Prostate Cancer Grading
From Gleason to a Contemporary Patient Centric Grading System
Jonathan I. Epstein
Original Gleason System

• First reported in 1967 - 270 men

• Modified 1974 – 1032 men

• Modified 1977 – 2911 men
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%.
Historical Prevalence of Gleason Score 2-4

- In the 1990s, 22% of prostate needle biopsies had as the highest grade a Gleason score of 2-4.
Gleason Score 2-4 on Needle Should Not Be Made
Editorial AJSP (Epstein), 2000

1) Poor reproducibility among experts for lower grade tumors.

2) Correlation with the prostatectomy score for Gleason 2-4 tumors is poor and up to 50% of the corresponding prostatectomies may have extraprostatic extension.

3) Gleason 2-4 may misguide clinicians and patients into believing that there is an indolent tumor.
Low Grade Prostate Cancer Does Exist

- Transition zone
- Small foci
- Seen on TURP – often indicates “insignificant” cancer
- Rarely sampled on needle biopsy – not indicate “indolent” tumor
The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma


Epstein, Jonathan I ; Allsbrook, William C Jr; Amin, Mahul B; Egevad, Lars L and the ISUP Grading Committee
WHY THE NEED FOR A CONSENSUS ON GLEASON GRADING?
Gleason’s Era

- More advanced clinical disease
- Fewer RPs which were not processed in entirety
  - Grading of multiple nodules
  - Tertiary patterns
- Needle biopsy only a few thick cores
  - Grading thin needle cores
  - Grading multiple cores from different sites
- Lesions diagnosed differently with more modern tests
- New entities
PROSTATIC ADENOCARCINOMA
(Histological Patterns)
Gleason Pattern 3

- Individual discrete glands with well-formed lumina
Level 1 ? Pattern 4
Level 2 – Glands Open Up Pattern 3
Gleason Pattern 3

- Small well-circumscribed cribriform glands with uniform round evenly distributed lumina
Grading of Invasive Cribriform Carcinoma on Prostate Needle Biopsy

An Interobserver Study among Experts in Genitourinary Pathology

Mathieu Latour, MD,* Mahul B. Amin, MD,§ Athanase Billis MD,¶ Lars Egevad MD, PhD,‖
David J. Grignon, MD,# Peter A. Humphrey, MD, PhD,** Victor E. Reuter, MD, † †
Wael A. Sakr, MD, ‡‡ John R. Srigley MD, §§ Thomas M. Wheeler, MD, §§§
Ximing J. Yang, MD, PhD, §§§ and Jonathan I. Epstein, MD* † †
Consensus Conference on Grading of Prostatic Carcinoma

Chicago
November, 2014
All Cribriform Cancer Glands are Graded as Gleason Pattern 4
PROSTATIC ADENOCARCINOMA

(Histological Patterns)

1

2

3

4

5

D. F. Gleason, M.D.
Gleason Pattern 4

- Poorly-formed glands
Gleason Pattern 4

- Fused glands
Gleason Pattern 4

- Cribriform glands
Gleason Pattern 4

- Glomeruloid glands
PROSTATIC ADENOCARCINOMA
(Histological Patterns)
Gleason Pattern 5

- No gland formation or glands with necrosis
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

jepstein@jhmi.edu
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

- 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-Treatment Cancer – HT or RT

If histologically, ordinary prostate cancer is seen, 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)

- Only do IHC if the overall highest grade per part in the case would change depending on whether IDC or infiltrating high grade carcinoma
The International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma

Chicago
November, 2014
67 Pathology Experts in Prostate Cancer from 21 Countries

20 Urology, Oncology, and Radiation Oncology Experts
Reporting Rules for Gleason Grading
Tertiary Patterns

No longer Used for Two Patterns
With Very Minor Component of Higher Grade

- 4+4=8 with minor pattern 5 behaves like 4+5=9 so now just called 4+5=9.

- 3+3=6 with minor pattern 4 is now called 3+4=7 with recording the percent pattern 4 ranging from 1%-approaching 50%.

- Optional how to record percent pattern 4 (per part or per case)
Rationale for Reporting Percent Pattern 4
The major advantage for patient care to record the percent pattern 4 on needle for Gleason 3+4=7 is 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.
The amount of pattern 4 may not only be 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.
PRACTICALITY

When a pathologist grades a specimen as 3+4 or 4+3, (s)he already has to decide what part of the tumor is pattern 4 or 3 such that to give a percent should not be that much extra effort.

“Interobserver reproducibility of reporting percent GG4/5 on prostate biopsies is at least as good as that of reporting Gleason score.” (J Urol 2004; 171:664-7)

Interobserver reproducibility of percent Gleason Pattern 4 on prostate biopsies is about 80%. (ASJP 2016; 40: 1686-1692).
BORDERLINE 3+3 vs 3+4

Having to record less than 5 percent pattern 4 in a borderline case between 3+3 and 3+4 should prompt the pathologist to verify that the pattern 4 is definitive.
Personal Preferences in My Practice

• I do not record percent pattern 4 in small foci of 3+4=7 or 4+3=7.

• I record: <5%, 10%, 20%, 30%, 40%, approaching 50%, 60%, 70%, 80%, 90%

• I do not record percent pattern 4 if any other core has Gleason score 9 or 10.

• If borderline between lower and higher grade cancer, I assign the lower grade and look at levels.
Clinical Utility of Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens

Eur Urol 2016
Sauter et al.
Tertiary Patterns

Three Patterns With Very Minor Component of Higher Grade

• On RP if pattern 5 is <5% and 3rd most common pattern then report 3+4=7 with tertiary pattern 5. If >5% then is the secondary pattern (ie. 3+5=8).

• On needle bx. if pattern 5 is 3rd most common pattern, regardless of percentage, then include in score (ie. 3+5=8) (most common + highest grade).

• Only use “tertiary” for 3+4=7 with <5% (tertiary) pattern 5 or 4+3=7 with <5% (tertiary) pattern 5 on RP
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.
NEEDLE BIOPSY WITH DIFFERENT CORES SHOWING DIFFERENT GRADES

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

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.
Impetus for a New Prostate Cancer Grading System
Movement to Rename Gleason Score 6 as not Cancer
The Word “Cancer” Drives Overtreatment

- Fear of death from cancer likely plays some role, and removing the label “cancer” could reduce unnecessary treatment of low grade disease.

- Proposed name: IDLE (indolent lesion of epithelial origin) (Esserman, Lancet Oncol et al., 2013)
Precedent in Other Organs

- Soft tissue: Well-differentiated liposarcoma in extremities renamed: **Atypical lipomatous tumor (ALT)**

- Bladder: Subset of low grade Papillary urothelial carcinoma renamed: **Papillary urothelial neoplasm of low malignant potential (PUNLMP)**

- Thyroid: Encapsulated follicular variant papillary thyroid carcinoma renamed: **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)**.
Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

H. Ballentine Carter, Alan W. Partin, Patrick C. Walsh, Bruce J. Trock, Robert W. Veltri, William G. Nelson, and Donald S. Coffey, The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD
Eric A. Singer, National Cancer Institute, National Institutes of Health, Bethesda, MD
Jonathan I. Epstein, The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD

When is Prostate Cancer Really Cancer?

David M. Berman, MD, PhD, Jonathan I. Epstein, MD
Arguments in Favor of Retention of Gleason Score 6 Cancer

• Morphological

• Molecular

• 20% undersampling of higher grade cancer with Gleason 6 on biopsy

• Patients will be lost to follow-up if called IDLE tumor
Gleason Score 6 Prostatic Adenocarcinoma Should Still be Called “Cancer”

- Rather there is a need to change what patients think when they hear they have Gleason score 6 cancer.

- Urologists need to reassure and educate patients.

- Modify how we report prostate cancer grade to more accurately reflect their behavior.
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
Qualitative Study About Grading

• 7 focus groups with n=37 prostate cancer patients in two clinical settings from 2015-2016

• Majority of patients (84%) agreed that it would be clearer if grades were reported on a scale of 1-5 instead of 6-10

• 88% would prefer to hear they have “Group 1” rather than “Gleason 6”

• 80% would feel more comfortable choosing active surveillance with “Group 1” versus “Gleason 6”

Loeb et al. (Unpublished data)
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 System:
Inconsistent & Inaccurate Grouping

Various combinations have been used in the literature including some of the highest impact studies:

Prostate Cancer Outcomes Study (NEJM): 2-4; 5-7; 8-10
Scandinavian Prostate Cancer Group Study (NEJM): 2-6, 7; 8-10
Prostate Cancer Intervention vs. Observation (NEJM): 2-6; 7-10
Prostate Cancer Prevention Trial (NEJM): 2-6; 7-10
D’Amico Risk Classification
Stratification

• Low Risk: T1C/T2a & PSA ≤10 & Gleason ≤6

• Intermed. Risk: T2b or PSA 10-20 or Gleason 7

• High Risk: T2c or PSA >20 or Gleason 8-10
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

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<td><strong>Total</strong></td>
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## RP Grade

### 5 Year Biochemical Risk Free Survival

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<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>
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<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>
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<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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# Biopsy Grade Meta-Analysis

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<td>6,137</td>
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<tr>
<td>Memorial</td>
<td>5,791</td>
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<td>CCF</td>
<td>2,146</td>
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<td><strong>Total</strong></td>
<td><strong>16,176</strong></td>
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Radiation Therapy

- CCF 2495 (45%)
- MSKCC 3006 (55%)
- Brachy 3361 (61%)
- EBRT 2140 (39%)
- Peri-RT 1845 (34%)
- HT
VALIDATION OF A CONTEMPORARY PROSTATE CANCER GRADING SYSTEM WITH LONG TERM OUTCOME

B J Cancer
Berney D., et al.
2016
Multiple Additional Studies Validating New Grading System

Correlating with BCR, distant metastases, mortality following RT and radical prostatectomy
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)

Starting in January 2018, it will be mandatory for pathology laboratories accredited by CAP to use the new grading system in parallel to the Gleason grading system and to report percent pattern 4 for Gleason score 3+4=7 on needle biopsy.

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

Optional: Percent pattern 4 for 4+3=7 on needle biopsy
• Mandatory to report Grade Groups and tertiary pattern 5 on RP

• **Radical Prostatectomy**: Adenocarcinoma of the prostate Gleason score 3+4=7 (Grade Group 2) with tertiary (<5%) pattern 5.

• Optional to report percent pattern 4 for Gleason 7 on RP
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