Data From 5 Institutions

- Since 2005 – Modified Gleason grades
- **University of Pittsburgh** – J. Nelson, A. Parwani
- **MSKCC** – V. Reuter, S. Fine, A. Vickers, J. Eastham, D. Sjoberg
- **CCF** – C. Magi-Galluzzi, E. Klein, J. Ciezki, C. Reddy
- **Karolinska** – L. Egevad, P. Wiklund, T. Nyberg
- **Johns Hopkins** – J. Epstein, M. Han
# RP Grade Meta-Analysis

<table>
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<th>Hosp</th>
<th>Freq.</th>
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<tbody>
<tr>
<td>Pittsburgh</td>
<td>2,102</td>
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<tr>
<td>Karolinska</td>
<td>3,763</td>
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<tr>
<td>Hopkins</td>
<td>6,137</td>
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<tr>
<td>Memorial</td>
<td>6,673</td>
</tr>
<tr>
<td>CCF</td>
<td>2,170</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>20,845</strong></td>
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# RP Grade

## 5 Year Biochemical Risk Free Survival

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gleason</th>
<th>BRFS</th>
<th>95% Confidence Intervals</th>
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<tbody>
<tr>
<td>1</td>
<td>3+3=6</td>
<td>96%</td>
<td>94%-95%</td>
</tr>
<tr>
<td>2</td>
<td>3+4=7</td>
<td>88%</td>
<td>87%-89%</td>
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<tr>
<td>3</td>
<td>4+3=7</td>
<td>63%</td>
<td>61%-65%</td>
</tr>
<tr>
<td>4</td>
<td>4+4=8</td>
<td>48%</td>
<td>44%-52%</td>
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<tr>
<td>5</td>
<td>9-10</td>
<td>26%</td>
<td>23%-30%</td>
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Multiple Additional Studies Validating New Grading System

Correlating with BCR, distant metastases, mortality following RT and radical prostatectomy
### 2016-2017 Review of the Literature

**How Grades Listed From Ideal to Least Ideal**

<table>
<thead>
<tr>
<th>Order to Ideal</th>
<th>2016 (n=601)</th>
<th>2017 (n=541)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>( \leq 6, 3 + 4 = 7 ) (3+4=7, 4+3=7, 8, 9-10)</td>
<td>71 (11.8%)</td>
<td>132 (34.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \leq 6, 3 + 4 = 7, 4+3=7, 8-10)</td>
<td>108 (18.0%)</td>
<td>79 (14.6%)</td>
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<tr>
<td>( \leq 6, 7, 8, 9, 10)</td>
<td>44 (7.3%)</td>
<td>38 (7.0%)</td>
<td>&lt;0.001</td>
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<tr>
<td>( \leq 6, 7, 8-10)</td>
<td>219 (36.4%)</td>
<td>161 (29.8%)</td>
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<tr>
<td>( \leq 7, 8-10 ) OR &lt;6, 7-10</td>
<td>159 (26.5%)</td>
<td>131 (24.2%)</td>
<td></td>
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</tbody>
</table>
More Accurately Reflects Biology of Disease than Current System

Grade Group 1 (as opposed to 6/10): Excellent prognosis – no metastases. Avoids issues of GS<6

Grade Group 2 (as opposed to 7/10): Very good prognosis – rare metastases

Grade Group 3 (4+3 and 3+4 both = GS7 – D’Amico): Greater distinction from Grade Group 2
More Accurately Reflects Biology of Disease than Current System

Grade Group 4 (as opposed to combined 8-10): Better prognosis than 9-10.

Grade Group 5: No need to distinguish 9 vs 10.
The new grading system was recently accepted

2016 World Health Organization (WHO)
Pathology & Genetics:
Tumours of the Urinary System and Male Genital System

College of American Pathologists (CAP)

**Needle Biopsy:** Adenocarcinoma of the prostate Gleason score 3+4=7 (Grade Group 2) with 20% pattern 4 involving 80% of 1 core.

**Radical Prostatectomy:** Adenocarcinoma of the prostate Gleason score 3+4=7 (Grade Group 2) with minor tertiary pattern 5.
Join us at:
www.gupathsociey.org
Controversy Gleason Score 3+5 & 5+3

- Conflicting studies on whether 3+5=8 & 5+3=8 should be in Grade Group 4 (along with Gleason score 4+4=8) or Grade Group 5 (along with Gleason Score 9-10)

- Needle Bx: Separate cores with 3+3=6 and 5+5=10. If average could be 3+5=8 or 5+3=8. If highest grade core would be 5+5=10.

- RP: Separate nodules with 3+3=6 and 5+5=10. If average or not process to determine if separate, then could be 3+5=8 or 5+3=8. If highest grade nodule would be 5+5=10.
How Common is 5+3=8?

• Our prior multi-institutional study of over 20,000 men using highest grade core or highest grade nodule

• Only 4/20,824 (0.02%) radical prostatectomies and 6/16,172 (0.04%) needle biopsies were Gleason score 5+3=8