Why grade tumours?

- Groups of patients
  - Clinical trials
    - Groups have to comparable
  - Survival analysis
    - Surgeons, Areas (eg. Wales vs. England)
- Individual patient
  - Prognosis
  - Management

Grading tumours

- Groups of patients
  - Borderline grades cancel each other
  - Inter-observer reproducibility less important
  - Fewer tiers the better?
- Individual patient
  - Arbitrary lines in continuum
  - More tiers the better?
  - Inter-observer reproducibility critical

Classical Gleason System

- Prospective study, >4000 pts, 1960-75
- Pre-PSA
- Most (86%) advanced cancer
- Specimen type
  - TURBT, open prostatectomy, 14 gauge needle bx
- Pre-immunohistochemistry
- Before variants described

Classical Gleason System: Principles

- Low-medium power assessment
- Based only on architecture
- Not by worst grade
- Grade only included if at least 5%
- Rules same for all specimen types
- Tertiary grade not included in score

Gleason Score: Not by the Worst Grade

- Minor component (eg. 6%) lower grade improves prognosis?
- Rationale:
  - volume of high-grade important?
  - marker of less aggressive behaviour?
    - 4 + 3: slower transformation to high-grade
    - 4 + 4: faster transformation
  - 4 + 4 and 4 + 3: separate diseases?
    - de-novo pattern 4 vs. transformation of 3
**Why was Gleason System Adopted?**

- Simple
- Quick
- Low/medium power evaluation
- Gleason’s diagram of patterns easy to follow
- Based on follow-up data

**ISUP 2005 Modifications**

- Use of Gleason scores 2-4
- Grading cribriform cancer
- Definition of pattern 4
- Grading variants
- Grading limited (<5%) secondary pattern
- Reporting tertiary pattern

**Gleason Score 2-4**

- **Needle biopsy**
  - Pattern 1: never
  - Pattern 2: very rarely
- **TURPs**
  - Uncommon
  - Prognosis same as Gleason 5-6
- **Radicals**
  - Occasionally
  - Small anterior transition zone tumours

**Rationale for Gleason Score 2-4 Changes**

- Gleason 2-4 tumours generally small anterior tumours
- Not sampled by needle biopsy
- Most (?) all Gleason’s 1 + 1 = 2 cancers were adenosis
- “Tip of iceberg phenomenon”

**Cribriform Cancers**

- Almost all pattern 4
- Cribriform pattern 3 very rare
  - Many of Gleason’s cribriform pattern 3 were high-grade PIN or intraductal cancer
  - Criteria for cribriform pattern 3 vs. 4 arbitrary and poorly reproducible (size, outline etc)
  - Cribriform pattern 3 generally associated with usual pattern 4

**Pattern 4**

- Poorly formed glands included in pattern 4
Grading Variants

- Ductal carcinoma: pattern 4
  - Pin-like ductal cancer: pattern 3
- Pseudohyperplastic cancer: pattern 3
- Mucinous carcinoma
  - Cribriform glands: pattern 4
  - Discrete glands: no consensus

Grading Variants (2)

- Small cell carcinoma
  - do not grade
- Cancer with vacuoles
  - ignore vacuoles
- Foamy gland cancer
  - ignore foamy cytoplasm
- Cancer with glomerulations
  - no consensus

<5% Lower Grade

- No change from original Gleason system
- Ignore in all specimens
- RCPath dataset: mention as tertiary grade

<5% Higher Grade

- Needles biopsies
  - Include as secondary grade
- TURPs and Radicals
  - No consensus

Tertiary Pattern (of Higher Grade)

- Needle biopsy
  - Include as secondary grade
- Radicals
  - Comment as tertiary pattern
  - Epstein: tertiary pattern as secondary grade if >5%

EXEMPLARY (ISUP 2005)

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Needle Biopsy</th>
<th>Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 4 5</td>
<td>97% 3%</td>
<td>3 + 4</td>
</tr>
<tr>
<td></td>
<td>3% 97%</td>
<td>4 + 4</td>
</tr>
<tr>
<td></td>
<td>60% 38% 2%</td>
<td>3 + 5</td>
</tr>
<tr>
<td></td>
<td>60% 33% 7%</td>
<td>3 + 5</td>
</tr>
</tbody>
</table>

Epstein JI. J Urol 183:433-440,2010
**Needle Biopsy with Cores Showing Different Grades**

- **Cores submitted separately**
  - Score each core separately
- **Multiple cores in container**
  - No consensus
  - ? Score each core separately
  - ? Give score for container

### Scenario 1

- **Gleason score**:
  - Traditional: $3 + 4 = 7$
  - ISUP 2005: $4 + 4 = 8$

### Scenario 2

- **Gleason score**:
  - Traditional: $3 + 4 = 7$
  - ISUP 2005: $4 + 4 = 8$

### Radical:

- Scenario 1: $3 + 3$ and $4 + 4$
  - (ISUP 2005 correct as prognosis will be of $4 + 4$ tumour)

- Scenario 2: $3 + 4 = 7$
  - (ISUP 2005 will over-grade in this scenario)

### My Approach

- **Overall Gleason score**: $3 + 4 = 7$
Overall Gleason score 3 + 4 = 7. However, core E contains 7mm focus of only pattern 4 suggesting possibility of a separate 4 + 4 = 8 tumour.

**Radical with Multiple Tumours**
- Assign separate score to each dominant tumour
- Prognosis will be of 4 + 4 = 8 rather than 3 + 4 = 7

**2005 ISUP Modified Gleason System: Implications**
- Gleason inflation
  - Most common Gleason score 7
    - Upscoring in 35% cases
      - 90% of these due to highest core scoring
      - 10% due to revised 5% rule and tertiary rule

**Intraductal Prostatic Carcinoma**
- Almost always associated with invasive cancer
- Invasive adenocarcinoma growing within benign ducts
- Generally associated with high volume, high-grade, high-stage prostate cancer

**Intraductal Cancer: to Grade or Not to Grade**
- **No:** Epstein
  - Only invasive cancers graded
  - Comment: generally associated with aggressive invasive cancer
- **Yes:** Van der Kwast, Srigley

**Grading Intraductal Cancer: My Approach**
- **Yes** if morphologically unequivocal
- Grading is for predicting prognosis
- Ductal cancers graded pattern 4 even if morphologically pattern 3
- If no, then all high grade cancers would need immuno?
Grading: Intrinsic Problems

- Arbitrary lines
  - Morphological continuum
  - Clinical continuum

What is Glandular Fusion?

- Not true fusion
- Increasing architectural complexity resulting to apparent fusion
  - Convoluted growth pattern with budding?
- Similar to atypical endometrial hyperplasia (back to back glands)

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Borderline Gleason Pattern 4

- How much complexity is required to diagnose pattern 4?
- Pattern 3 to 4 is a morphological continuum

Gleason Patterns 3 – 5: A clinical continuum

- Risk of extraprostatic extension
  - 1%  5%  10%  15%  20%  25%  30%

At what risk of EPE should the cut off between pattern 3 and 4 be?

Grading: Intrinsic Problems

- Rigid rules
  - 1 size fits all
  - No room for judgement
2 Different Scenarios, 1 Gleason Score
ISUP 2005: both Gleason score 4 + 4 = 8

Gleason Grading: **Pitfalls**
- Small foci mis-interpreted as low grade
- Tailing of angulated pattern 3 glands mis-interpreted as pattern 5
- Tangential sectioning mimicking fusion
- Cribriform PIN mimicking cribriform 4
- Artificial overgrading with Rx effects
  - Gland atrophy mimics fusion

Common Medicolegal Situations and How to Avoid Them:
Jonathan I. Epstein, MD