PROBLEM ISSUES WITH GLEASON GRADING OF ADENOCARCINOMA OF THE PROSTATE

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DISCLOSURE
- I have nothing to disclose

GLEASON GRADE DRAWING

- “Simplified drawing of histologic patterns, emphasizing degree of glandular differentiation in relation to stroma” – DONALD F. GLEASON, 1977

GLEASON GRADING NON-ISSUES

- Gleason grade is one of the most powerful, if not the most powerful indicator of outcome for patients with prostate cancer
- Gleason grade is in routine clinical use
NEEDLE BIOPSY GLEASON GRADE: CLINICAL UTILITY

- Predict prognosis
- Predict small, potentially harmless cancers
- Select patients for active surveillance
- Used in treatment selection (both primary and adjuvant)
- Predict response to therapy
- Used as criterion (usually one of many) for enrollment into clinical trials

ISSUES WITH GLEASON GRADING

- Application: intraprostatic cancer only, without treatment effect
- Adoption of modified Gleason grading schemes
- Upgrading and downgrading
- Subjectivity and reproducibility
- Overgrading and undergrading
- Detection of high-grade adenocarcinoma
- High-grade patterns not in ISUP 2005
- High-grade tertiary pattern
- Outcome of 8 vs. 9-10 and prognostic grade groups
- %4/5 high-grade cancer
- High-grade cancer at margins
- Added value of molecular markers

APPLICATION OF GLEASON GRADING TO TISSUE SAMPLES

- Assign Gleason grade to all prostatic tissue samples, even to minimal carcinoma in needle biopsy tissue
- Not applicable to FNA samples
- Not applicable to carcinoma outside the prostate, or to metastatic deposits

2010 AJCC Anatomic Stage/Prognostic Groups

The 2009 Anatomic Stage/Prognostic Groups incorporate serum PSA level and Gleason score:

<table>
<thead>
<tr>
<th>Anatomic Stage</th>
<th>Prognostic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA 1-10</td>
<td>Gleason 6</td>
</tr>
<tr>
<td>PSA 11-20</td>
<td>Gleason 7</td>
</tr>
<tr>
<td>PSA 21-30</td>
<td>Gleason 8</td>
</tr>
<tr>
<td>PSA 31-40</td>
<td>Gleason 9</td>
</tr>
<tr>
<td>PSA 41-50</td>
<td>Gleason 10</td>
</tr>
<tr>
<td>PSA 51-60</td>
<td>Gleason 11</td>
</tr>
<tr>
<td>PSA 61-70</td>
<td>Gleason 12</td>
</tr>
<tr>
<td>PSA 71-80</td>
<td>Gleason 13</td>
</tr>
<tr>
<td>PSA 81-90</td>
<td>Gleason 14</td>
</tr>
<tr>
<td>PSA 91-100</td>
<td>Gleason 15</td>
</tr>
<tr>
<td>PSA &gt;100</td>
<td>Gleason 16</td>
</tr>
</tbody>
</table>

When either PSA or Gleason is not available, grouping should be determined by T stage and/whichever of the either PSA or Gleason is available.
GLEASON GRADING NOT RECOMMENDED

EFFECT OF ANDROGEN DEPRIVATION THERAPY ON GLEASON GRADE

MODIFIED ISUP GLEASON SCHEME 2005 AND AFIP 2011 SCHEME

INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY (ISUP) CONSENSUS CONFERENCE : HIGHLIGHTS

- Modification: Vast majority of cribriform carcinomas are pattern 4
- Single cells – not pattern 3
- Variants: can grade adenocarcinoma variants. Don’t grade small cell carcinoma
GLEASON GRADE PATTERN 4: CRIBRIFORM GLANDS

CRIBRIFORM ADENOCARCINOMA
- Rounded cribriform 3s usually associated with typical cribriform 4
- Chromosomal abnormalities more like 5
- Outcome: associated with biochemical failure, metastasis-free survival, and disease specific survival after radical prostatectomy

Outcome data from:
- Mod Pathol 2015; 28:457

COLLEGE OF AMERICAN PATHOLOGISTS 2009 AND ISUP 2005 RECOMMENDATIONS FOR LIMITED SECONDARY PATTERN <5%
- In needle biopsy specimens where there is a minor component and where the secondary component is of higher grade it should be reported. So: 96% 3 and 4% 4, score = 7
- If the secondary pattern is lower grade, it need not be reported. So: 96% pattern 4 and 4% pattern 3, score = 8

GLEASON SCORE 2-4 IN NEEDLE BIOPSY: PITFALL
- In needle biopsy tissue do not equate minimal amount of carcinoma with score 2-4
- Ideally should be a rare to non-existent diagnosis in peripheral zone needle biopsy tissue
APPLICATION OF ISUP MODIFIED GLEASON GRADING SYSTEM TO NEEDLE BIOPSY: PERCENTAGE OF CASES IN EACH CATEGORY (J Urol 180:548, 2008)

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Standard Gleason</th>
<th>Modified Gleason</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>5-6</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>8-10</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

Modified Gleason scoring showed stronger association with outcome after radical prostatectomy.

INCREASING GLEASON GRADE OVER TIME AND THE WILL ROGERS EFFECT

- When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.
- For prostate cancer upgrading has resulted in an apparent improvement in clinical outcomes. JNCI 97:1248, 2005

APPLICATIONS OF THE MODIFIED GLEASON GRADING SCHEME

- Overall 6 of 8 studies demonstrate improvement using modified rather than classical grading (reviewed in Int Urol Nephrol 2013).
- Modified Gleason score was a more accurate predictor of prognosis than original score (Berney DM et al. BJU Int 2007; 100: 1240).
- Validation of prognostic value of modified Gleason grading system after upgrading of classic Gleason grade 3+3=6 to modified score of 7 or 8 (Am J Surg Pathol 2012; 36:838)

Classical Gleason Grading vs. Modified Gleason Grading: Clinical Outcome

- FIGURE 3. Metastasis-free survival stratified by classical Gleason score (cGS) and modified Gleason score (mGS). Log-rank P=0.009, Log-rank P=0.04. AJSP 2012; 36:838
VALUE OF CLASSIFICATION OF PURE MODIFIED PATTERN 3

- Pure modified Gleason score 6 is relatively indolent:
- 6s do not metastasize to lymph nodes (>14,000 cases) (AJSP 2012; 36:1346)
- No cancer-specific deaths after radical prostatectomy (BJU Int July 2014; Epub)

UPGRADING AND DOWNGRADING: CORRELATION OF NEEDLE BIOPSY AND WHOLE GLAND GLEASON GRADE

- 43% exact correlation; within 1 score unit for 77% of 3,789 cases (pre-ISUP 2005)
- Upgrading: 35% 6s in needle to 7 or greater at RP (Epstein JI: The Gleason Grading System, 2013)
- Downgrading: 25% 7 or greater in needle to less than 7 at RP (J Urol 2008; 179:1335)
- Sources of error: borderline cases, tissue sampling error, tissue distortion, pathologist experience, observer variability, not accounting for tertiary grade

PREDICTORS OF UPGRADING AND DOWNGRADING

- Clinical sampling: # needle cores taken
- Age and clinical stage: not helpful (but stage is present in nomograms and age in one)
- Serum PSA: often correlates with upgrading
- Prostate size: Larger size associated with less upgrading
- Cancer extent on biopsy: ½ of papers positive
- Perineural invasion: 3 studies positive
- Imaging: More studies needed

REPRODUCIBILITY (pre 2005 ISUP)

- Exact intraobserver agreement in 42-78% in 5 studies; within +/- 1 score unit in 72-87% of cases
- Exact interobserver agreement in 36-81% (median 61%) in 9 studies; slight to substantial agreement as assessed by kappa (0.13-0.78)
REPRODUCIBILITY
(pre 2005 ISUP)

- Highest levels of agreement attained with use of whole mounts, by urologic pathologists, and after educational programs (such as courses and web-based tutorial)
- Experience and education most critical in enhancing reproducibility

CAUSES OF POOR REPRODUCIBILITY

- Pre 2005 ISUP
  - Undergrading
  - Cribriform proliferations
  - Low-grade carcinomas
  - Borderline patterns that are at the interface between two patterns
  - Larger tumors with more than two patterns
  - Hum Pathol 32:74, 2001

- Current issues:
  - Definition of fused glands
  - Tangential sectioning of 3s vs. poorly-formed 4s
  - Number of single cells needed to diagnose 5
  - Grade heterogeneity with multiple cores positive

OVERGRADING OF PATTERN 3 AS 4

- Crowded glands
- Pattern 3B (small glands)
- Tangentially sectioned glands
- Branching glands
- Crush or poor sectioning artifact
- Glands with perineural invasion
- Collagenous micronodules

Epstein JI: *The Gleason Grading System*, 2013

CROWDED 3 VS. FUSED 4
HIGH-GRADE DIAGNOSIS CHALLENGE: 3B VS. POORLY FORMED GLANDS

- PATTERN 3A
- PATTERN 3B

HIGH-GRADE DIAGNOSIS CHALLENGE: FUSION VS. TANGENTIAL SECTION

UNDERGRADING IN NEEDLE BIOPSY TISSUE

- MINIMAL AMOUNT OF CARCINOMA DOES NOT EQUAL LOW-GRADE CARCINOMA
- DIFFICULT TO APPRECIATE INFILTRATIVE PATTERNS

GLEASON GRADE 3 +3 = SCORE OF 6
UNDERGRADING PATTERN 5

- In one series of 59 needle core cases, pattern 5 was missed by referring pathologist in 58% of cases.
- Patterns missed: comedonecrosis (100%), cords (55%), single cells (51%), and solid sheets (39%).
- Pattern 5 more often missed when it was not the primary pattern.

AJSP 2011; 35:1706

UNDERDIAGNOSIS OF PATTERN 5 in RADICAL PROSTATECTOMY

FOAMY GLAND ADENOCARCINOMA: PATTERN 5 MISSED

DETECTION OF HIGH GLEASON GRADE CRITICAL

J Urol 185:869, 2011
HIGH-GRADE GLEASON PATTERN 4 in NEEDLE BIOPSY

- Ill-defined glands with poorly-formed glandular lumina (57%)
- Fused microacinar glands (53%)
- Cribriform glands (25%)
- Chains (4%)
- Glomeruloid (3%)
- Hypernephromatoid (0.3%)

GLEASON GRADE PATTERN 4: CHAINS

GLEASON GRADE PATTERN 4: GLOMERULOID STRUCTURES

Issue: Some have graded as 3

GLEASON GRADE PATTERN 4: HYPERNEPHROMATOID
HIGH-GRADE GLEASON PATTERN 5 in NEEDLE BIOPSY

- Single cells (53%)
- Single file (40%)
- Cords (35%)
- Small solid nests (24%)
- Solid sheets (19%)
- Comedocarcinoma (2%)
- Solid cylinders (0.3%)

PATTERN 5 NOT RECOGNIZED in ISUP 2005

- SINGLE FILE (some may consider cords – but cords are thick rope-like structures)
- SMALL SOLID NESTS
- SOLID CYLINDERS

GLEASON GRADE PATTERN 5: SINGLE CELLS

GLEASON GRADE PATTERN 5: LINEAR ARRAY
GLEASON GRADE PATTERN 5: CORDS

GLEASON GRADE PATTERN 5: SMALL SOLID NESTS

GLEASON PATTERN 5: SMALL SOLID NESTS

GLEASON GRADE PATTERN 5: SOLID SHEETS

NOT IN ISUP 2005; PROPOSED AS 5: AJSP 2012; 36:900-907
GLEASON GRADE PATTERN 5: COMEDONECROSIS

GLEASON GRADE PATTERN 5: SOLID CYLINDERS

MINIMAL SCORE 8-10 ADENOCARCINOMAS

- 5% of Gleason score 8-10 adenocarcinomas measure < 1 mm
- Most common pattern: poorly-formed glands
- ASJP 29: 962-968, 2005

CLINICAL SIGNIFICANCE OF DIAGNOSTIC RECOGNITION OF MINIMAL ADENOCARCINOMA: SOME ARE HIGH-GRAD

HIGH GLEASON GRADES COMMONLY ADMIXED
- Mean of 3.6 patterns per needle biopsy case (range 1-8) in a series of 268 Gleason score 8-10 cases
- Only 12% of cases were pure single pattern
- Most common pure patterns: fused glands and poorly formed glands
AJSP 36:900-907, 2012

MOST COMMON ADMIXTURE: PATTERN 4 WITH 3
PLCO TRIAL: 859 RADICALS

ISSUE: HOW TO HANDLE CASES WITH APPARENT EQUAL MIX OF 3 AND 4?

HIGH-GRADE DIAGNOSIS CHALLENGE: SMALL SOLID NESTS VS. POORLY FORMED GLANDS

HIGH-GRADE DIAGNOSIS CHALLENGE: HOW MANY SINGLE CELLS NEEDED FOR 5?
ISSUE: NO DATA ON THRESHOLD FOR AMOUNT OF HIGH-GRADE 4/5 IMPACTING OUTCOME

- Survey study: 17% of urologic pathologists would diagnose pattern 5 on needle biopsy when single cells, strands, or nests were identified at 400X; 83% would diagnose 5 when seen at less than 400X (Hum Pathol 2005; 36:5)

- “Single cells/cords > 10 or 6 to 10 in a cluster” achieved consensus for Gleason pattern 5 (AJSP 2015; Epub ahead of print)

- Neither study linked method or threshold to clinical endpoints

PROGNOSTIC GRADE GROUPS

- GROUP I: Gleason score < 7
- GROUP II: Gleason score 3 + 4 = 7
- GROUP III: Gleason score 4 + 3 = 7
- GROUP IV: Gleason score 8
- GROUP V: Gleason score 9-10

BJU Int 111:753-760, 2013

MODIFIED GLEASON SCORE 8 VS. 9-10

%4/5 GLEASON GRADE IN RELATION TO FAILURE AFTER SURGERY

JAMA 281:1395, 1999
PERCENTAGE OF HIGH-GRADE PATTERN 4/5

- Proposed as a significant prognosticator (JAMA 281:1395, 1999)
- Mainly tested in radical prostatectomy cases
- In needle biopsy is variably related to % 4/5 in whole gland, with high false negative rate (J Urol 165:114, 2001)
- Not established: increments to use
- Currently experimental – not demonstrated to be more significant than standard Gleason grading (WHO Prognostic Factors Meeting 2004, ISUP 2005)

REPORTING % 4 IN GLEASON SCORE 7

- Particularly important for Gleason grade 3 + 4 = 7
- Recommended by 2014 ISUP Gleason Grading Meeting and WHO 2015
- 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)

CONSEQUENCE OF TERTIARY HIGH-GRADE CANCER IN RADICAL PROSTATECTOMIES


TERTIARY GLEASON PATTERN IN RADICAL PROSTATECTOMIES

- “When a tumor contains tertiary high grades, the tumor should be graded routinely with a comment in the report noting the presence of the tertiary element.”
GLEASON GRADE AT SURGICAL MARGIN IS AN INDEPENDENT INDICATOR OF OUTCOME


GLEASON GRADE AND GENE EXPRESSION PROFILING

- "There was a readily detectable and statistically significant signature of Gleason score" (Cancer Cell 1:203, 2002)
- 2011 to 2013: 11, 31, and 32 gene sets provided added value beyond Gleason grade

IMMUNOHISTOCHEMICAL MARKERS FOR HIGH-GRADE CARCINOMA DO NOT EXIST

- Gleason grade 5 + 3 = 8

CLINICAL GENE EXPRESSION PROFILING

- 46 gene expression signature including 31 cell cycle progression genes
- 17 gene Genomic Prostate Score
- Both used in conjunction with Gleason grade in needle core and serum PSA level
- Both tests have the potential to increase number of patients undergoing active surveillance
- Not proven in prospective clinical trials to improve quality of life or survival
SOMATIC COPY NUMBER ALTERATIONS: GRADE 3 VS. 4

- Whole genome sequencing and DNA copy number profiling for 57 prostate cancers
- Recurrent somatic copy number alterations (SCNAs) in Gleason grade pattern 4 vs. 3 (right)
- Cell 153:666-677, 2013

THE CANCER GENOME ATLAS

Genomic copy number alterations increase with Gleason scores.

28,000 men died of prostate cancer in 2014

THE TEST OF TIME