3+3=1! Changes in the Gleason Grading System

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Gleason Grading System

- Dr. Donald Gleason, the Chief of Pathology at the Veteran’s Hospital in Minnesota
- Based on a study of 270 men with prostate cancer from 1959 through 1964
- Based on Histologic patterns of the PA
- As most cases have two histologic patterns, a score was created that added the two most common grade patterns in the tumor
- We have scores ranging from 2 to 10
Gleason Score

Gleason Grade

PROSTATIC ADENOCARCINOMA
(Histologic Grades)

1977

ISUP Modified Gleason Grade

2005
Gleason Pattern 4

B: Poorly formed glands, pattern 4

C: Cribriform glands, pattern 4

Carinoma cell clusters with no glandular luminal formation.

Large glands compartmentalized by cellular bridges.
Gleason Grading System

- Significant revisions – 2005, the most current being the 2014 ISUP
- It is the single most powerful predictor of prostate cancer prognosis and directs clinical management
- Continues to have deficiencies that can potentially impact patient care
Gleason Grading System

• **Gleason’s original data**
  - GS 2-5 comprised 28%
  - GP 4 (GS 7, 8, 9) comprised 12%

• **Danneman et al**
  - GS 2-5 comprised 27% in 1998
  - GS 2-5 comprised 1% in 2011
  - GS 7 comprised 38% in 2011

• Grade scores 2-5 have disappeared from clinical practice

• Many former Gleason score 6 tumors are now reclassified as Gleason score 7 in the modified system.
Gleason Grading System

• Multiple modifications – much more complex than its original version
  – Confusing for the patients and the clinicians
• Gleason 6 is now recommended as the lowest grade to be assigned on prostate biopsy
• Counterintuitive in that the Gleason scale ranges from 2 to 10
Gleason Grading System

• Modern Gleason score 6 tumors have a more restrictive definition, much better prognosis than reported in the older literature
• No pure Gleason score 6 tumors are associated with disease recurrence after radical prostatectomy
• Rarely lymph node metastases occur
Is 6(3+3) a cancer?

• Pure Gleason score 6 (3+3) on radical prostatectomy
  – Does not metastasize
  – Incapable of regional lymph node metastases
  – Organ confined, margin negative – excellent prognosis

• Should it be designated as cancer?
  – To avoid fear and consequent overtreatment of a proportion of potentially indolent prostate cancers

• Pathologists point
  – Still a cancer
  – Same morphologic and molecular features as higher grade PA
  – Lack of basal cell layer
  – Potential to locally invade
  – When present in a biopsy, upgrading at RP is seen in 17% to 36%
  – Patients on active surveillance may not adhere to long term follow-up because they have been told that do not have cancer
Need for a New Grading System

• When patient’s are told that they have a Gleason score 6 out of 10, it implies that there prognosis is intermediate
• This information contributes to their fear of having a more aggressive cancer rather than having the best prognosis
• Overtreatment
Risk Stratification

- Urologists use Gleason score along with other clinical variables to create risk stratification for patient management.
- Diversity in literature regarding Gleason score grouping

<table>
<thead>
<tr>
<th>Prostate Cancer Outcomes Study</th>
<th>Scandinavian Prostate Cancer Group Study</th>
<th>Prostate Cancer Prevention Trial and Prostate Cancer Intervention versus Observation Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>2-6</td>
<td>2-6</td>
</tr>
<tr>
<td>5-7</td>
<td>7</td>
<td>7-10</td>
</tr>
<tr>
<td>8-10</td>
<td>8-10</td>
<td></td>
</tr>
</tbody>
</table>
Risk Stratification

- The most common risk stratification system used for prostate cancer is the D’Amico classification
- National Comprehensive Cancer Network (NCCN)
- Stratifies prostate cancer based on
  - Serum PSA
  - Clinical stage
  - Biopsy Gleason score
    - Low risk (2-6)
    - Intermediate risk (7) – both 7(3+4) and 7(4+3)
    - High risk (8-10) – 8 is not distinguished from 9-10
Gleason Grading System

• Many clinicians consider Gleason score 7 on biopsy to be intermediate risk, multiple studies have shown that Gleason score $4 + 3 = 7$ demonstrates worse pathological stage and biochemical recurrence rates than $3 + 4 = 7$.
There is need for a New Grading System to better align the Grades with Prognosis
New Grading System

• The new Grade Group System Dr. Epstein from John Hopkins in 2013
  – 7869 patients who underwent RP at John Hopkins
  – Validated on 20,845 patients from 5 academic institutions
• “New Grading System,” is “novel grouping” of a much modified original Gleason grading system
• Simple, easy to follow
• Least number of grades
• Each grade having its own distinct prognosis
New Grading System

• Five distinct Grade Groups based on the modified Gleason score groups
  – Grade Group 1 = Gleason score $\leq 6$
  – Grade Group 2 = Gleason score $3 + 4 = 7$
  – Grade Group 3 = Gleason score $4 + 3 = 7$
  – Grade Group 4 = Gleason score 8
  – Grade Group 5 = Gleason scores 9 and 10
New Grading System - Initial Data from John Hopkins

• 7869 men undergoing RP without tertiary pattern since 2004
• Median follow-up of 2 years (1-7 yrs range)
• The 5-year biochemical risk-free survivals for the 5 Grade Groups based on radical prostatectomy were
  – Grade Group 1 – 96.6%
  – Grade Group 2 -  88.1%
  – Grade Group 3 – 69.7%
  – Grade Group 4 – 63.7%
  – Grade Group 5 – 34.5 %
    • (p < 0.001)

Kaplan-Meier analysis of Gleason score at RP pathological analysis
Biochemical Recurrence Free Survival

Pathological Gleason Sum

<table>
<thead>
<tr>
<th>Pathological Gleason Sum</th>
<th>Survival Rate (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3,548)</td>
<td>96.6% (210)</td>
</tr>
<tr>
<td>(1,972)</td>
<td>88.1% (74)</td>
</tr>
<tr>
<td>(603)</td>
<td>69.7% (19)</td>
</tr>
<tr>
<td>(142)</td>
<td>63.7% (3)</td>
</tr>
<tr>
<td>(197)</td>
<td>34.5% (4)</td>
</tr>
</tbody>
</table>

log-rank p < 0.001

Time, years

(≤6)
(3+4)
(4+3)
(8)
(8+3)
(9–10)
Kaplan-Meier analysis of Gleason score at biopsy pathological analysis

Biochemical Recurrence Free Survival
Biopsy Gleason Sum

- (≤6): 94.6% (251) at 8 years
- (3+4): 82.7% (35) at 6 years
- (4+3): 65.1% (18) at 4 years
- (8): 63.1% (7) at 2 years
- (9–10): 34.5% (2 at 4 years)

log-rank p < 0.001
New Grading System – Validation Study

• Multi-institutional study including Johns Hopkins Hospital, Memorial Sloan-Kettering Cancer Center (MSKCC), University of Pittsburgh, Cleveland Clinic and the Karolinska Institute validated the new grading system

• 20,845 radical prostatectomy cases 2005-2014

• 5501 men treated with radiotherapy at two academic centers (JHH and CC)

• Mean follow-up period, without biochemical recurrence for RP and radiation cohorts were 3 and 3.1 years.

Recurrence-free progression following radical prostatectomy stratified by prostatectomy grade

Green ≤6; Orange 3+4; Blue 4+3; Red 8; Purple ≥9

RFP = recurrence free progression
Recurrence-free progression following radiation stratified by pre-radiation therapy biopsy grade (entire cohort)

![Recurrence-free progression graph]

Number at risk:

- ≤6: 237, 211, 163, 147, 113, 85, 58, 33, 14, 0, 0
- 3+4: 355, 311, 247, 183, 132, 78, 54, 29, 13, 0, 0
- 4+3: 279, 248, 183, 142, 97, 68, 38, 13, 3, 0, 0
- 8: 235, 198, 147, 120, 89, 53, 33, 10, 3, 0, 0
- ≥9: 228, 184, 143, 111, 86, 54, 32, 17, 6, 0, 0
Proportion of patients undergoing adjuvant or neoadjuvant hormonal therapy among radiotherapy patients

<table>
<thead>
<tr>
<th>Gleason Score (Grade Group)</th>
<th>Radiation + Hormonal Therapy</th>
<th>Radiation Therapy Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (GG 1)</td>
<td>15%</td>
<td>85%</td>
</tr>
<tr>
<td>3+4 (GG2)</td>
<td>26%</td>
<td>74%</td>
</tr>
<tr>
<td>4+3 (GG3)</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>8 (GG4)</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>9-10 (GG5)</td>
<td>95%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Recurrence-free progression following radiation stratified by pre-radiation therapy biopsy grade (no hormone therapy cohort)
New Grading System

• While retaining the essence of the Gleason system, the new Grading Groups more closely reflect tumor behavior

• Classifies the PA into prognostically more accurate groups than current Gleason risk stratification groups ≤6, 7, 8-10

• Simplifies the Gleason grading system from 25 scores to 5 Grade Groups

• Lowest grade is 1 as opposed to 6, with the potential to reduce overtreatment of indolent PA
  – Will help patients to make a more rationale decision
New Grading System

• This new grade is currently in conjunction with the GS e.g. GS 6 (3+3) (Grade Group 1)
  GS 7 (3+4) (Grade Group 2)
Grade Groups 1-5

The new grading system and the terminology

“Grade Groups 1-5” has been accepted by the

World Health Organization 2016 edition of Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs.
Questions?