Implications of the International Society of Urological Pathology Modified Gleason Grading System

Lars Egevad, MD; Roberta Mazzucchelli, MD, PhD; Rodolfo Montironi, MD, FRCPath

• Context.—Histologic grading is the clinically most useful tissue-based predictor of prognosis for prostate cancer. Over the years, there has been a gradual shift in how the Gleason grading is applied in practice, with a general trend toward upgrading. A consensus conference was organized in 2005 by the International Society of Urological Pathology (ISUP) for standardizing both the perception of histologic patterns and how the grade information is compiled and reported.

Objective.—To review the implications of the ISUP modified Gleason grading system.

The Gleason grading system of prostatic carcinoma is the quintessential prognostic factor in predicting findings in radical prostatectomy, biochemical failure, local recurrences, and lymph node or distant metastasis in patients receiving no treatment, radiation therapy, radical prostatectomy, and other therapies, including cryotherapy and high-intensity focal ultrasound therapy. Clinicians use various tools, such as Partin tables or Kattan nomograms, to predict outcomes, including the pathologic stage or prognosis following radical prostatectomy or radiotherapy. All of these tools incorporate the Gleason score.

ORIGINAL GLEASON GRADING SYSTEM

In 1966, Donald F. Gleason, MD, PhD, first published a unique grading system for prostate cancer (PCa) based solely on the architectural pattern of the tumor, using a 5-point scale, where patterns 1, 2, and 3 represented tumors that most closely resembled normal prostatic glands, and patterns 4 and 5 were tumors showing increasingly abnormal glandular architecture (Table 1). An innovative aspect of this system, based on a study of 270 patients, was that, rather than assigning the worst grade as the grade of the carcinoma, the grade was defined as the sum of the 2 most common patterns and was reported as the Gleason score.

GLEASON MODIFICATIONS

By 1974, Gleason and the Veterans Administration Cooperative Urological Research Group expanded their study of the original Gleason system to 1032 men. Gleason pattern 4 was described in a figure legend as “raggedly infiltrating, fused-glandular tumor, frequently with pale cells, may resemble hypernephroma of kidney.” The Gleason system was further refined by Mellinger in 1977, when the papillary and cribriform tumor under Gleason pattern 3 was described as having a “smooth and usually rounded edge.” In describing the breakdown of Gleason patterns among 2911 cases, Gleason pattern 1 was seen in 3.5% of cases, pattern 2 in 24.4%, pattern 3 in 87.7%, pattern 4 in 12.1%, and pattern 5 in 22.6%. These percentages added up to approximately 150% because 50% of the tumors showed at least 2 different patterns.

In 1977, Gleason provided additional comments concerning the application of the Gleason system: “Grading is performed under low magnification.” He also stated that “an occasional small area of fused glands did not change a pattern 3 tumor to pattern 4. A small focus of disorganized cells did not change a pattern 3 or 4 tumor to pattern 5.” The only comment relating to tertiary patterns was “occasionally, small areas of a third pattern were observed.”

CHANGES IN PROSTATE CARCINOMA SINCE THE LATE 1960s

Diagnosis of PCa has changed dramatically since the late 1960s, when the Gleason grading system was described. In the 1960s, there was no screening for PCa, other than by digital rectal examination because serum prostate-specific antigen had not yet been discovered. In the Gleason 1974 study, most men had advanced disease with either local extension out of the prostate on digital rectal examination or distant metastases. Only 6% of

Data Sources.—Personal experience and review of the current literature.

Conclusions.—The recommendations regarding pattern interpretation and reporting are summarized. The practical consequences of the ISUP modification of the Gleason grading are reported. The prognostic importance of the Gleason score, its reproducibility, and its preoperative assessment are discussed. Subsequent proposals for slight modifications to the ISUP grading system are described.

patients had a nonpalpable tumor diagnosed by transurethral resection, and 8% of patients were diagnosed with a localized nodule on digital rectal examination.7

The method of obtaining prostate tissue was also different from today’s practice. Typically, only a couple of thick gauge needle biopsies were directed into an area of palpable abnormality, usually perineally. The use of 18-gauge, thin biopsy needles and the concept of sextant needle biopsies to more extensively sample the prostate were not developed until the 1980s.7 Consequently, the grading of prostate cancer in thin cores and in multiple cores from different sites of the prostate were not issues in the Gleason era.

In the 1960s, radical prostatectomy was relatively uncommon, prostates were not as often removed intact, and glands were not processed in their entirety or as extensively and systematically as currently seen. Further issues relating to radical prostatectomy specimens, such as the grading of multiple nodules within the same prostate, determining variants and variations of PCa, or dealing with tertiary patterns, were not addressed within the original Gleason system.

The Gleason system also predated the use of immunohistochemistry. It is likely that, with immunostaining for basal cells, many of the original Gleason 1 + 1 = 2 PCA would today be regarded as adenosis (atypical adenomatous hyperplasia), that is, a benign lesion.4 Similarly, many of the cases in 1966, diagnosed as cribriform Gleason pattern 3 carcinoma, would probably now be referred to as cribriform high-grade prostatic intraepithelial neoplasia, if labeled with basal cell markers.9

Forty Years After the Inception of the Gleason System

Nearly 40 years after its inception, the Gleason system remains one of the most powerful prognostic factors in PCa. In part, this system has remained timely by minor adaptations to accommodate the changing practice of medicine.10–12 However, certain aspects of the original Gleason system are interpreted differently in today’s practice. With such changes have come variations in applying the Gleason system among pathologists, with some differences by region and others dependent on other demographic factors. For example, pathologists older than 50 years diagnosed Gleason scores less than 4 on needle biopsy more often than did younger pathologists, who were trained to do so rarely, if ever.13 The assigning of an overall score to needle biopsy specimens with different grades on different cores is more often practiced in Europe than in the United States.14

2005 INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY MODIFIED GLEASON SYSTEM

The International Society of Urological Pathology (ISUP) convened a conference in 2005 in San Antonio, Texas, in an attempt to achieve consensus in controversial areas relating to the Gleason system (Tables 2 and 3). That conference led to the 2005 ISUP Modified Gleason System.15 The conference was preceded by an international consensus meeting, the “International Consultation on Predictors of Patient Outcome in Prostate Cancer,” sponsored by the World Health Organization, which took place in 2004 in Stockholm, Sweden.16 National groups, independent of the ISUP activities, had already started a revision of the Gleason system with proposals that preceded those included in the 2005 ISUP Modified Gleason System.17–18

It is outside the scope of this review to describe all the features included in the 2005 ISUP Modified Gleason System. Interested readers are referred to the conference proceedings.15 The main differences between the original Gleason system and the 2005 ISUP Modified Gleason System are reported in Table 4. Below, we’ve provided a brief summary of the ISUP modified Gleason grading system. Representative images of the various Gleason patterns and scores are shown in the Figure, A through F.

- The Gleason score is the sum of the primary (most predominant) Gleason grade and the secondary (second most predominant) Gleason grade. In needle biopsies, this definition is modified to include any component of higher grade (see below).
- A Gleason score of 1 + 1 = 2 is a grade that should not be diagnosed, regardless of the type of specimen, with only rare exception.

Table 1. The 5 Architectural Patterns According to the Original Gleason Grading System

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very well-differentiated, small, closely packed, uniform glands in essentially circumscribed masses</td>
</tr>
<tr>
<td>2</td>
<td>Similar to pattern 1 but with moderate variation in size and shape of glands and more atypia in the individual cells, cribriform pattern may be present, still essentially circumscribed, but more loosely arranged</td>
</tr>
<tr>
<td>3</td>
<td>Similar to pattern 2 but 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>
</tr>
<tr>
<td>4</td>
<td>Large clear cells growing in a diffuse pattern resembling hypernephroma; may show gland formation</td>
</tr>
<tr>
<td>5</td>
<td>Very poorly differentiated tumors; usually solid masses or diffuse growth with little or no differentiation into glands</td>
</tr>
</tbody>
</table>

Table 2. Controversial Areas of the Original Gleason Grading System Reviewed at the 2005 International Society of Urological Pathology (ISUP) Conference

<table>
<thead>
<tr>
<th>Area</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>General applications of the Gleason grading system</td>
<td></td>
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<tr>
<td>Gleason patterns</td>
<td></td>
</tr>
<tr>
<td>Grading variants and variations of acinar adenocarcinoma of the prostate</td>
<td></td>
</tr>
<tr>
<td>Reporting secondary patterns of lower grade when present to a limited extent</td>
<td></td>
</tr>
<tr>
<td>Reporting secondary patterns of higher grade when present to a limited extent</td>
<td></td>
</tr>
<tr>
<td>Tertiary Gleason patterns</td>
<td></td>
</tr>
<tr>
<td>Percentage of patterns 4 to 5</td>
<td></td>
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<tr>
<td>Radical prostatectomy specimens with separate tumor nodules</td>
<td></td>
</tr>
<tr>
<td>Needle biopsy with different cores showing different grades</td>
<td></td>
</tr>
</tbody>
</table>
A. Prostate cancer Gleason score 3 + 3 = 6. Light staining glands with oval, rounded contour. This pattern would be diagnosed a decade ago by many pathologists as Gleason pattern 2. However, the tumor shows some infiltration between the benign glands (right), and there is considerable variation in glandular diameter and distribution, which favors a diagnosis of Gleason pattern 3. B, Prostate cancer Gleason score 3 + 3 = 6. Minimal focus of cancer with bland features. The malignant glands infiltrate between benign glands and are irregularly distributed, which favors a grading of Gleason pattern 3. C, Prostate cancer Gleason score 4 + 4 = 8. Gleason pattern 4 of a fusion type. Glands are fused into a mazelike conglomerate. D, Prostate cancer Gleason score 4 + 3 = 7. Gleason pattern 4 of the cribriform type. These cribriform glands are too irregular for cribriform pattern 3. E,
• The diagnosis of Gleason scores 2 through 4 on needle biopsies should be reported rarely, if ever (Table 5).

• Individual cells would not be allowed within Gleason pattern 3.

• Most cribriform patterns are diagnosed as Gleason pattern 4, with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3 (see below).

• Grading variations of acinar adenocarcinoma include the tumor being graded solely on the underlying architecture (Table 6). For instance, pseudohyperplastic cancer should be assigned a Gleason score of 3 + 3 = 6.

• Grading variants of adenocarcinoma include ductal adenocarcinomas, which should be graded as Gleason score 4 + 4 = 8, whereas prostatic intraepithelial neoplasia–like adenocarcinoma should be graded as Gleason pattern 3 and ductal adenocarcinoma with comedonecrosis should be graded as Gleason pattern 5, retaining the diagnostic term ductal adenocarcinoma to denote unique clinical and pathologic findings. There is no consensus on the way mucinous (colloid) carcinoma should be scored. Some authors think that all mucinous carcinomas should be assigned a Gleason score of 8, whereas others say the extracellular mucin should be ignored and the tumor should be graded on the underlying architectural pattern. The grading of glomeruloid glands is another controversial area in the modified Gleason system (see below). Small cell carcinoma should not be assigned a Gleason grade. The appropriateness of assigning a Gleason score to sarcomatoid carcinoma is uncertain. In general, a Gleason grade is not assigned to the sarcomatoid component, whereas the glandular component is graded in the usual manner.

• Secondary patterns of lower-grade cancer when present to a limited extent should be ignored and not reported in the setting of a high-grade cancer and ignored and not reported if they occupy less than 5% of the tumor area.

• High-grade tumor of any quantity on needle biopsy should be included and reported within the Gleason score.

• For tertiary Gleason patterns, the typical situation on biopsy includes tumors with patterns 3, 4, and 5 in various proportions. Such tumors should be classified overall as high grade (Gleason scores 8–10), given the presence of high-grade tumor (patterns 4 and 5) on needle biopsy. On needle biopsies with patterns 3, 4, and 5, both the primary pattern and the highest grade should be recorded. For a radical prostatectomy specimen, the Gleason score is based on the primary and secondary patterns, with a comment added about the tertiary pattern.

• Whether the actual percentage of a 4- or 5-pattern tumor should be included in the report is not clear based on published data to date, and if the percentage emerges as an important parameter, meaningful, discriminatory cutoff points for the percentage of patterns 4 or 5 will need to be defined. If one wants to include that information in addition to the routine Gleason score, doing so is acceptable.

• For needle biopsies with different cores showing different grades, the pathologist should assign individual Gleason scores to separate cores if the cores are submitted in separate containers or if the cores are in the same container but their location is specified by the urologist (ie, by different color inks). In addition to giving separate cores individual Gleason scores, an optional, overall score can be given at the end of the case. If more than one core contains cancer with multiple cores per container, some authors think each core should be graded separately, whereas other authors think an overall grade should be given for the involved cores per specimen container. In cases in which a container contains multiple pieces of tissue and it is unclear whether one is looking at an intact core, an overall score should be given for that container.

### Changes to Patterns 3 and 4

The general theme of the changes to patterns 3 and 4 was to limit the definition of pattern 3 carcinoma and to widen the scope of pattern 4 carcinoma. As in the original Gleason description, pattern 3 carcinomas are composed of discrete, circumscribed, and infiltrative glands with well-formed glandular lumina. In the 2005 ISUP Modified Gleason System, very small, well-formed glands were still considered within the spectrum of Gleason pattern 3; however, a departure from the original Gleason system was that “individual cells” are not allowed within Gleason pattern 3.5

A further area of divergence from the original Gleason system was the controversial area of cribriform Gleason.

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Table 3. The 5 Architectural Patterns According to the 2005 International Society of Urological Pathology Modified Gleason System

<table>
<thead>
<tr>
<th>Pattern 1</th>
<th>Pattern 2</th>
<th>Pattern 3</th>
<th>Pattern 4</th>
<th>Pattern 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscribed nodule of closely packed, but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)</td>
<td>Like pattern 1, fairly circumscribed, but at the edge of the tumor nodule, there may be minimal infiltration; glands are more loosely arranged and not quite as uniform as pattern 1</td>
<td>Discrete glandular units: typically, smaller glands than seen in Gleason patterns 1 or 2; infiltrates in and among nonneoplastic prostate acini; marked variation in size and shape; smoothly circumscribed, small, cribriform nodules of tumor</td>
<td>Fused microacinar glands: ill-defined glands with poorly formed glandular lumina; large, cribriform glands; cribriform glands with an irregular border; hypernephromatoid</td>
<td>Essentially no glandular differentiation, composed of solid sheets, cords, or single cells; comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses</td>
</tr>
</tbody>
</table>

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pattern 3. Within the original Gleason illustrations of pattern 3, large, cribriform glands are depicted with rounded and smooth contours. Gleason never conducted any studies that specifically addressed the prognostic differences between the rounded glands he considered cribriform pattern 3 and the irregular glands he also called cribriform pattern 3. At the ISUP 2005 conference, the consensus was that almost all of those cribriform patterns should be diagnosed as Gleason pattern 4. The consensus panel required extremely stringent criteria for the diagnosis of cribriform pattern 3, which included only rounded, well-circumscribed glands of the same size as normal glands; that is, cribriform Gleason pattern 3 PCa should morphologically resemble cribriform high-grade prostatic intraepithelial neoplasia but show diagnostic features of infiltrating carcinoma such as the following:

- Glands are negative for basal cell markers,
- Glands are back to back, ruling out high-grade prostatic intraepithelial neoplasia, or
- Glands should exhibit pathognomonic features of carcinoma, such as perineural invasion or extraprostatic extension.

In contrast, pattern 4, which was originally limited to fused or irregularly contoured cribriform structures, was widened in scope. With rare exceptions, almost all cribriform morphologies were accepted as Gleason pattern 4. Although not included in the original Gleason depictions, a consensus was reached that ill-defined glands with poorly formed glandular lumina, a pattern that often accompanies fused glands, warranted a diagnosis of Gleason pattern 4.

The grading of glomeruloid glands is another controversial area in the modified Gleason system. Glomeruloids are dilated glands containing intraluminal cribriform structures with a single point of attachment, resembling a renal glomerulus. According to some experts at the 2005 ISUP consensus conference, the rare case of Gleason score 3 + 3 = 6, admixed with small glomeruloid glands, should be scored as 3 + 3 = 6. Other experts in the field felt that all glomeruloid structures should be assigned a Gleason pattern 4. Larger glomeruloid structures are uniformly accepted by urologic pathologists as Gleason pattern 4. Consequently, either approach was deemed acceptable for practicing pathologists until future data indicated which method was more accurate.

### EFFECT OF THE MODIFIED GLEASON GRADING SYSTEM

#### Upgrading

The primary result of limiting the definition of Gleason pattern 3 and expanding the definition of pattern 4 has been Gleason grade migration or upgrading. In many settings, Gleason pattern 3 carcinoma, previously the most common pattern on needle biopsy, has become less common than pattern 4. In one recent study comparing the original and modified Gleason system on needle biopsy material, cancers with a Gleason score of 6 decreased from 48% to 22% of the total, whereas cancer with Gleason score 7 increased from 25% to 68%. Not surprisingly, the magnitude of this shift depends somewhat on the study population, and it is less dramatic in clinical settings with a greater proportion of early stage disease, as seen in a study by Billis et al, where the proportion of needle biopsies with a Gleason score of 6 was 68%, decreasing to 49% using the modified grading scheme. Correspondingly, Gleason 7 went from 26% to 39% with application of the modified grade criteria.

#### Biopsy Versus Radical Prostatectomy Gleason Score

Several studies have addressed the correlation and sources for the discrepancies between Gleason scores in needle biopsies and corresponding radical prostatectomy specimens: sampling error, borderline cases, pathology error, and pathologists’ experience.

The most common type of sampling error occurs when there is a higher-grade component present within the

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**Table 4. Differences Between the Original Gleason System and the 2005 International Society of Urological Pathology (ISUP) Modified Gleason System**

<table>
<thead>
<tr>
<th>Original Gleason System</th>
<th>2005 ISUP Modified Gleason System</th>
</tr>
</thead>
<tbody>
<tr>
<td>A diagnosis of GS &lt; 4 possible on NB</td>
<td>GS of NB specimens &lt; 4 rarely, if ever, made</td>
</tr>
<tr>
<td>Cribriform glands with rounded and smooth contours as well as with an irregular outer border are diagnosed as Gleason pattern 3.</td>
<td>Most cribriform patterns would be diagnosed as Gleason pattern 4, whereas specimens with only rare cribriform lesions would satisfy the diagnostic criteria for cribriform pattern 3.</td>
</tr>
<tr>
<td>The same GS is used for NB and RP specimens</td>
<td>Different GS used for NB and RP specimens</td>
</tr>
<tr>
<td>High-grade tumor of small quantity (&lt;5%) on NB should be excluded based on GS (5% threshold rule)</td>
<td>High-grade tumor of any quantity on NB should be included within the GS</td>
</tr>
<tr>
<td>Tumors on NB should be graded by listing the primary and secondary patterns, ie, excluding tertiary pattern</td>
<td>For the tertiary pattern on NB specimens, both the primary pattern and the highest grade should be recorded</td>
</tr>
<tr>
<td>The GS of RP specimens should be assigned based on the primary and secondary patterns</td>
<td>For RP specimens, the pathologist should assign the GS based on the primary and secondary patterns; a comment should be added on the tertiary pattern</td>
</tr>
<tr>
<td>Separate or overall scoring to assess all grades of NB specimens</td>
<td>When NB specimens show different grades in separate cores, individual GS should be assigned to these cores (separate scoring)</td>
</tr>
<tr>
<td>The grade of the largest portion should be assigned, even if the second largest portion is of higher grade</td>
<td>When RP specimens show different grades in separate tumor nodules, a separate GS should be assigned to each of the dominant tumor nodules</td>
</tr>
</tbody>
</table>

* Abbreviations: GS, Gleason score; NB, needle biopsy; RP, radical prostatectomy.

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**Table 5. Reasons for Not Assigning Gleason Scores 2 Through 4 on Needle Biopsy**

1. Cancer with Gleason scores 2 through 4 is extraordinarily rare in needle biopsies as compared with transurethral resection specimens
2. There is poor reproducibility among experts for lower-grade tumors
3. The correlation with the prostatectomy score for tumors with a Gleason score of 2 through 4 is poor
4. A “low” score of Gleason 2 through 4 may misguide clinicians and patients into believing that there is an indolent tumor
radical prostatectomy that is not sampled on needle biopsy. This typically occurs when a needle biopsy tumor is graded as Gleason score 3 + 3 = 6 and a Gleason pattern 4, which was not sampled on the biopsy, exists in the prostatectomy, resulting in a prostatectomy Gleason 3 + 4 = 7. A common pathology error is seen when pathologists assign a Gleason score of less than 4 on a needle biopsy, which is, in fact, a Gleason score 5 to 6 or higher. When there is a limited focus of small glands of cancer on needle biopsy, it is a Gleason pattern 3 or higher by definition. Gleason pattern 3 consists of small glands with an infiltrative pattern. Biopsying an adenocarcinoma with a Gleason score of less than 6 is unlikely to result in just a few neoplastic glands because low-grade adenocarcinoma grows as nodules of closely packed glands rather than scattered, infiltrating glands. Undergrading may result from difficulty in recognizing an infiltrative growth pattern or failing to recognize the presence of small areas of gland fusion.

An important effect of modifying the Gleason grading has been to improve the agreement between Gleason scores on needle biopsy and radical prostatectomy. Before the 2005 ISUP modification, the agreement of Gleason scores between biopsy and radical prostatectomy specimens ranged from 28% to 68% in most studies. This relatively low level of agreement was predominantly due to the undergrading of low-grade carcinomas in needle biopsies, whereas the agreement was more exact in high-grade carcinomas. Biopsies have been found to undergrade carcinomas in 24% to 60% of cases, whereas overgrading is less common, occurring in 5% to 32% of cases.

Results on the concordance of the Gleason scores between needle biopsy and radical prostatectomy when the ISUP revision was issued conflict. In a recent study by Helpap et al, overall exact agreement between needle biopsy and radical prostatectomy specimens increased from 58% to 72% when using the modified system. As in the past, most of the cases without perfect correlation were due to undergrading (73%). When analyzed by Gleason score, agreement using the modified system was excellent for a biopsy Gleason score of 3+4=7 (88%) and reasonable for 4+3=7 (68%) but was quite poor for 3+3=6 (28%). The proportion of radical prostatectomy specimens that were assigned a score of 6 or 7 increased from 68% to 89% with the introduction of the ISUP 2005 modified Gleason score. As many as 82% of cases were assigned a Gleason score of 7. Agreement improves when cases are grouped into a few categories. Furthermore, Ozok et al showed that agreement between needle biopsies and radical prostatectomy specimens in 97 men improved from 31.9% to 44.3% with the ISUP grading system.

Other studies failed to demonstrate significantly improved agreement. In a study by Uemura et al, the concordance rates for needle biopsies and radical prostatectomy specimens between the original Gleason system and the ISUP modified system were 67% and 70%, respectively. Similarly, Zareba et al showed the biopsy–radical prostatectomy did not significantly affect the Gleason score agreement (63.4% and 65.5%, respectively).

### Observer Reproducibility

Exact intraobserver agreement on Gleason scores was reported in 43% to 78% of cases, and agreement within plus or minus one Gleason score unit was reported in 72% to 87% of cases. Gleason wrote that he duplicated exactly his previous histologic scores approximately 50% of the time. Highly variable levels of interobserver agreement on Gleason scores have also been reported, with a range of 36% to 81% for exact agreement and 69% to 86% within plus or minus one Gleason score unit.

An important consequence of changes to the definition of Gleason pattern 4 has been an improvement in interobserver reproducibility. Most studies using the modified Gleason system have shown that overall interobserver reproducibility hovers around 80%. Again, grouping the cases into fewer categories contributes to these results. In an early study on the reproducibility of a modified Gleason score, including primary and highest Gleason pattern in radical prostatectomy specimens, Glaessgen et al found that weighted k was almost identical for conventional and modified Gleason scores. That study did not, however, take into account the effect of changes in pattern interpretation. Although this improvement may be due, in part, to the decreased diagnosis of carcinomas with low Gleason scores (Gleason scores 2–5) on needle biopsy using the modified system, there has also been improvement in the reproducibility of Gleason

<table>
<thead>
<tr>
<th>Table 6. Grading Variations and Variants of Prostate Adenocarcinoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Pseudohyperplastic Adenocarcinoma</strong></td>
</tr>
<tr>
<td>These cancers should be graded as Gleason score 3 + 3 = 6 with pseudohyperplastic features, in large part, based on the recognition that they are most often accompanied by more-ordinary Gleason score 3 + 3 = 6 adenocarcinoma</td>
</tr>
<tr>
<td><strong>Foamy Gland Carcinoma</strong></td>
</tr>
<tr>
<td>Whereas most cases of foamy gland carcinoma would be graded as Gleason score 3 + 3 = 6, higher-grade, foamy gland carcinomas exist and should be graded accordingly based on the pattern</td>
</tr>
</tbody>
</table>

### Table 7. Reasons for Assigning Gleason Pattern 4 to Cribriform Glands

1. Candidate cribriform pattern 3 cancers almost always occur in association with typical Gleason pattern 4 cancer elsewhere in the case
2. The rarity of candidates for cribriform Gleason pattern 3
3. Within these rare candidates, the lack of interobserver reproducibility by experts on assessing the diagnostic criteria proposed to distinguish cribriform Gleason pattern 4 from Gleason pattern 3
4. Conceptually, the change in grade from pattern 3 to pattern 4 would be expected to be reflected in a distinct architectural paradigm shift where cribriform as opposed to individual glands are formed, rather than merely a subjective continuum of differences in size, shape, and contour of cribriform glands
pattern 4 carcinomas. In a recent study, which evaluated reproducibility for each Gleason score group under the modified system, there was 68% congruence for Gleason score 7, compared with 27% in 1994, a finding that underscores the importance of the modifications to Gleason pattern 4 definitions.29,30

**Correlation of Gleason Score With Patient Outcomes and Pathologic Stage**

The true test of the validity of the new Gleason system is its correlation with patient outcomes. However, it will be some time before a sufficient follow-up period has elapsed to do those studies. Both studies by Uemura et al22 and Billis et al23 demonstrated that the Gleason scores on needle biopsies using the modified, but not the original, Gleason system correlated with progression after radical prostatectomy. Tsivian et al31 similarly found that the modified Gleason score, when analyzed in prognostic grade groups (<7, 7, and >7), predicted biochemical recurrence after radical prostatectomy better than did the original Gleason score groups. In a large study of 454 transurethral resections and 347 needle biopsies, Berney et al32 reported significant upgrading of biopsies initially graded in 1990–1996 and then regraded and published in 2007. Whereas the initial grades did not correlate with survival outcome, the newly recorded grades did.32 In the only study favoring the original over the modified Gleason system for progression, Delahunt et al33 reported that the original Gleason grading system outperformed the modified system in predicting prostate-specific antigen nadir following external beam radiotherapy and hormone therapy. However, prostate-specific antigen nadir is not currently considered the best endpoint for predicting failure following radiotherapy.

Until more time has elapsed for follow-up studies, surrogate predictors of patient outcome have been used, such as the pathologic stage of the tumor at radical prostatectomy. One recent study34 looking at the correlation among pathologic stage and the conventional and modified Gleason systems applied to radical prostatectomy specimens found that the only significant change in stage distribution was seen for Gleason score 7, where pT2 was the most common stage with modified grading (54%) and pT3 was most common with conventional grading (67%). Strikingly, 95% of Gleason score 3 + 4 = 7 tumors were stage pT2, whereas 79% of Gleason score 4 + 3 = 7 tumors were stage pT3 to pT4. That dramatic difference in clinical stage between 3 + 4 = 7 and 4 + 3 = 7 carcinomas is likely due to the inclusion of cases previously considered Gleason score 6 in the 3 + 4 = 7 category under the modified system. Whether the distinction between 3 + 4 = 7 and 4 + 3 = 7 under the new grading system will affect clinical decision-making remains to be seen.34

**CLINICAL IMPLICATIONS OF THE MODIFIED GLEASON GRADING SYSTEM**

One notable consequence of the Gleason modifications is that it is increasingly difficult to compare data sets assessing patient outcomes in prostate cancer over time. Today’s cases of Gleason score 6 are a homogenous group of tumors lacking cribriform and poorly formed glands, and are, therefore, associated with a better prognosis. An example can be seen in a study30 analyzing 38 cases that were diagnosed before the consensus conference as organ-confined, margin negative, Gleason score 6 PCa, which were treated with radical prostatectomy in 1983–2005 and which had biochemical progression. On review of these older Gleason score 6 cases, 24 (63%) would be considered to have some Gleason pattern 4 under today’s grading scheme, including poorly formed, fused, or cribriform glands. Based on the updated Gleason system, organ-confined, Gleason score 6, margin-negative cancer is virtually 100% curable.

**Effect of Upgrading on Treatment Decisions**

The most important clinical decision affected by the Gleason score on a needle biopsy is the mode of therapy offered. Historically, patients with high-grade tumors (traditionally Gleason score 8–10) have been discouraged from undergoing radical prostatectomy because of the high likelihood of disease not confined to the organ or even systemic disease at presentation. However, a number of more recent studies from the era after the introduction of prostate-specific antigen (almost all using conventional Gleason grading) have suggested that men with high-grade tumors may do better than we previously thought after surgical monotherapy. Thus, the tendency toward upgrading may be balanced by an increasing trend to perform radical prostatectomy in the context of higher-grade disease. Additionally, the preferred mode of therapy for Gleason score 7 tumors (intermediate grade) has always been ambiguous. Because the most noticeable consequence of the changing definition of Gleason pattern 4 is the regrouping of cases previously considered Gleason 6 into the Gleason 7 category, this particular modification to the Gleason system will likely have little effect on the decision to proceed to radical prostatectomy. Occasionally, radiotherapists have distinguished between Gleason 3 + 4 and 4 + 3 disease by whether the patient is a reasonable candidate for brachytherapy. The recent suggestion that modified Gleason score 3 + 4 = 7 tumors behave much like Gleason 6 tumors, whereas Gleason score 4 + 3 = 7 tumors behave more like high-grade tumors does indicate that refinement of Gleason pattern 4 definitions may have slightly shifted the traditional low-grade/high-grade cutoffs. However, those data used Gleason scoring from radical prostatectomies rather than from needle biopsies. Because sampling is an unavoidable issue on needle biopsy, it is unlikely that any refinement of the Gleason system will make the distinction between 3 + 4 = 7 and 4 + 3 = 7 into a reliable basis for determining appropriate therapy at this time.30

There is also a need to better define the detection threshold for a small amount of Gleason pattern 5. Experts have claimed that they require a cohesive focus of epithelial structures without lumina, seen at a power lower than ×40.35 Yet, more stringent criteria is needed because a diagnosis of a minute component of a Gleason pattern 5 tumor on a needle biopsy may move the Gleason score to 4 + 5 = 9 or 3 + 5 = 8, which is likely to affect the treatment decision.

**SUBSEQUENT PROPOSALS FOR SLIGHT MODIFICATIONS OF THE ISUP GRADING SYSTEM**

The recent recommendation is that all cribriform patterns be diagnosed as Gleason pattern 4 rather than Gleason pattern 3.19,20,36 This recommendation has been based on a reproducibility study by Latour et al37 and is supported by nuclear DNA studies. Latour et al28 selected 30 needle biopsy cases that possibly represented cribriform
Gleason pattern 3 cancer. Thirty-six digital images were taken and sent to 10 experts in prostate pathology. Consensus was defined when at least 7 of 10 experts (70%) agreed on the grade. Experts reached consensus on 67% (24 of 36) of the images (pattern 4, n = 23; pattern 3, n = 1). Of the 12 images where consensus was not reached, 7 (58%) favored pattern 4 (6 of 10 experts [60%] agreed), 1 (8%) favored pattern 3 (6 of 10 experts [60%] agreed), and 4 (33%) were equivocal (<6 experts agreed). The most common criteria used to diagnose pattern 4 in the 23 pattern 4 images where consensus was reached were (in frequency from high to low): irregular contour, irregular distribution of lumens, slitlike lumens, large glands, number of glands, and small lumens. In the only pattern 3 image on which consensus was reached, the criteria used were regular contour, small glands, regular distribution of lumens, and uniform, round lumens. Discrepancy between experts was qualified as primarily objective (different criteria present) in 38%, subjective (different interpretation of the same criteria) in 12%, and mixed (both objective and subjective) in 50%. The most frequent situation with different interpretations of the same criteria was regular versus irregular contours and small versus large glands, with the former being more common. Even in this highly selected set of images thought to be the best candidates for cribriform pattern 3 from a busy consultation service, most experts interpreted the cribriform patterns as pattern 4. Moreover, most of the cribriform foci investigated (73%) were associated with more definitive pattern 4 elsewhere on the needle biopsy specimen.

In a recent study, prostate needle biopsies containing carcinoma with glomeruloid features were examined to establish whether there was an association between glomerulations and the presence of concurrent high-grade carcinoma. Glomerulations were overwhelmingly associated with high-grade cancer on the same core, were composed predominantly of Gleason pattern 4 (80% of cases), and often appeared to represent a morphologic transition to larger cribriform glands. Only a few glomerulations were surrounded exclusively by pattern 3 cancer (16% of cases). Although this was an association study without clinical follow-up, the weight of the current evidence suggests that glomerulations most likely represent an early stage of cribriform pattern 4 cancer and should likely be graded as pattern 4.

Gleason Grading System Supplemented with Nuclear Morphology and Immunohistochemistry

The Gleason system and its ISUP revision are based on the architectural patterns of PCa. The contribution of nuclear morphology and immunohistochemistry to its further refinement has been investigated only to a limited extent. It is worth mentioning the proposal made by the late F. K. Mostofi, MD, in 1999, in a meeting in Paris, France, sponsored by the World Health Organization, to supplement the Gleason system with the World Health Organization nuclear grading scheme. The proposal was based on his experience that patients with a Gleason score of 6 or higher can be stratified based on the World Health Organization nuclear grading and that such stratification has a prognostic importance. This was recently confirmed in a morphometric study in which it was shown that nuclear signature is important in better-defining risk groups in patients with PCa.

There are some cases in the description of the Gleason grading system that are right at the interface between 2 different patterns, leading to interobserver and possibly intraobserver variability. In particular, one of the major challenges for pathologists is the identification of small areas of fusion in the presence of a predominantly grade 3 background whose recognition will yield a Gleason score of 7. There are few immunohistochemical studies, to our knowledge, addressing this issue. Richardson et al investigated IGBPFB2 and found the marker to be superior to morphology in defining gland fusions and, therefore, in separating Gleason pattern 4 from Gleason pattern 3.

Conclusions

The primary result of limiting the definition of Gleason pattern 3 and expanding the definition of pattern 4 is Gleason grade migration or upgrading, both in needle biopsies and radical prostatectomy specimens. There are clinical consequence to upgrading the Gleason score, for instance, in the type of therapy offered to an individual patient with PCa. For example, patients with high-grade tumors from biopsies could be discouraged from undergoing active surveillance. The true test of the validity of the 2005 ISUP Modified Gleason System is its correlation with patient outcomes. Few studies have yet been published assessing those correlations. Uemura et al found that the 2005 ISUP modified Gleason score of needle biopsy specimens was significantly associated with biochemical recurrence-free survival after radical prostatectomy. They concluded that the ISUP system is clinically useful for determining the most appropriate treatments for patients with early stage PCa. However, it will be some time until studies with sufficient follow-up periods are published.

The urologists and uropathologists have to be aware of the effect of the Gleason system used on patient prognosis and treatment. The pathology report and the clinical records have to clearly indicate which system is adopted for each individual patient.

References

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