Current Perspectives on the Gleason Grading of Prostate Cancer
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• Context.—Since its description in 1966 by Donald Gleason, the Gleason grading has remained a cornerstone in the diagnosis and management of prostate cancer. With widespread use of the prostate specific antigen screening, the diagnosis and management patterns of prostate cancers have dramatically changed. In addition, better understanding of the morphologic spectrum of prostate cancer and its subsequent outcome have prompted the refinement of the grading criteria and reporting practices applicable to contemporary practice management.

Objective.—To present contemporary perspectives and approaches to the Gleason grading of prostate cancer.

Data Sources.—Personal practice experience, review of medical literature, and excerpts from the 2005 International Society of Urological Pathology Consensus Statement on Gleason Grading of Prostate Cancer.

Conclusions.—This review addresses the trend in contemporary practice toward a grading shift, with rare utilization of Gleason patterns 1 and 2, and discusses the refinement of histologic criteria for Gleason patterns 3 and 4; approaches to Gleason grading in the setting of unusual variant morphologies of prostate cancer; significance of higher tertiary pattern 5; and practice recommendations for reporting in the setting of extended multiple core biopsies and multifocal prostate cancers in radical prostatectomy. Finally, the impact of consensus recommendations in current practice, its limitations and pitfalls, are also addressed.

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GLEASON GRADING
Historical Perspective

In 1966, Donald F. Gleason, created the Gleason grading system based on low-power architectural features of prostate cancer. The original description of this system was based on a study of 270 patients from the Minneapolis Veterans Administration Hospital (Minneapolis, Minnesota). Later in 1974, the study was expanded to include 1032 men. With additional experience, Gleason made further refinements to the system in 1974 and 1977. In this architectural system, all tumors fall into a 5-grade system representing a continuum of progressively complex morphologies. Another unique aspect of the system is that rather than being assigned a worst grade, a tumor is assigned an average grade comprising the most prevalent and the second most prevalent pattern (Gleason score = primary + secondary pattern).

Of the many proposed systems over time for the grading of prostate cancer, currently the most widely accepted and used is the Gleason system. Most recently, the system has been endorsed by the World Health Organization.

Numerous reports have confirmed the significance of Gleason score in predicting outcome after no treatment, treatment with radical prostatectomy, and radiation therapy. For patients receiving neoadjuvant or adjuvant hormonal therapy, Gleason grade is an independent predictor of biochemical failure. Patients with low Gleason score (6 or lower) are often candidates for an active surveillance program, previously referred to as “watchful waiting therapy.” A Gleason score of 7 is usually associated with a critical decision-making step—patients usually need some form of definitive therapy. And finally, patients with Gleason score of 8–10 are often candidates for adjuvant therapy or radiation treatment.

Several groups have developed nomograms for predicting pathologic stage and outcome based on clinical stage, serum prostate specific antigen (PSA), and biopsy Gleason score. The best known of these nomograms are the Partin tables and Kattan nomograms. Similarly, models for predicting risk of disease progression for patients treated with radiation therapy and other therapy settings have been proposed.

Changes and Trends in the Practice Patterns for the Diagnosis and Management of Prostate Cancer Since the Introduction of Gleason Grading

In the last 40 years the diagnosis and management of prostate carcinoma has dramatically changed. With the widespread use of PSA screening, there has been a remarkable shift in disease staging toward low-volume, low-stage prostate cancers. Because of this trend, extended and saturation biopsy templates are increasingly used instead of limited, targeted biopsies to improve prostate cancer detection. Surgical pathologists are increasingly

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faced with the task of grading prostate cancer in cores submitted from separate sites. The concept of atypical cribriform lesions and adenosis has improved with widespread use of immunohistochemistry. In addition, we now need to address the issue of grading some of the newly described variants or patterns of adenocarcinoma of the prostate and the issue of higher tertiary grade pattern. The correlation between biopsy and radical prostatectomy specimens still remains a problem, specifically and significantly the undergrading of the biopsy specimen. These trends have prompted the refinement of the grading criteria and reporting practices applicable to contemporary practice management.

**Current Concepts in the Gleason Grading of Prostate Cancer**

This review attempts to systematically address contemporary thinking on Gleason grading, key issues from the 2005 International Society of Pathologists Consensus Gleason Grading Statement, and select recent literature on this subject.

**Gleason Grade 1 or 2 Should Be Rarely, if Ever, Assigned in the Biopsy Setting.**—The first and foremost important lesson that was learned, and now widely practiced, is that the diagnosis of low-grade Gleason score 2–5 prostate carcinomas in the setting of needle biopsy (NBX) should be made with extreme caution. Such diagnosis on final radical prostatectomy was proved wrong most of the time. Therefore, even though, conceptually, the definition of pattern 1 and pattern 2 remain essentially that defined by Gleason, its application in the contemporary biopsy setting is rather obsolete. Most cases that were diagnosed as Gleason score 1 + 1 = 2 in the time of Gleason would be considered, today, atypical adenomatous hyperplasia by basal cell immunohistochemistry. This grade should not be assigned (with only extremely rare exceptions), regardless of the type of specimen. These patterns occasionally exist on prostate transurethral resection and in multifocal low-grade tumors within the radical prostatectomy specimens. Because of poor reproducibility, lack of good correlation with prostatectomy grade, sampling issues, and potentially misleading clinical implications, Gleason score 2–5 on needle biopsy should “rarely, if ever” be assigned when all classic criteria are present and diagnosis of adenosis is excluded. The major limitation of a diagnosis of Gleason score 4 on needle biopsy is that one may not see the edge of the entire lesion. Therefore, most such lesions in NBX are diagnosed as 3 + 2 = 5 or 2 + 3 = 5, with a comment stating that the corresponding prostatectomy specimen will almost always have a higher grade.

**Gleason Grade in the Biopsy Setting Essentially Starts With Gleason Grade 3.**—From a practical standpoint, Gleason grading in contemporary practice starts with pattern 3. Gleason pattern 3 represents the most common Gleason pattern encountered on NBX. The presence of variably sized individual glands, typically smaller than those seen in Gleason pattern 1 or 2, infiltrating between the benign glands, represents the classic spectrum of Gleason pattern 3. In contrast to the original description by Gleason, individual cells are no longer allowed in Gleason pattern 3. Minute foci of individual, infiltrating tumor glands, seen frequently in NBXs, represent pattern 3 + 3 = 6 (Figure 1, A).

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**Figure 1.** Select morphologic representations of current concepts and pitfalls in the grading of Gleason grade 3 prostate cancers. A, Variably sized, discrete glands infiltrating between benign glands; despite very small tumor focus, the lesion should be graded as 3 + 3 = 6. B, A rare example of cribriform lesion, which may be graded as Gleason pattern 3. It typically has small cribriform glands, round and regular in contour, with regular lumina and may mimic cribriform intraepithelial neoplasia. C, Tangentially cut glands at the periphery of the tumor nodule mimic poorly formed glands associated with Gleason pattern 4 prostate cancer (hematoxylin-eosin, original magnifications ×200).
Prostate cancer with cribriform architecture is now rarely considered representative of Gleason pattern 3 or a lower pattern. Only rare cribriform lesions consisting of round, regular glands, essentially of the same size as normal glands, may qualify as pattern 3 (Figure 1, B). Cribriform Gleason pattern 3 lesions morphologically resemble high-grade cribriforming prostate intraepithelial neoplasia (PIN) but may be separated from the latter (1) if a large number of glands are negative for basal cell markers; (2) if specific features of cancer exist, such as perineural invasion or extraprostatic extension; or (3) if there is evidence of adjacent conventional carcinoma. In a recent article, a group of expert urologic pathologists performed an analysis of small invasive cribriform carcinomas thought to be representative of cribriform Gleason 3 in biopsy specimens. The overall interobserver reproducibility was not good and most lesions were favored to be a spectrum of Gleason pattern 4. This study again emphasizes that, in needle biopsy, most cribriform carcinomas should be classified as Gleason pattern 4 or higher.

Prostate cancer may demonstrate branching or “U”-shaped glands, which is not considered as evidence of fusion and should be regarded as pattern 3.

Most (>95%) Cribriform Cancers Are Considered a Spectrum of Gleason Pattern 4.—A major departure from the original Gleason system is that most cribriform carcinomas (>95%) are in fact considered Gleason pattern 4 or pattern 5 (with comedonecrosis) carcinomas, with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3, as described earlier. The original Gleason system recognized many of the cribriform processes as an example of Gleason pattern 2 or 3 cancer. However, studies have shown that cribriform carcinomas have an aggressive course. Gleason pattern 4 cribriform carcinoma spectrum is associated with (1) small but irregular cribriforming glands (Figure 2, A); (2) round and regular uniform cribriform cancers that are much larger than the normal prostate gland (Figure 2, B); and (3) adenocarcinoma with ductal differentiation, characterized by confluent cribriform glands lined by tall columnar epithelium and demonstrating slitlike pattern and papillary differentiation (Figure 3, A). A summary of the spectrum of cribriform carcinoma and its implications for grading is shown in Table 1.

Cluster(s) of Poorly Formed Glands, With Tangential Sectioning Ruled Out, Is Considered Gleason Pattern 4.—An interesting morphologic concept is that a cluster of poorly formed or ill-defined glands for which tangential sectioning is ruled out warrant the diagnosis of Gleason pattern 4 (Figure 2, C). Even though glands are discrete and not fused, they are very poorly formed with barely recognizable lumina. Caution should be exercised when using this feature, as it has significant potential for subjectivity for both overinterpretation and underinterpretation. Therefore, one should use strict criteria when using this feature. Tangential sectioning may mimic poorly formed glands. Therefore, the presence of a few, random, poorly formed glands within a cluster—which otherwise has well-formed lumina—or poorly formed glands seen specifically at the edge of a nodule does not qualify for pattern 4 (Figure 1, C). However, an entire cluster containing poorly formed glands would be difficult to justify by tangential sectioning and is regarded as pattern 4.
Description of the Amount of Pattern 4 in the Setting of Gleason Score 7 (3 + 4 Versus 4 + 3) Is Prognostically Important. —Presence of any Gleason pattern 4 is typically considered clinically significant prostate cancer and is often important in the clinical decision-making process. In the most recent Partin tables, Gleason score 7 (3 + 4) and Gleason score 7 (4 + 3) are considered separately for prognostic purposes. For Multiple Biopsy Cancer Cores With Different Gleason Grades, Providing the Grade for Individual Core(s) Informs the Underlying Gleason Grade of Radical Prostatectomy Specimens. —Another important issue in the multiple biopsy setting is how to assign a grade when different cores contain different Gleason grades. In this setting, should we give only a global Gleason score or a worst score? Emerging data suggest that individual Gleason scores should be assigned to separate cores as long as the cores are submitted in separate containers or if the cores are in the same container but their location is specified by the urologist. Giving an overall or gestalt Gleason grade is optional.

My colleagues and I recently looked at a series of 200 extended biopsy specimens with 10 or more cores whose results subsequently led to radical prostatectomy performed at University of Michigan (Ann Arbor, Michigan). Biopsy Gleason score was categorized as a global or gestalt or average score by combining grades of all cores, worst-or highest-volume grade based on grading of individually sampled cores. Overall worst Gleason score showed best correlation and, more importantly, the chances of upgrading at prostatectomy was least with this parameter. In another study, in which 1 core had Gleason score 4 + 4 and other cores had pattern 3, the pathologic stage at radical prostatectomy was comparable to that for cases in which all needle cores had Gleason score 4 + 4. A recent survey demonstrated that our surgical colleagues typically choose the highest grade from all the cores and label the patient’s disease with that grade.

Scenarios in which multiple cores are put in the same container without any identifiers or labeled only as “left” or “right” are relatively common. Currently there are no clear guidelines to address this issue. Recently, my colleagues and I simulated this scenario in our practice by artificially lumping the cores, as they were placed in the right or left side only, and then determined a global score (as if they were averaged as 1 single linear core), a worst Gleason pattern, and largest tumor volume Gleason score. Overall correlation was best with biopsy worst Gleason score and probability of significant upgrading were least with this parameter. These results suggest that...
when multiple intact cores are submitted in a container without specific site identifiers, Gleason score of individual core or worst pattern should be reported. When a container contains multiple pieces of tissue and it is uncertain if one is looking at an intact core, the consensus is that only an overall score should be given for that container.

The Presence of Higher-Grade Tumor on Needle Biopsy Should Be Reported.—The presence of any high-grade tumor on needle biopsy should be included in the Gleason score as long as it was identified at low to medium magnification. This is based on the assumption that the presence of any high-grade tumor sampled in needle biopsy most likely indicates a more significant tumor at radical prostatectomy.

The guidelines for this parameter in the setting of radical prostatectomy are not clear, but most agree that even limited higher-grade tumor should be reported in the context of either secondary or tertiary grade.

Significance and Reporting of Higher Tertiary Pattern 5 in the Biopsy and Prostatectomy Specimens.—The importance of tertiary Gleason pattern is typically manifest when it is of higher grade than secondary pattern. The typical scenario with tertiary patterns in biopsy specimens includes tumors with patterns 3, 4, and 5 in various proportions. Emerging data suggest that such tumors should be classified overall as high grade in NBX setting.

For needle biopsy specimens with patterns 3, 4, and 5, both the primary pattern and the highest grade should be recorded, that is, 3 + 5 = 8 (Figure 4). This recommendation is based on management decision issues. Most clinicians use Partin tables or a nomogram to predict outcomes such as pathologic stage or prognosis after radical prostatectomy or after radiation therapy. These algorithms typically use only primary and secondary patterns reported in the NBX specimen and, therefore, a tertiary pattern of higher grade would be ignored unless reported as a secondary pattern. In our recent experience, my colleagues and I correlated radical prostatectomy and pathologic outcomes for patients with biopsy Gleason score 3 + 4 or 4 + 3 without tertiary pattern 5, Gleason score 3 + 4 or 4 + 3 with tertiary pattern 5, and Gleason score 8–10 groups. Our study showed that the pathologic outcomes of patients with biopsy tertiary group 5 were comparable to outcomes of patients with biopsy Gleason score 8–10.

For the radical prostatectomy specimen, one assigns the Gleason score based on the primary and secondary patterns with a comment about the tertiary pattern when it is of higher grade. Mosse et al demonstrated that at radical prostatectomy, cases with Gleason score of 4 + 3 = 7 with a tertiary pattern 5 have worse pathologic behavior than cases with Gleason score of 4 + 3 = 7 without tertiary pattern 5, but they have a lower incidence of seminal vesicle invasion and lymph node metastases than those with Gleason score 4 + 5 = 9.

Emerging Concept of Intraductal Prostatic Carcinoma.—Some “invasive” Gleason pattern 3–5 prostatic carcinomas have basal cell layers, revealed by hematoxylin-eosin staining or, more commonly, by immunostaining. In the past, these lesions have been variably labeled as high-grade PIN or ductal-type prostatic adenocarcinoma. McNeal and Yemoto first raised the possibility that they may represent an aggressive form of prostatic adenocarcinoma, as they are almost never seen in the absence of an invasive component. If present, the invasive component is almost always high grade and has large tumor volume. The prognosis with cancer harboring these basal cell–positive cancer glands is worse. The term intraductal carcinoma of the prostate (IDC-P) was introduced. The importance of recognizing IDC-P is for its association with a poorer prognosis than that which would otherwise be attributed to either high-grade PIN or Gleason pattern 3 cancers.

The diagnosis of IDC-P in prostate biopsy specimens is difficult. Guo and Epstein published morphologic criteria in prostate biopsy specimens that define IDC-P as malignant epithelial cells filling large acini and prostatic ducts, with at least partial preservation of basal cells forming either (1) solid or dense cribriform patterns or (2) loose cribriform or micropapillary patterns with either marked nuclear atypia (nuclear size 6 normal or larger) or comedonecrosis. Reporting of IDC-P in prostate biopsy specimens deserves special mentioning. If a high-grade (Gleason pattern 4 or 5) invasive component is present with IDC-P, diagnosis of IDC-P seems to be of academic interest. However, when associated with a Gleason pattern 3 component, IDC-P should be documented and its poor prognostic significance should be mentioned. One solution could be grading IDC-P component as pattern 4 or 5. However, when IDC-P is not associated with an invasive component in prostate biopsy specimens, it is more difficult to distinguish it from...
cribiform high-grade PIN; it is prudent to diagnose it as IDC-P and to comment that IDC-P is often associated with high-grade invasive prostate cancer.

**Gleason Grading in the Setting of Select Unusual Morphologies and Patterns.**—**Foamy Gland Cancer.**—Even though foamy gland cancers appear morphologically banal, biologically they usually behave as intermediates to aggressive tumors. Many tumors in fact represent high Gleason-grade cancers.\(^3\) From a grading point of view, one should grade these tumors by overall architecture rather than by foamy appearance.

**Prostate Adenocarcinoma With Collagenous Micronodules.**—When one encounters collagenous micronodules, an intracellular eosinophilic material also considered a specific feature for prostate cancer, one should try to subtract this feature from the analysis and grade the tumor on the basis of its underlying architecture. Most such cases represent Gleason pattern 3.

**Large Duct Differentiation.**—The large duct differentiation, characterized by large glands with papillary and cribiform morphology and slitlike lumina and lined by columnar cells, represents Gleason pattern 4\(^4\) (Figure 3, A). If it contains comedonecrosis, it should be classified as pattern 5.

**Small Cell Carcinoma.**—The small cell neuroendocrine carcinomas should not be graded because of their unique tumor biology and therapeutic significance. Presence of such differentiation is significant and should be reported.

**Glomerulation.**—Infrequently, dilated glands may show cribiform proliferation that is not transluminal and that is referred to as glomeruloid pattern—another specific feature of prostate cancer (Figure 3, B). The grading of such pattern remains controversial, as some experts believe it should be scored as 4 while others would score it as 3. Most of the time, glomerulation is a very focal feature and can be potentially excluded from analysis. Personally, when glomerulation is important in the general architecture of the tissue, I consider it Gleason pattern 4.

**Colloid Carcinoma.**—Colloid carcinoma consisting of tumor with pools of extravasated mucin is another area of grading controversy. Previously, such tumors were typically considered high-grade Gleason 4 + 4 tumors. New data suggest that they are not uniformly aggressive tumors.\(^2\) One should again use the tissue architecture as a major feature to grade these tumors. If there are discrete glands floating within the pools of mucin, they should be considered as pattern 3 tumors (Figure 3, C), but if there are cribiform glands floating within the pools of mucin, they should be considered pattern 4 tumors.

The summary of different variant morphologies of prostate cancer and their proposed Gleason grading recommendations are listed in Table 2.

**Significance of Percentage of Gleason Pattern 4/5.**—Several studies\(^5,6\) have demonstrated the importance of percentage of pattern 4/5. This is particularly predictive of prognosis at extreme percentages. However, the percentage of pattern 4/5 on NBX has not been shown to correlate well with the percentage of pattern 4/5 in the corresponding radical prostatectomy specimen. Reporting of this parameter is optional.

**Gleason Grading in the Setting of Multifocal Prostate Cancers in Radical Prostatectomy Specimens.**—When I examine radical prostatectomy specimens, most prostate adenocarcinomas demonstrate a multifocal disease, generally consisting of a dominant tumor referred to as an index tumor and 1 or multiple separate additional tumors. Usually, the index tumor is considered to be biologically most significant in this setting.

It is well known that the multifocal tumors frequently demonstrate histologic heterogeneity and may have different Gleason grades in different foci. Index tumor usually drives the grade and stage in this type of case.\(^35\) For example, if the index tumor is 4 + 4 = 8 with smaller nodules demonstrating Gleason score 3 + 4 = 7 and 3 + 3 = 6, overall the tumor should be graded as 4 + 4 = 8, with a comment about the presence of smaller nodules of tumor with Gleason score of 3 + 4 and 3 + 3. Similarly, when 2 codominant tumors exist, with 1 of lower grade 2 + 2 = 4 in the transition zone and the other of grade 4 + 4 = 8 in the peripheral zone, it is important not to describe the overall grade as 4 + 2 = 6 or 2 + 4 = 6 but rather to call it 4 + 4 = 8, with a comment describing a second codominant nodule. Rarely, one may have a nondominant nodule of higher grade. Overall grading of the case in this setting is somewhat controversial. However, again in this setting, it is important to describe the grades of both nodules, as the grade of the nondominant nodule may still drive the outcome. In our overall experience, this approach also helps to better explain the correlation between biopsy and radical prostatectomy specimens.

**The Impact of the 2005 International Society of Urological Pathology Consensus Gleason Grading**

Billis et al\(^9\) studied the ability of the conventional and modified Gleason score in preoperative needle biopsies to predict recurrence after radical prostatectomy. Modified, but not conventional, Gleason score predicted PSA failure outcome better in the cancers diagnosed in the same biopsy specimens. This article is one of the first to provide important evidence-based feedback about the clinical impact of the 2005 revised Gleason grading system.

**Challenges.**—The Gleason grading system is certainly not without limitations. The very concept that the histologic patterns represent a continuum ensures that gray zones will be encountered and hence, also, a problem of reproducibility. This limitation has been documented by several studies for both interobserver and intraobserver variability.

A major limitation of the system is poor agreement between biopsy and prostatectomy Gleason score.\(^37-39\)

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**Table 2. Gleason Grading of Unusual Subtypes and Patterns of Prostate Cancer**

<table>
<thead>
<tr>
<th>Histologic Type or Pattern</th>
<th>Gleason Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foamy gland pattern</td>
<td>Graded by underlying architecture</td>
</tr>
<tr>
<td>Pseudohyperplastic tissue</td>
<td>3</td>
</tr>
<tr>
<td>Atrophic tissue</td>
<td>3</td>
</tr>
<tr>
<td>Large duct carcinoma</td>
<td>4; with evidence of necrosis, 5</td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Adenosquamous and squamous carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Glomeruloid pattern</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Collagenous micronodules</td>
<td>Usually 3, graded by underlying architecture (subtract collagenous micronodules from analysis)</td>
</tr>
<tr>
<td>Mucinous (colloid) carcinoma</td>
<td>3 or 4, graded by underlying architecture</td>
</tr>
</tbody>
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Only in about one-third of cases does such agreement typically exist, with another one-third having a prostatectomy score that is \( \pm 1 \) the score of a needle biopsy. For the remaining one-third, the difference is 2 or more. Factors that contribute to such discrepancies include tumor heterogeneity, sampling errors, intervariability and intra-variability, and interpretive errors. Surgical pathologists typically have a tendency to underestimate the biopsy specimens. Recent studies suggest that this discrepancy is reduced when more extended biopsy approach protocols are adopted.

**References**


