The New ISUP Modified Gleason Grading System & ICCR Datasets for Prostate Cancer

Professor James Kench
Royal Prince Alfred Hospital
Gleason Scoring of Prostate Adenocarcinoma

• Gleason grading system was proposed almost 50 yrs ago

• Several modifications
  – 2005 International Society of Urological Pathology (ISUP) consensus meeting
  – 2014 ISUP Prostate Cancer Grading Panel consensus meeting

*Epstein JI et al AJSP 2005;29:1228*
2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma

- Chicago
- November 1st 2014
- 67 invited “prostate cancer pathology experts”
  - 17 countries (3 Aust, 1 NZ)
- 17 “clinical leaders”, urologists, radiation & medical oncologists
  - 1 NZ urologist
• Ambitious agenda for 7 hours
  (incl. “working lunch”)
Gleason Scoring

2005 International Society of Urological Pathology (ISUP) revisions

Unchanged at 2014 Meeting

- **highest grade** (previously score = dominant grade + second most dominant grade)
  - Grade 1 should never be used in core biopsy reports (most represent adenosis)
  - Score 2+2=4 should “rarely, if ever” be assigned based on a core biopsy

*Epstein JI et al AJSP 2005;29:1228*
Gleason Scoring

2005 International Society of Urological Pathology (ISUP) revisions (cont.)

• For **radical prostatectomy specimens** now:
  – Range of patterns accepted for grade 4 increased
    • “ill-defined glands with poorly formed glandular lumina” now included
    • But “very small well-formed glands” still grade 3

At 2014 ISUP Consensus Meeting
All cribriform glands are now Pattern 4

– Comment on tertiary pattern

At 2014 ISUP Consensus Meeting
No agreement on how to include tertiary pattern in the overall grade

Epstein JI et al AJSP 2005;29:1228
2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma

Proceedings will be reported in 2 papers

1. Issues we all agree on (submitted to AJSP)
   – Updated def’n of various grade patterns
   – New “ISUP” grading system

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1. Issues we all agree on (submitted to AJSP)
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2. Issues that are more “complicated”
   - Cases with minor component of high grade tumour (incl “tertiary grade”)
   - % pattern 4
   - Case vs specimen vs core level reporting for needle core biopsies
• All cribriform glands should be assigned pattern 4
• Previous cribriform pattern 3 associated 73% cases with obvious coexistent pattern 4
• Pattern 3 cribriform carcinoma had poor reproducibility anyway

Glomeruloid glands should be assigned pattern 4
• Mucinous carcinoma of the prostate should be graded according to its underlying growth pattern
Intraductal carcinoma of prostate (IDC-P) without invasive carcinoma should not be assigned a Gleason grade.

A comment as to its “invariable” assoc with aggressive prostate cancer should be made.
## New ISUP Grading System for Prostate Cancer

<table>
<thead>
<tr>
<th>2005 Modified Gleason Grading</th>
<th>2015 ISUP Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3, 3+2, 2+3, 2+2</td>
<td>1</td>
</tr>
<tr>
<td>3+4</td>
<td>2</td>
</tr>
<tr>
<td>4+3</td>
<td>3</td>
</tr>
<tr>
<td>4+4, 3+5, 5+3</td>
<td>4</td>
</tr>
<tr>
<td>4+5, 5+4, 5+5</td>
<td>5</td>
</tr>
</tbody>
</table>
New ISUP Grading System for Prostate Cancer

Histological definition of new grading system

Grade 1 – Only individual discrete well-formed glands

Grade 2 – Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands

Grade 3 – Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands

Grade 4
- Only poorly-formed/fused/cribriform glands or
- Predominantly well-formed glands and lesser component lacking glands
- Predominantly lacking glands and lesser component of well-formed glands

Grade 5 – Lack gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands
<table>
<thead>
<tr>
<th><strong>2005 Modified Gleason</strong></th>
<th><strong>2015 ISUP Grading</strong></th>
</tr>
</thead>
</table>
| In contemporary practice 6 (3+3) is usually the lowest score assigned:  
   (that means patients are told they have a 6 out of 10 carcinoma and assume an intermediate prognosis) | 2015 ISUP Grade 1 is equivalent to 2005 Mod Gleason score ≤6:  
   (but 1 out of 5 is a better reflection of excellent prognosis associated with this pattern) |
| Inappropriate grade combinations sometimes used for prognosis and therapy  
   (e.g. 2-4, 5-7, 8-10 in Prostate Cancer Outcomes Study) | Avoids this and also distinguishes between 3+4=7 vs 4+3=7 |
New ISUP Grading System for Prostate Cancer

Validation

• Multi-institutional (4) study of 20,845 radical prostatectomy cases with mean follow up of 3.0 years

• The 5 year biochemical risk-free survival for ISUP grades 1-5 were 96%, 88%, 63%, 48% & 26%

• Similar prognostic curves and HR for 16,176 prostate needle biopsies

Epstein JI, Zelefsky MJ, Sjoberg DD et al. Submitted for publication
Figure 3. Recurrence-free progression following radical prostatectomy stratified by grade (green line - Gleason score 6 [Grade Group 1], orange – Gleason score 3+4 [Grade Group 2], dark blue - Gleason score 4+3 [Grade Group 3], brown – Gleason score 8 [Grade Group 4], gray – Gleason score ≥9 [Grade Group 5]).
New ISUP Grading System

So where are we now?

• First paper outlining new ISUP grading system submitted but not published yet
• Second, more contentious paper not drafted yet
• Agreement that to avoid confusion the new grading system should not have the name Gleason in its title (although it’s still based on Gleason patterns!)

New ISUP Grading System

So where are we now?

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• New grading system has been accepted by WHO for 2016 edition of *Pathology & Genetics: Tumours of the Urinary System and Male Genital Organs*
• Recommendation for pathology reports to include both new ISUP grade and 2005 modified Gleason grading for next 2-3 years

New ISUP Grading System

So where are we now?

• First paper outlining new ISUP submitted but not published yet
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• But, new grading system has been accepted by WHO for 2016 edition of *Pathology & Genetics: Tumours of the Urinary System and Male Genital Organs*
• Recommendation for pathology reports to include both new ISUP grade and 2005 modified Gleason grading for next 2-3 years
• Needs robust validation based on clinical endpoints, eg bone mets, disease specific mortality

International Collaboration on Cancer Reporting

- 2011 began as a quadripartite alliance, 5 countries
- 2013 European Society of Pathology joined
- now worldwide involvement, IARC & WHO link
International Collaboration on Cancer Reporting

• Aims to harmonise pathology reporting internationally
  – Development of agreed upon, evidence based datasets for each major cancer
  – Standardised elements, terminology and definitions for cancer reporting

http://www.iccr-cancer.org/
ICCR

Why does this matter to clinicians and researchers?

Facilitates

• inclusion of complete, accurate and standardised data in pathology reports

• comparison of cohorts from different centres
  – vital for obtaining robust pathology data for multicentre *clinical trials*, epidemiology research, patterns of care studies etc

• uploading of path data into registry or clinical databases
  – ideally from drop down menus, XML, HL7 archetypes

• biobanking collection from multiple centres
## Additional File 1  
NHMRC Evidence Hierarchy: designations of ‘levels of evidence’ according to type of research question (including explanatory notes)

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention ¹</th>
<th>Diagnostic accuracy ²</th>
<th>Prognosis</th>
<th>Aetiology ³</th>
<th>Screening Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation</td>
<td>A prospective cohort study⁷</td>
<td>A prospective cohort study</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation⁶</td>
<td>All or none⁸</td>
<td>All or none⁸</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
</tbody>
</table>
| III-2 | A comparative study with concurrent controls:  
- Non-randomised, experimental trial⁹  
- Cohort study  
- Case-control study  
- Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial | A retrospective cohort study | A comparative study with concurrent controls:  
- Non-randomised, experimental trial  
- Cohort study  
- Case-control study |
| III-3 | A comparative study without concurrent controls:  
- Historical control study  
- Two or more single arm study ¹⁰  
- Interrupted time series without a parallel control group | Diagnostic case-control study⁶ | A retrospective cohort study | A case-control study | A comparative study without concurrent controls:  
- Historical control study  
- Two or more single arm study |
| IV    | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard)¹¹ | Case series, or cohort study of persons at different stages of disease | A cross-sectional study or case series | Case series |
# ICCR Prostate Ca (Rad Prostatectomy) Dataset

## Table 2. Required (‘core’) elements for the prostate cancer structured reporting protocol (radical prostatectomy)

<table>
<thead>
<tr>
<th>Data element</th>
<th>Consensus response values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PSA</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Specimen weight (prostate – seminal vesicles)</td>
<td>Grams</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>Present/absent</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Present/absent</td>
</tr>
<tr>
<td>Histological tumour type</td>
<td>Expanded WHO classification list</td>
</tr>
<tr>
<td>Histological grade</td>
<td>Gleason 1, 2 and 3 grades, and score</td>
</tr>
<tr>
<td>Extraprostatic extension</td>
<td>Present/not identified/indeterminate</td>
</tr>
<tr>
<td>Extent of extraprostatic extension</td>
<td>Focal/non-focal</td>
</tr>
<tr>
<td>Seminal vesicle status</td>
<td>Involved/not involved/not applicable</td>
</tr>
<tr>
<td>Surgical margin status</td>
<td>Involved/not involved/not applicable</td>
</tr>
<tr>
<td>Location(s) of any involved surgical margin</td>
<td>Apical, bladder neck, anterior, lateral, posterolateral, posterior, other (specify)</td>
</tr>
<tr>
<td>Number of positive lymph nodes</td>
<td>Number</td>
</tr>
<tr>
<td>Number of lymph nodes examined</td>
<td>Number</td>
</tr>
<tr>
<td>Pathological staging (AJCC/UICC 7th edition)</td>
<td>pT and pN with suffixes as required</td>
</tr>
</tbody>
</table>

## Table 3. Recommended (‘non-core’) elements for the prostate cancer structured reporting protocol (radical prostatectomy)

<table>
<thead>
<tr>
<th>Data element</th>
<th>Consensus response values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen dimensions (prostate)</td>
<td>mm, three dimensions</td>
</tr>
<tr>
<td>Maximum dimension (of each seminal vesicle)</td>
<td>mm</td>
</tr>
<tr>
<td>Laterality of any lymph nodes submitted</td>
<td>Right, left, bilateral</td>
</tr>
<tr>
<td>Intraglandular extent of tumour</td>
<td>Percentage of prostate involved</td>
</tr>
<tr>
<td>Maximum size of dominant nodule</td>
<td>mm</td>
</tr>
<tr>
<td>Location(s) of extraprostatic extension</td>
<td>Apical, bladder neck, anterior, lateral, posterolateral, posterior, other (specify)</td>
</tr>
<tr>
<td>Bladder neck status</td>
<td>Involved/not involved/not applicable</td>
</tr>
<tr>
<td>Extent of surgical margin involvement (total)</td>
<td>mm (along involved margin)</td>
</tr>
<tr>
<td>Lymphovascular (lymph-vascular) invasion</td>
<td>Present/not identified/indeterminate</td>
</tr>
<tr>
<td>Laterality of positive lymph nodes</td>
<td>Right, left, bilateral/not applicable</td>
</tr>
<tr>
<td>Maximum dimension of metastatic deposit in a positive lymph node</td>
<td>mm/not applicable</td>
</tr>
</tbody>
</table>
Currently a full ICCR Genitourinary suite of 13 datasets is being developed (in time for WHO GU Book publication 2016)

- Prostate
- Kidney
- Urinary bladder
- Testis & Penis

http://www.iccr-cancer.org/
Questions?