Prostate Cancer Grading

A Decade After the 2005 Modified Gleason Grading System

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• Since 1966, when Donald Gleason, MD, first proposed grading prostate cancer based on its histologic architecture, there have been numerous changes in clinical and pathologic practices relating to prostate cancer. Patterns 1 and 2, comprising more than 30% of cases in the original publications by Gleason, are no longer reported on biopsy and are rarely diagnosed on radical prostatectomy. Many of these cases may even have been mimickers of prostate cancer that were described later with the use of contemporary immunohistochemistry. The original Gleason system predated many newly described variants of prostate cancer and our current concept of intraductal carcinoma. Gleason also did not describe how to report prostate cancer on biopsy with multiple cores of cancer or on radical prostatectomy with separate tumor nodules. To address these issues, the International Society of Urological Pathology first made revisions to the grading system in 2005, and subsequently in 2014. Additionally, a new grading system composed of Grade Groups 1 to 5 that was first developed in 2013 at the Johns Hopkins Hospital and subsequently validated in a large multi-institutional and multimodal study was presented at the 2014 International Society of Urological Pathology meeting and accepted both by participating pathologists as well as urologists, oncologists, and radiation therapists. In the present study, we describe updates to the grading of prostate cancer along with the new grading system.

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The first publications on prostate cancer appeared in the first decade of the 20th century and were by Hugh Hampton Young, MD, a urologist from The Johns Hopkins Hospital and a founder of the *Journal of Urology* in 1917, who developed the technique of perineal prostatectomy more than a hundred years ago.[1] In 1909, Young described his experience with 111 patients with prostate cancer and acknowledged the contribution of pathologist John T. Geraghty, MD, who described pathologic findings in 9 autopsies, 6 radical prostatectomies (RPs), and 24 *partial* prostatectomies.[2] The author noted that "the histologic character of cancer of the prostate is very variable" and described acinar, scirrhous, and solid patterns of growth. Interestingly, intraductal spread of carcinoma was also noted. Subsequent reports on prostate cancer mostly followed Broders' approach of grading carcinomas based on "the percentage of undifferentiated cells."[3,4]

In 1966, Donald Gleason, MD, developed the classification of prostatic carcinomas on material from a group of Veterans Administration Hospitals. In a major departure from prior classifications, Gleason used prostate cancer histologic architectural pattern, rather than cytology, for assigning the grade. The classification was developed using biopsies, transurethral resections, and RPs from 270 patients.[5] Because most of the specimens showed more than one pattern of carcinoma, it was suggested to assign two patterns to each case in the order of dominance. This grading system was subsequently tested to predict prostate cancer–related mortality in 1032 patients.[6] Since then, the system has received a worldwide acceptance and is referred to as the Gleason grading system.[7]

RATIONALE FOR MODIFICATION OF THE GLEASON SYSTEM

The underlying principles of the Gleason grading system and its contributions to prostate cancer clinical management retain relevance and influence more than half a century from the time of its development. However, a number of new pathologic and clinical discoveries, changes in prostate cancer screening and detection, and development of new clinical and pathologic methodologies justify the need for revising the original grading system.

The original works by Gleason were performed on morphology alone without immunohistochemistry. It is very likely that some of the originally described patterns 1 and 2 that constituted a third of cancer in Gleason's 1974 publication were actually more recently described mimickers of carcinoma, such as adenosis or partial atrophy.[6,8] Gleason recommended reporting the primary (most common) and secondary (second most common) patterns, whereas a minor component of higher-grade cancer, if present, was not mentioned in the report. Consequently, the issues of

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tertiary patterns of higher grade on RPs and biopsies were not dealt with. Gleason did not provide recommendations on reporting multiple cores involved by cancer from different sites or reporting different tumor nodules of different grade in RPs. Whereas in Gleason's era only a few large-gauge needles were directed into palpable tumors, with discovery of prostate-specific antigen testing, contemporary practice typically samples at least 12 cores, with 1, 2, or 3 cores per container.[9] Finally, some new patterns of prostatic carcinoma have been described in more recent times that needed incorporation into the Gleason grading system.[10–16]

To address the above needs, two consensus conferences were held by the International Society of Urological Pathology (ISUP). Only pathology experts were involved in the 2005 ISUP conference. In the 2014 consensus conference, in addition to 67 pathology experts from 17 countries, there were 17 urologists, oncologists, and radiation oncologists who met to resolve both matters that were unresolved from the 2005 meeting as well as new grading issues that arose in the interim 10 years. The key findings from these two conferences are described below.

GLEASON PATTERNS 1 TO 5

Gleason Patterns 1 to 2

In 2000, one of the current authors (J.I.E.) wrote an editorial entitled, "Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made."[17] This recommendation was based on: (1) poor reproducibility even among experts; (2) poor correlation with RP grade, with almost all cases showing higher grade at resection; and (3) that a diagnosis of Gleason score 2 to 4 may misguide clinicians and patients into believing that the patient has an indolent tumor. The 2005 consensus conference softened this proposal, recommending 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*."[7] The 2014 conference removed the caveat and agreed with the 2000 editorial.[8]

Gleason Pattern 3

A major point of divergence from the original Gleason system is with the assignment of grade to cribriform glands. Within Gleason's original illustrations of his cribriform pattern 3, he depicts large cribriform glands.[18] Cases graded prior to 2005 as Gleason pattern 3 included large cribriform glands that today would uniformly be called Gleason pattern 4.[19,20] It was agreed in the 2005 consensus that the vast majority of cribriform patterns be diagnosed as Gleason pattern 4, with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3.[7] However, at the 2005 conference, when various images of these rare candidates for cribriform Gleason pattern 3 were shown to the participants of the consensus meeting, almost none of them were uniformly accepted as cribriform pattern 3 based on subtle features. A subsequent study, led by one of the current authors and published in 2008, found that even in a highly selected set of images thought to be the best candidates for cribriform pattern 3, most experts interpreted the cribriform patterns as pattern 4.[21] The authors of this study concluded that all cribriform structures should be interpreted as Gleason pattern 4 and not pattern 3.[22] This was formally accepted in the 2014 consensus conference, based both on the poor interobserver reproducibility of experts in diagnosing cribriform Gleason pattern 3 cancer and subsequent numerous studies demonstrating that cribriform glands, regardless of morphology, were associated with an adverse prognosis.[8,20,23,24]

The glomeruloid pattern of prostate cancer has a very typical morphology of a cribriform structure protruding inside a dilated cancer gland and only focally being attached to it, creating an architectural resemblance of a kidney glomerulus (Figure 1, A). Gleason did not describe the grading approach to glomeruloid structures. However, in his work from 1966 there are clear-cut glomeruloid structures in a pattern that he described as pattern 2 (Figure 1, B, in Gleason[5]). The grading of glomeruloid glands was controversial and unresolved in the 2005 consensus conference. In a subsequent 2009 work by Lotan and Epstein,[11] only a minor percentage of cancers with glomeruloid patterns were associated with Gleason pattern 3, and it was suggested that Gleason pattern 4 be assigned to glomeruloid structures. We confirmed this approach, demonstrating that cases with glomeruloid structures and otherwise Gleason pattern 3 disease were capable of regional lymph node metastases and should be assigned Gleason pattern 4.[20] In two recent studies it was shown that glomeruloid structures should be considered as an early stage of cribriform Gleason pattern 4.[23,24] In the 2014 consensus meeting, there was uniform agreement to consider glomeruloid structures as Gleason pattern 4.[8]

The original Gleason pattern 4 consisted almost entirely of cribriform patterns with a minor component of fused glands. Ill-defined glands with poorly formed glandular lumina were not discussed or depicted by Gleason in either Gleason pattern 3 or 4. It was the consensus of the 2005 conference that poorly formed glands should not be considered Gleason pattern 3. Consequently, only individual, well-formed glands were allowed for Gleason pattern 3.[7]

Gleason Pattern 4

As described above, based on the 2005 and 2014 conferences, Gleason pattern 4 now consists of either: (1) cribriform glands (including the glomeruloid pattern); (2) poorly formed glands; and (3) fused glands. Gleason's description of a *hypernephromatoid* pattern 4 was not clear and is no longer recommended to be used. Occasional seemingly poorly formed or fused glands between well-formed glands are insufficient for a diagnosis of Gleason pattern 4 because they could represent tangential sections of adjacent well-formed glands.[25] In order to avoid overdiagnosing Gleason pattern 4 in this setting, the cluster of poorly formed glands should be seen at magnification ×10. If a focus of cancer is borderline between Gleason patterns 3 and 4, one should assess the focus on levels, and if still borderline then should assign Gleason pattern 3.[26]

Gleason Pattern 5

Gleason pattern 5 remains essentially the same as Gleason's original scheme. Gleason pattern 5 is composed of: (1) solid nests, (2) cords of cells, (3) individual cells, or (4) nests or cribriform glands with unequivocal necrosis. The one clarification made in the 2014 conference was that solid medium to large nests with rosettelike spaces, where the attempt at glandular differentiation was too poor, should be graded as Gleason pattern 5. Gleason pattern 5 is frequently underdiagnosed on prostate needle biopsy.[27]

One of us (J.I.E.) has demonstrated that in approximately 50% to 60% of cases submitted in consultation at the

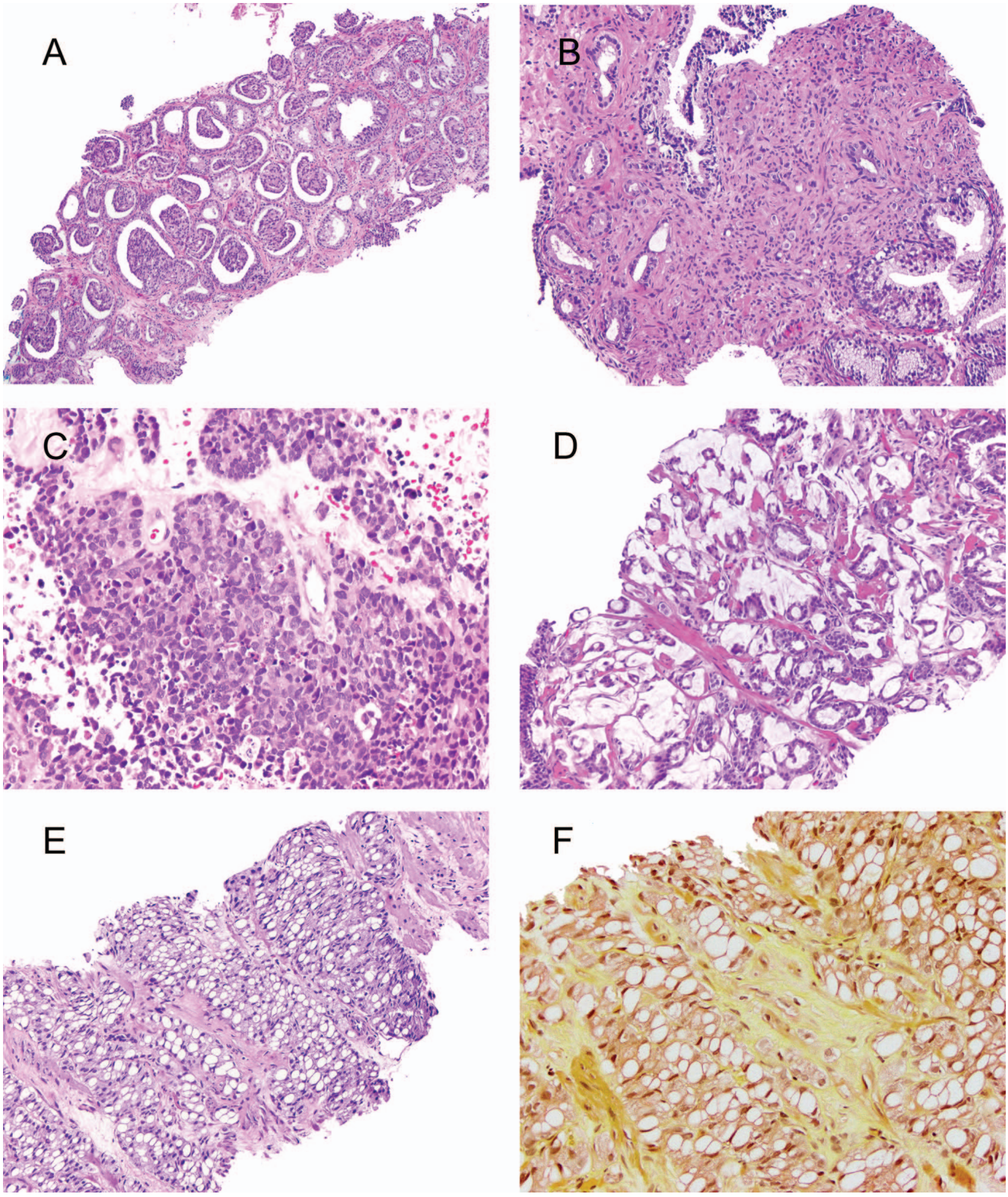

Figure 1. *A, Needle core biopsy, with the majority of cancer forming glomeruloid structures, Gleason score 4 + 4 = 8/Grade Group 4. B, Combination of patterns 5 (right-hand side) and 3 (left-hand side), Gleason score 5 + 3 = 8/Grade Group 4. C, Small cell carcinoma of the prostate; no Gleason score is assigned. D, Mucinous prostatic adenocarcinoma composed of well-formed glands, Gleason score 3 + 3 = 6/Grade Group 1. E, Prostatic adenocarcinoma with intracytoplasmic vacuoles forming signet ring–like cells, Gleason score 5 + 5 = 10/Grade Group 5. F, Same case as E, with intracytoplasmic vacuoles that lack mucin and should be mentally subtracted for grading (hematoxylin-eosin, original magnifications ×10 [A], ×40 [B and C], and ×20 [D and E]; mucicarmine, original magnification ×40 [F]).*

request of patients or clinicians, pattern 5 was underdiagnosed.[27,28] Pattern 5 is more commonly missed when it is not the primary pattern, and the solid-sheet pattern was most readily identified correctly as Gleason pattern 5.[28] A recent study assessed the interobserver variability on the interpretation of limited amount of pattern 5 in biopsy specimens between 16 urologic pathologists.[29] Although large collections of single cells or clusters achieved consensus of Gleason pattern 5, small nests and single cells/cords of 5 or fewer cells achieved consensus against pattern 5. Most of the experts considered diagnosing pattern 5 only when present on more than 1 level. Although in most of the biopsy cases pattern 5 will be associated with pattern 4, in a minor proportion of biopsies pattern 5 may be the primary or secondary grade in otherwise Gleason pattern 3 disease (Figure 1, B). In a recent study describing 462 men with Gleason score 8 cancer on biopsy, 421 (91.1%) had Gleason score 4 + 4 = 8, and only 41 (8.9%) had a combination of patterns 3 and 5.[30]

Two reports suggest that Gleason score 8 cases with pattern 5 differ in prognosis from those with 4 + 4 = 8 disease.[30,31] One of these studies included patients from 1998 to 2012 who underwent radiation and/or androgen deprivation therapy 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.[30] No comparison was performed between the outcomes of Gleason score 3 + 5 = 8 and 5 + 3 = 8, and cases from before the 2005 ISUP conference would have been graded significantly differently 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.[31] Although 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 of 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 a large multi-institutional study with genitourinary pathology experts from 2005–2014, of 20 845 RP specimens, there were 39 cases (0.2%) with 3 + 5 = 8 and 4 (0.02%) with 5 + 3 = 8 (J.I.E., unpublished data).[32] Similarly, of 16 172 needle biopsy cases, there were only 44 (0.3%) with 3 + 5 = 8 and 6 (0.04%) with 5 + 3 = 8 (J.I.E., unpublished data). These data indicate that Gleason score 5 + 3 = 8 cancer on needle biopsy or RP almost never occurs in clinical practice.

VARIANTS OF PROSTATE CANCER

The overall rule in grading variants of prostate cancer is to grade the underlying pattern in a fashion analogous to that of usual prostate adenocarcinoma. Individual, well-formed glands are Gleason pattern 3, cribriform/poorly formed/fused glands are Gleason pattern 4, and lack of gland formation and necrosis are Gleason pattern 5. In cases with mixed usual prostatic adenocarcinoma and variant morphology, both the usual acinar prostate carcinoma and variants are graded. The only exception to this rule is small cell carcinoma that is not assigned a grade.

Small Cell Carcinoma

Small cell carcinoma of the prostate is an aggressive high-grade neuroendocrine carcinoma with the diagnostic features similar to those described in pulmonary small cell carcinoma (Figure 1, C).[33] Despite the lack of gland formation similar to Gleason pattern 5, small cell carcinoma has a unique morphology, and more importantly has a worse prognosis with different treatment than poorly differentiated prostatic adenocarcinoma.[34] Consequently, small cell carcinoma should be diagnosed without assigning a Gleason grade. However, many cases are a mixture of high-grade acinar carcinoma and small cell carcinoma.[34,35] In such cases, the prostatic adenocarcinoma component should be given a Gleason score, although the small cell carcinoma component is still not graded.

Mucinous Prostatic Adenocarcinoma

This variant is diagnosed in the presence of extraglandular mucin. In RP specimens, a designation of mucinous adenocarcinoma should be rendered when more than 25% of tumor nodule is represented by mucinous carcinoma.[12,23,36] In biopsy specimens, the term "adenocarcinoma with mucinous features" should be used. In the 2005 ISUP consensus meeting there was no agreement regarding the grading of mucinous prostatic adenocarcinoma (Figure 1, D). This is in part related to conflicting evidence in limited prior publications.[12,37,38] In 2006, Lane et al[36] assessed 12 cases of mucinous prostatic adenocarcinoma and concluded that this type of prostate cancer did not impart an aggressive clinical behavior. In a subsequent study of 47 cases of mucinous adenocarcinoma at RP, only 1 patient had regional lymph node metastases and 1 patient progressed 3 years after RP.[39] Finally, in a recent work by the current authors, we conducted a case-control study of 184 cases of Gleason score 7 (both 3 + 4 and 4 + 3) at RP and demonstrated that cancers with regional lymph node metastases were less likely to be mucinous (1.1%) than those without (6.5%).[23] Thus, in 2014 an agreement was reached that mucinous adenocarcinoma should be graded based on the underlying pattern as if extraglandular mucin were not present.[8]

Adenocarcinoma With Signet Ring Cell–like Features

This pattern is usually seen in high-grade cancers (Figure 1, E). It differs from true signet ring cells, seen, for example, in gastric carcinomas, in that the intracytoplasmic vacuole in prostate cancer is clear and does not contain mucin (Figure 1, F).[40] Although older works, including original publications by Gleason, suggested assigning pattern 5 to cancers with signet ring cell–like pattern,[5,41] it is now recognized that such findings can be seen in lower-grade prostate cancer (Figure 2, A), and even high-grade prostatic intraepithelial neoplasia and intraductal prostatic carcinoma.[42] The consensus is that the intracytoplasmic vacuoles should not influence the grade, and, akin to mucinous carcinoma, the grade should be assigned based on the underlying architectural pattern as if the intracytoplasmic vacuoles were not present.[7]

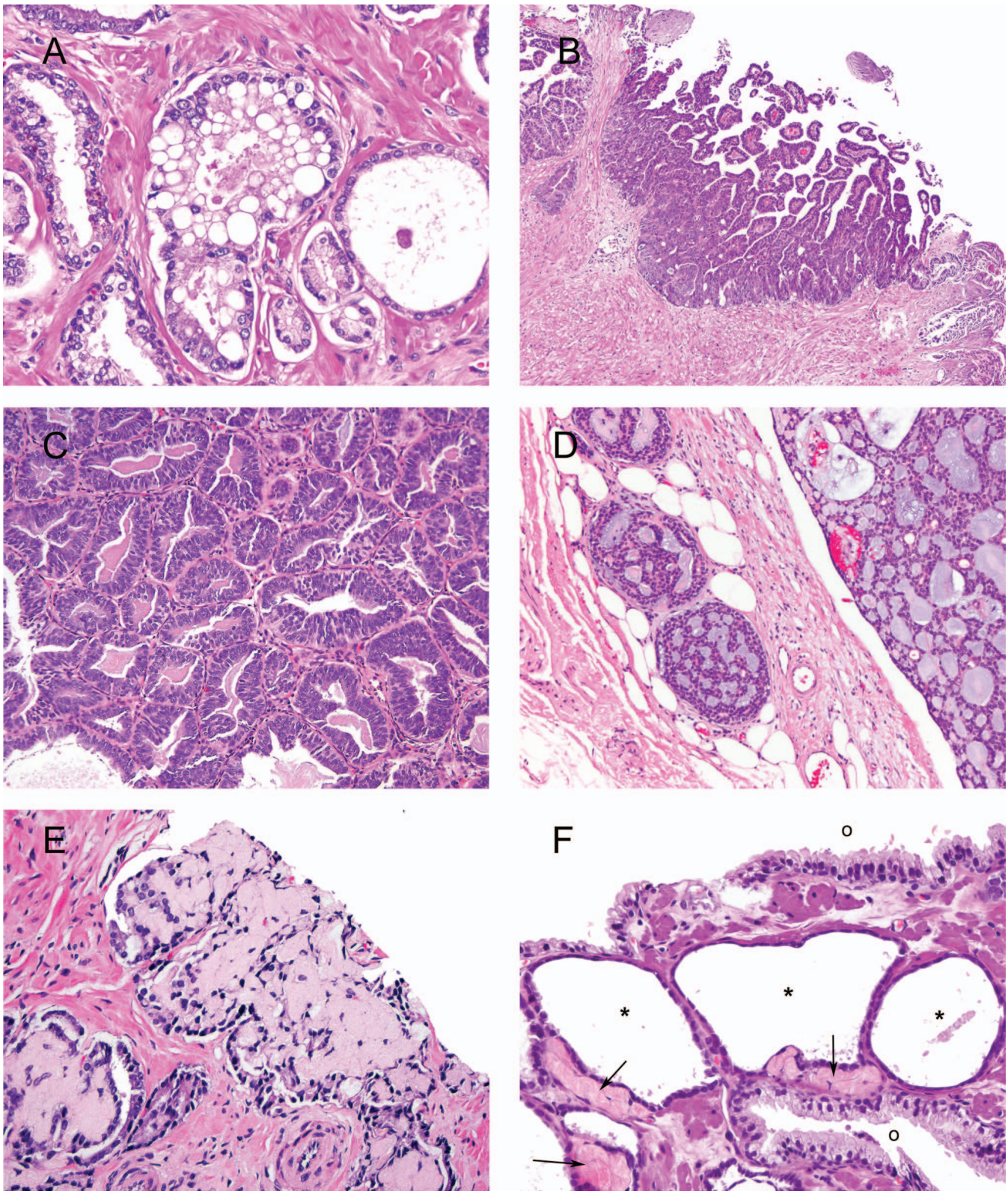

Figure 2. *A, Gleason pattern 3, with well-formed glands with intracytoplasmic vacuoles. B, Prostatic duct adenocarcinoma with papillary fronds, Gleason score 4 + 4 = 8/Grade Group 4. C, Prostatic intraepithelial neoplasia-like prostatic duct adenocarcinoma, Gleason score 3 + 3 = 6/Grade Group 1. D, Adenoid cystic–like prostatic basal cell carcinoma with extraprostatic extension; no Gleason score is assigned. E, Mucinous fibroplasia in prostatic adenocarcinoma. Despite a more complex architecture, Gleason score 3 + 3 = 6/Grade Group 1 should be assigned. F, Atrophic prostatic adenocarcinoma (*) infiltrating between benign glands (o) with mucinous fibroplasia (arrows), Gleason score 3 + 3 = 6/Grade Group 1 (hematoxylin-eosin, original magnifications ×40 [A, E, and F] and ×20 [B through D]).*

Prostatic Duct (Ductal) Adenocarcinoma

Prostatic duct adenocarcinoma is distinctive, with its tall, pseudostratified columnar cells, as opposed to the simple cuboidal or short columnar cytology seen in usual acinar prostate adenocarcinoma (Figure 2, B).[16] It is infrequent in its pure form and is often seen in specimens composed of a mixture of usual acinar and prostatic duct adenocarcinoma. In some cases prostatic duct adenocarcinoma can be seen within ducts retaining a patchy basal cell layer.[43]

Most prostatic duct adenocarcinomas have a cribriform pattern and are graded as Gleason pattern 4.[7] A relatively unique morphology seen in ductal adenocarcinoma is papillary architecture with true fibrovascular cores, typically mixed with cribriform glands, that is also graded as pattern 4. If necrosis is present, then Gleason pattern 5 is assigned. Gleason pattern 3 is given to the more recently described "prostatic intraepithelial neoplasia-like ductal adenocarcinoma," composed of discrete, often dilated individual glands lined by pseudostratified columnar cells lacking basal cells (Figure 2, C).[44]

Basal Cell Carcinoma

Basal cell carcinoma of the prostate has a broad spectrum of patterns, including individual glands resembling basal cell hyperplasia; medium-sized nests, some with central tubule formation; large nests with necrosis; and cribriform glands, which can in some cases resemble adenoid cystic carcinoma seen in the salivary gland. The presence of solid patterns with necrosis and high Ki-67 nuclear labeling index may distinguish more aggressive variants. However, many basal cell carcinomas have a cribriform pattern associated with a relatively indolent clinical course characterized by local infiltration as opposed to distant metastases (Figure 2, D).[45] Consequently, the Gleason system does not apply to basal cell carcinomas, although a comment should be made on the expected behavior based on the morphology (ie, presence or absence of large, solid nests with necrosis).

VARIANT HISTOLOGY OF USUAL (ACINAR) PROSTATIC ADENOCARCIOMA

Mucinous Fibroplasia

Mucinous fibroplasia (also known as collagenous micronodules) is an ingrowth of paler-appearing connective tissue often associated with intraluminal mucin, leading to distortion of the gland mimicking a higher-grade pattern (Figure 2, E and F).[7] The grading of mucinous fibroplasia was not revisited in 2014 and the agreement was retained from 2005 to mentally subtract the mucinous fibroplasia and grade the underlying morphology. It may be difficult to determine whether glands are truly fused or merely connected to other glands as a result of the fibroplasia, so that diagnosing Gleason pattern 4 in the setting of mucinous fibroplasia should only be made if unequivocal cribriform glands are present.

Foamy Gland Carcinoma

Initial descriptions of this variant were individual glands of carcinoma containing abundant xanthomatous-appearing cytoplasm and were graded as Gleason pattern 3 (Figure 3, A).[46] Subsequently, prostate carcinomas with foamy cytoplasm with Gleason patterns 4 and 5 architecture have been reported.[47] Foamy gland cancer should be graded based on underlying morphology, and this subtype by itself does not affect the prognosis.

Paneth Cell–like Neuroendocrine Differentiation

The term *Paneth cell–like change* has been used to describe distinctive eosinophilic neuroendocrine cells that can be seen in benign prostate glands, high-grade prostatic intraepithelial neoplasia, intraductal carcinoma, and usual acinar adenocarcinoma of the prostate (Figure 3, B).[33] In some cases the tumor cells do not have prominent pink granules and appear as small, poorly formed glands or ribbons of cells with distinctive deeply amphophilic cytoplasm and bland cytology.[14,15] These Paneth cell–like foci may be present in well-formed glands of Gleason pattern 3 but also can be present in cords or ribbons of cells with bland cytology, where, if strictly applying the Gleason grading system, one would assign a Gleason pattern 5. However, it can be questioned whether these cords/ribbons should be graded as pattern 5 because of their bland cytology, typically limited nature, and frequent association with lower-grade acinar adenocarcinoma. We do not assign a Gleason score to neuroendocrine cancers composed of cords/ribbons of cells but comment as to their generally favorable prognosis based on the limited data available. However, there have been anecdotal cases where such a tumor progressed to metastatic disease with small cell carcinoma.

Treated Prostatic Adenocarcinoma

Adenocarcinoma with radiation effect typically manifests as individual cells with abundant vacuolated cytoplasm and pyknotic nuclei without prominent nucleoli (Figure 3, C). Cancers that show radiation therapy effect have been associated with a better prognosis than tumors that appear unaltered by radiation.[48] A Gleason grade should not be assigned, because of artifactual therapy-related changes in the morphology that mimic higher-grade cancer. Similarly, cancers with hormone therapy effect appear higher grade and should not be assigned a Gleason score. If a specimen from a patient with a history of radiation or hormonal therapy shows cancer not altered by the therapy, the comment should be made that carcinoma lacks treatment effect and the appropriate Gleason grade should be assigned.

Pseudohyperplastic Prostatic Adenocarcinoma

This variant consists of large glands with branching and papillary infolding, architecturally resembling benign glands that can also be present in areas of perineural invasion (Figure 3, D).[49,50] Based on its underlying pattern, pseudohyperplastic cancer is graded as Gleason score $3 + 3 = 6$.

Intraductal Carcinoma of the Prostate

Contemporary literature often attributes the original description of intraductal carcinoma of the prostate (IDC-P) to Kovi et al[51] (1985) and McNeal and Yemoto[19] (1996), who noted its association with higher-grade cancer and interpreted it as a secondary spread inside the ducts rather than a precursor lesion. However, as early as 1909, Dr Geraghty, a pathologist working with Hugh Hampton Young at The Johns Hopkins Hospital, stated: "Cancer of the prostate spreads in two ways, by direct extension through the stroma and by extension along the ducts. As a result of this duct extension one sometimes sees masses of cancer cells filling the acini, the intervening tissue being

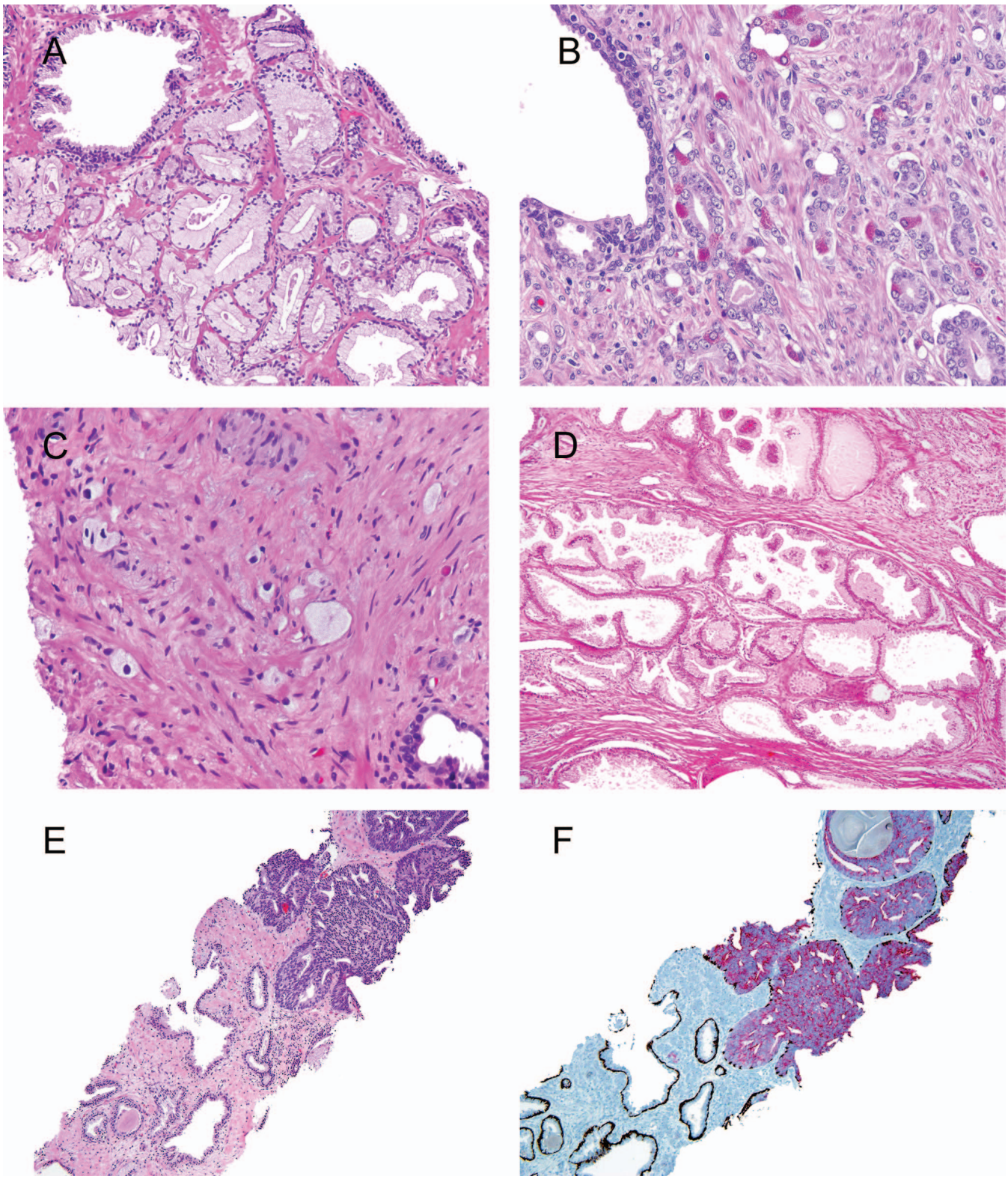

Figure 3. *A, Foamy gland prostatic adenocarcinoma, Gleason score 3 + 3 = 6/Grade Group 1. B, Prostatic adenocarcinoma with focal Paneth cell–like neuroendocrine differentiation, Gleason score 3 + 4 = 7/Grade Group 2. C, Prostatic carcinoma with radiation-related changes; no Gleason score is assigned. D, Pseudohyperplastic prostatic adenocarcinoma, Gleason score 3 + 3 = 6/Grade Group 1. E, Intraductal prostatic carcinoma with a dense cribriform proliferation; no Gleason score is assigned. F, Same case as in E, with PIN-4 immunostain demonstrating the presence of basal cells and immunoreactivity with racemase in the area of intraductal prostatic carcinoma (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B and C]; and ×10 [D and E]; original magnification ×10 [F]).*

entirely normal."[2] The most commonly used contemporary definition of IDC-P is by Guo and Epstein,[52] requiring an intraductal growth with either: (1) solid pattern; (2) dense cribriform morphology, defined as greater than 70% epithelium as opposed to lumens; or (3) loose cribriform and/or micropapillary lesions with either marked nuclear atypia (6× normal) or comedonecrosis (Figure 3, E and F). The above criteria of IDC-P were derived based on architectural patterns or cytologic features that clearly exceed those of high-grade prostatic intraepithelial neoplasia.

Most cases of IDC-P reflect adjacent high-grade carcinoma involving ducts and acini in a retrograde fashion, which has been termed by some as "regular IDC-P."[53] In contrast, "precursor IDC-P" is found without a nearby invasive component, representing a de novo intraepithelial lesion as opposed to retrograde extension by invasive carcinoma. Regular IDC-P (ie, associated with invasive carcinoma) is associated with higher grade and stage cancer and an increased risk of progression following treatment compared with precursor IDC-P.[53] We have previously shown that among Gleason score 7 cancers with lymph node metastases, the incidence of IDC-P is twice as common compared with cases without metastatic disease.[23] In a study by Robinson and Epstein,[54] the authors reported RP findings from 66 men with IDC-P on biopsy without invasive cancer. Most men had advanced-stage disease, pT3a or higher, and the median Gleason score was 8. In only 2 men was there precursor IDC-P as the sole finding in RP. In other studies the presence of IDC-P on biopsy was demonstrated as an independent factor in multivariate analysis predicting biochemical recurrence in men treated by radiation and RP.[23,55,56]

In support of grading IDC-P is that when seen on biopsy without invasive carcinoma, Gleason score 7 or higher will be present in 90% of corresponding RP specimens. When IDC-P is associated with invasive cancer on biopsy, the invasive cancer is almost always Gleason score of 7 or higher. However, precursor IDC-P without infiltrating carcinoma or only seen with Gleason score 3 + 3 = 6 cancer can be seen at RP.[57] In these cases, had a Gleason score been assigned to the cribriform or solid IDC-P it would have labeled the patient as having a poor prognosis when in fact the prognosis was excellent. A total of 82% of ISUP 2014 consensus participants voted that IDC-P should not have a grade assigned and its presence should be documented separately in the reporting.[8] A comment should be made describing its common association with high-grade prostate cancer. Intraductal carcinoma of the prostate should be included in the percentage of core involved by cancer.

A NEW CONTEMPORARY PROSTATE CANCER GRADING SYSTEM

Problems With the Current Gleason System

First, Gleason scores 2 to 5 are currently no longer assigned and certain patterns that Gleason defined as a score of 6 are now graded as 7, thus leading to contemporary Gleason score 6 cancers having a better prognosis than historic score 6 cancers.

Second, in practice, the lowest score now assigned is 6, although it is on a scale of 2 to 10. This leads to a logical yet incorrect assumption on the part of patients that the cancer on biopsy is in the middle of the grade scale, compounding the fear of a cancer diagnosis, thus leading to an expectation that definite treatment is always necessary.

Third, combining Gleason scores into a 3-tier grouping (6, 7, 8–10) is used most frequently for prognostic and therapeutic purposes, despite 3 + 4 = 7 versus 4 + 3 = 7 and 8 versus 9 to 10 having very different prognoses.[8]

Development of a New Grading System

As a result of the first two problems noted above, it has been questioned whether Gleason score 3 + 3 = 6 should retain the designation of cancer or be relabeled as indolent lesion of epithelial origin to avoid fear and consequential overtreatment of a proportion of potentially indolent prostate cancers.[58] This is also based on the observations from the two studies showing that using a contemporary grading approach, pure Gleason score 3 + 3 = 6 at RP is incapable of regional lymph node metastasis.[20,59] At RP, pure Gleason score 3 + 3 = 6, organ-confined, margin-negative disease has an excellent prognosis, with only occasional men demonstrating detectable prostate-specific antigen that may be in part due to the presence of benign glands at the margin and the use of ultrasensitive methods.[60–62] From a pathologist's viewpoint, Gleason score 6 is still cancer, with many of the same morphologic and even molecular features of higher-grade cancer, a lack of a basal cell layer, and the potential to locally invade.[63,64] Furthermore, whereas pure Gleason score 3 + 3 = 6 cancer at RP may be associated with a favorable clinical course, when present on biopsy, upgrading at RP can be seen in 17% to 36% of cases.[65–68] Renaming Gleason score 3 + 3 = 6 cancer as an indolent lesion of epithelial origin tumor on biopsy carries the risk that patients on active surveillance will not adhere to long-term follow-up because they have been told they do not have *cancer*. Rather than renaming Gleason score 3 + 3 = 6 cancer as an indolent lesion of epithelial origin tumor, a new grading system for prostate cancer is needed to better align the grades with prognosis.

If one were starting de novo in developing a new prostate cancer grading system, the goal would be a simple system with the least number of grades, each with its own distinct prognosis. The Grade Groups (Table) were originally developed by the senior author of this work in 2013 on the data from 7869 patients who underwent RP at The Johns Hopkins Hospital, Baltimore, Maryland,[69] and more recently validated on 20 845 patients from 5 academic institutions.[32] The 5-year biochemical risk-free survivals for the 5 Grade Groups based on RP grade were 96%, 88%, 63%, 48%, and 26% (Figure 4). The 5 Grade Groups were also predictive for biopsy grade followed by RP or radiation therapy.

Benefits of the New Grading System

First, the New Grading System Provides More Accurate Grade Stratification Than Current Applications of the Gleason System.—In clinical practice, Gleason score 7 disease is often considered one grade regardless of pattern composition (3 + 4 versus 4 + 3). The most common prognostic classification system used for prostate cancer in clinical practice is the D'Amico/National Comprehensive Cancer Network system, which divides prostate cancer into low-, intermediate-, and high-risk disease.[70] In the intermediate category, one of the criteria is Gleason score 7 cancer. Based on this risk stratification, treatment protocols have been developed without recognizing the extensive literature showing the significantly different prognosis between Gleason scores 3 + 4 versus 4 + 3 prostate

New Grading System Morphologic Patterns and Grade Group Pattern Composition	
Grade Group	**Pattern Definition**
Grade Group 1 (Gleason score ≤6)	Only individual, discrete, well-formed glands
Grade Group 2 (Gleason score 3 + 4 = 7)	Predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform glands
Grade Group 3 (Gleason score 4 + 3 = 7)	Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands[a]
Grade Group 4 (Gleason score 8)	Only poorly formed/fused/cribriform glands *or* Predominantly well-formed glands with a lesser component lacking glands[b] *or* Predominantly lacking glands with a lesser component of well-formed glands[b]
Grade Group 5 (Gleason scores 9–10)	Lacks gland formation/necrosis with or without poorly formed/fused/cribriform glands[a]

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

cancers.[71–73] Similarly, Gleason scores 8 to 10 are combined together as high-risk disease, despite numerous studies demonstrating that Gleason scores 9 to 10 are associated with a significantly worse prognosis. Having a distinct Grade Group 2 for Gleason score 3 + 4 = 7 and Grade Group 3 for Gleason score 4 + 3 = 7 will prevent combining these two very different prognostic groups of cancer for both prognostic and treatment purposes. Similarly, Grade Groups 4 and 5, representing Gleason score 8 and Gleason scores 9 to 10, respectively, will allow better stratification and foster future studies to determine whether Grade Group 5 cancers need more intensive therapy.

Second, the New Grading System Is Simple, With 5 Grade Groups as Opposed to 25 Scores Depending on Various Gleason Pattern Combinations.—The current Gleason system, with its primary and secondary patterns, is a complicated and nonintuitive grading system, whereas grading systems used for other tumors usually range simply from 1 to 3 (well, moderately, and poorly differentiated), or low to high grade. For nonurologists and patients, the system is confusing and difficult to understand. As patients increasingly have access to their medical records and are becoming more involved in their medical care, men with prostate cancer read their pathology reports and need to understand the terminology better.

Third, the Lowest Grade in the New System Is 1 as Opposed to 6 in the Gleason System.—There is wide recognition that many Gleason score 6 cancers can be followed with active surveillance. However, active surveillance is still not widely accepted in many parts of the world because of the fear of not being treated definitively for cancer. In addition, a sizable amount of men abandon active surveillance despite favorable clinical and pathologic findings because of this anxiety.[74,75] Compounding this fear is that the lowest grade assigned in the Gleason system is 6 out of a scale of 2 to 10, implying that a 6 is in the middle of the grading scale in terms of aggressiveness.[8] In talking to patients on a daily basis, we have had to reassure numerous men that their Gleason score 6 cancer is the lowest grade possible. In addition, some patients with Gleason score 3 + 4 = 7 had thought they were going to die in the near future because their score of 7 was closer to the highest grade of 10 than the lowest grade of 2. With the new grading system, patients can be reassured that they have a Grade Group 1 out of 5, which is the lowest grade, or a Grade Group 2 out of 5, which is still a relatively low grade.

A New Grading Photomicrograph Montage

One of the most enduring graphics in surgical pathology is the Gleason schematic diagram drawn in the 1960s and early 1970s. Because of changes in the Gleason system

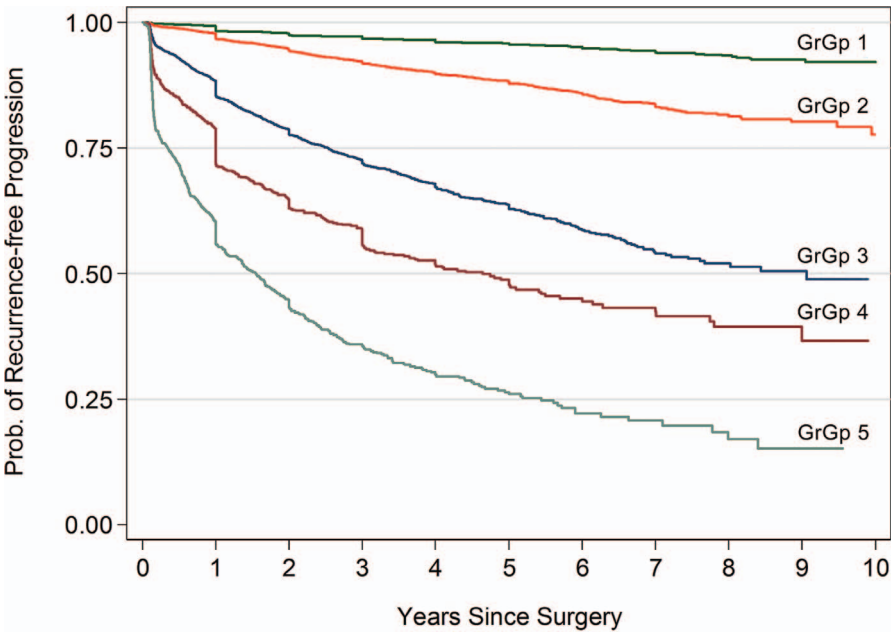

Figure 4. *Biochemical recurrence-free survival after radical prostatectomy according to Grade Group (GrGp).*

A. Apex, right lateral:
- Prostatic adenocarcinoma, Gleason score 3 + 3 = 6 (Grade Group 1) involving 70% of one (1) core.
- Length of cancer is 7 mm.

B. Mid, right lateral:
- Benign prostate tissue.

C. Base, right lateral:
- Prostatic adenocarcinoma, Gleason score 4 + 3 = 7 (Grade Group 3) involving 70% of one (1) core.
- Length of cancer is 3 mm.
- Percentage of pattern 4 = 70%.

D. etc

Diagnostic comment:

Gleason scores can be grouped and range from Grade Group 1 (most favorable) to Grade Group 5 (least favorable).

References: *BJU Int.* 2013;111:753–760 and *Eur Urol.* Published online ahead of print July 9, 2015.

Figure 5. *Example of a biopsy report using both Gleason score and Grade Group.*

outlined above, the diagram has undergone several significant modifications, most recently in 2014. However, the latest schematic diagram still suffers from including patterns 1 and 2, despite their near extinction from practice. In addition, a schematic diagram—even one developed with contemporary technologies—cannot depict morphology as accurately as a photomicrograph. In response to these issues, a contemporary prostate cancer grading photomicrograph montage was created.[8]

Terminology for the New Grading System

There has been some confusion and controversy in the recent literature regarding the name of the new system. As noted earlier, the new grading system was first described in 2013 by work done at The Johns Hopkins Hospital by one of us (J.I.E.) and was verified by a large multi-institutional study led by the same author, both prior to the 2014 consensus conference. The new system was termed *Grade Groups*. The data from these two studies, and the rationale and evidence in support of the new grading system were presented to the attendees of the 2014 conference, where 90% voted to accept the new grading system. Although the 2005 and 2014 ISUP consensus conferences, which were both led by one of us (J.I.E.) were instrumental in many of the grade changes outlined in this article and will be influential in the new grading system's eventual broader acceptance, the ISUP conferences did not come up with the concept, nor did they do the research that lead to the new 5 Grade Groups grading system. To therefore rename the grading system solely as the *ISUP Grading System* is misleading and inaccurate. Proponents of crediting the new system to ISUP argue that because the initial study describing Grade Groups was in 2013 and the validation study was finished before the 2014 consensus conference, then the changes from the 2014 conference were not incorporated within the data. However, the key recommendation from the 2014 consensus conference that all cribriform cancers are pattern 4 was already adopted by the groups that participated in the Hopkins and validation studies. As described earlier in this article, the 2005 consensus conference allowed only *rare* cribriform glands as pattern 3. However, by 2008 even those cases were recognized as pattern 4.[21] The 2014 consensus conference officially proclaimed what was already in practice shortly after the 2005 conference. Consequently, grading data from 2005 forward can be accepted as contemporary grades. The 2016 edition of the World Health Organization's *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs* refers to the new grading system simply as *Grade Groups 1–5* as originally described[69] to be reported along with the Gleason score for the foreseeable future. As a result of significant differences in criteria and reporting compared with Gleason's original grading system, we have regarded the newly proposed grades as a "new grading system," although one could also consider it as a "novel grouping" of a much modified original Gleason grading system.

REPORTING BIOPSY AND RP SPECIMENS

Needle Biopsy Specimens

To ease the transition to the new grading system, it was agreed upon that both the Gleason grade and the Grade Group would be included in the reports.[8] In our reports we provide a diagnostic comment with the references and explanation of the Grade Groups (Figure 5). Each core is assigned a separate grade.[76] For specimens with multiple cores submitted in a single container, each core should be interpreted separately if they are differentially inked to correlate to where they were taken from in the gland.[7] If there are multiple cores without designation in the same container, experts are split as to whether to still assign different scores to different cores or just provide a single score for the container. If the specimen shows fragmented cores with different grades, then we report the overall grade for the entire fragmented specimen as if it was one core.

It is optional whether to provide a summary overall (average or global) score to the entire case. The difficulty with doing so relates to the multifocal nature of prostate cancer. For example, one could have several cores with Gleason score $4+4=8$ and other cores with $3+3=6$ and $3+4=7$. If this reflected a single tumor nodule, the overall grade could be $3+4=7$ or $4+3=7$. However, it could also reflect sampling separate tumor nodules of $4+4=8$ and $3+4=7$ or $4+3=7$. In our opinion it is best left to the clinician, who may have more information than the pathologist in terms of findings on imaging studies, to determine the overall grade. In general, pathologists in the United States

do not assign an overall grade at the end of the case, and clinicians use the core with the highest grade in a biopsy to determine the prognosis and therapy.

RP Specimens

Each separate tumor nodule should be assigned an individual Gleason score/Grade Group.[7,8] It is particularly important when there are 2 or more spatially separate tumor nodules with different grades. The nodule defining the prognosis is usually the largest nodule with the highest stage and grade cancer. However, occasionally there may be a smaller nodule that is of the highest grade, which will be recorded as the grade for the case for prognostic and adjuvant therapy purposes. This requires that RPs be processed in an organized fashion where one can assess the relationship between the sections with cancer. If prostatectomy specimens are not submitted in their entirety, there are partial submission techniques to maximize identification of key pathologic parameters.[77–80] It should be recognized that African American patients have a tendency to have dominant tumor nodules located in the anterior gland that could be sampled less by partial submission protocols.[66,67] In addition to the tumor's Gleason score, the grade of the tumor at a positive margin site, as well as the length of positive margin, is also prognostic and should be reported.[81–83]

Percent Pattern 4

There are multiple advantages to reporting percent pattern 4 both in needle biopsy and RP specimens. The 2014 consensus conference recommends reporting the percent pattern 4, with discretion regarding how to record it. These authors record percent pattern 4 for each core with Gleason score 7, unless there are several cores with Gleason score 7 in a jar, whereby the overall percent pattern 4 is recorded for that jar. One option is to record percent pattern 4 in intervals of less than 5%, 5%, 10%, 20%, 30%, 40%, approaching 50%, 60%, 70%, 80%, and 90%. An alternative would be less than 5%, 5% to less than 25%, 25% to less than 50%, 50% to less than 75%, and 75% to less than 100%. It is most critical to determine whether the percent pattern 4 is very limited (ie, borderline between Gleason scores $3+3=6$ and $3+4=7$), close to 50% (ie, borderline between Gleason scores $3+4=7$ and $4+3=7$), or closer to 90% (ie, borderline between Gleason scores $4+3=7$ and $4+4=8$). If there is Gleason score 9 to 10 on any core, we do not record the percent pattern 4 for Gleason score 7 on other cores, because it will not affect therapy. We also do not record percent pattern 4 in a small focus of Gleason score 7 cancer occupying less than 5% of a core because grading only a few glands can radically change the percent pattern 4. The following are the advantages of reporting percent pattern 4:

1. Currently, many pathologists use two different grading systems for needle biopsy and RP specimens. One situation is with a tumor with more than 95% pattern 3 and a minimal amount of pattern 4. In needle biopsies, any pattern 4 is factored into the grade (ie, Gleason score $3+4=7$). In RPs, if pattern 4 is less than 5%, then some pathologists would grade it as Gleason score $3+3=6$ with tertiary pattern 4, and if greater than 5%, then it would be graded as Gleason score $3+4=7$. If the percent pattern 4 is recorded for both specimens, there would be a uniform grading system in this situation, grading these cases as Gleason score $3+4=7$ and noting the percent pattern 4. Also, the 5% cutoff used for reporting Gleason score $3+3=6$ with tertiary pattern 4 on RP as opposed to Gleason score $3+4=7$ is arbitrary. By recording the percent pattern 4, there would be a sliding scale of the percent pattern 4.
2. The major advantage for recording the percent pattern 4 is on biopsies for men being considered for active surveillance. For the appropriate patient, Gleason score $3+3=6$ is accepted for men to undergo active surveillance.[67,84] However, there may be some men, depending on age, comorbidity, extent of cancer, magnetic resonance imaging findings, patient desire, etc, who could be candidates for active surveillance with Gleason score $3+4=7$ if the pattern 4 is limited.[26] Currently, this information is not transparent in pathology reports.
3. The amount of pattern 4 is not only used for active surveillance but could be used for radiation therapy as well. Currently, there are different radiation therapy protocols for Gleason score $3+4$ versus Gleason score $4+3$. A case that is borderline between these two grades would be apparent if the percent pattern 4 was recorded, and then other factors (clinical stage, prostate-specific antigen, number of cores positive, etc) could be used to decide therapy.
4. When pathologists grade specimens as Gleason scores $3+4=7$ or $4+3=7$, they already have to decide what tumor is pattern 4 or 3, such that to give a percent should not be that much extra effort.
5. Interobserver reproducibility of reporting percent patterns 4/5 on prostate biopsies is at least as good as that of reporting Gleason score.[85] However, although cribriform patterns 4 are more easily recognized, there is significant interobserver variability in the diagnosis of small-volume pattern 4 composed of poorly formed glands even between urologic surgical pathologists.[25]
6. Borderline cases exist between Gleason scores $3+4$ and $4+3$ that we currently have to flip a coin to decide. If we record percent pattern 4, these ambiguous cases will be evident regardless of whether we diagnose Gleason score $3+4=7$ with approaching 50% pattern 4, or Gleason score $4+3=7$ with 60% pattern 4. This could also help explain potential differences in grading the same case between pathologists.
7. Having to record the percent poorly formed/fused/cribriform glands in a borderline case between Gleason scores $3+3$ and $3+4$ is another way of having pathologists check again to specifically identify the foci that lack well-formed glands before verifying that there is pattern 4.
8. Increasing percent pattern 4, quantified in a continuous scale, is associated with an increased risk of biochemical failure after RP.[86]

Tertiary Patterns

Numerous studies have demonstrated that a tertiary (third most common) pattern in RP specimens is prognostic, basically worsening the prognosis yet not as bad as the next higher score.[87–90] A controversy that was resolved in the 2014 consensus conference was that in order for percent of pattern 5 to be considered as a tertiary pattern it should occupy less than 5% of the tumor nodule. In the past, others

allowed a much greater percent of pattern 5 as long as it was the third most common pattern. On RP, 3 + 4 = 7 with less than 5% pattern 5 is called 3 + 4 = 7 with tertiary 5 (Grade Group 2 with minor high-grade pattern), and 3 + 4 = 7 with more than 5% pattern 5 is called 3 + 5 = 8 (Grade Group 4). On RP, 4 + 3 = 7 with less than 5% pattern 5 is called 4 + 3 = 7 with tertiary 5 (Grade Group 3 with minor high-grade pattern), and 4 + 3 = 7 with more than 5% pattern 5 is called 4 + 5 = 9 (Grade Group 5). For example, the prognosis of 3 + 4 = 7 with tertiary pattern 5 is in between 3 + 4 = 7 and 4 + 3 = 7. The grade Gleason score 3 + 3 = 6 with tertiary pattern 4 will no longer be used. As discussed above, these will be graded as Gleason score 3 + 4 = 7 with 5% or less pattern 4. Similarly, Gleason score 4 + 4 = 8 with tertiary pattern 5 is no longer recommended because the prognosis is the same as Gleason score 4 + 5 = 9.

Tertiary patterns are not recorded on needle biopsy. The usual situation with 3-grade patterns is a core with Gleason patterns 3, 4, and 5. The Gleason score is determined by adding the most common pattern with the highest-grade pattern and typically not mentioning the remaining pattern. As it relates to three patterns on needle biopsy: 3 + 4 = 7 with a lesser amount of 5 is called 3 + 5 = 8 (Grade Group 4), and 4 + 3 = 7 with a lesser amount of 5 is called 4 + 5 = 9 (Grade Group 5).

SUMMARY

As the clinical field of prostate cancer has changed dramatically during the last few decades, so too has the grading of prostate cancer. These changes will enable clinicians to better manage prostate cancer patients, which is the ultimate goal of any grading system. Initially, the new grading system for prostate cancer will be a "translation" from the much modified original Gleason system (ie, Gleason score 3 + 3 = 6 = Grade Group 1). However, ultimately pathologists and clinicians will learn the new system directly (ie, Grade Group 1 = discrete, well-formed glands) without the need to "think in Gleason."

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