Gleason Grading of Core prostatic Biopsies and Digital Pathology

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WSI/VM current utility

• Educational
• Training or proficiency testing
• Seek for second opinion specialist in difficult cases
• Remote frozen sections diagnosis
• Limited-to-Not in use as routine primary diagnosis
• **Prostate pathology**: allowed us to undertake a novel approach to inter-observer variability in Gleason grading of bx.
WSI/VM

• Similar to standard imaging
  – brightness, navigation, different magnifications, focus…

• Might be superior to standard
  – extreme low-power for structure evaluation, reducing risk of missing small separated fragments, no need to transpor slides, better efficacy in postgraduate education

• Facilitates quantitation

• Simultaneous viewing of several slides in same monitor.
WSI/VM some problems

• High quality scanners needed
• High quality monitors needed
• Scanning slides at 40X>>Slow
• That limit utility in routine practice
• Large size of pathology digital files
• There is a need to establish a practical work flow
WSI/VM in prostate bx

- Pbx well suited for VM-Small biopsies-small files
  - Low-medium power
  - Architecture
  - Cytologic features
- VM superior to standard microscopy
- Gleason score requires evaluation of all core and all cores to assess the proportion of Gleason patterns.
WSI/VM in prostate bx

- WSI/VM may assess tumor volume
- Examining multiples slides in the same monitor is very useful in assessing basal cell status (IHC) for diagnosis of small foci.
- Z-scanning particularly useful to assess subtle nuclear/nucleolar changes of great importance in Pbx
  - Large digital files
  - More time to scan slides
WSI/VM in prostate bx

- Several core analysis (i.e. Template-20)
- May require large files
- More time to scan the slides
- Major limitation to use VM in routine practice
- Similar problems in RP specimens
- Main current utility of WSI/VM
  - Education
  - Proficiency testing
  - Inter-observer evaluation
  - Expert second-opinion consultation
WSI/VM in prostate bx
ENUP experience

• Gleason practice between experts and general pathologists

• Advantages:
  • Marking the areas easy
  • Different pathologists in different countries
  • WSI/VM allowed to identify controversial vs. areas easier to grade
  • Identified areas of consensus

Fig. 1. Prostate needle biopsy with tumour marked by red lines. The green areas represent areas marked by participants as Gleason pattern 4 and yellow areas as Gleason pattern 5. The darker the colour, the more often the grade had been assigned.
Utility of whole slide imaging and virtual microscopy in prostate pathology

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The study identified significant disagreement among experts on borderline Gleason score 6–7 cases using ISUP revision of Gleason grading of prostate cancer. A major source of disagreement was the detection threshold for minimal Gleason pattern 4 in needle biopsies. However, using WSI/VM with heat mapping enabled identification of a set of consensus cases that will be used to aid standardization of Gleason grading in Europe.
Prostate Cancer

Gleason Score Basic Practice

- Most common Gleason score
- UROPATHOLOGIST: 7
  - Good correlation with Radical Prostatectomy
- General Pathologist: 6 or Less
  - Poor correlation with Radical Prostatectomy
Se basa en la frecuente heterogeneidad histológica del cáncer de próstata.

Gleason Score: **Patron** más frecuente + patrón secundario más frecuente
The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD, * William C. Allsbrook, Jr, MD, † Mahul B. Amin, MD, ‡ and Lars L. Egevad, MD, PhD, § and the ISUP Grading Committee
Grading according to the Gleason system

Original Gleason

ISUP 2005 Gleason

Gleason with proposed refinements and modifications to ISUP 2005

Hum Pathol 23;273-79, 1992

Am J Surg Pathol 29;1228-42, 2005

J Urol 183;433-40, 2010

SCHEDULE

• Introduction - Jonathan Epstein, Baltimore, MD
  1) Grading cribriform prostate cancer
  2) Grading glomeruloid prostate cancer
  3) Proposal for a new grading system
  4) Handling minor (tertiary) patterns in new grading system
The reasons behind variation in Gleason grading of prostatic biopsies: areas of agreement and misconception among 266 European pathologists.

**CONCLUSION:**
Misinterpretation of ISUP 2005 is widespread, and may explain the variation in Gleason scoring seen. Clarity and uniformity in teaching ISUP 2005 recommendations is necessary.

- Cribriform glands GS 3 >> 51%
- Necrosis GS 5 >> 62%
- Tertiary GS5 >> 58%
Cribriform
GLEASON GRADING SYSTEM

- Developed from 1960-1975 and based on follow-up of 5,000 prostate cancer patients
- Employs extent of glandular differentiation and pattern of growth
- Nuclear atypia, mitoses not used
MORTALITY BY GLEASON SCORE

All Patients
N = 2911

All Deaths
Cancer Deaths

Deaths/Patient-Year

N = (14) (84) (68) (558) (1240) (256) (537) (61) (93) = 2911

Primary + Secondary Pattern
Total and cancer death rates by histologic score.

60% of cases were needle biopsy
GLEASON GRADING SCHEME

: RULES

• Categorize patterns with 4-10X lens
• Primary grade pattern (predominant by area) and secondary grade pattern added to yield histologic score (range 2-10)
• If only one grade, double to give Gleason score
Pattern 1

Monolayer microglands
Similar gland size
Separate glands for basal membrane
Pushing growth, well defined
Pattern 2
Monolayer glands medium size
Round to oval glands
Glands separation up to one gland
Diameter average
Masses less well defined
Grading according to the Gleason scheme:

**General applications of the Gleason grading system:**

- A Gleason score of $1+1=2$ is a grade that should not be diagnosed regardless of type of specimen (*Extremely Rare Exceptions*)
- The diagnosis of Gleason 2-4 score should not be made on needle biopsies
  - Gleason score 2-4 cancer is *extraordinarily rare* in needle biopsies as compared to transurethral resection specimens
  - There is *poor reproducibility* among experts for lower grade tumors
  - The correlation with the prostatectomy score for Gleason 2-4 tumors is poor
  - A "low" score of Gleason 2-4 may misguide clinicians and patients into believing that there is an indolent tumor
Pattern 3

Ill-defined infiltrating edges
Wide stromal separation
Very small gland (corner)
Micropapillary pattern

No Cribriform allowed
No single cells allowed
Grading according to the Gleason scheme:

- Patron mas comun en la biopsia de aguja
- “Individual cells” would not be allowed within Gleason pattern 3.
- No cribriform patterns are diagnosed as Gleason pattern 3 Most cribriform lesions are now accepted as HIGH GRADE PIN.
Pattern 4
Fused glands without stroma
Cribriform pattern without well defined edges
Clear cell features
<table>
<thead>
<tr>
<th>Gleason Pattern</th>
<th>Original Gleason 1966&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Gleason Modifications 1974/77&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ISUP Modified Gleason 2005&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Epstein J Urol proposed modifications 2010&lt;sup&gt;23&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gleason Pattern 3</strong></td>
<td>Marked irregularity in size and shape of glands, with tiny glands or individual cells invading stroma away from circumscribed masses, or solid cords and masses with easily identifiable glandular differentiation within most of them.</td>
<td>May be papillary or cribriform which vary in size and may be quite large, but the essential feature is the smooth and usually rounded edge around all the circumscribed masses of tumour.</td>
<td>Discrete glandular units Infiltrates in and amongst non-neoplastic prostate acini. Marked variation in size and shape. Smoothly circumscribed small cribriform nodules of tumor.</td>
<td>Discrete glandular units Infiltrates in and amongst non-neoplastic prostate acini. Marked variation in size and shape.</td>
</tr>
<tr>
<td><strong>Gleason Pattern 4</strong></td>
<td>Large clear cells growing in a diffuse pattern resembling hypernephroma; may show gland formation.</td>
<td>Raggedly infiltrating, fused-glandular tumour. Glands are not single and separate, but coalesce and branch.</td>
<td>Fused microacinar glands Ill-defined glands with poorly formed glandular lumina. Irregular Cribriform glands. Hypernephromatoid</td>
<td>Fused microacinar glands Ill-defined glands with poorly formed glandular lumina. Smoothly circumscribed small cribriform nodules of tumour. Hypernephromatoid</td>
</tr>
</tbody>
</table>
Grading according to the Gleason scheme:

- **Percentage of Gleason 4 pattern in Gleason score 7 tumors**: In recently generated nomograms, patients with Gleason score **4+3** (i.e., the primary or most predominant Gleason grade is 4; this means that more than 50% of the neoplasia shows pattern 4) vs. **3+4** (i.e., the primary or most predominant Gleason grade is 3; this means that more than 50% of the neoplasia shows pattern 3) are stratified differently, underscoring the importance of the relative amount of pattern 4.

- It has been proposed to add in the report the “%” of Gleason 4 in 3+4/4+3 cases. **Currently is optional**
Kaplan–Meier curve showing Gleason 4+3 versus 3+4 prostate cancer.
Pattern 5

Loss glandular aspect
Isolated cells
Comedon aspect
Gradación de Gleason: Subgrupos terapéuticos Generalidades

• Gleason 6 bajo grado
  – Vigilancia activa, braqui, cirugia, terapia parcial

• Gleason 7 grado intermedio
  – Variable, en general no braqui, no vigilancia, Rx externa, cirugia

• Gleason 8-10 alto grado
  – Variable, Rx externa
TABLE 9.5 Prognostic Grade Grouping

Gleason score 2–6, Prognostic Grade Group I/V
Gleason score 3 + 4 = 7, Prognostic Grade Group II/V
Gleason score 4 + 3 = 7, Prognostic Grade Group III/V
Gleason score 8, Prognostic Grade Group IV/V
Gleason score 9–10, Prognostic Grade Group V/V

Pierorazio et al 2013 BJU Int
Correlación del grado de Gleason entre biopsia y prostatectomía radical
Gleason score correlation Biopsy/Prostatectomy

215 patients.

Exact correlation... 50%
Undergraded ......... 39%
Overgraded .......... 11%

AJSP, 2001
Cost-Benefit and Outcome Analysis: Effect of Prostate Biopsy Undergrading

Angelo J. Cambio, Lars M. Ellison, Karim Chamie, Ralph W. deVere White, and Christopher P. Evans

OBJECTIVES
Brachytherapy is a widely used treatment for localized prostate cancer (CaP) and is only appropriate as monotherapy for low-risk cancer. The predicted response to therapy is defined by the pretreatment parameters, of which the biopsy Gleason grade is central. However, the biopsy grade often misrepresents the true pathologic grade. We examined the impact of incorrect biopsy grading on brachytherapy outcomes.

METHODS
We constructed a decision analytic model to assess the theoretical performance of brachytherapy for a theoretical cohort of men with Gleason score 6 CaP who underwent radical prostatectomy. The variables regarding biopsy Gleason scores and the correlation with the surgical specimen findings were generated from the institutional data. The ranges for these variables, biochemical performance of brachytherapy, costs, and disease state utilities, were obtained from a data review.

RESULTS
For the base case, 67% of biopsy grades correlated with the pathologic grade. With this concordance, 8% of failures could be attributed, in part, to undergrading. On the basis of the model assumptions, as concordance worsened to 50%, the rate of undergraded failures increased to 12%. After adjusting for the quality of life associated with higher-grade disease and the risk of biochemical failure, the aggregate cost of treatment of biopsy grade 6 disease was increased by 8% because of undergrading ($75,700 versus $81,500 per case). The bulk of this effect was the cost of failure among patients with undergraded disease.

CONCLUSIONS
Brachytherapy for Gleason score 6 disease is reported to have excellent results. Undergrading of prostate biopsies can negatively affect clinical outcomes and increase treatment costs. Although the risk is low, it should be considered when counseling patients with CaP. UROLOGY 69: 1152–1156, 2007. © 2007 Elsevier Inc.
Clinical Predictors of Gleason Score Upgrading

Implications for Patients Considering Watchful Waiting, Active Surveillance, or Brachytherapy

METHODS. The authors identified 175 cases of low-risk prostate cancer treated with radical prostatectomy. By using logistic regression analysis, 11 a priori-defined preoperative risk factors were evaluated for their ability to predict upgrading from Gleason 6 at biopsy to Gleason $\geq 7$ at radical prostatectomy. An internally validated nomogram using all clinical variables was subsequently created to help physicians identify patients who had undetected high-grade disease.

RESULTS. A total of 60 (34%) patients were upgraded to high-grade disease. On multivariate analyses, both prostate-specific antigen (PSA) level ($P = .02$) and the level of pathologist expertise ($P = .007$) were predictive of upgrading. The predictive nomogram contained these variables plus age, digital rectal examination, transrectal ultrasound results, biopsy scheme applied (sextant vs extended), presence of prostatic intraepithelial neoplasia, prostate gland volume, and percentage of cancer in the biopsy. The nomogram provided acceptable discrimination (C statistic 0.71).

CONCLUSIONS. The authors identified significant predictors of upgrading for patients diagnosed with low-risk prostate cancer. A nomogram based on these study findings could help physicians further risk-stratify patients with low-risk prostate cancer before embarking on treatment. Caution should be exercised in recommending nonradical therapy to individuals with a high probability of undetected high-grade disease. Cancer 2007;109:2432–8. © 2007 American Cancer Society.
CORRELATION OF NEEDLE BIOPSY AND WHOLE GLAND GLEASON GRADE

• 43% exact correlation; within 1 score unit for 77% of 3,789 cases

• Sources of error: undergrading, tissue sampling error, tissue distortion, pathologist experience, and observer variability
Modified Gleason scoring showed stronger association with outcome after radical prostatectomy.
ACTIVE SURVEILLANCE : ELIGIBILITY

• Needle biopsy Gleason score : 6 or less
• Serum PSA : less than 10 ng/ml
• % positive cores : less than 33%
• % single core involvement : less than 50%
• PSA kinetics : stable

Cancer 112:1650-1659, 2008
GLEASON GRADING AFTER RADIATION AND HORMONAL THERAPY

- Gleason system was developed for patients without prior treatment.
- Gleason grading can be utilized after radiation therapy if there is no evidence of radiotherapy treatment effect.
- Consensus: Grading should not be done after hormonal therapy.

BEFORE

AFTER
GENE EXPRESSION PROFILING BY GLEASON SCORE

CANCER CELL 1:203, 2002

PNAS 101:811, 2004
GLEASON GRADE AND GENE EXPRESSION PROFILING

• Gene expression profiling has led to the discovery of genes whose expression is associated with grade. Examples: IGFBP 2, 3, and 5 and Col1A2 (Cancer Res 61:5974, 2001; Cancer Cell 1:203, 2002)

• 41 genes associated with high-grade prostate cancer (PNAS 101:811, 2004)

• 86 genes distinguish low-grade vs. high-grade carcinoma (PNAS 103:10991, 2006)

• “There was a readily detectable and statistically significant signature of Gleason score” (Cancer Cell 1:203, 2002)

• PIM1 kinase, identified by profiling, found to provide added value to grade in prediction of outcome (Nature 412:822, 2001)
Conclusiones

• El grado de Gleason tiene un excelente valor predictivo en PCA
• Es necesario corregir la práctica del Gleason con actividades formativas
THE TEST OF TIME