The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

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Abstract: In November, 2014, 65 prostate cancer pathology experts, along with 17 clinicians including urologists, radiation oncologists, and medical oncologists from 19 different countries gathered in a consensus conference to update the grading of prostate cancer, last revised in 2005. The major conclusions were: (1) Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology; (2) Glomeruloid glands should be assigned a Gleason pattern 4, regardless of morphology; (3) Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern rather than grading them all as pattern 4; and (4) Intraductal carcinoma of the prostate without invasive carcinoma should not be assigned a Gleason grade and a comment as to its invariable association with aggressive prostate cancer should be made. Regarding morphologies of Gleason patterns, there was clear consensus on: (1) Gleason pattern 4 includes cribriform, fused, and poorly formed glands; (2) The term hypernephromatoid cancer should not be used; (3) For a diagnosis of Gleason pattern 4, it needs to be seen at 10x lens magnification; (4) Occasional/seemingly poorly formed or fused glands between well-formed glands is insufficient for a diagnosis of pattern 4; (5) In cases with borderline morphology between Gleason pattern 3 and pattern 4 and crush artifacts, the lower grade should be favored; (6) Branched glands are allowed in Gleason pattern 3; (7) Small solid cylinders represent Gleason pattern 5; (8) Solid medium to large nests with rosette-like spaces should be considered to represent Gleason pattern 5; and (9) Presence of unequivocal comedonecrosis, even if focal is indicative of Gleason pattern 5. It was recognized by both pathologists and clinicians that despite the above changes, there were deficiencies with the Gleason system. The Gleason grading system ranges from 2 to 10, yet 6 is the lowest score currently assigned. When patients are told that they have a Gleason score 6 out of 10, it implies that their prognosis is intermediate and contributes to their fear of having a more aggressive cancer. Also, in the literature and for therapeutic purposes, various scores have been incorrectly grouped together with the assumption that they have a similar prognosis. For example, many classification systems consider Gleason score 7 as a single score without distinguishing 3 + 4 versus 4 + 3, despite studies showing significantly worse prognosis for the latter. The basis for a new grading system was proposed in 2013 by one of the authors (J.I.E.) based on data from Johns Hopkins Hospital resulting in 5 prognostically distinct Grade Groups. This new system was validated in a multi-institutional study of over 20,000 radical prostatectomy specimens, over 16,000 needle biopsy specimens, and over 5,000 biopsies followed by radiation therapy. There

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was broad (90%) consensus for the adoption of this new prostate cancer Grading system in the 2014 consensus conference based on: (1) the new classification provided more accurate stratification of tumors than the current system; (2) the classification simplified the number of grading categories from Gleason scores 2 to 10, with even more permutations based on different pattern combinations, to Grade Groups 1 to 5; (3) the lowest grade is 1 not 6 as in Gleason, with the potential to reduce overtreatment of indolent cancer; and (4) the current modified Gleason grading, which forms the basis for the new grade groups, bears little resemblance to the original Gleason system. The new grades would, for the foreseeable future, be used in conjunction with the Gleason system [ie. Gleason score 3 + 3 = 6 (Grade Group 1)]. The new grading system and the terminology *Grade Groups 1-5* have also been accepted by the World Health Organization for the 2016 edition of Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs.

Key Words: prostate cancer, grading, Gleason

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In 2005, the International Society of Urological Pathology conducted a consensus conference on Gleason grading that updated the grading system to more contemporary practice.[1] Changes to the original Gleason grading system agreed upon at the meeting are listed in Table 1. In 2014, it was recognized that there was a need for further modifications to prostate cancer grading based on: (1) the lack of consensus of certain grading issues, many of which were not resolved in the 2005 meeting; (2) a realization that some grading issues were not covered in 2005; (3) since 2005, there has been new pertinent research; and (4) changes in prostate cancer practice has led some clinicians to challenge the existing grading system, necessitating a response by the Pathology community.[2] To address these issues, the International Society of Urological Pathology conducted another consensus conference in Chicago that was attended by 65 prostate cancer pathology experts from 19 different countries on November 1, 2014. In this conference, treating physicians were proactively involved and participated in the proceedings; 17 clinical leaders in the field of prostate cancer including urologists, radiation oncologists, and medical oncologists participated. The participants, including clinicians, had the option of voting on all of the issues presented. The proceedings from the Chicago Grading Meeting, dealing with the definition of various grade patterns and the consensus recommendation and proposal to adopt a new grading system, are presented herein. A separate manuscript will present how the grades are reported in special circumstances, such as cases with a minor component of high-grade tumor, tertiary grade patterns, utilization of percent pattern 4, and case versus core level reporting.

TABLE 1. ISUP 2005 Modifications to Grading of Prostate Cancer

Poorly formed glands were classified as Gleason pattern 4
Restricted criteria were defined to distinguish cribriform pattern 4 vs. cribriform pattern 3
In needle biopsy specimens, the primary pattern + worst (not secondary) pattern were recommended to be included in the needle biopsy score
In needle biopsy specimens, very small amounts of lower-grade cancer occurring in the setting of extensive high-grade cancer were recommended to be ignored when assigning the score
Codified that the diagnosis of Gleason patterns 1 and 2 were not to be made in biopsy specimens
Discussed and recommended grading of existing variants of prostate cancer and variations in prostate cancer—small cell; mucinous; ductal; signet ring cell–like; and newly described variants—foamy; pseudohyperplastic; cancers with treatment affect
Provided recommendations of handling tertiary patterns in RP specimens
Provided recommendations of grading multiple cores from different sites
Provided recommendation of handling nodules of different grades in RP specimens

DETAILS REGARDING THE PROCEEDINGS OF THE CONSENSUS CONFERENCE

Presentations were made on preselected issues by 6 members of the International Society of Urological Pathology organizing committee (authors of the paper). All invited committee members (listed collaborators on the paper) participated on site or joined the proceedings remotely through a webinar. An audience response system was used to record votes on issues including those who participated remotely. The presentations emphasized a critical review of literature to ensure that the recommendations made were evidence based. It was recognized during the discussions at the meeting that levels of evidence, as utilized by many consensus conferences making recommendations, are not well suited for pathology-based observational and clinicopathologic research.

GRADING OF CRIBRIFORM GLANDS

Discussion and Presentation of New Research

In the original descriptions of the Gleason grading system, pattern 3 included both small and large cribriform glands.[3–7] The defining features based on Gleason's diagram was that in pattern 3 cribriform glands were relatively round and regular, whereas in pattern 4 they were more irregular with ragged edges. However, none of Gleason's studies addressed the prognostic differences between these 2 patterns of cribriform glands. Reports from some of the leading centers for prostate cancer treatment illustrate cases graded before 2005 as Gleason pattern 3 with large cribriform glands that today would uniformly be called Gleason pattern 4.[8,9] In 2005, the consensus meeting proposed more stringent criteria to distinguish cribriform pattern 3 and 4 glands.[1] Cribriform pattern 3 was restricted to the following 3 criteria: small cribriform glands with regular contour and round evenly spaced lumina. An interobserver study published in 2008 found only 1 consensus cribriform pattern 3 case out of 3590 prostate cancer and it was concluded that discrepant grading between experts on a given case was due to either application of different criteria or different

interpretation of the same criteria.[10] Iczkowski et al[11] in 2011 demonstrated that a cribriform pattern in radical prostatectomy (RP) specimens had the strongest association with biochemical failure after surgery. Both large and small cribriform glands were linked to failure. In 2014, a series of articles showed cribriform pattern to be associated with biochemical failure, extraprostatic extension, positive surgical margins, distant metastases, and disease-specific death.[12–15] In addition to consistent empiric data on the adverse prognostic influence of cribriform glands, conceptually one would expect the change in grade from pattern 3 to pattern 4 to be reflected in a distinct architectural paradigm shift where cribriform, as opposed to individual glands are formed, rather than merely a subjective continuum of differences in size, shape, and contour of cribriform glands.

Proposal and Vote

Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology (Fig. 1A). One hundred percent of the participants at the Chicago consensus meeting agreed on this proposal.

GRADING OF GLOMERULOID GLANDS

Discussion and Presentation of New Research

A related issue to cribriform glands is the grading of glomeruloid glands of prostate adenocarcinoma. Glomerulations consist of dilated cancer glands with cribriform cancer protruding into the lumen yet not attaching to the other side of the gland wall, superficially resembling a glomerulus. In the 2005 grading meeting, there was no consensus as to how this variant should be graded.[1] At this meeting approximately 50% of the pathologists preferred not to grade glomeruloid glands due to uncertainty of their behavior and the remaining half reported that they would grade this as Gleason pattern 4. In particular, there was controversy regarding small glomeruloid glands, with most experts grading large glomeruloid structures as Gleason pattern 4. In a study from Lotan and Epstein[16] in 2009, 84% of glomeruloid glands were associated with Gleason pattern 4 or higher cancer. This study also documented that there were often transitions between small and large glomeruloid glands and cribriform pattern 4.

Proposal and Vote

Glomeruloid glands should be assigned a Gleason pattern 4, regardless of morphology (Fig. 1B). One hundred percent of the participants at the Chicago consensus meeting agreed on this proposal.

GRADING MUCINOUS ADENOCARCINOMA OF PROSTATE

Discussion and Presentation of New Research

On the basis of older studies with limited number of cases, there was a lack of consensus at the 2005 grading meeting relating to the grading of mucinous adenocarcinoma of the prostate.[1] Approximately one half of the participants voted that, by definition, all mucinous carcinomas are Gleason pattern 4, whereas the other one half favored grading the tumor based on the underlying architecture. In most cases of mucinous carcinoma, a cribriform architecture predominates that would be graded as Gleason pattern 4 by either method, although in a minority of cases mucinous adenocarcinomas consist of individual round glands. In one study, 11/12 (91.7%) patients with mucinous carcinoma and 9/14 (64.3%) with focal mucinous differentiation at RP were clinically and biochemically free of disease, with none dying of cancer.[17]In this study, no difference in biochemical free or overall survival was seen between patients with mucinous carcinoma and those with usual prostatic adenocarcinoma. Osunkoya et al[18] studied 47 mucinous carcinomas at RP. Only 1 (2.1%) patient showed progression 3 years after his RP with an actuarial 5-year progression-free survival of 97.2%. Using the Kattan nomogram, the predicted mean 5-year prostate specific antigen (PSA) progression-free risk for nonmucinous prostate cancer with the same PSA and postoperative findings as in this study was 85.4%. The conclusions from the both of these studies were that mucinous adenocarcinoma of the prostate treated by RP is not more aggressive, and possibly even less aggressive than nonmucinous prostatic adenocarcinoma.

Proposal and Vote

Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern rather than grading them all as pattern 4 (Fig. 1C). Ninety-one percent of the participants agreed with this proposal.

GRADING OF INTRADUCTAL CARCINOMA OF THE PROSTATE

Discussion and Presentation of New Research

Kovi et al[19] in 1985 and McNeal[8] later in 1996 first documented that spread of adenocarcinoma within prostatic ducts were associated with higher-grade cancer and was considered to be progression of established invasive cancer rather than a precursor to it. Guo and Epstein[20] first established criteria for intraductal carcinoma of the prostate (IDC-P) on biopsy in 2006 and in a limited number of cases documented that subsequent RPs had aggressive disease (Table 2). Dense cribriform glands were defined as those where the epithelial component was $\geq 70\%$ epithelium surrounded by basal cells. In 2010, Robinson and Epstein[21] expanded the study to 66 cases with only IDC-P on biopsy. Of the 21 RPs available for review, pathologic stage was pT3a in 8 (38%), pT3b in 3 (13%), and pT2 in 8 (38%). IDC-P only without identifiable invasive cancer was seen in 2 (10%) cases. The median Gleason score was 8. The authors of these studies recommended definitive therapy for men with IDC-P on needle biopsy, even in the absence of pathologically documented invasive prostate cancer. There have been several subsequent works documenting the adverse prognosis of IDC-P on biopsy. Zhao et al[22] studied 278

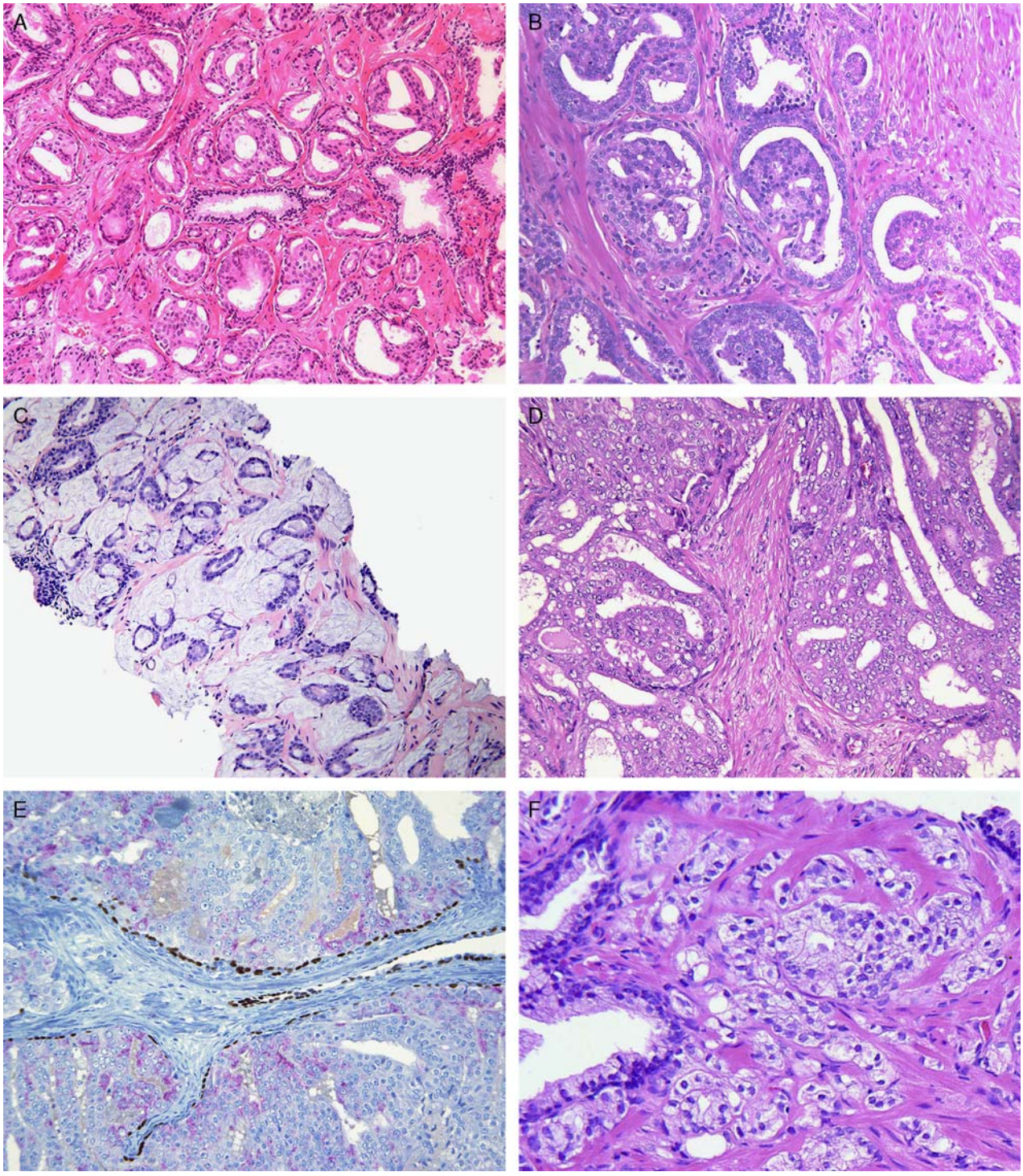

FIGURE 1. A, Gleason pattern 4 consisting of small round cribriform glands; before the 2014 consensus conference these were variably graded as either Gleason pattern 3 or 4. B, Small glomeruloid glands graded as Gleason pattern 4; there was no consensus as to how to grade in the 2005 conference. C, Mucinous carcinoma composed of discrete well-formed glands of Gleason pattern 3; before the 2014 consensus conference there was controversy how to grade. D, IDC with dense cribriform glands, which is not assigned a grade, an issue not discussed in the 2005 conference. E, Same case as (D) with p63-positive basal cells (brown chromogen) verifying carcinoma is intraductal. F, Predominantly poorly formed glands of Gleason pattern 4.

TABLE 2. Criteria for IDC[20]

Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells and:
Solid or dense cribriform pattern
Or
Loose cribriform or micropapillary pattern with either:
Marked nuclear atypia: nuclear size 6 × normal
Necrosis

men with metastatic prostate cancer diagnosed by needle biopsy and IDC-P was found in 57/278 (20.5%) cases. IDC-P was predictive of decreased cancer-free survival even in a subset of men with Gleason score ≥ 8 cancer. Watts et al[23] prospectively collected 1176 needle biopsies, with 33 (2.8%) cases having IDC-P and 3 (0.26%) lacking concomitant invasive carcinoma. The Gleason score was 7 in 16 (53.3%), 8 in 4 (13.3%), and 9 in 10 (33.3%) cases. Of 9 patients treated by RP, SV invasion was seen in 4 (44%) cases. Van der Kwast analyzed 118 intermediate-risk prostate cancer patients treated by radiation and 132 high-risk patients treated by either radiation alone or radiation with long-term androgen deprivation.[24] IDC-P on the biopsy was an independent prognosticator of early biochemical relapse and metastatic failure. In a recent biopsy study on IDC-P, 73 cases with IDC-P and Gleason score $3+3=6$ as the highest grade on biopsy, were evaluated.[25] Of 62 with follow-up, 4 had metastatic disease at diagnosis treated with chemotherapy and ADT. Of the 16 RPs, 3(19%) had only Gleason score $3+3=6$.

There have also been studies evaluating the significance of IDC-P at RP when associated with invasive prostatic adenocarcinoma. In a series of 184 Gleason score 7 RPs with lymph node metastases, 42.4% in the metastatic group demonstrated IDC-P compared with only 20.6% in a control group without lymph node metastases.[26] Kimura an colleagues reported on 206 high-risk prostate cancer patients treated with RP. In multivariate analysis, IDC-P was significantly associated with biochemical-free recurrence and cancer-specific survival.[27] In another study, multivariate analysis similarly showed IDC-P associated with invasive carcinoma at RP to be an independent predictor for biochemical recurrence.[28] Of the 901 RPs, the group distinguished 141 (15.6%) where IDC-P was associated with adjacent invasive carcinoma from 14 (1.5%) cases where the IDC-P was distant from invasive cancer. The former they termed *regular* IDC and the latter *precursor* IDC. *Regular* IDC-P had significantly higher Gleason score, higher pathologic stage, and lower 5-year biochemical-free survival than *precursor* IDC-P. Prostate cancer with Gleason score ≥ 8 in at RP was observed in 73 (52%) cases with *regular* IDC-P versus 3 (21%) cases with *precursor* IDC-P. The authors concluded that IDC-P does not always represent intraductal spread of preexisting high-grade invasive carcinoma, and at least a subset of IDC-P could be a precursor lesion of invasive carcinoma.

Whether IDC-P should be graded or not, and if so how it should be graded was debated at the Chicago meeting. This issue was not discussed in the 2005 grading consensus meeting. The arguments for and against grading IDC-P are listed in Table 3. Immunohistochemistry was advised for cases where the results of the studies would change the case's overall grade.

Proposal and Vote

IDC-P without invasive carcinoma should not be assigned a Gleason grade (Figs. 1D, E). A comment as to its invariable association with aggressive prostate cancer should be made. Eighty-two percent voted for this proposal.

MORPHOLOGIES INCLUDED IN GRADING PATTERNS

A presentation followed by discussion included clarification and update on how different morphologic patterns should be included in the different Gleason grade patterns. The results and recommendations are summarized in Table 4 (Figs. 1F, 2).

A NEW GRADING SYSTEM FOR PROSTATIC ADENOCARCINOMA

There are several reasons why a new grading system, which was based on extensive modifications of the original Gleason system was proposed for prostatic adenocarcinoma at the meeting in Chicago.

Problems With the Gleason Grading System Scale

The reporting of Gleason scores 2 to 5 has virtually disappeared from current clinical practice. In Gleason's original data, Gleason scores 2 to 5 were seen in 27.9% of cases.[7] In one study, it was shown that in 1991, 24% of pathologists rendered a diagnosis of Gleason score 2 to 4 which decreased to 2.4% in 2001.[29] In another study analyzing biopsies from 2002 to 2003, only 1.6% were graded as Gleason score 2 to 4 which compared with

TABLE 3. Pros and Cons of Grading IDC-P

Pros
Even when IDC alone present on biopsy, 90% will have Gleason score > 7 at RP
When IDC and invasive cancer on biopsy, almost always Gleason score > 7, so already Gleason pattern 4
Hard to tell IDC vs. cribriform Gleason pattern 4 cancer and may need to do immunohistochemistry on multiple parts to distinguish
Several studies demonstrating correlation of IDC with increased stage and prognosis
Cons
Approximately 10% of IDC found at RP are not closely associated with invasive carcinoma and appear to be a precursor lesion as opposed to invasive cancer extending into ducts
In the uncommon setting of IDC only on biopsy, 10% no invasive carcinoma at RP. If had called $4+4=8$ on biopsy would have labeled the patient as having poor prognosis when in fact the patient is 100% cured with IDC only
In the uncommonly setting of IDC and $3+3$ on biopsy, approximately 20% have $3+3=6$ only at RP and would have been incorrectly labeled as having pattern 4 on biopsy
In other organ systems, intraductal lesions are not graded with the same grading system as the invasive component

TABLE 4. Morphologies Within Gleason Patterns

1. Gleason pattern 4 includes cribriform, fused, and poorly formed glands.
   VOTE: 100% Yes
2. The term hypernephromatoid cancer should not be used.
   VOTE: 78% Yes
3. For a diagnosis of Gleason pattern 4, it needs to be seen at ×10 lens magnification.
   VOTE: 78% Yes
4. Occasional/seemingly poorly formed or fused glands between well-formed glands is insufficient for a diagnosis of pattern 4.
   VOTE: 85% Yes
5. All glomeruloid glands should be graded as Gleason pattern 4 regardless of morphology.
   VOTE: 100% Yes
7. In cases with borderline morphology between Gleason pattern 3 and pattern 4 and crush artifacts, the lower grade should be favored.
   VOTE: 98% Yes
8. Branched glands are allowed in Gleason pattern 3.
   VOTE: 94% Yes
9. Small solid cylinders represent Gleason pattern 5.
   VOTE: 87% Yes
10. Solid medium to large nests with rosette-like spaces should be considered to represent Gleason pattern 5.
    VOTE: 88% Yes
11. Presence of unequivocal comedonecrosis, even if focal is indicative of Gleason pattern 5.
    VOTE: 94% Yes
12. Rarely, discrete glands (otherwise pattern 3) with necrotic debris within the lumens represents Gleason pattern 5.
    VOTE: 49% Yes

22.3% of the biopsies in 1994.[30,31] Helpap and Egevad[32] demonstrated that from 1996-2000 to 2005, reported Gleason scores 2 to 4 decreased from 2.7% to 0% and reported Gleason score 5 decreased from 12.2% to 0.3%. The Gleason grading system ranges from 2 to 10, yet 6 is the lowest score currently assigned. When patients are told that they have a Gleason score 6 out of 10, it implies that their prognosis is intermediate and contributes to their fear of having a more aggressive cancer.

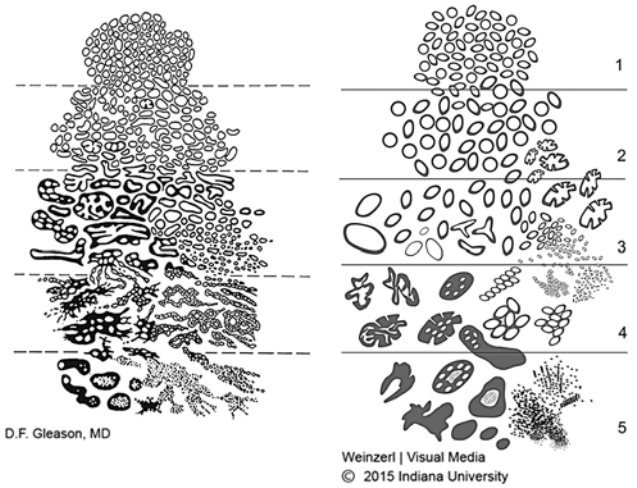

FIGURE 2. Prostatic adenocarcinoma (histologic patterns): original (left) and 2015 Modified ISUP Gleason schematic diagrams.

Use of Inaccurate Grade Combinations for Prognosis and Therapy

In the literature and for therapeutic purposes, various scores have been grouped together with the assumption that they have a similar prognosis. Analysis of some of the highest impact articles on prostate cancer in the last few years reveals some of the Gleason score groupings that have been utilized: 2 to 4; 5 to 7; 8 to 10 (Prostate Cancer Outcomes Study)[33] 2 to 6; 7; 8 to 10 (Scandinavian Prostate Cancer Group Study); 2 to 6; 7 to 10 (Prostate Cancer Prevention Trial & Prostate Cancer Intervention vs. Observation Trial).[34,35] The most common risk stratification used in prostate cancer, especially with radiation therapy, is the National Comprehensive Cancer Network (NCCN) and D'Amico classification systems.[36] These systems stratify prostate cancer based on serum PSA values, clinical stage, and biopsy grade into low-risk, intermediate-risk, and high-risk groups, with Gleason scores 2 to 6; 7; and 8 to 10, respectively. In addition to the lack of uniformity of the various score groupings, which preclude meaningful comparisons between studies, the combinations that have been used have significant flaws. As noted above, Gleason scores 2 to 4 virtually never exist on current biopsy material, with many of the cases in Gleason's era that predated the use of modern techniques probably representing adenosis, a mimic of cancer. Studies combining Gleason scores 6 and 7 span tumors ranging from those with an almost uniformly excellent prognosis (3+3) to those where a high percent of disease will progress following therapy (4+3). All of the above classification systems consider Gleason score 7 as a single score without distinguishing 3+4 versus 4+3, despite studies showing significantly worse prognosis for the latter.[37–48] Combining Gleason scores 7 to 10 includes patients with an excellent prognosis (3+4) along with patients who have a high likelihood of cancer-related death (5+5). Even within the high Gleason score group of 8 to 10, prior studies have also noted the adverse prognosis associated with Gleason pattern 5.[49–53] A grading system should distill grades of prostate cancer down to the lowest number of grades where each has a unique prognosis.

Response to Proposals by Clinicians to Redefine Gleason Score 6 Cancer as Not Cancer

It has been questioned as to whether or not Gleason score 6 prostatic adenocarcinoma should be classified as cancer given its more favorable prognosis. It has also been proposed that the alternative term IDLE Tumor (indolent lesion of epithelial origin) be used to ameliorate the fear associated with the term "cancer."[2] Despite these arguments, there are numerous morphologic, molecular, and clinical reasons why the designation "cancer" should be retained for Gleason score 6 tumors.[54,55] This proposal results from the frequent overtreatment of Gleason score 6 cancer which is, in part, due to patient's concern at being diagnosed with a malignancy. The current Gleason grading system contributes to this fear by assigned a score of 6 out of 10 for the lowest possible grade of tumor.

Proposal for New Grading System

The basis for a new grading system that included grade groups was proposed in 2013 by one of the authors (J.I.E.) based on data from Johns Hopkins Hospital.[56] The grading system is based on the modified (2005 and 2014) Gleason score groups shown in Table 5, resulting in 5 prognostically distinct grade groups. As opposed to Gleason patterns 1 to 3, grade group 1 is composed of individual discrete glands regardless of circumscribed/infiltrative pattern, uniformity of gland size and shape, or amount of intervening stroma. A multi-institutional study, based upon 2005 grading criteria was undertaken with Johns Hopkins Hospital, Memorial Sloan-Kettering Cancer Center (MSKCC), University of Pittsburgh, Cleveland Clinic, and the Karolinska Institute to validate the new grading system.[57]

Follow-up was available on 20,845 RP cases with a mean follow-up period, without progression, of 3.0 years. The biochemical-free progression curves are shown in Figure 3. The hazard ratios of grade groups 2 to 5 relative to grade group 1 were: 2.2, 7.3, 12.3, and 23.9, respectively. This means, for example, that grade group 3 (Gleason 4 + 3 = 7) has a 7.3 times likelihood of progression compared with grade group 1 (Gleason 3 + 3 = 6). The 5-year biochemical risk-free survival for the 5 grade groups based on RP grade were 96%, 88%, 63%, 48%, and 26%. The 5 grade groups were shown to be more accurate in predicting progression than the 3 Gleason score groups (≤6, 7, 8 to 10) used in the NCCN and Kattan clinical risk groups. Similar prognostic curves and hazard ratios were generated from a series of 16,176 prostate needle biopsies from 4 of the same institutions; Karolinska Institute lacked central review of externally performed needle biopsies. In a cohort of 5501 men treated with radiation therapy at MSKCC and Cleveland Clinic, the 5 grade groups were also predictive of outcome once concomitant hormone therapy was factored into a multivariate analysis.

TABLE 5. Histological Definition of New Grading System

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 lesser component of poorly- formed/fused/cribriform glands
Grade Group 3 (Gleason score 4 + 3 = 7) – Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands†
Grade Group 4 (Gleason score 4 + 4 = 8; 3 + 5 = 8; 5 + 3 = 8) Only poorly-formed/fused/cribriform glands *or* Predominantly well-formed glands and lesser component lacking glands†† or Predominantly lacking glands and lesser component of well-formed glands††
Grade Group 5 (Gleason scores 9-10) – Lacks gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands†

†For cases with > 95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of < 5% well-formed glands is not factored into the grade.

††Poorly-formed/fused/cribriform glands can be a more minor component.

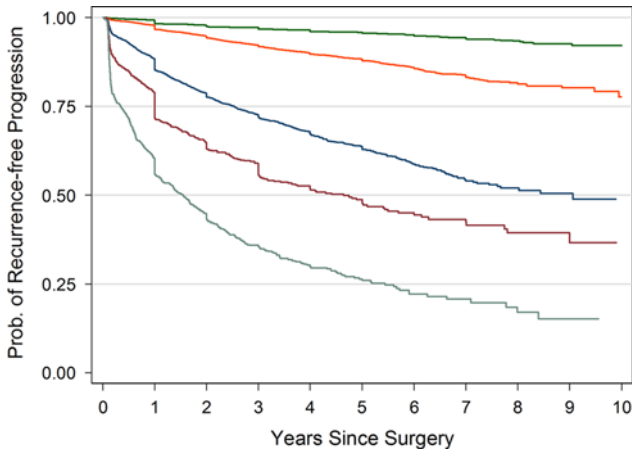

FIGURE 3. Biochemical recurrence-free progression after RP stratified by grade (green line—Gleason score 6 [grade group 1], orange—Gleason score 3+4 [grade group 2], dark blue—Gleason score 4+3 [grade group 3], brown—Gleason score 8 [grade group 4], gray—Gleason score ≥9 [grade group 5]).

The new grading system has as its foundation the 1967 to 1973 Gleason system, yet is based on extensive subsequent research that incorporates significant changes from the original system in its definition and application. Although retaining the practice of combining the most common and secondmost common tumor patterns, there have been many changes to Gleason's recommendations, first in 2005 and more recently as a result of the 2014 grading conference.[1] There has been an almost complete disappearance of Gleason scores 2 to 5. Poorly formed glands and some cribriform glands were considered as Gleason pattern 3 in the original system, yet upgraded to Gleason pattern 4 in the modified system. In the original Gleason system, large cribriform glands, that in current practice would universally be graded as pattern 4, were typically graded as Gleason pattern 3.[8,9] Even the overall concept of summing the 2 most common patterns has been modified depending on whether on needle biopsy or RP and on the extent of the minor lower grade component. As a result of significant differences in criteria and reporting compared with the 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.

The new grading system more accurately reflects prostate cancer biology than the Gleason system. Grade group1 out of 5 (better characterizes the tumor than reporting as Gleason score 6 out of 10) has an excellent prognosis within 1 large multi-institutional study with no potential for lymph node metastases.[9] Patients could be reassured that they have a grade group 1 tumor on biopsy that is the lowest grade tumor possible, which in most cases can be followed with active surveillance. However, follow-up is still needed as in approximately 20% of cases there is higher-grade cancer in the prostate that has not been sampled.[58] In addition to biopsy grade, the decision

as to whether a patient is a candidate for surveillance is complex and factors in multiple clinical findings, as well as extent of cancer on biopsy and serum PSA levels. Grade group 2 out of 5 (as opposed to Gleason score 7 out of 10) has a very good prognosis with rare metastases. Grade group 3 out of 5 has a significantly worse prognosis than grade 2 as opposed to Gleason score 7, which combines Gleason scores 3 + 4 and 4 + 3. Grade group 4 out of 5 is not considered the highest grade (as opposed to Gleason scores 8 to 10) and has a significantly better prognosis than grade group 5 (Gleason scores 9 to 10). Finally, grade group 5 obviates the need to distinguish between Gleason scores 4 + 5, 5 + 4, and 5 + 5 just as grade group 1 makes irrelevant the distinction between Gleason scores 2 + 2, 2 + 3, 3 + 2, and 3 + 3.

Following discussion at the 2014 Chicago grading meeting, there was a proposal for the adoption of this new prostate cancer Grading system based on the observations that: (1) the new classification provided more accurate stratification of tumors than the current system; (2) the classification simplified the number of grading categories from Gleason scores 2 to 10, with even more permutations based on different pattern combinations, to grades 1 to 5; (3) the lowest grade is 1 not 6 as in Gleason, with the potential to reduce overtreatment of indolent cancer; and (4) the current modified Gleason grading, which forms the basis for the new grade groups, bears little resemblance to the original Gleason system. The new grades would, for the foreseeable future, be used in conjunction with the Gleason system: *Gleason score 3 + 3 = 6* (*grade group 1*). Ninety of the participants at the Chicago grading meeting voted in support of adopting the new grading system. The new grading system and the terminology "Grade Groups 1-5" has also been accepted by the World Health Organization for the 2016 edition of *Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs*.

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