The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

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Donald F. Gleason in 1966 created a unique grading system for prostatic carcinoma based solely on the architectural pattern of the tumor.[3,14,22] 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, based on a study of 270 patients from the Minneapolis Veterans Administration Hospital, is seen in Table 1.

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).[14] 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 (Table 1).

By 1974, Gleason and the Veterans Administration Cooperative Urological Research Group expanded their study to 1032 men.[15] 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."[23] These modifications of the Gleason system are depicted in Table 1. 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%.[23] These percentages added up to approximately 150% because 50% of the tumors showed at least two different patterns.

In 1977, Gleason provided additional comments concerning the application of the Gleason system.[16] "Grading is performed under low magnification (40–100×)." He also stated "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."

WHY THE NEED FOR A CONSENSUS ON GLEASON GRADING?

It is a testament to the enduring power of the original Gleason grading system that it is the accepted grading system throughout the world, despite its inception almost 40 years ago. How many other things in medicine have stood the test of time so well? Nonetheless, medicine in general and prostate carcinoma in specific has changed dramatically since the late 1960s, when the Gleason grading system was derived. In the 1960s, there was no screening for prostate cancer other than by digital rectal examination, as serum PSA had not yet been discovered. In Gleason's 1974 study, most (86%) of the men had advanced disease with either local extension out of the prostate on clinical examination or distant metastases. Only 6% of patients had nonpalpable tumor diagnosed by transurethral resection and 8% of patients were diagnosed with a localized nodule on rectal examination.[15] The method of obtaining prostate tissue was also very different from today's practice. Typically, only a couple of thick-gauge needle biopsies were directed into an area of palpable abnormality. 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.[17] Consequently, the grading of

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TABLE 1. Gleason System

Original Gleason System: 1966 & 1967
Pattern 1: Very well differentiated, small, closely packed, uniform, glands in essentially circumscribed masses
Pattern 2: 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
Pattern 3: 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
Pattern 4: Large clear cells growing in a diffuse pattern resembling hypernephroma; may show gland formation
Pattern 5: Very poorly differentiated tumors; usually solid masses or diffuse growth with little or no differentiation into glands
Gleason's Modifications: 1974 & 1977
Patterns 1 & 2: Unchanged
Pattern 3: Adds to earlier description: may be papillary or cribriform (1974), which vary in size and may be quite large, but the essential feature is the smooth and usually rounded edge around all the circumscribed masses of tumor (1977)
Pattern 4: Adds to earlier description: raggedly infiltrating, fused-glandular tumor (1974); glands are not single and separate, but coalesce and branch (1977)
Pattern 5: Adds to earlier description: can resemble comedocarcinoma of the breast (1977); almost absent gland pattern with few tiny glands or signet cells (1977)

prostate cancer in thin cores and in multiple cores from different sites of the prostate were not issues in Gleason's 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 to the degree currently seen. Further issues relating to radical prostatectomy specimens such as the grading of multiple nodules within the same prostate 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 Gleason's original 1 + 1 = 2 adenocarcinomas of the prostate would today be regarded as adenosis (atypical adenomatous hyperplasia). Similarly, many of the cases in 1967 diagnosed as cribriform Gleason pattern 3 carcinoma would probably be currently referred to as cribriform high grade prostatic intraepithelial neoplasia, if labeled with basal cell markers.[1]

Another issue not dealt with in the original Gleason grading system is how to grade newly described variants of adenocarcinoma of the prostate. Some of the more common variants where grading controversy exists include: mucinous carcinoma, ductal adenocarcinoma, foamy gland carcinoma, and pseudohyperplastic adenocarcinoma of the prostate. In addition, there are certain patterns of adenocarcinoma of the prostate such as those with glomeruloid features and mucinous fibroplasia (collagenous micronodules) where the use of Gleason grading was not defined.

The application of the Gleason system for all of the reasons noted above varies considerably in contemporary surgical pathology practice and has led to several recent attempts to achieve consensus on Gleason grading.

RECENT WORLD HEALTH ORGANIZATION CONSENSUS STATEMENTS ON THE GLEASON SYSTEM

The 2004 *World Health Organization Classification of Tumors*: *Pathology and Genetics*: *Tumors of the Urinary System and the Male Genital Organs* summarized the current state of Gleason grading.[12] A follow-up international consensus meeting on "International Consultation on Predictors of Patient Outcome in Prostate Cancer" sponsored by the World Health Organization took place in 2004 in Stockholm, Sweden.[2,13] Although both of these meetings provided a current analysis of Gleason system, they were restricted to a relatively limited number of participants for both financial and logistical reasons. In an attempt to elicit input from a greater representation of the urologic pathology community, a survey on Gleason grading was sent to 91 pathologists with 67 respondents.[9] Although the survey provided useful information as to the worldwide practice of the Gleason grading system among urologic pathologists, certain questions were ambiguous and were interpreted differently by different respondents. In addition, the survey provided unidirectional responses to questions, not allowing for back-and-forth discussions of controversial areas.

2005 ISUP CONSENSUS CONFERENCE

The authors of the Gleason grading survey convened a group of urologic pathologists 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. The goal of the meeting was to achieve consensus among leading urologic pathologists in specific areas of Gleason grading, including areas where there is currently either a lack of data or scant information as to the optimal method of grading. In the latter instances, the consensus was based on personal and institutional experience with a large number of cases. More than 70 urologic pathologists were invited to attend, with most not in attendance having a conflict in their schedule. Only one invitee declined participation, stating that the Gleason system in its original form should not be altered and hence there was no need for a consensus conference. For the purposes of this meeting, we defined "consensus" when two thirds of the participants were in agreement, although for almost all of the issues discussed a much higher degree of agreement was reached. With rare

exception, there was uniformity of opinion between the consensus opinion from the Gleason survey and those who attended the 2005 ISUP consensus conference. The current manuscript was circulated to all those listed in Table 2 who have accepted their name to be associated with this consensus statement, recognizing that by doing so it does not mean that they are in agreement with all of the consensus statements, but rather that they are in overall acceptance of most of the views expressed by both the survey and the ISUP consensus meeting.

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 4× or 10× lens.[16] After one assesses the case at scanning magnification, one may proceed to use the 20× 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 20× to confirm its presence. However, one should not initially use the 20× or 40× objectives to look for

TABLE 2. Participants in Gleason Survey and ISUP Consensus Meeting

Participant	Country	Participant	Country
Mahul B. Amin*†	USA	Peter A. McCue†	USA
Ferran Algaba*	Spain	John McNeal*	USA
William Allsbrook*†	USA	Gregor Mikuz*	Austria
Alberto Ayala*	USA	Rodolfo Montironi*	Italy
Sheldon Bastacky*†	USA	Robin Moseley*	UK
Aasmund Berner*†	Norway	Ray Nagle*	USA
Athanase Billis*†	Brazil	Tipu Nazeer*†	USA
Antonio López Beltrán†	Spain	Stig Nordling*	Finland
Liliane Boccon-Gibod*†	France	Gerald O'Dowd*	USA
Christer Busch*	Norway	Esther Oliva*†	USA
Liang Cheng†	USA	Roberto Orozco*	Guatemala
John Cheville*	USA	Kathleen O'Toole*	USA
Stephen Cina*	USA	Chin-Chen Pan*†	Taiwan
Francisco Civantos*†	USA	Constance Parkinson*	UK
Cynthia Cohen*†	USA	Robert O. Petersen*	USA
Michael B. Cohen*†	USA	Carl-Gustaf Pihl*	Sweden
Milton Datta†	USA	Galina Pizov†	ISRAEL
Charles Davis*†	USA	Andrew Renshaw†	USA
Brett Delahunt*†	New Zealand	Victor Reuter*†	USA
Warick Delprado*†	Australia	Jae Ro*	South Korea
Anthony di Sant'Agnese*	USA	Mark Rubin*	USA
John N. Eble*†	USA	Hemamali Samaratunga*†	Australia
Lars Egevad*†	Sweden	Thomas Sebo*†	USA
Jonathan I. Epstein*†	USA	Isabell Sesterhenn*†	USA
Fang Fan*	USA	Maria Shevchuk*†	USA
Christopher S. Foster†	UK	John R. Srigley*†	Canada
Masakuni Furusato†	Japan	Sueli Suzigan†	Brazil
Paul B. Gaudin*†	USA	Hiroyuki Takahashi†	Japan
Neal Goldstein*	USA	Pheroze Tamboli†	USA
David J. Grignon*†	USA	Bernard Têtu*†	Canada
Hans Hamberg*	Sweden	Satish Tickoo†	USA
Burkhard Helpap*	Germany	John E. Tomaszewski†	USA
Puay Hoon Tan*†	Singapore	Patricia Troncoso*†	USA
Peter A. Humphrey*†	USA	Lawrence D. True*†	USA
Kenneth A. Iczkowski*†	USA	Toyonori Tsuzuki*†	Japan
Sonny Johansson*	USA	Theo van der Kwast*†	Canada
Edward C. Jones*†	Canada	Thomas M. Wheeler*†	USA
Hillel Kahane*	USA	Kirk J. Wojno*†	USA
Howard Levin*	USA	Ximing Yang*	USA
Scott Lucia†	USA	Robert H. Young*†	USA

*Gleason Survey participant.
†ISUP Consensus Meeting participant.

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 (Fig. 1).

GLEASON PATTERNS

Gleason Score 1 + 1 = 2

It was the consensus that a Gleason score of 1 + 1 = 2 is a grade that should not be diagnosed regardless of the type of specimen, with extremely rare exception (Table 3). 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 3–4

These low-grade tumor scores were assigned by members of the consensus panel occasionally on transurethral resection specimens (TURPs) and in multifocal low-grade tumors within radical prostatectomy specimens (Fig. 2). In contrast to Gleason's diagram and text, the consensus was that cribriform patterns are not allowed within Gleason pattern 2. A controversial area is whether a diagnosis of Gleason score 3 or 4 should be made on needle biopsy. Reasons why such a diagnosis is usually inaccurate are: 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 score 3 to 4 may misguide clinicians and patients into believing that the patient has an indolent tumor.[11,34] It was the consensus of the group that, rather than stating categorically that a Gleason score 4 on needle biopsy should "never" be made, this diagnosis should be made "rarely, if ever." Whereas recommending that the diagnosis of Gleason score 4 on needle biopsy should be made "rarely, if ever" is similar to "never," it does allow for the exceedingly rare case where low-grade cancer has been sampled on needle biopsy. The consensus conference cautioned that, although the potential exists for rendering a diagnosis of Gleason score 4 on needle biopsy, it is a diagnosis that general pathologists should almost never make without consultation. Even when the exceedingly rare Gleason score 4 cancer is diagnosed on needle biopsy by an expert, a note should be added that almost always a higher grade cancer will be seen in the corresponding prostate (if examined at radical prostatectomy). The major limitation of rendering a diagnosis of Gleason score 4 on needle biopsy is that one cannot see the entire edge of the lesion to determine if it is completely circumscribed. Consequently, most of the lesions that appear to be very low grade on needle biopsies are diagnosed by urologic pathologists as Gleason score 2 + 3 = 5 or 3 + 2 = 5 (Fig. 3). Some participants stated that if the location of the needle biopsy were from the transition zone or possibly at the apex, where many lower-grade cancers are found, that might factor into diagnosing the rare Gleason score 4 on needle biopsy.

TABLE 3. 2005 ISUP Modified Gleason System

Pattern 1:
- Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

Pattern 2:
- Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration
- Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

Pattern 3:
- Discrete glandular units
- Typically smaller glands than seen in Gleason pattern 1 or 2
- Infiltrates in and amongst nonneoplastic prostate acini
- Marked variation in size and shape
- Smoothly circumscribed small cribriform nodules of tumor

Pattern 4:
- Fused microacinar glands
- Ill-defined glands with poorly formed glandular lumina
- Large cribriform glands
- Cribriform glands with an irregular border
- Hypernephromatoid

Pattern 5:
- Essentially no glandular differentiation, composed of solid sheets, cords, or single cells
- Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

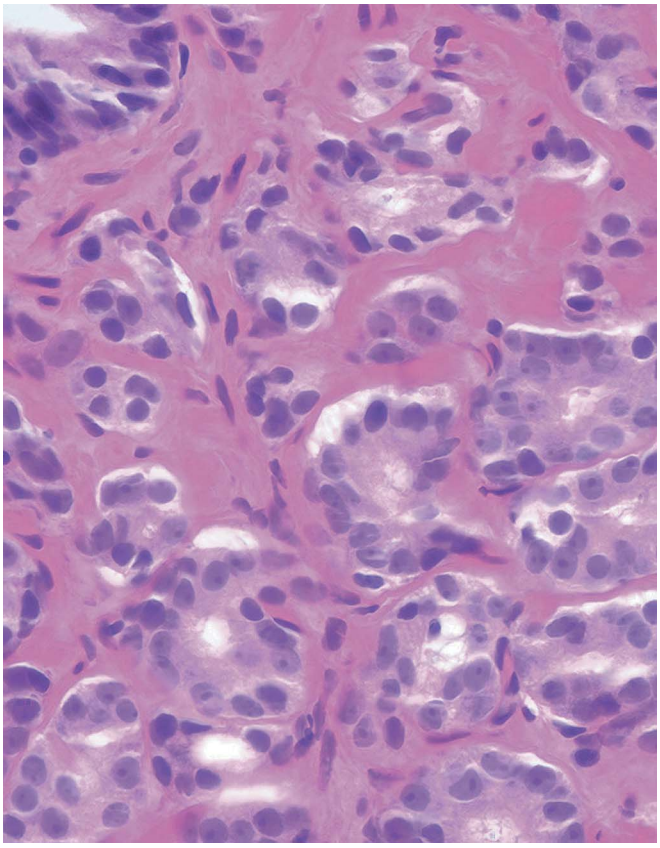

FIGURE 1. Adenocarcinoma, Gleason score 3 + 3 = 6 with rare poorly formed glands probably representing tangential sectioning of well formed glands and are only identified at high magnification (original magnification ×40).

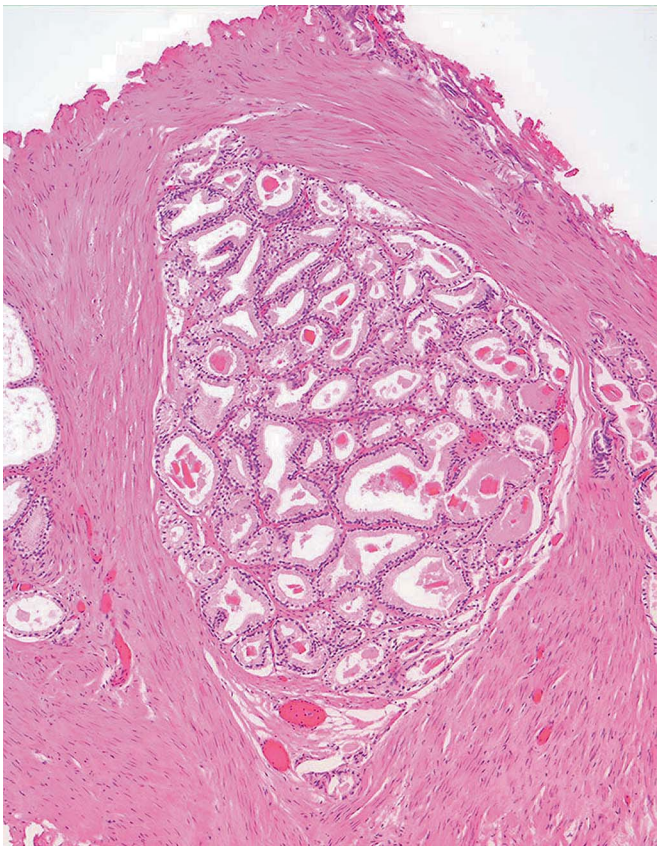

FIGURE 2. Gleason score 1 + 2 = 3 nodule of cancer on TURP, verified immunohistochemically with negative stains for basal cells.

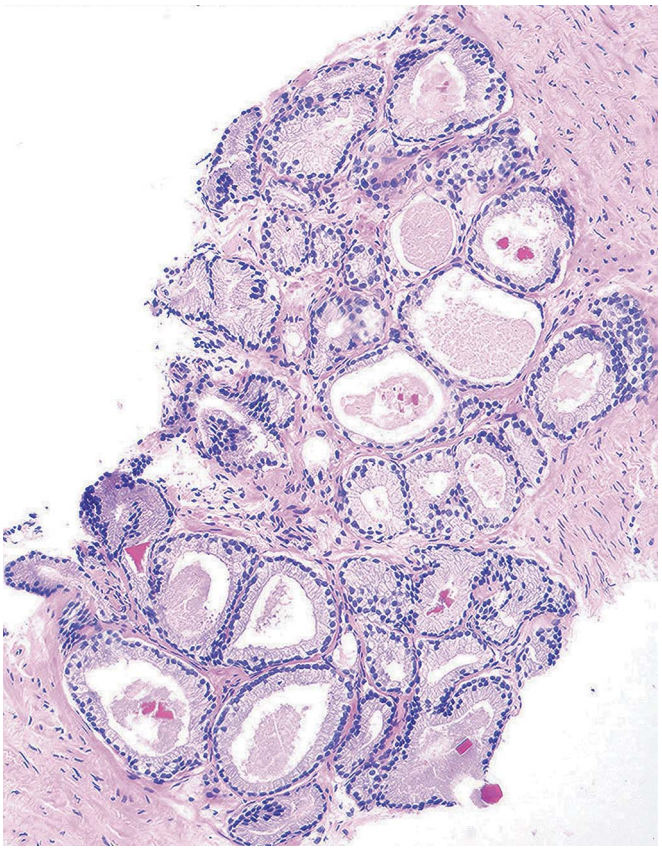

FIGURE 3. Gleason score 2 + 3 = 5 adenocarcinoma on needle biopsy, where the inability to see whether the lesion is fully circumscribed mitigates against grading as Gleason score 2-4.

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 (Fig. 4). 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 (Fig. 3D in reference 23). The consensus panel required extremely stringent criteria for the diagnosis of cribriform pattern 3, with remaining cribriform patterns typically falling into Gleason pattern 4. The criteria used to diagnose cribriform pattern 3 were rounded, well-circumscribed glands of the same size of normal glands (Fig. 5). 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. A minority of the consensus panel used additional criteria to diagnose Gleason cribriform pattern 3, such as the requirement of evenly spaced lumina or that the bridges within the cribriform glands had to be of uniform thickness and no thicker than the width of the luminal spaces. Cribriform Gleason pattern 3 cancer should morphologically resemble cribriform high-grade prostatic intraepithelial neoplasia, yet are diagnostic of infiltrating carcinoma based on: 1) a large number of glands are negative for basal cell markers; 2) the glands are back-to-back, ruling out high-grade prostatic intraepithelial neoplasia; or 3) the glands are exhibiting pathognomonic features of carcinoma such as perineural invasion or extraprostatic extension. It was the consensus that most of cribriform patterns be diagnosed as Gleason pattern 4 with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3.

Gleason Pattern 4

A controversial area where consensus was reached was that ill-defined glands with poorly formed glandular lumina also warrant the diagnosis of Gleason pattern 4 (Fig. 6). 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 (Fig. 7). It was also noted that in most cases ill-defined glands with poorly formed glandular lumina are accompanied by fused glands (Fig. 8). Very small, well-formed glands still are within the spectrum of Gleason pattern 3 (Fig. 9). This definition differs from Gleason's original description of pattern 4, which only included the hypernephromatoid pattern.[14] Only in subsequent years were fused glandular masses added to the definition.[23] The schematic diagram of Gleason pattern 4 consists almost entirely of cribriform patterns without depicting fused glands or ill-defined

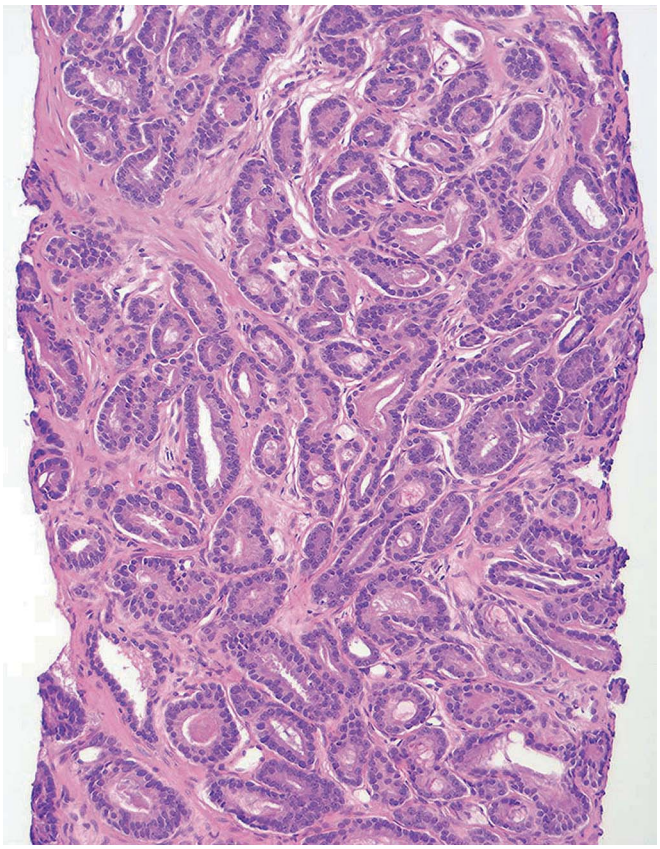

FIGURE 4. Gleason score 3 + 3 = 6 prostate carcinoma composed of small discrete glands.

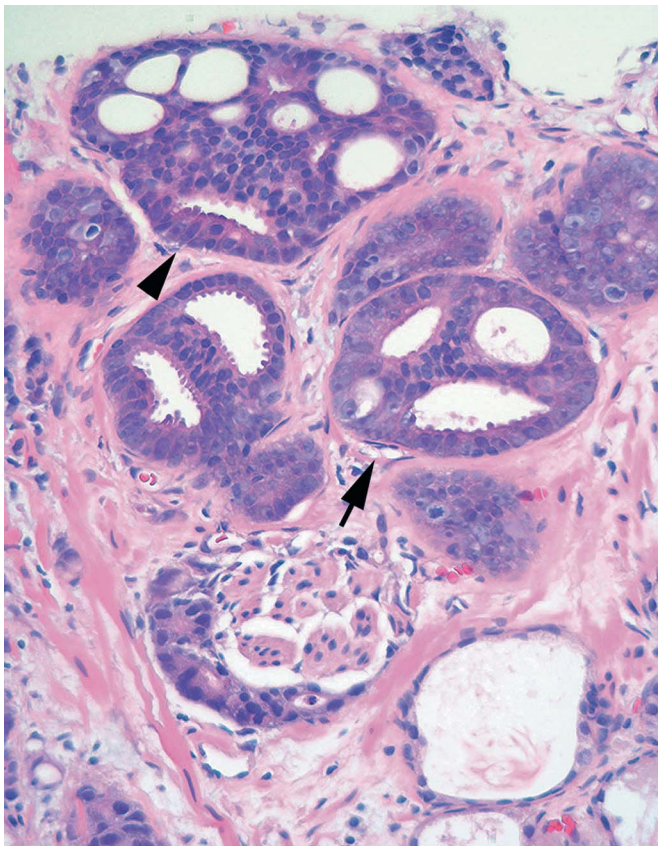

FIGURE 5. Cribriform prostate cancer with perineural invasion. Cribriform pattern 3 consists of oval-round smoothly circumscribed cribriform glands, which approximate the size of benign glands (arrow). Other cribriform glands with even slight irregularities to their border warrant a diagnosis of pattern 4 (arrowhead).

glands with poorly formed glandular lumina (Fig. 10). Gleason pattern 4 closely resembling renal cell carcinoma (hypernephromatoid pattern) makes up only a very small percentage of Gleason pattern 4 cases.

Gleason Pattern 5

Although typically one sees comedonecrosis with solid nests, occasionally one can see necrosis with cribriform masses that by themselves might be cribriform pattern 4. If there is true comedonecrosis, the consensus was that these patterns should be regarded as Gleason pattern 5 (Fig. 11). One must be stringent as to the definition of comedonecrosis, requiring intraluminal necrotic cells and/or karyorrhexis, especially in the setting of cribriform glands.

Modified Gleason Diagram

The schematic diagram of the modified Gleason's grading system, reflecting changes described above and in Table 3, is depicted in Figure 12.

GRADING VARIANTS AND VARIATIONS OF ACINAR ADENOCARCINOMA OF THE PROSTATE

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 described them as signet cells under pattern 5 tumor.[16] The panel concluded that, although typically vacuoles are seen within Gleason pattern 4 cancer, it may be seen within Gleason pattern 5 and even Gleason pattern 3 tumors (Fig. 13). The consensus was that tumors should be graded, as if the vacuoles were not present, by only evaluating the underlying architectural pattern.

Foamy Gland Carcinoma

In an analogous fashion to handling cancers with vacuoles, it was the consensus of the panel that in grading foamy gland carcinomas one should ignore the foamy cytoplasm and grade the tumor solely based on the underlying architecture.[25,35] Whereas most cases of foamy gland carcinoma would be graded as Gleason score 3 + 3 = 6, higher-grade foamy

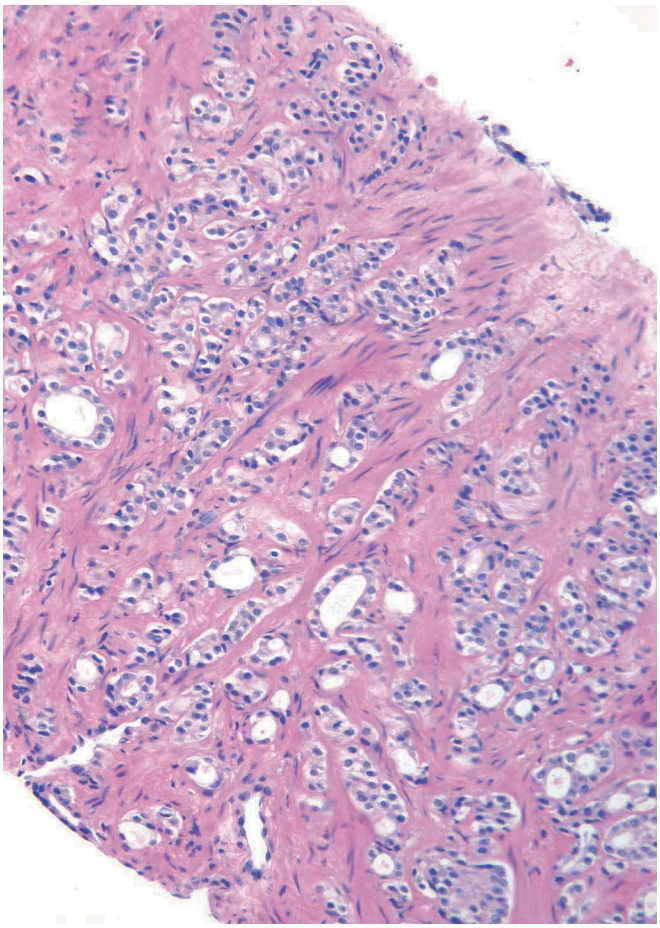

FIGURE 6. Gleason score 4 + 3 = 7 adenocarcinoma, where pattern 4 component consists of discrete yet poorly formed glands.

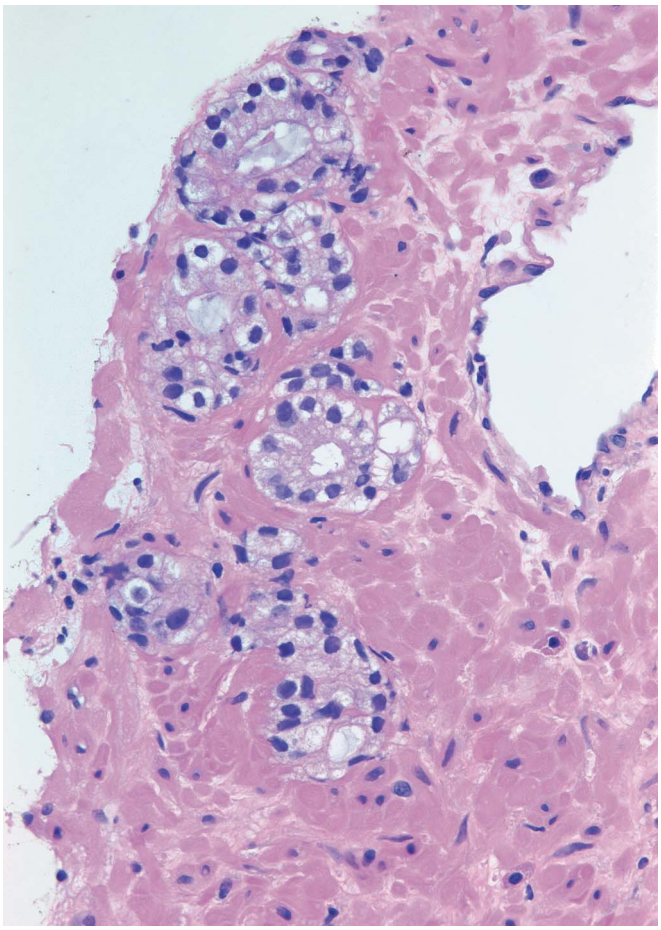

FIGURE 7. Adenocarcinoma, Gleason score 3 + 3 = 6 with tangential sectioning of a few glands.

gland carcinomas exist and should be graded accordingly based on the pattern.

Ductal Adenocarcinoma

Ductal adenocarcinomas of the prostate most commonly are composed of either papillary fronds or cribriform structures.[6] Less frequently, there exists a pattern consisting of individual glands lined by tall pseudostratified columnar cells. Ductal adenocarcinomas are recognized as being aggressive tumors with most studies showing comparable behavior to acinar cancer with a Gleason score 4 + 4 = 8. The consensus of the panel was that ductal adenocarcinomas should be graded as Gleason score 4 + 4 = 8, whereas retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathologic findings. 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.

Colloid (Mucinous) Carcinoma

The majority of cases with colloid carcinoma consist of irregular cribriform glands floating within a mucinous matrix (Fig. 14).[10,30] It was the uniform consensus that these cases would be scored Gleason score 4 + 4 = 8. However, uncommonly one may see individual round discrete glands floating within mucinous pools. There was no consensus in these cases whether such cases should be diagnosed as Gleason score 4 + 4 = 8 or Gleason score 3 + 3 = 6. Approximately half of the group said that by definition all colloid carcinomas should be assigned a Gleason score of 8, whereas the other half felt that one should ignore the extracellular mucin and grade the tumor based on the underlying architectural pattern. Given the lack of consensus, either method would be acceptable for practicing pathologists until future data indicate which method is correct.

Small Cell Carcinoma

It was the consensus that small cell carcinoma of the prostate has unique histologic, immunohistochemical, and clinical features. 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.

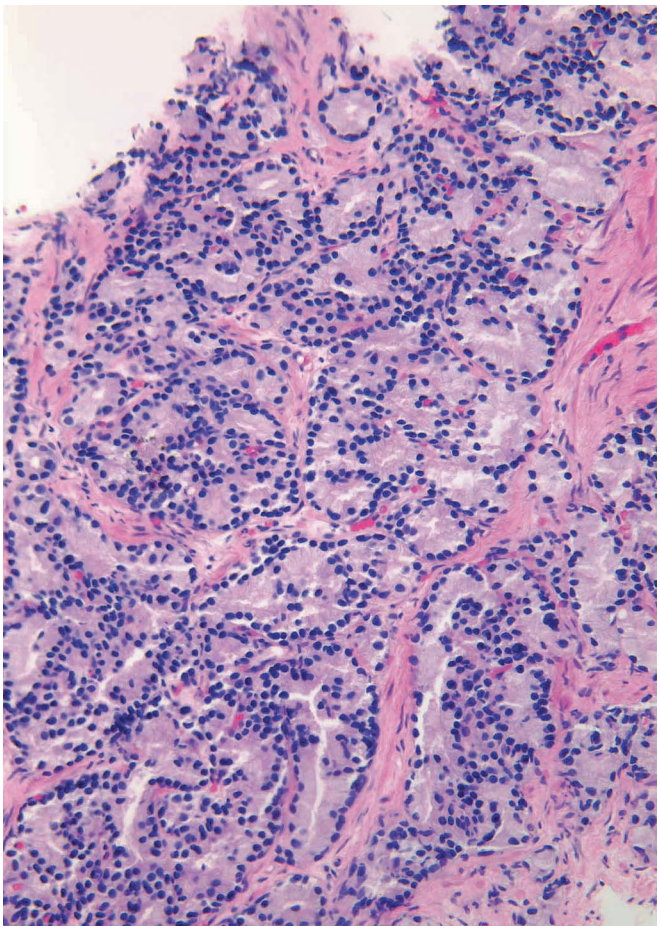

FIGURE 8. Gleason score 4 + 4 = 8 adenocarcinoma with fused glands.

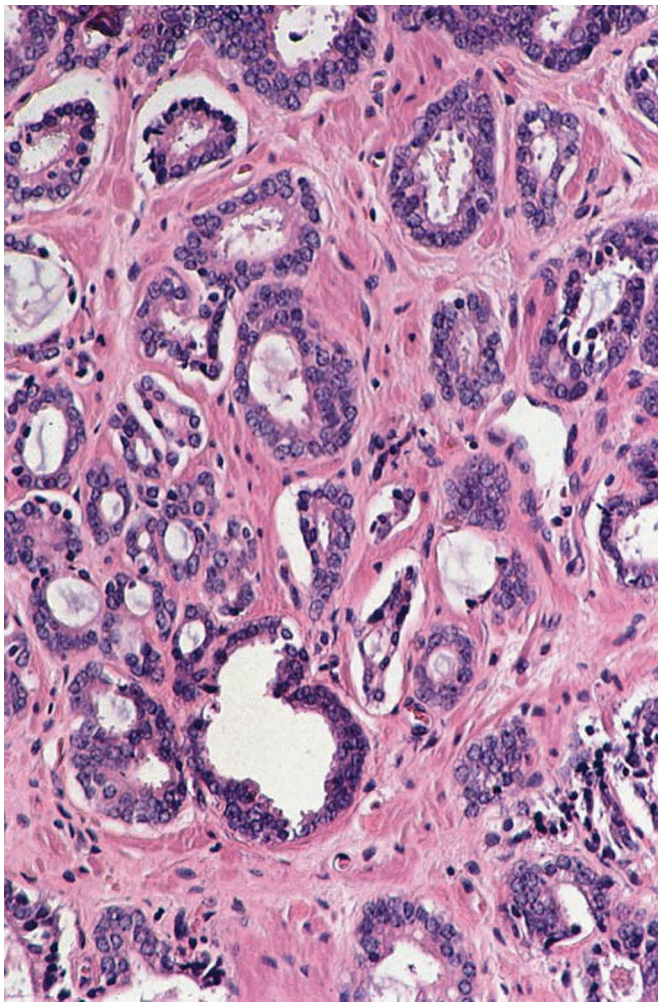

FIGURE 9. Gleason score 3 + 3 = 6 adenocarcinoma with small, yet well-formed neoplastic glands.

Adenocarcinoma With Focal Mucin Extravasation

There was consensus among the group that adenocarcinomas of the prostate with focal mucinous extravasation should not be by default graded as Gleason score 4 + 4 = 8. Rather, one should ignore focal mucinous extravasation and grade the tumor based on the underlying architecture of the glands. The distinction between focal mucinous extravasation and colloid carcinoma is the presence of epithelial elements floating within the mucinous matrix within the latter, whereas with mucinous extravasation there is only focal acellular mucin adjacent to cancer (Fig. 15).

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 often that of individual discrete rounded glands invested by loose collagen (Fig. 16).[4,5] It was the consensus of the panel that one should try to subtract away the mucinous fibroplasia and grade the tumor based on the underlying glandular architecture. The majority of these cases would accordingly be graded as Gleason score 3 + 3 = 6.

Glomeruloid Structures

An unusual pattern of prostate cancer is the presence of dilated glands containing a cribriform proliferation that is not transluminal (Fig. 17).[4,26] Rather, the cribriform formation is attached to only one edge of the gland resulting in the structure superficially representing a glomerulus. The grading of such structures was controversial within the panel. Approximately half of the group felt that as the prognostic significance of this pattern is unknown one should not assign a grade to glomeruloid patterns and rather just grade the surrounding tumor; in the rare case where the entire tumor is composed of glomeruloid glands, a grade of 3 + 3 = 6 should be assigned. The other half of the panel felt that these structures should be assigned a Gleason pattern 4. Because of the lack of consensus, either approach would be acceptable by practicing pathologists until future data indicate which method is more accurate.

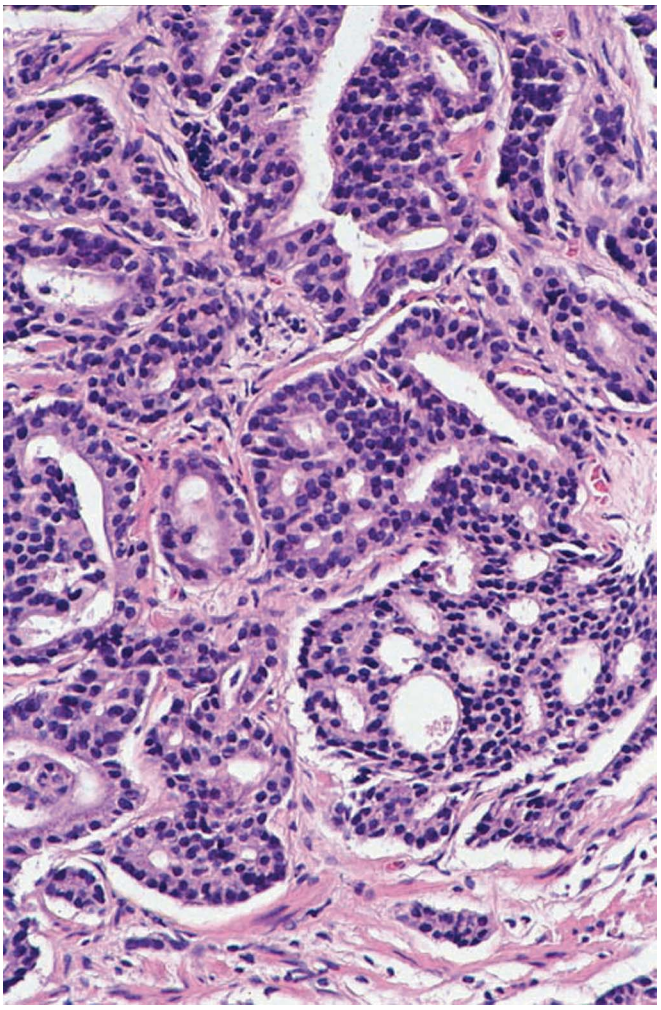

FIGURE 10. Adenocarcinoma Gleason score 4 + 4 = 8 with large irregular cribriform glands.

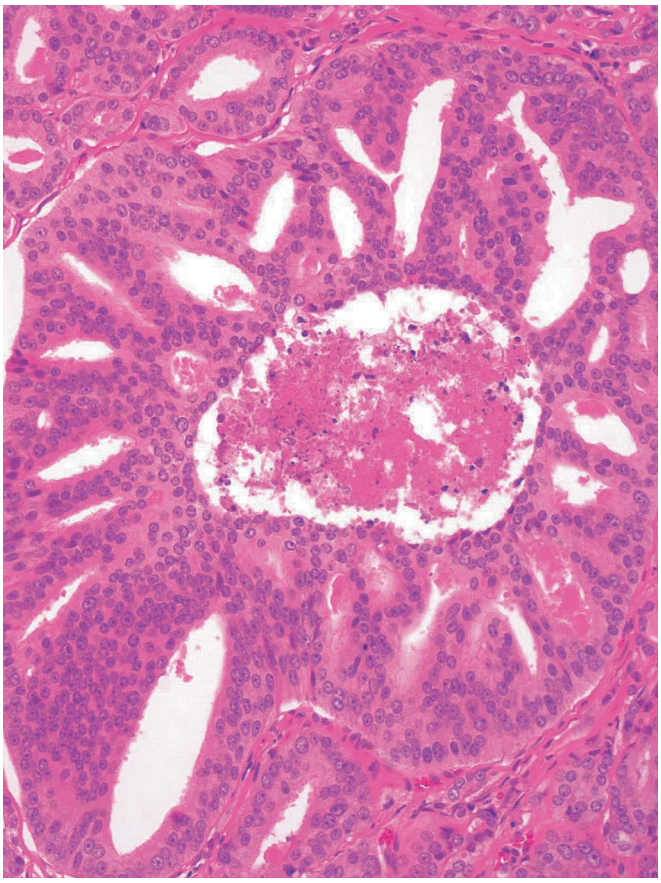

FIGURE 11. Gleason pattern 5 cancer with cribriform gland containing central comedonecrosis.

Pseudohyperplastic Adenocarcinoma

Rarely, adenocarcinomas of the prostate may architecturally resemble benign glands.[19,21] These typically consist of larger glands with papillary infolding and branching (Fig. 18). It was the consensus of the panel that these tumors should be graded as Gleason score 3 + 3 = 6 with pseudohyperplastic features. This is in large part based on the recognition that they are most often accompanied by more ordinary Gleason score 3 + 3 = 6 adenocarcinoma.

REPORTING SECONDARY PATTERNS OF LOWER GRADE WHEN PRESENT TO A LIMITED EXTENT

It was the consensus of the group that in the setting of high-grade cancer one should ignore lower-grade patterns if they occupy less than 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 $\geq$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 (Fig. 19). Given the significant potential in this scenario of a sampling error resulting from only limited cancer on biopsy, the presence of a relatively small amount of pattern 3 would most likely correspond to a Gleason score 7 tumor in the corresponding prostate. The same 5% cutoff rule for excluding lower-grade cancer also applies for TURPs and radical prostatectomy specimens, which in most cases would relate to extensive cancer with >95% Gleason pattern 4 tumor.

REPORTING SECONDARY PATTERNS OF HIGHER GRADE WHEN PRESENT TO A LIMITED EXTENT

It was the consensus of the group that 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

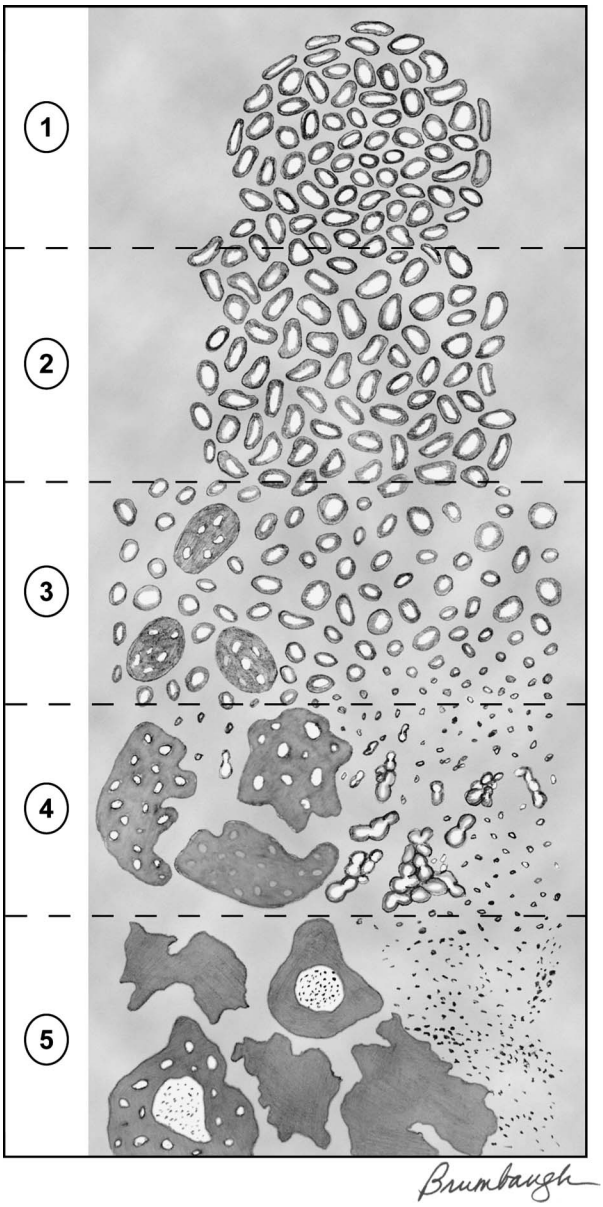

FIGURE 12. Schematic diagram of modified Gleason grading system.

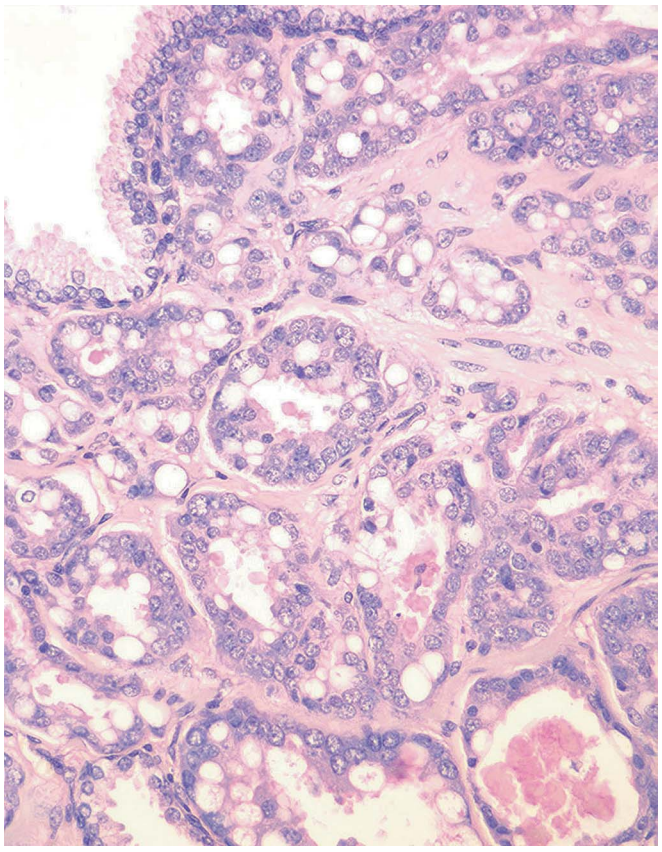

FIGURE 13. Adenocarcinoma of the prostate Gleason score 3 + 3 = 6 with prominent vacuoles.

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 because of 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 radical prostatectomy specimens with the analogous situation of a tumor nodule having 98% Gleason pattern 3 and 2% pattern 4, there was no consensus within the group. Approximately half of the group would diagnose these foci in an analogous fashion to that done on needle biopsy and interpret the case as Gleason score 3 + 4 = 7 regardless of the percentage of pattern 4. The other half would note these tumors as Gleason score 3 + 3 = 6 with a minor component of Gleason pattern 4. The rationale for the latter method is based on radical prostatectomy data; cancers with >95% Gleason pattern 3 and <5% pattern 4 have pathologic stages that are worse than a pure Gleason score 3 + 3 = 6 tumor yet not as adverse as a Gleason score 3 + 4 = 7 where pattern 4 occupies >5% of the tumor.[24,27]

TERTIARY GLEASON PATTERNS

Needle Biopsy

The typical scenario with tertiary patterns on biopsy includes tumors with patterns 3, 4, and 5 in various proportions. It was the uniform consensus of the group that such tumors should be classified overall as high grade (Gleason score 8–10) given the presence of high-grade tumor (patterns 4 and 5) on needle biopsy. It was the consensus that these tumors on needle biopsy should not be graded by listing the primary and secondary pattern with a note relating to the tertiary pattern. When the grade is assigned for management of the patient, notes are typically dropped and only the primary and secondary patterns are incorporated within the treatment plan. Many clinicians use various tables (ie, Partin tables) or

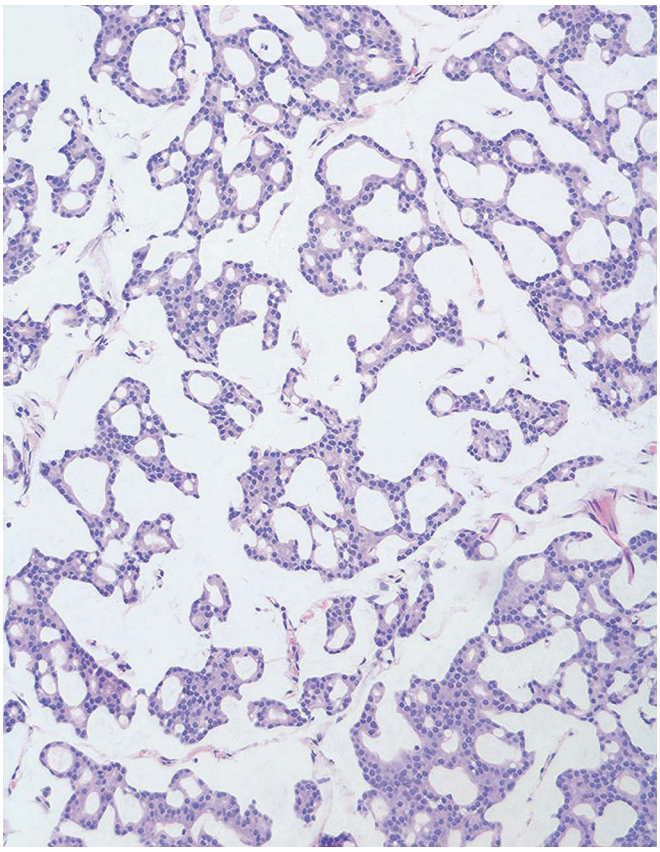

FIGURE 14. Gleason score 4 + 4 = 8 colloid cancer with irregular cribriform glands floating within mucinous lakes.

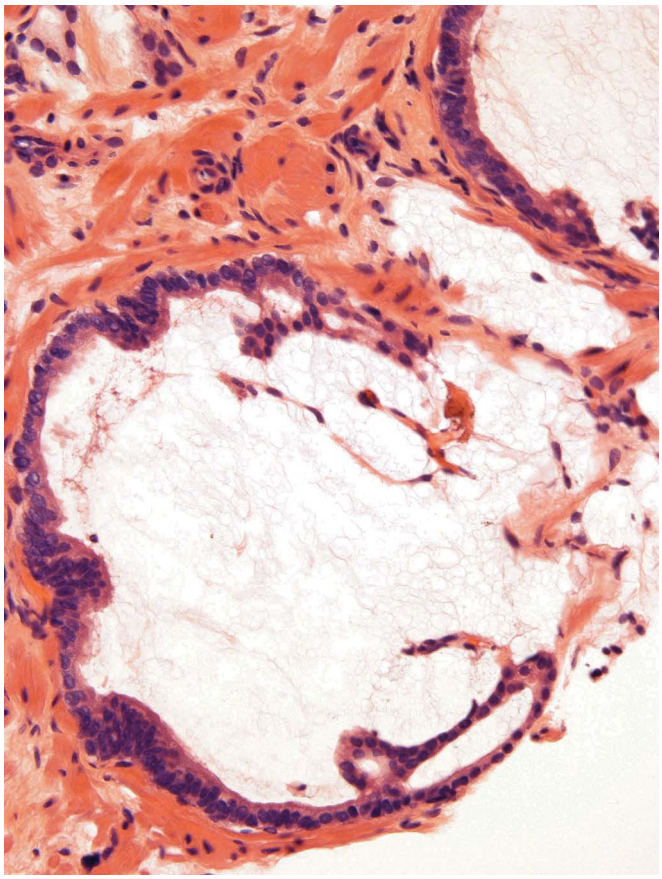

FIGURE 15. Minute focus of adenocarcinoma Gleason score 3 + 3 = 6 with focal mucin extravasation.

algorithms (ie, Kattan nomograms) to predict outcomes such as pathologic stage or prognosis following radical prostatectomy, and prognosis following radiotherapy.[8,28] All of these tables and nomograms incorporate the Gleason score without regard to a tertiary pattern mentioned in a note. For example, a tumor with a Gleason score 3 + 4 and a tertiary component of 5 on needle biopsy would be recorded for the purpose of these nomograms and tables as Gleason score 3 + 4 = 7. The consensus of the group was that on needle biopsies with patterns 3, 4, and 5, both the primary pattern and the highest grade should be recorded (Fig. 20). Consequently, tumors with Gleason score 3 + 4 and a tertiary pattern 5 would be recorded as Gleason score 3 + 5 = 8. In cases where there are three patterns consisting of patterns 2, 3, and 4, it was the consensus of the group that one would ignore the pattern 2 and the biopsy would be called Gleason score 3 + 4 = 7 or Gleason score 4 + 3 = 7, depending on whether pattern 3 or pattern 4 was more prevalent.

Radical Prostatectomy

In radical prostatectomy specimens, the situation is not analogous to that seen on needle biopsy, as one has the entire nodule available for examination. For example, tumors at radical prostatectomy that are Gleason score 4 + 3 = 7 with a tertiary pattern 5, whereas behaving worse than Gleason score 4 + 3 = 7 tumors without a tertiary pattern 5 have a much lower incidence of seminal vesicle invasion and lymph node metastases compared with tumors that are Gleason score 4 + 5 = 9.[24] Consequently, on radical prostatectomy specimens, it would be misleading to derive the Gleason score by adding the most common Gleason pattern and the highest Gleason pattern. It was the consensus of the group that for a radical prostatectomy specimen one assigns the Gleason score based on the primary and secondary patterns with a comment as to the tertiary pattern (Fig. 20).

PERCENT PATTERN 4–5

As a modification to the Gleason system, it has been proposed that one should record the percentage pattern 4/5 both on biopsy and radical prostatectomy specimens.[33] However, percent pattern 4/5 is only very predictive for prognosis in radical prostatectomy specimens at the extremes of the percentages. The percent of pattern 4/5 on needle biopsy has also been shown not to correlate well with the percentage of pattern 4/5 in the corresponding radical prostatectomy. It has also not been demonstrated that classifying tumors based on the percent pattern 4/5 is more predictive than Gleason score 2–4, 5/6, 3 + 4, 4 + 3, or 8–10. Also, assessing the percent of pattern 4 is difficult as patterns 3 and 4 are often intimately mixed. Consequently, it was the consensus of the group that

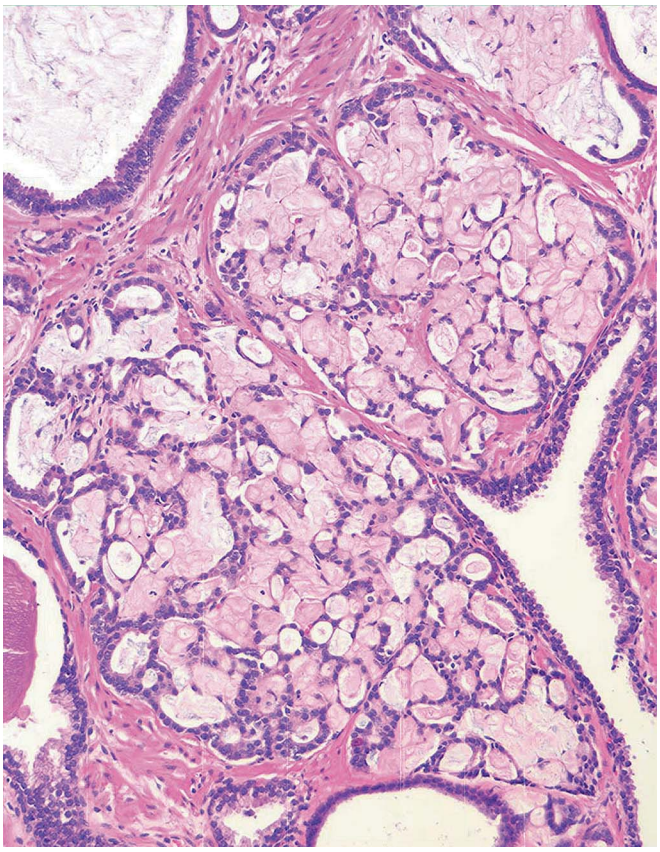

FIGURE 16. Gleason score 3 + 3 = 6 with extensive mucinous fibroplasia.

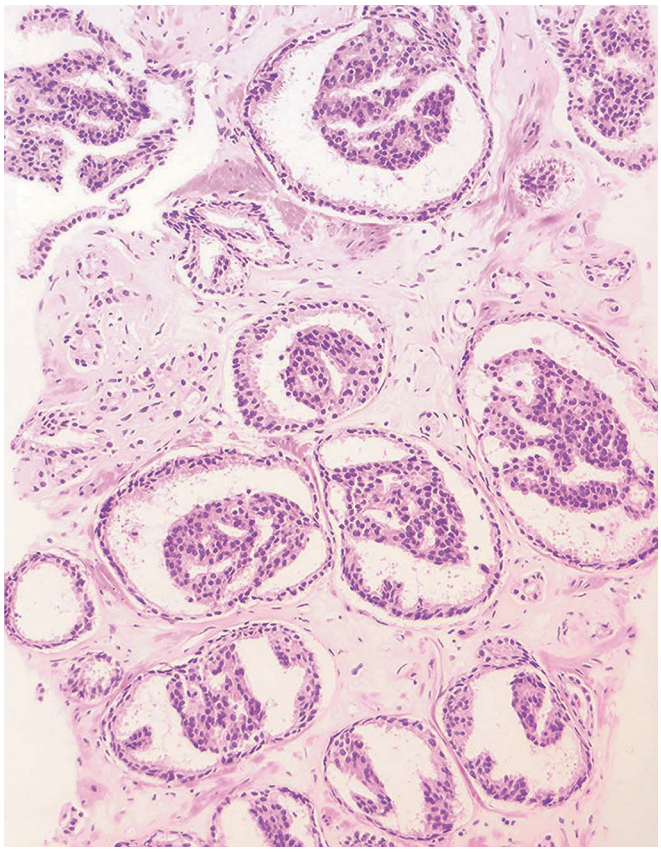

FIGURE 17. Cancer with prominent glomeruloid pattern.

percent pattern 4/5 should not be required or recommended as a method of Gleason grading. However, it remains an option if one wants to include this information in addition to the routine Gleason score.

RADICAL PROSTATECTOMY SPECIMENS WITH SEPARATE TUMOR NODULES

It was recommended that radical prostatectomy specimens should be processed in an organized fashion 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 a radical prostatectomy 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.[7,18,32] 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. It was the consensus of the group that 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. It was also recognized that if a tumor were graded, for example, as Gleason score 4 + 2 = 6 or 2 + 4 = 6, the presence of pattern 4 within such a diagnosis would not be emphasized and the patient would typically merely be recorded as having a Gleason score 6 tumor, which would not accurately reflect the nature of his lesion. The recommendation of the consensus conference was that one should assign a separate Gleason score to each dominant tumor nodule(s). With only a couple of exceptions, pathologists within the consensus conference who were authors of large radical prostatectomy series had already adopted this method of grading, and the prognostic impact of the Gleason score within these series already reflects this approach. 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 nondominant 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,

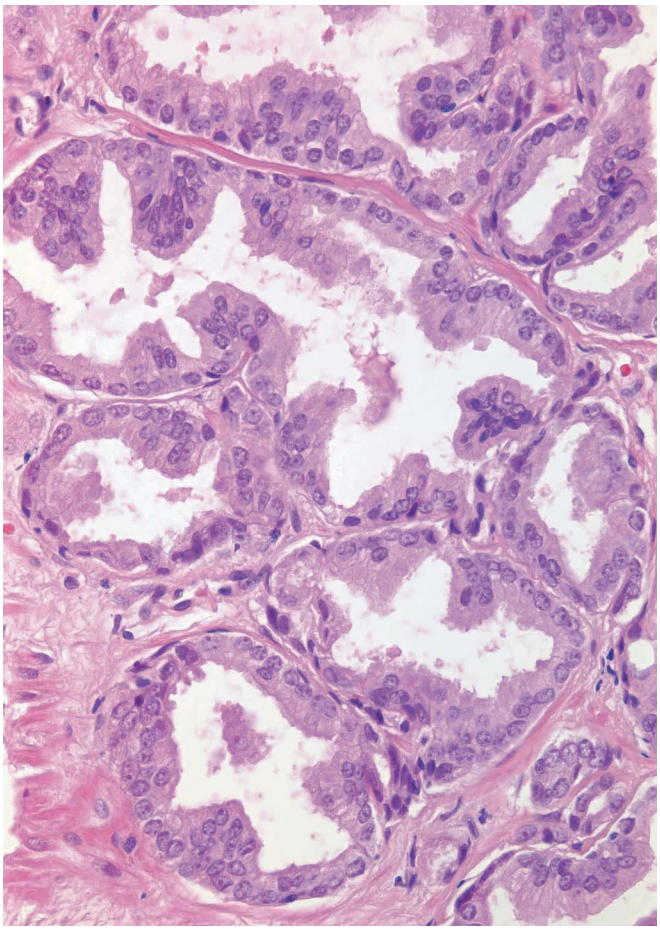

FIGURE 18. Gleason score 3 + 3 = 6 pseudohyperplastic adenocarcinoma.

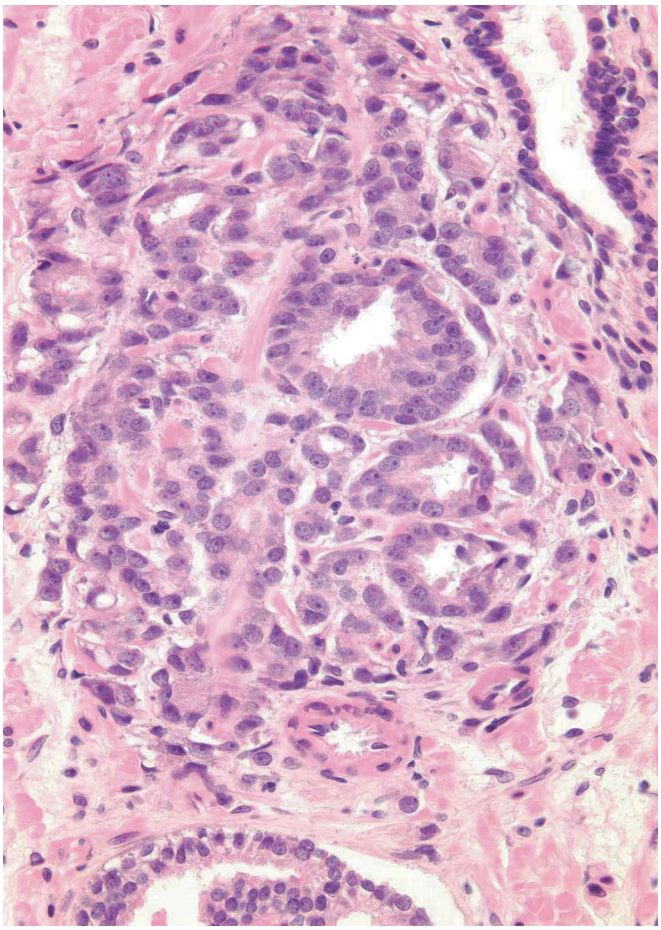

FIGURE 19. Small focus of Gleason score 4 + 3 = 7 on needle biopsy with poorly defined and fused glands of pattern 4, and a few well-defined glands of pattern 3 occupying >5% of the tumor area.

separate grades will be assigned to only one or at most two dominant nodules.

NEEDLE BIOPSY WITH DIFFERENT CORES SHOWING DIFFERENT GRADES

This issue assumes its greatest importance when one or more of the cores shows pure high-grade cancer (ie, Gleason score 4 + 4 = 8) and the other cores show pattern 3 (3 + 3 = 6, 3 + 4 = 7, 4 + 3 = 7) cancer. One option is to report the grades of each core separately, whereby the highest grade tumor (Gleason score 8) would typically be the one selected by the clinician as the grade of the entire case.[31] Others have proposed to give instead only one overall score for the entire case. For example, in a case with Gleason score 4 + 4 = 8 on one core with pattern 3 (3 + 3 = 6, 3 + 4 = 7, 4 + 3 = 7) on other cores, the overall score for the entire case, averaging all involved needle biopsies together as if they were one long positive core, would be Gleason score 4 + 3 = 7 or 3 + 4 = 7, depending on whether pattern 4 or 3 predominated. In the only study to address this issue, it was demonstrated that when one core is Gleason score 4 + 4 = 8 with other cores having pattern 3, the pathologic stage at radical prostatectomy is comparable to cases with all needle cores having Gleason score 4 + 4 = 8.[20] In another study, the highest Gleason score and the biopsy core with the highest tumor volume correlated best with final Gleason score at radical prostatectomy.[29] Additional support for giving cores a separate grade rather than an overall score for the entire case is that all of the various tables (ie, Partin tables) and nomograms that have been validated and proven to be prognostically useful have used the highest core grade of the given case in cases where there are multiple cores of different grades. In a recent survey of the Society of Urologic Oncology, 81% of urologists used the highest Gleason score on a positive biopsy, regardless of the overall percentage involvement, to determine treatment.[31] Consequently, the consensus of the group was to 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 addition to giving separate cores individual Gleason scores, one has the option to also give an overall score at the end of the case.

There was not a consensus as to how to grade different cores with different grades when the different cores were present within the same specimen container without a

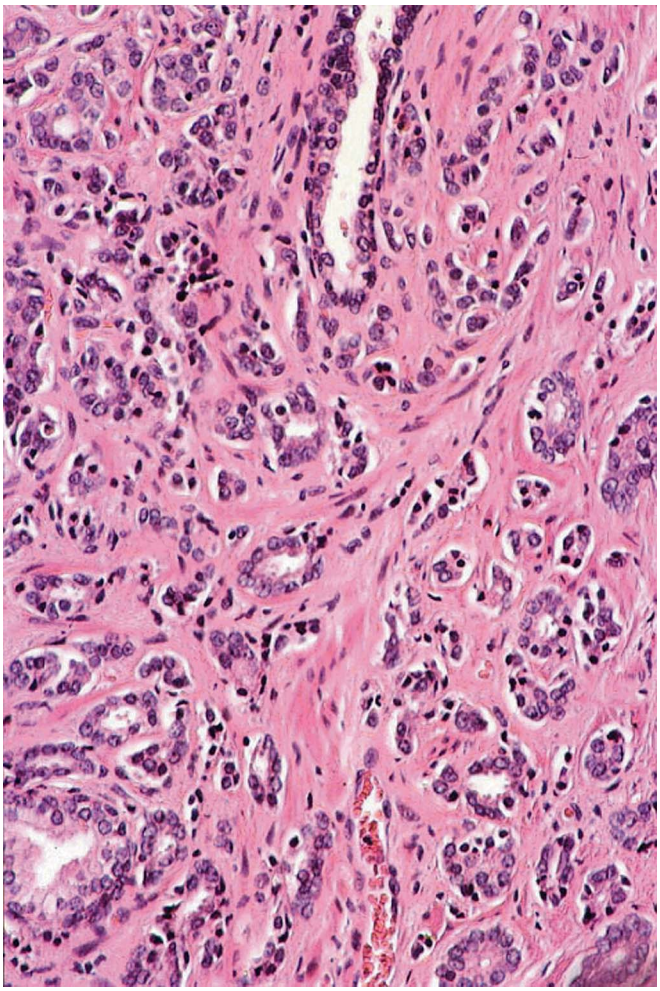

FIGURE 20. Tumor with patterns 3, 4, and 5. If present on a radical prostatectomy, it would be graded as ''Gleason score 3 + 4 = 7 with tertiary pattern 5.'' If present on a needle biopsy, it would be graded as ''Gleason score 3 + 5 = 8.''

designation as to site. For example, one may have two cores of tissue from the left base in one jar without further designation, or multiple cores divided into containers from the left and right side of the gland. If more than one core contained cancer in the setting of multiple cores per container, approximately half of the group said that one should still grade each core separately with the remaining half of the group saying that one should give an overall grade for the involved cores per specimen container. One rationale for this latter approach was that it is implicit that clinicians submitting multiple cores together in one container do not value the specific information derived from the cores within a given container.

It was emphasized that in cases with multiple cores per jar, cores often fragment where it becomes impossible or potentially misleading to give a Gleason score on a small tissue fragment. For example, to call Gleason score 4 + 4 = 8 on a tiny tissue fragment where there are other fragments with Gleason score 3 + 3 = 6 could be misleading; if the cores were intact and the tumor was all on one core, it would be assigned a Gleason score 3 + 4 = 7 or 4 + 3 = 7. In cases where a container contains multiple pieces of tissue and one cannot be sure if one is looking at an intact core, the consensus of the group was that one should only give an overall score for that container.

In summary, it is remarkable that nearly 40 years after the inception of the Gleason grading system it remains one of the most powerful prognostic predictors in prostate cancer. In part, this system has remained timely by minor adaptations of the system to accommodate the changing practice of medicine. However, with these changes have come variations in applying the Gleason system among pathologists with some differences regional in nature and others dependent on other demographic factors. For example, it was demonstrated that pathologists over 50 years of age tended to diagnose Gleason score 2–4 on needle biopsy to a statistically significantly higher frequency than younger pathologists, who were trained to do so rarely if ever.[9] The assigning of an overall score to needle biopsy specimens with different grades on different cores is more of a phenomenon practiced in Europe as compared with the United States.[9] Even within the United States, our consensus conference brought out many differences in how the Gleason system was applied. With the exception of only a few areas, clear consensus was reached by the majority of genitourinary pathologists who participated in this meeting. It is hoped that these consensus guidelines will help pathologists adapt the Gleason grading system to current day practice in a more uniform manner, whereas at the same time fostering collaborative studies to address controversial areas where data are currently lacking.

REFERENCES

1. Amin MB, Schultz DS, Zarbo RJ. Analysis of cribriform morphology in prostatic neoplasia using antibody to high molecular-weight cytokeratin. *Arch Pathol Lab Med*. 1994;118:260–264.
2. Amin M, Boccon-Gibod L, Egevad, et al. Prognostic and predictive factors and reporting of prostate carcinoma in prostate needle biopsy specimens. *Scand J Urol Nephrol*. 2005;39:20–33.
3. Bailar JC 3rd, Mellinger GT, Gleason DF. Survival rates of patients with prostatic cancer, tumor stage, and differentiation: preliminary report. *Cancer Chemother Rep*. 1966;50:129–136.
4. Baisden BL, Kahane H, Epstein JI. Perineural invasion, mucinous fibroplasia, and glomerulations: diagnostic features of limited cancer on prostate needle biopsy. *Am J Surg Pathol*. 1999;23:918–924.
5. Bostwick DG, Wollan P, Adlakha K. Collagenous micronodules in prostate cancer: a specific but infrequent diagnostic finding. *Arch Pathol Lab Med*. 1995;119:444–447.
6. Brinker DA, Potter SR, Epstein JI. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. *Am J Surg Pathol*. 1999;23:1471–1479.
7. Cohen MB, Soloway MS, Murphy WM. Sampling of radical prostatectomy specimens: how much is adequate? *Am J Clin Pathol*. 1994;101:250–252.
8. DiBlasio CJ, Rhee AC, Cho D, et al. Predicting clinical end points: treatment nomograms in prostate cancer. *Semin Oncol*. 2003;30:567–586.
9. Egevad L, Allsbrook WC, Epstein JI. Current practice of Gleason grading among genitourinary pathologists. *Hum Pathol*. 2005;36:5–9.
10. Epstein JI, Lieberman PH. Mucinous adenocarcinoma of the prostate gland. *Am J Surg Pathol*. 1985;9:299–308.
11. Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. *Am J Surg Pathol*. 2000;24:477–478.
12. Epstein JI, Algaba F, Allsbrook J, et al. Acinar adenocarcinoma. In: Eble JN, Sauter G, Epstein JI, et al, eds. *World Health Organization*

Classification of Tumours. *Pathology & Genetics*: *Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press, 2004:179–184.
13. Epstein JI, Amin M, Boccon-Gibod L, et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. *Scand J Urol Nephrol*. 2005;39:34–36.
14. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep*. 1966;50:125–128.
15. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol*. 1974;11:58–64.
16. Gleason DF. Histological grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic Pathology*: *The Prostate*. Philadelphia: Lea & Feibiger, 1977:171–198.
17. Hodge KK, McNeal JE, Terris MK, et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J Urol*. 1989;142:71–74.
18. Hall GS, Kramer CE, Epstein JI. Evaluation of radical prostatectomy specimens: a comparative analysis of sampling methods. *Am J Surg Pathol*. 1992;16:315–324.
19. Humphrey PA, Kaleem Z, Swanson PE, et al. Pseudohyperplastic prostatic adenocarcinoma. *Am J Surg Pathol*. 1998;22:1239–1246.
20. Kunz GM Jr, Epstein JI. Should each core with prostate cancer be assigned a separate Gleason score? *Hum Pathol*. 2003;34:911–914.
21. Levi AW, Epstein JI. Pseudohyperplastic prostatic adenocarcinoma on needle biopsy and simple prostatectomy. *Am J Surg Pathol*. 2000;24:1039–1046.
22. Mellinger GT, Gleason D, Bailar J 3rd. The histology and prognosis of prostatic cancer. *J Urol*. 1967;97:331–337.
23. Mellinger GT. Prognosis of prostatic carcinoma. *Recent Results Cancer Res*. 1977;61–72.
24. Mosse CA, Magi-Galluzzi C, Tsuzuki T, et al. The prognostic significance of tertiary Gleason pattern 5 in radical prostatectomy specimens. *Am J Surg Pathol*. 2004;28:394–398.
25. Nelson RS, Epstein JI. Prostatic carcinoma with abundant xanthomatous cytoplasm: foamy gland carcinoma. *Am J Surg Pathol*. 1996;20:419–426.
26. Pacelli A, Lopez-Beltran A, Egan AJ, et al. Prostatic adenocarcinoma with glomeruloid features. *Hum Pathol*. 1998;29:543–546.
27. Pan CC, Potter SR, Partin AW, et al. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens: a proposal to modify the Gleason grading system. *Am J Surg Pathol*. 2000;24:563–569.
28. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *JAMA*. 1997;277:1445–1451.
29. Poulos CK, Daggy JK, Cheng L. Preoperative prediction of Gleason grade in radical prostatectomy specimens: the influence of different Gleason grades from multiple positive biopsy sites. *Mod Pathol*. 2005;18:228–234.
30. Ro JY, Grignon DJ, Ayala AG, et al. Mucinous adenocarcinoma of the prostate: histochemical and immunohistochemical studies. *Hum Pathol*. 1990;21:593–600.
31. Rubin MA, Bismar TA, Curtis S, et al. Prostate needle biopsy reporting: how are the surgical members of the Society of Urologic Oncology using pathology reports to guide treatment of prostate cancer patients? *Am J Surg Pathol*. 2004;28:946–952.
32. Sehdev AE, Pan CC, Epstein JI. Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. *Hum Pathol*. 2001;32:494–499.
33. Stamey TA, McNeal JE, Yemoto CM, et al. Biological determinants of cancer progression in men with prostate cancer. *JAMA*. 1999;281:1395–1400.
34. Steinberg DM, Sauvageot J, Piantadosi S, et al. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. *Am J Surg Pathol*. 1997;21:566–576.
35. Tran TT, Sengupta E, Yang XJ. Prostatic foamy gland carcinoma with aggressive behavior: clinicopathologic, immunohistochemical, and ultrastructural analysis. *Am J Surg Pathol*. 2001;25:618–623.

