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Prostate cancer grading: a decade after the 2005 modified system

Jonathan I Epstein[1,2,3]

[1]Department of Pathology, The Johns Hopkins Medical Institution, Baltimore, MD, USA; [2]Department Urology, The Johns Hopkins Medical Institution, Baltimore, MD, USA and [3]Department of Oncology, The Johns Hopkins Medical Institution, Baltimore, MD, USA

This review article will cover the evolution of grading of prostate cancer from the original Gleason system in the 1960–1970s to a more patient-centric grading system proposed in 2013 from a group at Johns Hopkins Hospital, validated in 2014 by a large multi-institutional study, and subsequently accepted by the World Health Organization (WHO), College of American Pathology (CAP), and the AJCC TNM system. Covered topics include: (1) historical background; (2) 2005 and 2014 International Society of Urological Pathology Grading Conferences; (3) Description of Gleason patterns; (4) new approaches to display Gleason grades; (5) grading variants and variations of acinar adenocarcinoma; (6) reporting rules for Gleason grading reporting secondary patterns of higher grade when present to a limited extent; (7) reporting secondary patterns of lower grade when present to a limited extent; (8) reporting percentage pattern 4; (9) general applications of the Gleason grading system; (10) needle biopsy with different cores showing different grades; (11) radical prostatectomy specimens with separate tumor nodules; and (12) a new grading system for prostate cancer.
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Historical background

Donald F Gleason in 1966 created a unique grading system for prostatic carcinoma based solely on the architectural pattern of the tumor.[1,2] Another innovative aspect of this system was, rather than assigning the worst grade as the grade of the carcinoma, the grade was defined as the sum of the two most common grade patterns and reported as the Gleason score. The original description of this system was based on a study of 270 patients from the Minneapolis Veterans Administration Hospital.

Initially, Gleason intended to classify carcinomas into four patterns, but a small group of distinctive tumors (clear cell) was observed and they were placed in a separate fifth category (pattern 4). Certain aspects of the original Gleason system would be interpreted differently in today's practice. The cribriform pattern described as a component of Gleason's original patterns 2 and 3 would today typically be considered higher grade. Individual cells listed under Gleason's original pattern 3 would also be currently assigned a higher grade. Pattern 4 has become significantly expanded beyond Gleason's original description of tumors with clear cytoplasm that resembled renal cell carcinoma.

By 1974, Gleason and the Veterans Administration Cooperative Urological Research Group expanded their study 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%; 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 ~150%, as 50% of the tumors showed at least two different patterns.

In 1977, Gleason provided additional comments concerning the application of the Gleason system.[3] 'Grading is performed under low magnification (x40–100).' 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.' An

Correspondence: Dr JI Epstein, MD, Department of Pathology, The Johns Hopkins Medical Institution, 401N Broadway Street, Weinberg Building, Room 2242, Baltimore, MD 21231, USA.
E-mail: jepstein@jhmi.edu
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iconic schematic diagram was drawn by Gleason that achieved widespread popularity (Figure 1).

In 2000, an influential editorial was written that Gleason scores 2–4 should not be assigned to cancer on needle biopsy for several reasons: (1) poor reproducibility even among experts; (2) poor correlation with prostatectomy grade with almost all cases showing higher grade at resection; and (3) a diagnosis of Gleason scores 3 and 4 may misguide clinicians and patients into believing that the patient has an indolent tumor.[4] In a prior study from Johns Hopkins, we reported that only 1.6% of biopsies from other institutions were graded as Gleason scores 2–4 in 2002–2003, compared with 22.3% in 1994.[5] Consequently, most of the lesions that appear to be very low grade on needle biopsies are currently diagnosed by urological pathologists as Gleason score 3+3 = 6.

2005 and 2014 International Society of Urological Pathology grading conferences

A group of urological pathologists convened at the 2005 United States and Canadian Academy meeting in San Antonio in an attempt to achieve consensus in controversial areas relating to the Gleason grading system.[6] The aim of the meeting was to achieve consensus among leading urological pathologists in specific areas of Gleason grading, including areas where there was either a lack of data or scant information as to the optimal method of grading. Over 70 urological pathologists from around the world were invited to attend, with most attending. In 2014, over 80 expert pathologists, urologists, medical oncologists, and radiation oncologists attended a meeting in Chicago to: (1) resolve issues that lacked consensus in the earlier meeting; (2) deal with issues that were not discussed in the 2005 meeting; and (3) update guidelines based on interim research.[7]

Gleason patterns

Gleason Score 1+1 = 2

Gleason score of 1+1 = 2 is a grade that should not be diagnosed regardless of the type of specimen, with extremely rare exception. Most cases that were diagnosed as Gleason score 1+1 = 2 in the era of Gleason would today be referred to as adenosis (atypical adenomatous hyperplasia).

Gleason Scores 3 and 4

These low-grade tumor scores are occasionally assigned on transurethral resection specimens (TURPs) and in multifocal low-grade tumors within radical prostatectomy (RP) specimens. It is now accepted that Gleason scores 2–4 should not be assigned to cancer on needle biopsy for several reasons as described above.

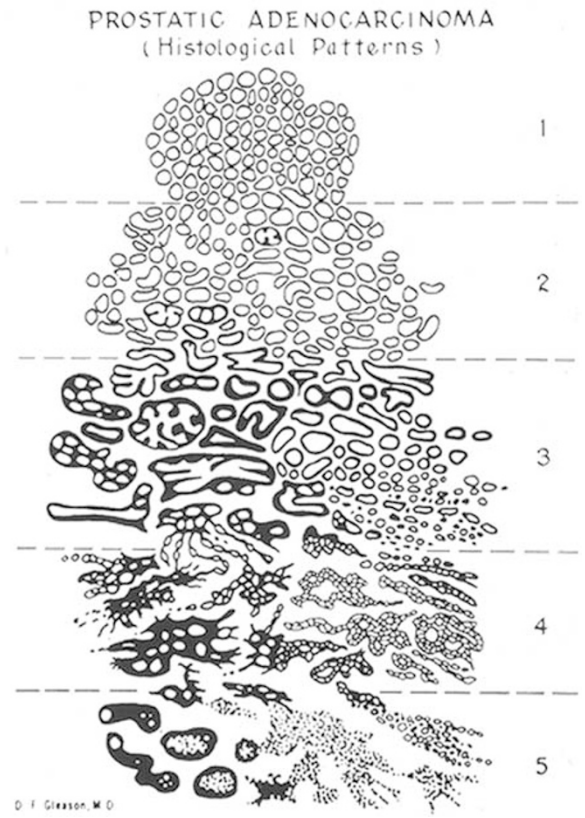


Figure 1 Original Gleason schematic grading diagram.

Gleason Pattern 3

A departure from the original Gleason classification system is that 'individual cells' would not be allowed within Gleason pattern 3. Rather, Gleason pattern 3 cancer consists of variably sized individual glands. A further area of divergence from the original Gleason system is the controversial area of cribriform Gleason pattern 3. Within Gleason's original illustrations of his cribriform pattern 3, he depicts large, cribriform glands that the consensus panel would uniformly diagnose as cribriform pattern 4. Before 2005, it was the routine to grade large cribriform glands as pattern 3 (Figure 2).[8,9] In 2005, the consensus required extremely stringent criteria for the diagnosis of cribriform pattern 3, with remaining cribriform patterns typically falling into Gleason pattern 4. The 2005 criteria used to diagnose cribriform pattern 3 were rounded, well-circumscribed glands of the same size of normal glands with uniform round evenly distributed lumina. When various images were shown to the consensus panel of potential candidates for cribriform Gleason pattern 3, almost none of them met the criteria based on subtle features, such as slight irregularities of the outer border of the cribriform glands. Subsequent to the 2005 meeting, this author reviewed 3590

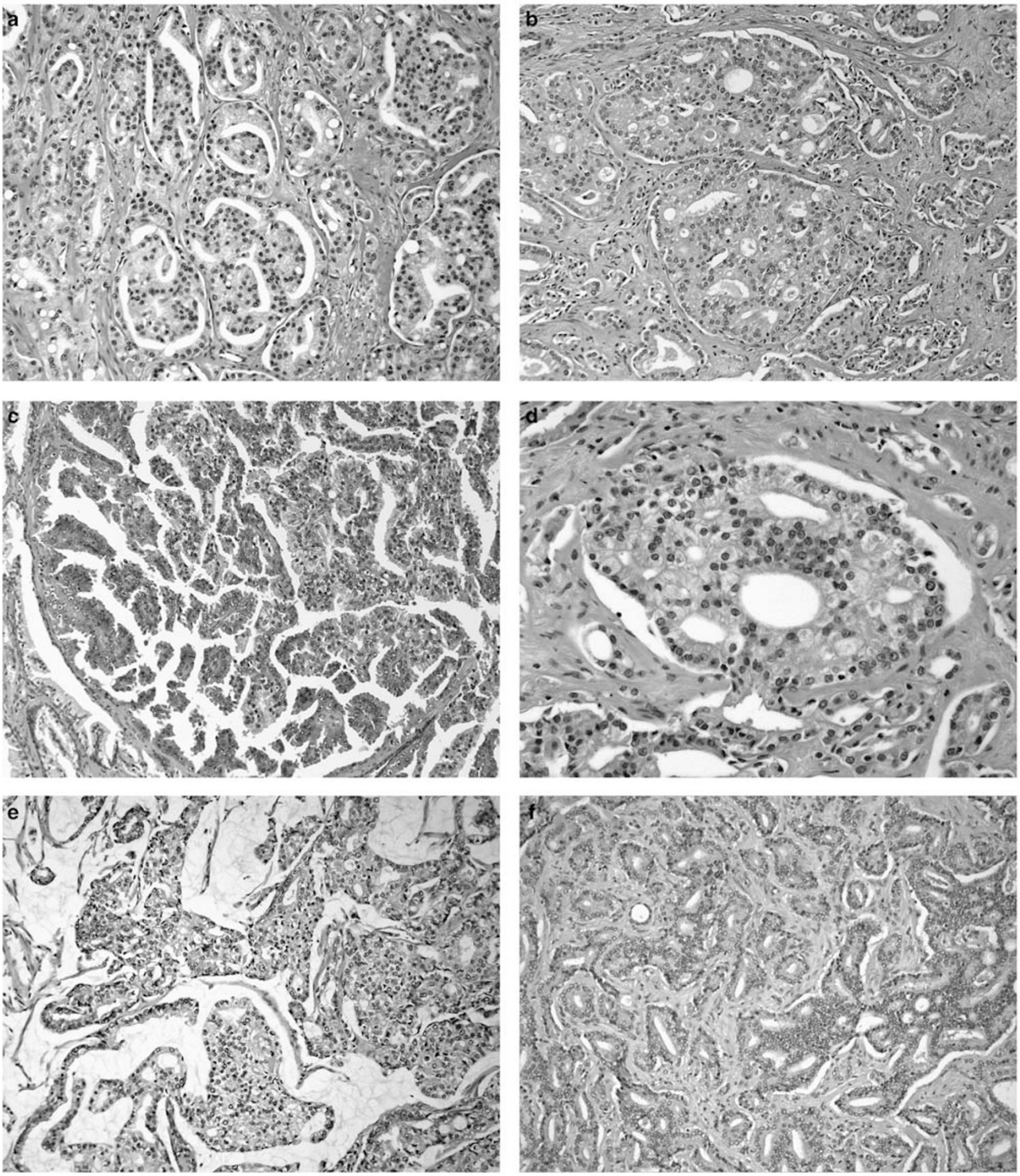


Figure 2 Images graded from several large academic prostate centers before 2005 as Gleason score 3+3 = 6 with lymph node metastases. Currently, all these images would be graded as having a component of Gleason pattern 4. (**a**) Glomeruloid glands transitioning to small cribriform glands. Original magnification, 20x. (**b**) Medium to large irregular cribriform glands. Original magnification, 20x. (**c**) Papillary prostatic ductal adenocarcinoma. Original magnification, 20x. (**d**) Small more regular cribriform gland. Original magnification, 40x. (**e**) Cribriform glands floating within mucin. Original magnification, 10x. (**f**) Medium-sized irregular cribriform glands (modified from Ross *et al*[9]). Original magnification, 10x.

consecutive prostate cancers sent to this author over 7 months; 30 needle biopsy cases were selected that possibly represented cribriform Gleason pattern 3 cancer.[10] Thirty-six digital images were taken and sent to 10 experts in prostate pathology with a consensus defined when at least 7/10 experts agreed

on the grade. Even in this highly selected set of images thought to be the best candidates for cribriform pattern 3 from a busy consult service, most experts interpreted the cribriform patterns as pattern 4. Conceptually, one would expect the change in grade from patterns 3 to 4 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.

The only reason why cribriform pattern 3 even exists is because of the original Gleason schematic diagram. Gleason never specifically published the prognostic difference between what he called cribriform Gleason pattern 3 compared with Gleason pattern 4. Many of Gleason's cribriform Gleason pattern 3 cancers may not even have been infiltrating carcinomas due to the lack of availability of immunohistochemistry for basal cell markers. Today we might have diagnosed them either as cribriform high-grade PIN or intraductal carcinoma of the prostate (concepts not present in Gleason's era). Subsequently, there have been several studies demonstrating the adverse prognosis associated with cribriform glands.[11–13] Based on all the above data, it was accepted in the 2014 grading conference that all cribriform cancer should be interpreted as Gleason pattern 4 and not pattern 3.

Gleason Pattern 4

In 2005 it was accepted that ill-defined glands with poorly formed glandular lumina also warrant the diagnosis of Gleason pattern 4. Only a cluster of such glands, where a tangential section of Gleason pattern 3 glands cannot account for the histology, would be acceptable as Gleason pattern 4. In most cases, ill-defined glands with poorly formed glandular lumina are accompanied by fused glands. Very small, well-formed glands still are within the spectrum of Gleason pattern 3.

Glomeruloid Structures

Glomeruloid glands in prostatic adenocarcinoma are characterized by dilated glands containing intraluminal cribriform structures with a single point of attachment, resembling a renal glomerulus (Figure 2a).[14] On prostate biopsy, glomeruloid glands are exclusively associated with carcinoma and not associated with benign mimickers. A study of ours subsequent to the consensus conference indicated that glomerulations were overwhelmingly associated with concurrent Gleason pattern 4 or higher-grade carcinoma.[15] In several cases, transition could be seen among small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer. Glomerulations represent an early stage of cribriform pattern 4 cancer and are best graded as Gleason pattern 4.

Gleason Pattern 5

Gleason pattern 5 consists of individual cells, cords of cells, and sheets of tumor. Although typically one sees comedonecrosis with solid nests, occasionally one can see necrosis with cribriform masses that should be graded as Gleason pattern 5. One must be stringent as to the definition of comedonecrosis, requiring intraluminal necrotic cells and/or karyorrhexis, especially in the setting of cribriform glands. We have noted in two studies using different patient populations the tendency for pathologists to undergrade Gleason pattern 5 in almost 50% of cases sent for a second opinion at the request of the patient of urologist where this author has diagnosed Gleason pattern 5.[16,17] Pattern 5 was missed more frequently when it was not the primary pattern.

New approaches to display Gleason grades

For the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs, a revised schematic diagram was created with the assistance of David Grignon at the Indiana University School of

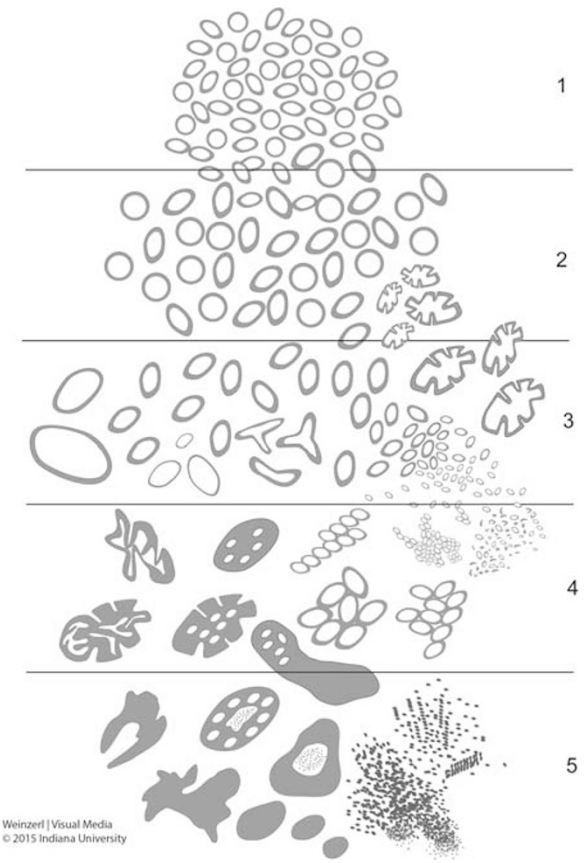
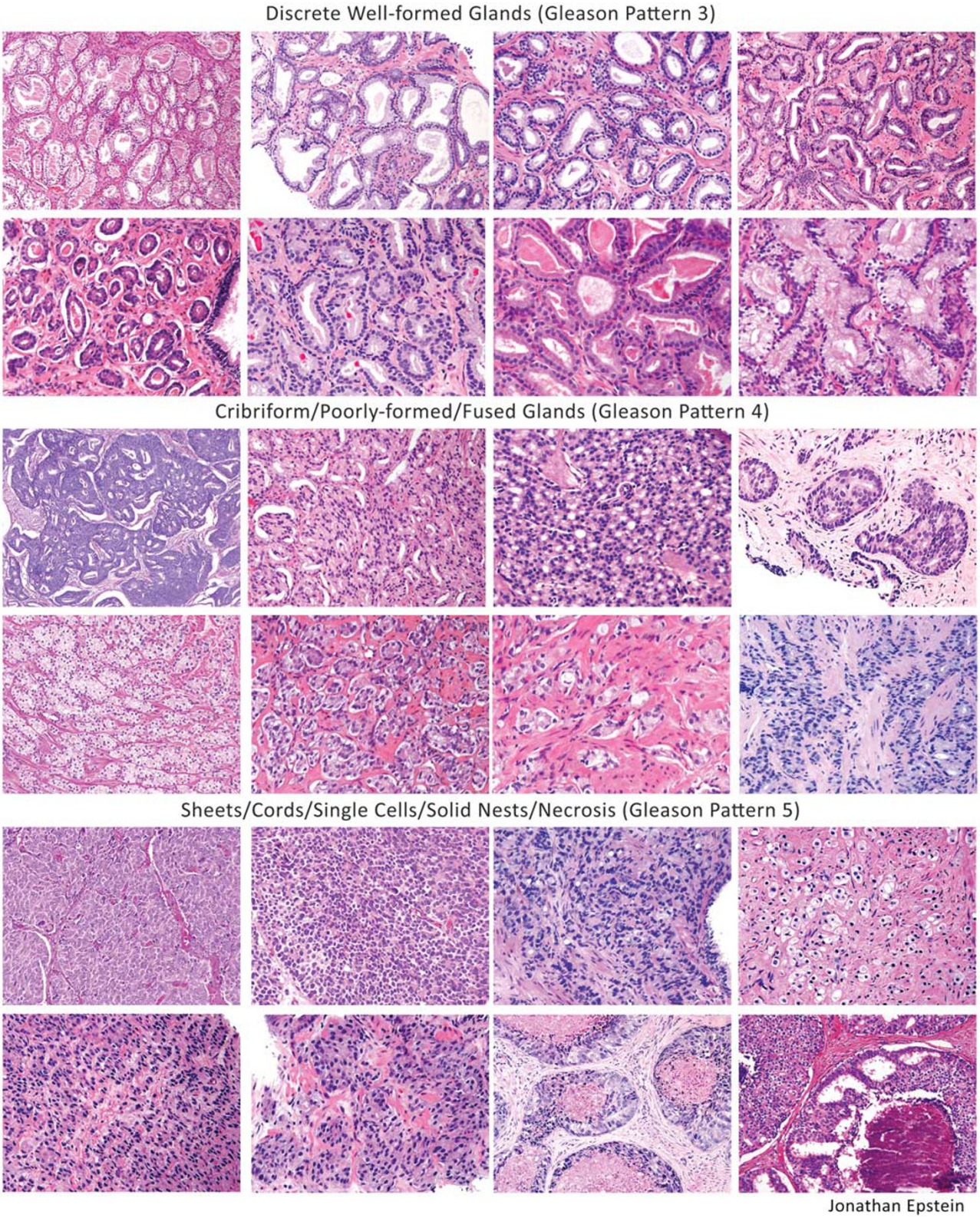


Figure 3 Current modified schematic Gleason diagram (courtesy of David Grignon, Indiana University Medical Center).

Medicine (Figure 3). Advantages of the new schematic diagram is that it depicts variants of Gleason pattern 3 including pseudohyperplastic, atrophic, and branching prostate cancer.

Another tool that can aid in the practical grading of prostate cancer is a photomontage that shows multiple photomicrographs of various morphologies, both classic and difficult to grade, covering Gleason patterns



3–5. It does not cover Gleason patterns 1 and 2, as in practice these are no longer in use (Figure 4).[18]

Grading variants and variations of acinar adenocarcinoma

A general rule that applies to variants, with the exception of small-cell carcinoma, is that variants should be graded, just the same as usual prostate adenocarcinoma, by evaluating the underlying architectural pattern.

Vacuoles

Adenocarcinomas of the prostate may contain clear vacuoles and these should be distinguished from true signet-ring carcinomas which contain mucin. Whereas vacuoles in adenocarcinoma of the prostate are not uncommon, true mucin-positive signet-ring cell carcinomas of prostate are exceedingly rare with only a handful of *bona fide* cases reported in the literature. Vacuoles may distort the architecture and it is controversial as to what grade should be assigned. Gleason's only mention of vacuoles

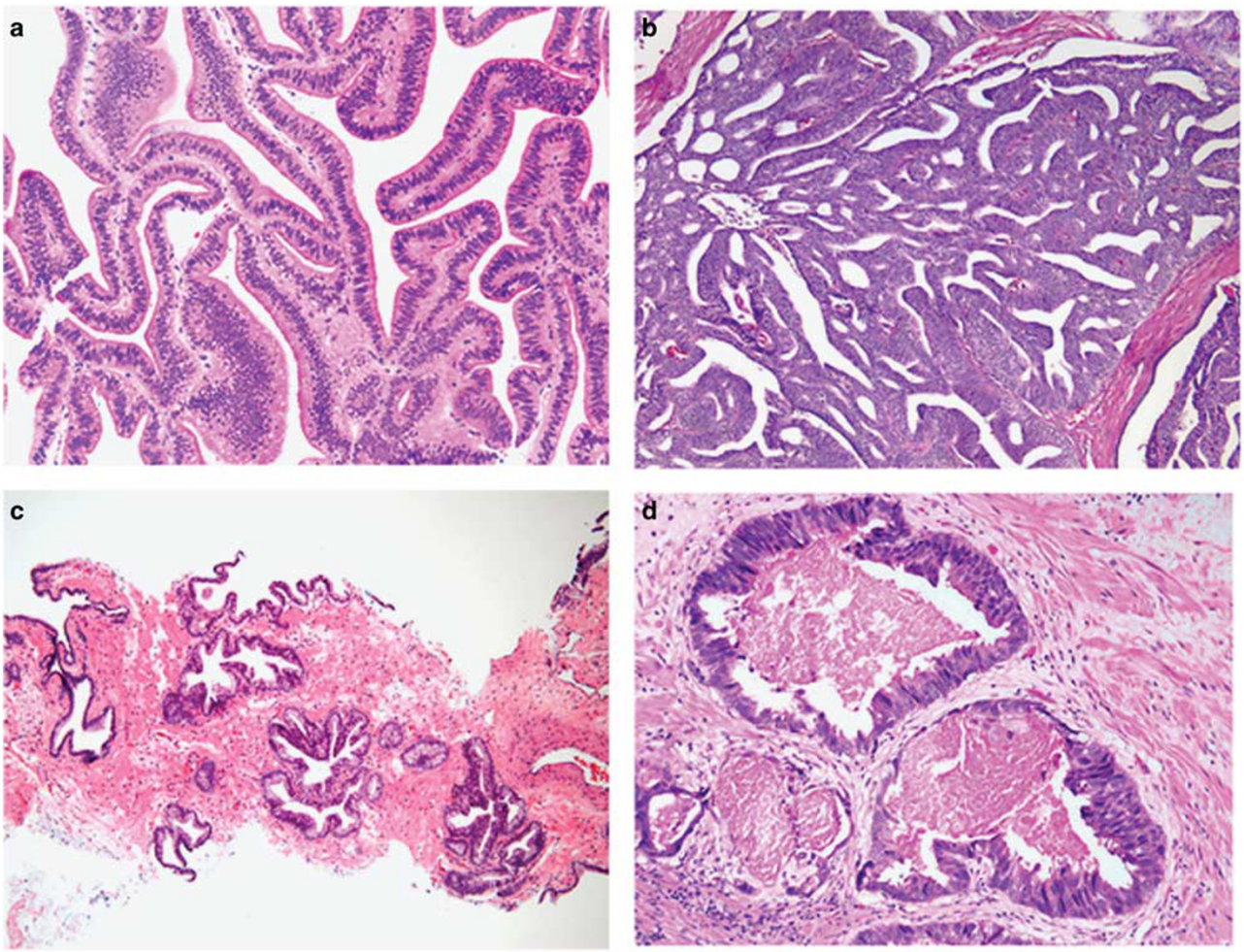


Figure 5 Prostatic ductal adenocarcinoma. (**a**) Papillary, Gleason pattern 4, original magnification, 20x. (**b**) Cribriform, Gleason pattern 4, original magnification, 10x. (**c**) PIN-like, Gleason pattern 3, original magnification, 10x. and (**d**) with necrosis, Gleason pattern 5, original magnification, 20x.

Figure 4 From left to right: (from reference 18). 1st Row: Closely packed uniform-sized and -shaped large glands. Large variably sized and shaped glands, some with infolding. Uniform medium-sized glands. Variably sized glands. 2nd Row: Occasional tangentially sectioned glands among well-formed small glands. Occasional tangentially sectioned glands among well-formed glands with open lumina. Back-to-back discrete glands. Branching glands. 3rd Row: Large irregular cribriform glands with well-formed lumina. Irregular cribriform glands with slit-like lumina, glomeruloid structures, and fused glands. Irregular cribriform glands with small round lumina. Small round cribriform glands. 4th Row: Poorly formed glands with peripherally arranged nuclei. Small poorly formed glands. Small poorly formed glands. Fused poorly formed glands. 5th Row: Sheets of cancer. Sheets of cancer with rosette formation. Small nests and cords of tumor with scattered clear vacuoles. Individual cells. 6th Row: Nests and cords of cells with only vague attempt at lumina formation. Solid nests of cancer. Solid nests with comedonecrosis. Cribriform glands with central necrosis.

described them as signet cells under pattern 5 tumor. Although typically vacuoles are seen within Gleason pattern 4 cancer, it may be seen within Gleason pattern 5 and even Gleason pattern 3 tumors. Tumors should be graded, as if the vacuoles were not present, by only evaluating the underlying architectural pattern.

Foamy Gland Carcinoma

In an analogous manner to handling cancers with vacuoles, in grading foamy gland carcinomas one should ignore the foamy cytoplasm and grade the tumor solely based on the underlying architecture. 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.[19,20]

Ductal Adenocarcinoma

Ductal adenocarcinomas of the prostate most commonly are composed of either papillary fronds or cribriform structures.[21] Ductal adenocarcinomas are recognized as being aggressive tumors with most studies showing comparable behavior to acinar cancer with a Gleason score 4+4 = 8. Papillary and cribriform and ductal adenocarcinomas should be graded as Gleason score 4+4 = 8, while retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathological findings (Figure 5). This can be achieved by diagnosing such a tumor as 'prostatic ductal adenocarcinoma (Gleason score 4+4 = 8).' In cases with mixed ductal and acinar patterns, the ductal patterns should be assigned Gleason pattern 4. The only exceptions to grading ductal adenocarcinoma as Gleason pattern 4 are: (1) PIN-like ductal adenocarcinoma; and (2) ductal adenocarcinoma with comedonecrosis. PIN-like ductal adenocarcinoma consists of individual glands lined by tall pseudostratified columnar cells resembling high-grade prostatic intraepithelial neoplasia.[22] Its prognosis appears comparable to Gleason pattern 3. Although it has not been specifically studied, ductal adenocarcinoma with comedonecrosis is graded as Gleason pattern 5.

Colloid (Mucinous) Carcinoma

The majority of cases with colloid carcinoma consist of irregular cribriform glands floating within a mucinous matrix.[23,24] These cases would be scored Gleason score 4+4 = 8 (Figure 2e). The excellent prognosis of mucinous carcinomas in two large studies of mucinous carcinoma at RP supports grading mucinous prostate carcinomas based on the underlying architectural pattern rather than assuming that all of these tumors are aggressive.[7,25,26]

Small-Cell Carcinoma

Small-cell carcinoma of the prostate has unique histological, immunohistochemical, and clinical features.[27] Comparable to its more common pulmonary counterpart, chemotherapy is the mainstay of therapy for prostatic small-cell carcinomas. These clinicopathologic features differ from those associated with Gleason pattern 5 prostatic acinar carcinoma, such that small-cell carcinoma should not be assigned a Gleason grade.

Mucinous Fibroplasia (Collagenous Micronodules)

The delicate ingrowth of fibrous tissue seen with mucinous fibroplasia can result in glands appearing to be fused resembling cribriform structures, although the underlying architecture is really that of individual discrete rounded glands invested by loose collagen. The tumor should be graded on the underlying glandular architecture, whereby the majority are graded as Gleason score 3+3 = 6.[14] Only when there are distinct cribriform glands in areas of mucinous fibroplasias does this author diagnose Gleason pattern 4.

Pseudohyperplastic Adenocarcinoma

Uncommonly, adenocarcinomas of the prostate share some architectural features with benign glands, including larger size, branching, and papillary infolding. These cancers should be graded as Gleason score 3+3 = 6 with pseudohyperplastic features.[28,29] This convention is in large part based on the recognition that they are most often accompanied by more ordinary Gleason score 3+3 = 6 adenocarcinoma.

Post-Treatment Cancer: Hormone Therapy and Radiation Therapy

If histologically ordinary prostate cancer is seen, which resembles non-treated cancer, the diagnosis of 'Cancer without significant treatment affect' is given and a Gleason grade is assigned. If cancer is present, yet shows treatment affect, then the diagnosis is 'Cancer with significant treatment affect' and a grade is not assigned.

Reporting rules for Gleason grading reporting secondary patterns of higher grade when present to a limited extent

High-grade tumor of any quantity on needle biopsy, as long as it was identified at low to medium magnification (see General Applications of the Gleason Grading System) should be included within the Gleason score. Any amount of high-grade tumor sampled on needle biopsy most likely indicates a

more significant amount of high-grade tumor within the prostate due to the correlation of grade and volume and the problems inherent with needle biopsy sampling. Consequently, a needle biopsy that is entirely involved by cancer with 98% Gleason pattern 3 and 2% Gleason pattern 4 would be diagnosed as Gleason score 3+4 = 7.

In RP specimens with the analogous situation of a tumor nodule having 98% Gleason pattern 3 and 2% pattern 4, the current recommendation is to grade these foci in an analogous manner to that done on needle biopsy and interpret the case as Gleason score 3+4 = 7 and record the percentage of pattern 4.

The prognostic significance of minor high-grade patterns in RP specimens were first analyzed in 2000 by Pan *et al*,[30] who used the term *tertiary grade pattern*.[30] The original Gleason grading system did not account for more than two patterns. At the 2014 meeting, a review of the literature was presented summarizing studies on tertiary patterns where at least 50 RP specimens were analyzed. Of the eight articles that fulfilled this criteria, seven reported that tertiary grade patterns adversely affected prognosis.[31–38] A conflicting study by Isbarn *et al*[39] found that tertiary patterns < 5% was not associated with adverse prognostic findings at RP, although a potentially confounding factor in this study was the tertiary lower patterns (ie Gleason score 3+4 = 7 with tertiary pattern 2) was considered tertiary grade patterns, whereas most other studies evaluated only tertiary higher-grade patterns.[39] Based on these data, there was a consensus that tertiary grade patterns as an important prognostic factor. Subsequent to the 2014 meeting, there has been another large study on this topic further supporting the adverse prognostic significance of higher tertiary grade patterns.[40]

One of the confusing issues with the term *tertiary grade pattern* as it has been used in the past and still persists today is the use of the term *tertiary* for RP tumors sometime referred to cases with only two grade patterns, where the secondary higher-grade pattern was of very limited extent. For example, some pathologists grade RPs with 3+3 = 6 and < 5% pattern 4 as *3+3 = 6 with tertiary 4*, to contrast with 5–50% pattern 4, which they grade as *3+4 = 7*.[36] Using *tertiary* in this context, despite there not being three different grade patterns, accounts for the less adverse prognosis with very limited pattern 4 relative to greater amounts of pattern 4. With the adoption of reporting percentage Gleason pattern 4 in Gleason 3+4 = 7 as noted below, cases formerly reported as *Gleason score 3+3 = 6 with tertiary pattern 4* will now be recorded as *Gleason score 3 +4 = 7 with < 5% pattern 4.* Similarly, some pathologists graded tumors composed of > 95% Gleason pattern 4 and < 5% Gleason pattern 5 as *Gleason score 4+4 = 8 with tertiary pattern 5*.[36] Recent studies have shown that presence of limited (< 5%) Gleason pattern 5 in the context of Gleason score 4+4 = 8 imparts a poor prognosis equivalent to Gleason scores 9–10.[41] Although not discussed at the 2014 Consensus Conference, a collaborative study of 169 RPs performed at the Johns Hopkins Hospital and University of Pittsburgh has shown that the presence of < 5% Gleason pattern 5 in the context of Gleason score 4+4 = 8 results in a biochemical risk-free survival that is equivalent to Gleason scores 9 and 10.[41] At the 2014 Consensus Conference, there was agreement that the grading rule proposed in the 2005 Consensus Conference that on needle biopsies, *tertiary* is not used and rather the most common and highest grade patterns are summed together as the Gleason score.[6] For example, in a needle biopsy core with 70% Gleason pattern 3, 25% pattern 4 and 5% pattern 5, the tumor would be graded as *Gleason score 3+5 = 8.*

Another controversial aspect of the term *tertiary grade patterns* is whether there is an upper limit to the amount of Gleason pattern 5 that can still be considered as a tertiary pattern. The first article to investigate the prognostic significance of tertiary patterns from the Johns Hopkins Hospital referred to tertiary pattern 5 as 'very limited amounts of pattern 5'.[30] Subsequent works on this topic from the same institution more precisely restricted the use of 'tertiary pattern' to prostate adenocarcinoma at RP with < 5% pattern 5.[36] There is, however, a lack of consensus on whether there should be a minimum cutoff for the amount of percent pattern 5 in cases when pattern 5 is the third most common Gleason pattern. Choy *et al*[42] and Lucca *et al*[40] required < 5% Gleason pattern 5 for it to be considered tertiary pattern 5, but Adam *et al*[33] only required that pattern 5 be the third most common pattern, regardless of percentage. An argument for restricting the amount of percent pattern 5 to be designated as 'tertiary pattern 5' is that one could have, for example, an RP tumor nodule with 50% pattern 3, 30% pattern 4, and 20% pattern 5. With no limits on how much pattern 5 is allowed for a tertiary pattern, this tumor could be graded as *Gleason score 3+4 = 7 with tertiary pattern 5. Gleason score 3+4 = 7 with tertiary pattern 5* is typically considered only *Gleason score 3+4 = 7* for treatment purposes. A Gleason score 3+4 = 7 at RP has almost a 90% cure rate, which would give the misleading impression of a very favorable tumor, given that the tumor had 30% pattern 4 and 20% pattern 5. At the 2014 Consensus Meeting, 83% of participants favored the term of *minor high-grade pattern* over *tertiary grade pattern*. 'Minor' indicates that the high-grade pattern should be limited in extent, and not just the third most common pattern. The only cutoff that has been used in the literature with evidence-based data correlating with outcome has been < 5% for tertiary pattern 5. The term *tertiary* or *minor high-grade pattern* should only be used in the logical scenario when there are 3 grade patterns, such as with *3+4 = 7* or *4+3 = 7* with < 5% Gleason pattern 5 at RP.

Minor (tertiary) high-grade patterns do not change the Grade Groups (ie Gleason score 3+4 = 7 (Grade Group 2) with minor (tertiary) pattern 5). If Grade

Groups 1–5 eventually were to replace Gleason scores 2–10, the 2014 Consensus Conference suggested options how to incorporate tertiary patterns with Grade Groups. Suggestions included, for example, *Grade Group 2 with minor high-grade pattern* or *Grade Group 2*$^{+}$.[43]

In summary, the term 'tertiary' should only be used when there are three patterns with a very minor component of higher grade. On an RP, if pattern 5 is $<5\%$ and the third most common pattern then it should be reported as 3+4 = 7 with minor high-grade (tertiary) pattern 5. If pattern 5 is $>5\%$ then it is the secondary pattern (ie. 3+5 = 8). On needle biopsy, if pattern 5 is the 3rd most common pattern, regardless of percentage, then it is included in the Gleason score (ie 3+5 = 8) (most common+highest grade). Only use the term 'minor high-grade (tertiary) pattern' for Gleason score 3+4 = 7 with $<5\%$ pattern 5 or Gleason score 4+3 = 7 with $<5\%$ pattern 5 on RP.[43]

Reporting secondary patterns of lower grade when present to a limited extent

In the setting of high-grade cancer one should ignore lower-grade patterns if they occupy $<5\%$ of the area of the tumor. For example, a needle biopsy core that is 100% involved by cancer, with 98% Gleason pattern 4 and 2% Gleason pattern 3 would be diagnosed as Gleason score 4+4 = 8. These cases with extensive pattern 4 cancer, where a significant amount of tumor is available for examination, should be considered as high grade (Gleason score ≥ 8). At the other extreme, one can occasionally see small foci of Gleason pattern 4 on needle biopsy with a few glands of pattern 3. In the setting of very limited cancer on needle biopsy, the few glands of pattern 3 would typically occupy over 5% of the area of the tumor focus, and one would grade these tumors as Gleason score 4+3 = 7. The same 5% cutoff rule for excluding lower-grade cancer also applies for TURPs and RP specimens, which in most cases would relate to extensive cancer with $>95\%$ Gleason pattern 4 tumor.

Reporting percentage pattern 4

A major new recommendation that came from the 2014 Consensus Conference, subsequently supported by the 2016 WHO, was to report percent pattern 4 with Gleason score 7 in both needle biopsies and RP specimens.[43,44] This recommendation was supported by 75% of the conference pathologists and 100% of the clinicians, with an overall consensus of 79%.

The major advantage to report percent pattern 4 is for patient care.[43] Currently, active surveillance is typically restricted for men with Gleason score 3 +3 = 6. However, some urologists could consider this strategy for men with Gleason score 3+4 = 7 with limited percent pattern 4, especially in older men, or with increased comorbidity, or where cancer appears relatively small based on the extent of cancer on biopsy and/or imaging studies.[45,46] Recording the percent pattern 4 would also potentially be helpful in cases that are borderline between Gleason score 3 +4 = 7 or Gleason score 4+3 = 7, as there are different radiation therapy approaches for Gleason score 3 +4 = 7 (Grade Group 2) *versus* 4+3 = 7 (Grade Group 3).[47] By reporting the case as 3+4 = 7 (approaching 50% pattern 4) or 4+3 = 7 (60% pattern 4), the borderline nature of the case would be evident and clinicians could use other factors for guiding therapy.

Although recording the percent pattern 4 introduces an extra step in the evaluation of prostate specimens, it is relatively minimal. Pathologists have to decide what part of the tumor is pattern 4 or 3 when assigning a Gleason score so that estimating percent pattern 4 is not that much extra effort. Assessing the percent Gleason pattern 4 is relatively reproducible, with substantial agreement within $\pm 10\%$ in cases.[48] Cases where patterns 3 and 4 are intermingled are more difficult to assess for percent pattern 4.[49] We have shown that there is only moderate interobserver agreement for assessing the percent pattern 4 with $<10\%$ involvement of the core by cancer, as a few glands of a given pattern can markedly affect the percent of Gleason pattern 4.[48] As a result, some experts do not record percent pattern 4 in small foci of Gleason score 7 tumors on needle biopsy, although other experts routinely reports percent pattern 4 for call cases of Gleason score regardless of tumor extent.

It was the majority opinion of the 2014 Consensus Meeting that the method by which the percent pattern 4 should be recorded remains optional, both for the core and case level. One option is to record the percentages as follows: <5, 10, 20, 30, and 40%, approaching 50% for Gleason score 3+4 = 7, and 60, 70, 80 and 90% for Gleason score 4+3 = 7, which is the personal preference of the current author. Another alternative would be $<5\%$, 5–$<25\%$, 25–$<50\%$, 50–$<75\%$, and 75–90%. Given the inherent large sampling error with needle biopsies, it does not make sense to record more precise percentages (ie 13%). Although not discussed at the 2014 Consensus meeting, some experts do not record percent of Gleason pattern 4 if any other core has Gleason score 9 or 10 (Grade Group 5), as the latter grades drive therapy and prognosis.[43] Although not discussed at the 2014 Consensus meeting, it is the personal preference of this author and several other urological pathology experts to record percent pattern 4 for those cores with Gleason score 7 if the highest core is Gleason score 4+4 = 8, as it can still provide useful information for the clinician.[43] For example, if in addition to a core with Gleason score 4+4 = 8, there are other cores with 4+3 = 7, with 80–90% pattern 4 that informs the clinician that the overall tumor grade is closer to a Gleason score 8.

Subsequent to the 2014 Consensus Conference, studies have demonstrated that increasing percent pattern 4 at RP correlates with an increased risk of biochemical recurrence after RP.[42,50,51] There have also been several publications showing that percent pattern 4 on needle biopsy can improve prediction of upgrading at RP and of adverse findings at RP and biochemical recurrence after RP.[52,53]

General applications of the Gleason grading system

As described by Gleason, the initial grading of prostate carcinoma should be performed at low magnification using a x4 or x10 lens. After one assesses the case at scanning magnification, one may proceed to use the x20 lens to verify the grade. For example, at low magnification one may have the impression of fused glands or necrosis, but may require higher magnification at x20 to confirm its presence. However, one should not initially use the x20 or x40 objectives to look for rare fused glands or a few individual cells seen only at higher power, which would lead to an overdiagnosis of Gleason pattern 4 or 5, respectively (Figure 6). If the tumor is borderline between lower- and higher-grade cancer, I assign the lower grade so as to not result in overtreatment. In cores with borderline grade, additional levels are often helpful to clarify the grade.

Needle biopsy with different cores showing different grades

A controversial area discussed at the 2014 Consensus conference is how to handle cases where multiple cores with different Gleason scores are positive for cancer. Should the overall grade be the core with the highest grade or does one assign the grade by mentally adding all the cancer together as if it was one long core? Whether the highest grade per core or the overall score is used impacts a significant number of cases.[54] Most studies show that the highest Gleason score on a given core correlates better with stage and Gleason score at RP than the average or most frequent grade among the cores.[55–58] Fewer studies show no significant difference in biochemical recurrence and prostate cancer death whether recording as the case grade either the higher Gleason score or the average Gleason score.[59,60] All of the commonly used tables (ie Partin tables) and nomograms (Kattan nomograms) to predict prognosis and stage have used the highest core grade in the case.[61,62] In general, clinicians use the highest Gleason score per part in a case for prognosis and therapeutic purposes, which was also the viewpoint of clinicians attending the 2014 Consensus Conference. The problem with using the average grade is that when there are multiple cores with different grades, it can be difficult and subjective to determine if one is dealing with two separate tumors with differing grades *versus* a single tumor with grade heterogeneity. At the 2014 Consensus Conference, 65% of pathologists and clinicians stated that the highest grade core should be used for clinical decision making and 10% favored using the global grade for the entire case (25% said either option was acceptable). Only 3% of the experts at the 2014 Consensus Conference recommended reporting only the average or global grade for the entire case with approximately one-quarter of them providing the overall grade in addition to the individual core grade, both practices more commonly seen outside the United States. The remaining majority of the pathologists at the 2014 Consensus Conference report out the individual Gleason scores per part, which is standard practice in the United States.

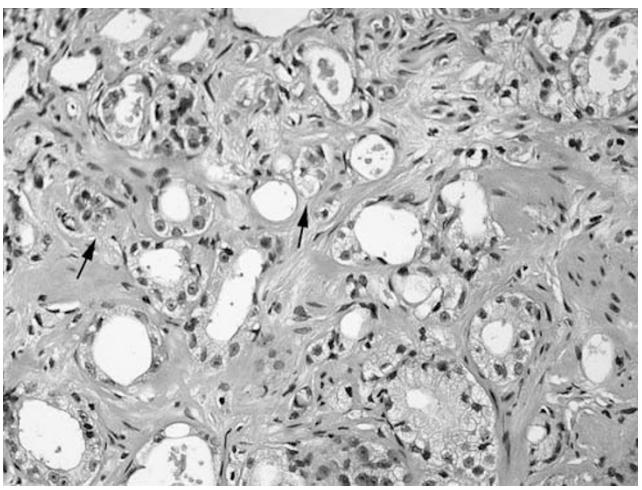


Figure 6 Gleason pattern 3 with a few glands (arrows) that appear poorly formed but are likely tangential sections off of adjacent small well-formed glands. Original magnification, 40x.

When multiple cores having different grades are present in the same specimen container, the recommendation at the 2014 Consensus Conference was equally split between assigning a grade to each positive core *versus* a global grade for each specimen container, with the same conclusion as the 2005 consensus: Assign individual Gleason scores to separate cores as long as the cores were submitted in separate containers or the cores were in the same container yet specified by the urologist as to their location (ie by different color inks). In cases where there are different undesignated cores with different grades in the same specimen container, it is optional whether to assign individual grades to different cores or a global grade for the specimen container. In addition to giving separate cores individual Gleason scores, one has the option to also give an overall score at the end of the case.[6] As currently cores are almost always submitted per part based on a specific site (ie not just left *versus* right), one can assume that all the cores in a given part (if not inked differentially) came from roughly the same location within the prostate so that only one grade averaging all the

positive cores per part should be reported. In cases with multiple fragmented cores in a jar, there was a 97% agreement to give a global Gleason score for that jar. For example, diagnosing Gleason score 4+4 = 8 on a tiny tissue fragment where there are other fragments with a greater amount of Gleason pattern 3 could be in error; if the cores were intact and the tumor was all on one core, it would be assigned a Gleason score 3+4 = 7.

RP specimens with separate tumor nodules

RP specimens should be processed in an organized manner where one can make some assessment as to whether one is dealing with a dominant nodule or separate tumor nodules. This does not necessarily require serially sectioning and embedding an RP in its entirety. Rather, multiple sampling techniques have described how one can subtotally submit the prostate yet still maintain orientation to distinguish between different tumor nodules.[63–65] This issue becomes critical in the situation where one has a higher-grade peripheral nodule and a smaller, typically transition zone, lower-grade nodule. One can have a nodule of Gleason score 4+4 = 8 within the peripheral zone and a Gleason score 2+2 = 4 nodule within the transition zone. Occasionally these Gleason score 2+2 = 4 transition zone tumors may even reach relatively sizable proportions, although typically they are organ confined. If one were to assign an overall score considering all of the tumor within the prostate as one lesion, the score of such a tumor would be Gleason score 4 +2 = 6 or Gleason score 2+4 = 6. Such a grade would be misleading as it is not logical to expect that the presence of a lower-grade tumor that is discrete from a separate high-grade tumor nodule could in some way mitigate the poor prognosis associated with the higher-grade tumor nodule. One should assign a separate Gleason score to each dominant tumor nodule(s). Most often, the dominant nodule is the largest tumor, which is also the tumor associated with the highest stage and highest grade. In the unusual occurrence of a non-dominant nodule (ie smaller nodule) that is of higher stage, one should also assign a grade to that nodule. If one of the smaller nodules is the highest grade focus within the prostate, the grade of this smaller nodule should also be recorded. In general, this will be the exception; in most cases, separate grades will be assigned to only one or at most two dominant nodules.

A new grading system for prostate cancer

Should Gleason Score 6 Cancer be Renamed as Non-Cancer

Overtreatment of low-grade prostate cancer (Gleason score ≤ 6) is a recognized problem today with systematic prostate gland sampling triggered by PSA measurements. Fear of death from cancer likely has some role, and removing the label 'cancer' could reduce unnecessary treatment of low-grade disease.[66] Two studies showing that using a contemporary grading approach, pure Gleason score 3 +3 = 6 at RP is incapable of regional lymph node metastasis.[9,67] At RP, pure Gleason score 3+3 = 6, organ-confined, margin-negative disease has an excellent prognosis with only occasional men demonstrating detectable PSA.[68,69] As a result of, it has been questioned if Gleason score 3+3 = 6 should retain the designation of cancer or be relabeled as indolent lesion of epithelial origin (IDLE) to avoid fear and consequential overtreatment of a proportion of potentially indolent prostate cancers.[70] Although renaming Gleason score 6 adenocarcinoma as 'not cancer' seems farfetched, there is a precedent in other organ systems to rename indolent malignancies with a non-cancerous term to avoid overtreatment. Some examples include: (1) renaming well-differentiated liposarcoma in the extremities as *atypical lipomatous tumor*;[71] (2) changing the designation of a subset of bladder tumors previously diagnosed as low-grade papillary urothelial carcinoma to papillary urothelial neoplasm of low malignant potential;[72] and (3) most recently reclassifying encapsulated follicular variant papillary thyroid carcinoma to *n*oninvasive follicular thyroid neoplasm with papillary-like nuclear features.[73]

From a pathologist's viewpoint, Gleason score 6 is still cancer with many of the same morphological features of higher-grade cancer, along with a lack of a basal cell layer and the potential to locally invade.[74] Gleason pattern 3 cancer harbors many of the molecular alterations associated with higher-grade cancers including overexpression of α-methylacyl-CoA racemase, glutathione *S*-transferase hypermethylation and downregulation, and TMPRSS2:ERG gene fusions.[75] From a clinical perspective, renaming Gleason score 3+3 = 6 as an IDLE tumor on biopsy carries the risk that patients on active surveillance will not adhere to long-term follow-up as they have been told they do not have *cancer*. The need for close follow-up results from the risk of unsampled higher-grade carcinoma. The likelihood of upgrading from a Gleason score ≤ 6 on biopsy to Gleason score ≥ 7 at RP has been reported to be as high as 36%.[76] If Gleason score 6 on biopsy was not labeled as *cancer*, the potential for higher grade or more extensive disease might be ignored, and compliance with recommendations for careful monitoring may not occur.

Problem with the Current Gleason Scale

Consequently, Gleason score 6 prostatic adenocarcinoma should still be called cancer. However, there is a need to change what patients think when they hear they have Gleason score 6 cancer. Urologists need to

reassure and educate patients, and pathologists need to modify how we report prostate cancer grade to more accurately reflect their behavior. A major problem with the current application of the Gleason grading system is that Gleason score 6 is the lowest grade reported on biopsy, although the scale goes from 2–10. What other grading system starts with a 6? Patients are told they have a Gleason score of 6 out of 10 and logically but incorrectly think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer. I routinely talk to patients on a daily basis regarding their pathology on prostate needle biopsy as it relates to treatment and prognosis. The first thing I tell them when describing their Gleason score 6 cancer is that it is the lowest possible grade. An anecdotal experience I had talking with a particular patient exemplifies the problem with the current Gleason scale. A man that I recently diagnosed as having Gleason score 3+4 = 7 on biopsy called me, literally in tears. His wife was recently diagnosed with a glioblastoma and he feared that given that his prostate cancer grade was a 7, which was close to 10 (the worst grade), he might not be alive to take care of his wife. I was able to reassure him that from his cancer's standpoint it has approximately an 88% cure rate and even if it did recur it would not do so symptomatically for many years. The power of how prostate cancer grades are reported was also recently shown in a study of prostate cancer patients in two clinical settings from 2015 to 2016.[77] The men were told that there is a new grading system for prostate cancer with grades ranging from 1 to 5, where Grade Group 1 is equivalent to Gleason score 6. The majority of patients (84%) agreed that it would be clearer if grades were reported on a scale of 1–5 instead of 6–10. Eighty-eight percent of the men would prefer to hear they have 'Grade Group 1' rather than 'Gleason 6', and, most importantly, 80% would feel more comfortable choosing active surveillance with 'Grade Group 1' *versus* 'Gleason 6'.

Problems with Gleason System Grouping

In the literature and for therapeutic purposes, various Gleason scores have been incorrectly grouped together based on the assumption that they have a similar prognosis. Analyzing some of the highest impact articles on prostate cancer in the past few years reveals some of the Gleason score groupings that have been used: 2–4, 5–7, 8–10 (Prostate Cancer Outcomes Study);[78] 2–6, 7, 8–10 (Scandinavian Prostate Cancer Group Study); and 2–6, 7–10 (Prostate Cancer Prevention Trial and Prostate Cancer Intervention *versus* Observation Trial).[79,80] The most common risk stratification used in prostate cancer is the D'Amico classification also used by the National Comprehensive Cancer Network.[81] It stratifies prostate cancer based on serum PSA values, clinical stage, and biopsy score into low-, intermediate-, and high-risk groups incorporating Gleason scores into a three-tiered Gleason score grouping (2–6, 7, and 8–10). In addition to the lack of uniformity of the various score groupings, precluding meaningful comparisons between studies, the combinations used have significant flaws. Gleason scores 2–4 virtually never exist on current biopsy material. Many of these cases in Gleason's era, predating the use of modern immunohistochemistry, probably represent adenosis, a mimicker of cancer. Studies combining Gleason scores 6 and 7 span tumors with almost a uniformly excellent prognosis (3+3) to those with a substantial likelihood of progressing following therapy (4+3). In the former, many men are candidates for active surveillance, whereas in the latter typical treatment is either by surgery or combination androgen deprivation and radiation therapy. All of the above classification systems consider Gleason 7 as a single score without distinguishing 3+4 *versus* 4+3, despite studies, showing a significantly worse prognosis for the latter.[82–84] Combining scores 7–10 includes cases with an excellent prognosis with an 88% cure rate (3+4) along with those that have a high prostate cancer-specific lethality (5+5). Even within the high score group of 8–10, we have demonstrated that Gleason scores 9–10 have twice as poor a prognosis than Gleason score 8, an observation supported by multiple studies noting the adverse prognosis associated with Gleason pattern 5.[85–91]

Proposal for a New Grading System

Although Gleason scores range from 2 to 10, there are 25 potential scores (1+1, 1+2, 1+3, 1+4, 1+5, 2+1, etc). If one were coming up with a new grading system starting from scratch one would want to distill it down to a simple system with the least number of grades, each with their distinct prognosis. Based on a series of 6462 men treated by RP where both the needle biopsy and RP were graded using the current modified Gleason grading system, this author showed both for biopsy and for RP that the following Gleason grade groups accurately reflects prognosis: Gleason score 2–6 (Prognostic Grade Group 1); Gleason score 3+4 = 7 (Prognostic Grade Group 2); Gleason score 4+3 = 7 (Prognostic Grade Group 3); Gleason score 8 (Prognostic Grade Group 4); and Gleason scores 9–10 (Prognostic Grade Group 5).[85]

In a recent meta-analysis of over 20 000 men treated by RP from five institutions, Grade Groups were strongly correlated with risk of biochemical recurrence after surgery.[92] Assigning a risk of 1 to Gleason score 6, the relative risks of progression for Grade Groups 2–5 were 2.6, 8.5, 16.8, and 29.3. The 5-year biochemical risk-free survival was 97.5%, 93.1%, 78.1%, 63.6%, and 48.9% for Grade Groups 1–5, respectively. These grade grouping was also validated on biopsy correlating with risk of progression after RP and following radiation therapy.

Table 1 Definition of Grade Groups

Grade Group 1 (3+3 = 6)—Only individual discrete well-formed glands
Grade Group 2 (3+4 = 7)—Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
Grade Group 3 (4+3 = 7)—Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands[a]
Grade Group 4 (Gleason score 8) Only poorly formed/fused/cribriform glands[a] *or* Predominantly well-formed glands and lesser component lacking glands[b] Predominantly lacking glands and lesser component of well-formed glands[b]
Grade 5 (Gleason scores 9 and 10)—Lack gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands[a]

[a]For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at RP, the component of <5% well-formed glands is not factored into the grade.[b]Poorly formed/fused/cribriform glands can be a more minor component.

Following these initial studies, there have been numerous works that have validated the new grading system following RP and radiation therapy, including its correlation with prostate cancer death and distant metastases.[60,93–101]

These new Grade Groups were formally accepted by the 2016 World Health Organization (WHO and it was accepted that at least for the foreseeable future, Grade Grouping would be report alongside the Gleason score (ie Gleason score 3+4 = 7 (Grade Group 2)), with eventually possibly replacing it in the future. The new system has also been accepted by the College of American Pathologists where it will be mandatory to report Grade Groups starting in 2018, and the AJCC Cancer Staging Manual 8th Edition. The histological definition of the five grades in the new grading system is depicted in Table 1. While in the foreseeable future, one would think of the new Grade Groups in terms of their equivalence to the corresponding Gleason grade, if eventually Grade Groups replaces the Gleason system, then the definitions of the Grade Groups would be based on the descriptive text shown in Table 1.

There has been some controversy relating to Grade Group 4, which includes Gleason scores 3+5 = 8 and 5+3 = 8, reporting that Gleason score 8 cases with pattern 5 has a worse prognosis from those with 4 +4 = 8 disease.[102,103] One of these studies included patients from 1998 to 2012 and concluded that prostate cancer-specific mortality was higher when any percent of pattern 5 was present compared with Gleason score 4+4 = 8 disease.[102] No comparison was performed between the outcomes of Gleason score 3 +5 = 8 and 5+3 = 8, and cases from before the 2005 International Society of Urological Pathology (ISUP) conference would have been graded significantly different from current practice. Another study extracted data from the Surveillance, Epidemiology, and End Results (SEER) database and concluded that prostate cancer-specific mortality was similar for Gleason score 4+4 = 8 and 3+5 = 8 prostate cancer, and the prognosis of patients with Gleason score 5 +3 = 8 was more similar to those with Gleason score 9 disease.[103] Another recent study also showed that the prognosis is not different in Gleason score 3+5 = 8 and 4+4 = 8 cancers.[104] While SEER provides a large database for retrospective prostate cancer research, it is not controlled for the consistency of reporting/grading and the data are extracted from pathology reports in hospitals without central re-review of the slides, with most institutions lacking genitourinary pathology experts. One potential error is to grade the overall tumor as 5+3 = 8 in an RP if there are separate nodules of 5+5 = 10 and 3+3 = 6. Similarly, a case may have been incorrectly issued a grade of 5+3 = 8 on needle biopsy if there were separate cores with 5 +5 = 10 and 3+3 = 6. In both these scenarios, the cases should be graded as 5+5 = 10 so that it would be expected that their prognosis would be worse than Gleason score 8. In another study of Grade Group 4 tumors, 295 (27.1%), 651 (59.8%), and 143 (13.1%) patients had pathologic Gleason scores 3+5, 4+4, and 5+3.[105] The relatively high percentage of cases with 3+5 and 5+3 calls into question on how these tumors were graded. The study lacks a single pathologist amongst the authors, no details were provided on how the grades were assigned, and the grade was solely based on review of pathology reports. They reported patients with Gleason pattern 3+5 were at lower risk of biochemical recurrence compared to those with 4+4.

In a large multi-institutional study with genitourinary pathology experts from 2005 to 2014, out of 20 845 RP specimens, there were 39 (0.2%) cases with 3+5 = 8 and 4 (0.02%) with 5+3 = 8 (unpublished data).[92] Similarly, out of 16 172 needle biopsy cases, there were only 44 (0.3%) with 3+5 = 8 and 6 (0.04%) with 5+3 = 8 (unpublished data). These data indicate that Gleason score 5+3 = 8 cancer on needle biopsy or RP almost never occurs in clinical practice.

Summary

The grading of prostate cancer has evolved significantly since Gleason's original description in the 1960–70s. Based on ISUP consensus conferences in 2005 and 2015, many of the original Gleason pattern 3 morphologies have now been shifted to Gleason pattern 4 with a relatively better prognosis for current Gleason score 6 tumors. Even the basic definition of Gleason grading by adding the most prevalent and second most prevalent patterns to arrive at a score has changed on needle biopsy where the most prevalent pattern is added to the highest grade. Grading has also evolved with new rules for grading of prostate cancer variants and variant morphologies, as well as for needle biopsies and radical prostatectomies. A new simple, intuitive grading system has been accepted clinicians with

better stratification of patients into distinct grade grades, which has implications for treatment. Grade Group 1/5 emphasizes the generally indolent behavior of Gleason score 6 prostate cancer to permit more rational and less emotional decision making for treatment, likely increasing the appropriate use of active surveillance in these men. Grade Group 2/5 can reassure patients of its very good prognosis with only rare metastases, as opposed to Gleason score 7, which is closer to Gleason score 10 than Gleason score 2, implying aggressive disease. Grade Group 3/5 with a significantly worse prognosis than Grade 2 reinforces their distinction as opposed to Gleason score 7, which combines Gleason scores 3+4 and 4 +3. Grade Group 4/5 (Gleason score 8) is not considered the highest grade with a significantly better prognosis than Grade Group 5 (Gleason scores 9 and 10), as opposed to the typical combining of Gleason scores 8–10. Grade Group 5 obviates the need to distinguish between Gleason scores 4+5, 5 +4, and 5+5 just as Grade Group 1 makes irrelevant the distinction between Gleason scores 2–6.

Disclosure/conflict of interest

The authors declare no conflict interest.

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