

Contemporary Gleason Grading of Prostatic Carcinoma

An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

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Abstract: The primary proceedings of the 2014 International Society of Urological Pathology Grading Conference were published promptly in 2015 and dealt with: (1) definition of various grading patterns of usual acinar carcinoma, (2) grading of intraductal carcinoma; and (3) support for the previously proposed new Grade Groups. The current manuscript in addition to highlighting practical issues to implement the 2014 recommendations, provides an updated perspective based on numerous studies published after the 2014 meeting. A major new recommendation that came from the 2014 Consensus Conference was to report percent pattern 4 with Gleason score 7 in both needle biopsies and radical prostatectomy (RP) specimens. This manuscript gives the options how to record percentage pattern 4 and under which situations recording this information may not be necessary. Another consensus from the 2014 meeting was to replace the term tertiary-grade pattern with minor high-grade pattern. Minor high-grade indicates that the term tertiary should not merely be just the third most common pattern but that it should be minor or limited in extent. Although a specific cutoff of 5% was not voted on in the 2014 Consensus meeting, the only quantification of minor high-grade pattern that has been used in the literature with evidence-based data correlating with outcome has been the 5% cutoff. At the 2014 Consensus Conference, there was agreement that the grading rule proposed in the 2005 Consensus Conference on needle biopsies be followed, that tertiary be not used, and that the most common and highest grade patterns be summed together as the Gleason score. Therefore, the term tertiary or minor high-grade pattern should only be used in RP specimens when there are 3 grade patterns, such as with $3+4=7$ or $4+3=7$ with <5% Gleason pattern 5. It was recommended at the 2014 Conference that for the foreseeable future, the new Grade Groups would be reported along

with the Gleason system. The minor high-grade patterns do not change the Grade Groups, such that in current practice one would, for example, report Gleason score $3+4=7$ (Grade Group 2) with minor (tertiary) pattern 5. It was discussed at the 2014 Consensus Conference how minor high-grade patterns would be handled if Grade Groups 1 to 5 eventually were to replace Gleason scores 2 to 10. In the above example, it could be reported as Grade Group 2 with minor high-grade pattern or potentially this could be abbreviated to Grade Group 2+. The recommendation from the 2014 meeting was the same as in the 2005 consensus for grading separate cores with different grades: 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). It is the practice of the majority of the authors of this manuscript that if the cores are submitted in a more specific anatomic manner than just left versus right (ie, per sextant site, MRI targets, etc.), that the grade of multiple cores in the same jar from that specific site are averaged together, given they are from the same location within the prostate. In cases with multiple fragmented cores in a jar, there was agreement to give a global Gleason score for that jar. The recommendation from the 2014 meeting was the same as in the 2005 consensus for grading separate nodules of cancer in RP specimens: one should assign a separate Gleason score to each dominant nodule(s). 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. An emerging issue in the studies and those published subsequent to the meeting was that cribriform morphology is associated with a worse prognosis than poorly formed or fused glands and in the future may be specifically incorporated into grading practice. We believe that the results from the 2014 Consensus Conference and the updates provided in this paper are vitally important to our specialty to promote uniformity in reporting of prostate cancer grade and in the contemporary management of prostate cancer.

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The Gleason grading system was first described by Dr Donald Gleason in 1966 with several subsequent revisions, the last in 1977.^{1–5} Over the next few decades, the Gleason grading system remained largely unchanged

until 2000, where there was an editorial by one of the current authors (J.I.E.) recommending that pathologists should not diagnose Gleason score 2 to 4 on needle biopsy.⁶ However, it was not until 2005 that there was a first formal revision to the Gleason system based on an International Society of Urological Pathology consensus conference held at the annual United States and Canadian Academy of Pathology meeting.⁷

Almost a decade later, in advance of influential nomenclature and standard setting publications of the World Health Organization (WHO) Classification of Tumours of the Urinary and Male Reproductive System and the American Joint Committee on Cancer (AJCC) TNM staging manual, both published in 2016,^{8,9} there was a need for another prostate cancer grading consensus conference. It was organized by the International Society of Urological Pathology and it took place in Chicago in 2014; the participation was multidisciplinary with pathologists, urologists, and urologic medical and radiation oncologists from multiple countries participating in this effort.¹⁰ The primary proceedings of this meeting were published promptly in 2015 and dealt with: (1) definition of various grading patterns of usual acinar carcinoma, its morphologic variations, and the variants of invasive carcinoma; (2) grading of intraductal carcinoma; and (3) support for the new Grade Groups along the lines first described in 2013.¹¹ Both the WHO and the AJCC publications endorsed this approach of grade grouping of prostate cancer because of the overarching advantages listed in Table 1.

The 2014 consensus conference has important implications in the daily practice of Gleason grading due to the endorsement by the WHO and AJCC. The co-chairs of the 2014 organizing committee (J.I.E.: Coeditor of the Third Edition of the WHO Classification of Tumours of the Urinary System and Male Genital Organs; P.A.H.: Coeditor of the Fourth Edition of the WHO Classification of Tumours of the Urinary System and Male Genital Organs), another member of the organizing committee (M.B.A.: Editor-in-Chief of the 2016 AJCC Staging Manual), along with another leader in the field (V.E.R.:

Coeditor of the Fourth Edition of the WHO Classification of Tumours of the Urinary System and Male Genital Organs) who attended the 2014 meeting felt for the pathology community it was critical to address the practice-related issues resulting from the recommendations and proceedings of the full consensus conference. We have also provided an updated perspective based on numerous studies published in this area after the November 2014 meeting. The topics included in this paper include: (1) recording percentage Gleason pattern 4, (2) grading tertiary patterns, (3) grading of multiple needle biopsy cores with different grades, (4) grading at the core versus the specimen (jar) level, and (5) grading of multiple nodules with different grades in radical prostatectomy (RP) specimens.

REPORTING PERCENTAGE PATTERN 4

A major new recommendation that came from the 2014 Consensus Conference was to report percent pattern 4 with Gleason score 7 in both needle biopsies and RP specimens. Although this issue was not completely resolved at the meeting, shortly after the meeting over e-mail discussions the topic was discussed in depth and voted upon by the attendees of the meetings. In addition to support by 75% of the conference pathologists, this recommendation was enthusiastically endorsed by 100% of the clinicians who were part of the Consensus Conference for an overall consensus of 79%. In addition, the 2016 WHO book recommends reporting of percentage of pattern 4 for Gleason score 7 adenocarcinoma.⁸ There are many advantages to report percentage pattern 4 in Gleason score 7 tumors.

(1) Consistency between needle biopsy core and RP grading:

As noted below, many pathologists use 2 different grading rules for needle biopsy and RP specimens. On needle biopsy, even if there is very limited Gleason pattern 4 present, it is factored into the grade. For example, a needle biopsy core with 98% Gleason pattern 3 and 2% Gleason pattern 4 is graded as Gleason score $3+4=7$. In RPs, if pattern 4 is <5% some pathologists would grade as Gleason score $3+3=6$ with tertiary pattern 4. By recording percent pattern 4 for both needles and RPs, there will be a uniform grading rule with all types of specimens with the example above graded as Gleason score $3+4=7$ with <5% pattern 4 for both the tumor on needle biopsy and RP.

(2) Consistency among pathologists in the grading of limited pattern 4 at RP:

In RPs, if pattern 4 is <5% some pathologists would grade as Gleason score $3+3=6$ with tertiary pattern 4 and others would grade as Gleason score $3+4=7$. By recording percent pattern 4 for RPs, there will be a uniform grading rule among pathologists to grade as Gleason score $3+4=7$ with <5% pattern 4.

(3) Potential positive impact on patient care—active surveillance:

The major advantage for patient care to record the percent pattern 4 on needles for Gleason $3+4=7$ would be for patients being considered for

TABLE 1. Major Contributions of Grade Group System

- (1) Gleason score 6 is the lowest grade currently reported although the scale goes from 2 to 10. Positioned in the middle of the Gleason scale, Gleason score 6 is a deterrent to enroll patients in active surveillance. In contrast, Grade Group 1 out of 5 accurately denotes that this grade is the lowest possible. This designation may help change the perception about the malignant potential of this common grade, which is usually indolent
- (2) Gleason score 7 is not homogenous. Gleason score $4+3=7$ has a much worse prognosis than Gleason score $3+4=7$. Having distinct Grade Groups 2 and 3 for $3+4=7$ and $4+3=7$, respectively, clearly separate these grades to account for their different prognoses and different treatment strategies, particularly in patients treated with radiation therapy
- (3) Gleason scores 8-10 are often considered as 1 group—high-grade disease. Grade Group 4 (Gleason score 8) with its better prognosis is separated from Grade Group 5 (Gleason scores 9-10) to better stratify patients into different treatment strategies.

active surveillance. For the appropriate patient, Gleason score $3+3=6$ is accepted for men to undergo active surveillance. However, select patients, depending on for example on age, comorbidity, extent of cancer, MRI findings, and patient choice, could be candidates for active surveillance with Gleason score $3+4=7$ if the pattern 4 is limited, and in particular if pattern 4 is $\leq 10\%$.^{12,13} Inclusion of percent pattern 4, currently not included in most pathology reports, would be beneficial in patients being considered for active surveillance.

- (4) Potential positive impact on patient care—radiation therapy: Knowledge of the extent of Gleason pattern 4 may also be helpful for planning radiation therapy. Currently, there are different radiation therapy approaches for Gleason score $3+4=7$ (Grade Group 2) versus $4+3=7$ (Grade Group 3).¹⁴ Some cases are borderline between the 2 grades and could be reported as either Gleason score $3+4=7$ or Gleason score $4+3=7$. Depending on whether $3+4$ or $4+3$, the percent pattern 4 could range from $<5\%$ to 90% and would not be evident in a report. By reporting the case as $3+4=7$ (approaching 50% pattern 4) or $4+3=7$ (60% pattern 4) the borderline nature of the case would be evident and clinicians could use other factors (such as serum PSA, number of cores positive for carcinoma, and imaging, etc.) for guiding therapy.
- (5) Practicality: When pathologists grade a specimen as $3+4$ (Grade Group 2) or $4+3$ (Grade Group 3), they already have to decide what part of the tumor is pattern 4 or 3 such that to give a percent should not be that much extra effort.
- (6) Interobserver reproducibility: Reporting percent Gleason grade 4/5 on prostate biopsies is at least as good as that of reporting Gleason score.¹⁵ In a more recent study, assessment of percent Gleason pattern 4 was relatively reproducible, with substantial agreement within $\pm 10\%$ in cases,¹⁶ although it may be a challenge to visually estimate percentage pattern 4 when patterns 3 and 4 are intermingled, which is a common occurrence.¹⁷
- (7) Quality control for identifying limited percent pattern 4: Having to record $<5\%$ pattern 4 in a borderline case between $3+3$ and $3+4$ should prompt the pathologist to verify that the pattern 4 is definitive. Indeed, 1 recommendation is the following: “Because of known interobserver variability associated with the identification of minor Gleason pattern 4 elements, prospective intradepartmental consultation with colleagues should be considered a cornerstone of quality assurance in this area.”¹³
- (8) Recording percentage Gleason pattern 4 will also allow the generation of additional data to validate its clinical utility and clinically relevant cutoff points.

It was the majority opinion of the 2014 Consensus Meeting that the method by which the percent pattern 4 should be recorded remains optional, both for the core and case level. For practical reporting purposes, there are

several approaches both using an eyeball estimate. One option is to record the percentages as follows: $<5\%$, 10% , 20% , 30% , 40% , approaching 50% for Gleason score $3+4=7$, and 60% , 70% , 80% , 90% for Gleason score $4+3=7$, which is the personal preference of the current authors. Another alternative would be $<5\%$, 5% to $<25\%$, 25% to $<50\%$; 50% to $<75\%$, and 75% to 90% . Given the inherent large sampling error with needle biopsies, recording more precise percentages than listed in the options above (ie, 13%) would entail extra effort but lack clinical relevance.

One study has demonstrated that there is only moderate interobserver agreement for assessing the percent pattern 4 when there is $<10\%$ involvement of the core by cancer.¹⁶ Given that in a small focus only a few glands of a given pattern can markedly affect the percent of Gleason pattern (GP4), some of the current authors do not record percent GP4 in small foci of Gleason score 7 tumors on needle biopsy. However, this practice is not uniformly accepted, and some of the current authors record the percent GP4 for Gleason score 7 regardless of the extent of cancer, recognizing that their clinicians are aware of inherent sampling problems.

Although not discussed at the 2014 Consensus meeting, the current authors do not record percent of Gleason pattern 4 if any other core has Gleason score 9 or 10 (Grade Group 5). In this scenario, the Grade Group 5 will end up driving therapy and prognosis, where recording the percentage of Gleason pattern 4 will no longer have any significant clinical relevance. We still record percent pattern 4 for those cores with Gleason score 7 if the highest core is Gleason score $4+4=8$, as it can still provide useful information for the clinician. For example, if there are other cores with $4+3=7$ with 80% to 90% pattern 4 that informs the clinician that the overall tumor grade is closer to a Gleason score 8.

Subsequent to the 2014 Consensus Conference, studies have demonstrated that increasing percent pattern 4 at RP correlates with an increased risk of biochemical recurrence after RP.^{18–20} There have also been several publications showing that percent pattern 4 on needle biopsy can improve prediction of upgrading at RP and of adverse findings at RP and biochemical recurrence after RP.^{21,22}

REPORTING MINOR HIGH-GRADE PATTERNS IN BIOPSIES AND RP SPECIMENS

The prognostic significance of minor high-grade patterns in RP specimens were first analyzed in 2000 by Pan et al,²³ who utilized the term tertiary-grade pattern. The original Gleason grading system did not account for >2 patterns. At the 2014 meeting, a review of the literature was presented summarizing studies on tertiary patterns where at least 50 RP specimens were analyzed. Of the 8 articles that fulfilled these criteria, 7 reported that tertiary-grade patterns adversely affected prognosis.^{24–31} On the basis of these data, there was a consensus that tertiary-grade patterns are an important prognostic factor.

Subsequent to the 2014 meeting, there has been another large study on this topic further supporting the adverse prognostic significance of higher tertiary-grade patterns.³²

One of the confusing issues with the term tertiary-grade pattern as it has been used in the past and still persists today is the use of the term tertiary for RP tumors with only 2 grade patterns, where the secondary higher grade pattern was of very limited extent. For example, some pathologists grade RPs with $3+3=6$ and <5% pattern 4 as $3+3=6$ with tertiary 4, to contrast with 5% to 50% pattern 4 that they grade as $3+4=7$.^{29,33} Using tertiary in this context, despite there not being 3 different grade patterns, accounts for the less adverse prognosis with very limited pattern 4 relative to greater amounts of pattern 4. With the adoption of reporting percentage Gleason pattern 4 in Gleason $3+4=7$ as noted above, cases formerly reported as Gleason score $3+3=6$ with tertiary pattern 4 will now be recorded as Gleason score $3+4=7$ with <5% pattern 4. Similarly, some pathologists graded tumors composed of >95% Gleason pattern 4 and <5% Gleason pattern 5 as Gleason score $4+4=8$ with tertiary pattern 5.²⁹ Although not discussed at the 2014 Consensus Conference, a collaborative study of 169 RPs performed at Johns Hopkins Hospital and University of Pittsburgh has shown that the presence of <5% Gleason pattern 5 in the context of Gleason score $4+4=8$ results in a biochemical risk-free survival that is equivalent to Gleason scores 9 to 10.³⁴ At the 2014 Consensus Conference, there was agreement that the grading rule proposed in the 2005 Consensus Conference that on needle biopsies, tertiary is not used and rather the most common and highest grade patterns are summed together as the Gleason score.⁷ For example, in a needle biopsy core with 70% Gleason pattern 3, 25% pattern 4, and 5% pattern 5, the tumor would be graded as Gleason score $3+5=8$.

Another controversial aspect of the term tertiary-grade patterns is whether there is an upper limit to the amount of Gleason pattern 5 that can still be considered as a tertiary pattern. In the initial article by Pan et al²³ from Johns Hopkins, tertiary pattern 5 referred to very limited amounts of pattern 5. Subsequent to this initial study, additional studies from that institution on the prognostic significance of tertiary pattern 5 were also restricted to cases with <5% pattern 5.²⁹ However, there has been no uniformity within the literature on this issue, with some using the cutoff of <5% Gleason pattern 5^{20,32} and others having no cutoff,²⁶ such that studies are not comparable. With no limits on the extent of pattern 5, one can have a RP nodule with up to 20% pattern 5, which is quite extensive, and still be called a tertiary pattern 5.²⁶ For example, a tumor nodule with 50% pattern 3, 30% pattern 4, and 20% pattern 5 could be graded as Gleason score $3+4=7$ with tertiary pattern 5. A problem with using tertiary in this manner is that often the tertiary grades are dropped as they are not incorporated within nomograms and prognostic tables. Consequently, Gleason score $3+4=7$ with tertiary pattern 5 is typically considered only Gleason score $3+4=7$ for treatment

purposes. Whereas a Gleason score $3+4=7$ at RP has almost a 90% cure rate, a case with 30% pattern 4 and 20% pattern 5 would be expected to have a much worse prognosis. Reporting cases as Gleason score $3+4=7$ with tertiary pattern 5 with no upper limit on the extent of Gleason pattern 5 can result in significant tumor undergrading and potential patient harm when applied clinically. At the 2014 Consensus Meeting, 83% of participants favored the term of minor high-grade pattern over tertiary-grade pattern. Minor high grade as the preferred synonym for tertiary indicates that the consensus was that the term tertiary should not merely be just the third most common pattern but that it should be minor or limited in extent. Although a specific cutoff of 5% was not voted on in the 2014 Consensus meeting, the only quantification of minor high-grade pattern that has been used in the literature with evidence-based data correlating with outcome has been the 5% cutoff. The term tertiary or minor high-grade pattern should only be used in the logical scenario when there are 3 grade patterns, such as with $3+4=7$ or $4+3=7$ with <5% Gleason pattern 5 at RP.

Another issue relating to minor high-grade (tertiary) patterns that was discussed at the 2014 Consensus Conference was how to incorporate minor high-grade patterns into the new grading system. It was recommended at the 2014 Conference that for the foreseeable future, the new Grade Groups would be reported along with the Gleason system. The minor high-grade patterns do not change the Grade Groups, such that in current practice one would, for example, report Gleason score $3+4=7$ (Grade Group 2) with minor (tertiary) pattern 5. It was discussed at the 2014 Consensus Conference how minor high-grade patterns would be handled if Grade Groups 1 to 5 eventually were to replace Gleason scores 2 to 10. In the above example, it could be reported as Grade Group 2 with minor high-grade pattern or potentially this could be abbreviated to Grade Group 2⁺.

GRADING CORE VERSUS JAR VERSUS CASE LEVEL

In cases where multiple cores are positive for cancer, different cores may have a different Gleason grade and grade grouping. This issue assumes its greatest importance when 1 or more of the cores shows pure high-grade cancer (ie, Gleason score $4+4=8$) and the other cores show pattern 3 cancer. Should the overall grade be the core with the highest grade or does one assign the grade by mentally adding all the cancer together as if it was one long core? Several studies have demonstrated that in cases with different cores having different grades, the highest Gleason score on a given core correlates better with stage and Gleason score at RP than the average or most frequent grade among the cores.³⁵⁻³⁸ Other studies show no significant difference in prognostic capacity for core with the worst Gleason score compared with overall score, with endpoints of biochemical recurrence and prostate cancer death.^{39,40} As was noted by the vast majority of clinicians

attending the 2014 Consensus Conference, in clinical practice typically the highest Gleason score is used to determine prognosis and treatment. 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 in cases where there are multiple cores of different grades.^{41,42} Whether the highest grade per core or the overall score is used impacts a significant number of cases.⁴³ In the 2014 Chicago meeting, different scenarios were presented as to whether the positive cores with different grades were ipsilateral, contralateral, adjacent, or separate. It was recognized that it was often not clear whether the high and lower grade cores represented a single tumor or multifocal tumors. In the former condition, one might propose to average all the positive cores to represent a single cancer with heterogeneous grades, and in the latter use the highest grade core to indicate a multifocal high-grade cancer. Clinicians attending the Chicago meeting almost universally stated that they would use the highest grade core in a given case to determine therapy and prognosis. When both pathologists and clinicians were polled on this issue, 65% stated that the highest grade core should be used for clinical decision making and 10% favored using the global grade for the entire case (25% said either option was acceptable). It was, however, recognized that whether to use the highest grade core or an average (global) grade also varied geographically with the latter approach used more commonly outside of the United States.

The result of the polling by the experts in Chicago on how grades should be reported when there are multiple positive cores is shown in Table 2. Only 3% of the experts recommended reporting only the average or global grade for the entire case with most recording the grade for each positive core. Approximately one quarter of the experts would provide the overall grade in addition to the individual core grade. As to the question how to grade cases when multiple cores having different grades are present in the same specimen container, the vote was equally split between assigning a grade to each positive core versus a global grade for each specimen container. Thus, the recommendation from the 2014 meeting was the same as in the 2005 consensus: Assign individual Gleason scores to separate cores as long as the cores are submitted in sep-

arate containers or the cores are in the same container yet specified by the urologist as to their location (ie, by different color inks). In cases where there are different un-designated cores with different grades in the same specimen container, it is optional whether to assign individual grades to different cores or a global grade for the specimen container. In addition to giving separate cores individual Gleason scores, one has the option to also give an overall score at the end of the case.⁷

It is the practice of the majority of the authors of this manuscript that if the cores are submitted in a more specific anatomic manner than just left versus right (ie, per sextant site, MRI targets, etc.), that the grade of multiple cores in the same jar from that specific site are averaged together, given they are from the same location within the prostate. In the 2005 Consensus Meeting, the practice of submitting cores only separated by laterality was still in practice by a significant number of urologists, which led some pathologists to recommend grading each core separately (even if not specified by ink), as the cores could have been sampled from very different regions of the prostate and may have represented multifocal tumor nodules.

In cases with multiple fragmented cores in a jar, there was a 97% agreement to give a global Gleason score for that jar. For example, diagnosing Gleason score $4+4=8$ on a tiny tissue fragment where there are other fragments with a greater amount of Gleason pattern 3 could be in error; if the cores were intact and the tumor was all on 1 core, it would be assigned a Gleason score $3+4=7$.

GRADING SEPARATE TUMOR NODULES IN A RP SPECIMEN

In 2005, the position on this issue was as follows: Most often, the dominant tumor is the largest tumor, which is also the tumor with the highest stage and grade. One should assign a separate Gleason score to each dominant nodule(s). 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.⁷ In the 2014 Consensus Conference, 90% of the participants agreed to adopt the 2005 Consensus guidelines. Each major tumor nodule should be graded separately. The rationale for grading each dominant tumor nodule separately is that one could have, for example, 2 separate tumor nodules. One could be high grade (ie, Gleason score $4+4=8$) and there could be a larger nodule of Gleason score $3+3=6$. If one were to average both nodules together, the grade would be Gleason score $3+4=7$, which is misleading as the prognosis of the tumor in the overall case would be expected to be based on the higher grade nodule that would not be mitigated by a separate lower grade tumor. To report each tumor nodule separately, the prostate should be submitted in a manner preserving anatomic location of

TABLE 2. Vote at the 2014 Consensus Meeting on Should We Provide a Grade for: (Multiple Choice)

	Responses [n (%)]
Each positive core	28 (45.2)
Each positive specimen jar	11 (17.7)
Whole case overall (global grade)	2 (3.2)
1+2	4 (6.5)
1+3	8 (12.9)
2+3	8 (12.9)
1+2+3	1 (1.6)
Total	62 (100)

each tumor slide so that this information can be discerned.

An area of controversy that arose at the 2014 Consensus Meeting was use of the terminology dominant nodule. The issue is that smaller nondominant nodule harbors the highest Gleason score in about 7% to 18% of cases.^{44,45} Furthermore, in 11% of cases the highest Gleason score, the largest tumor volume, and extraprostatic extension do not occur in the same tumor nodules.⁴⁵ In these situations, which should be designated the dominant nodule, the highest grade or the largest or the highest stage nodule? Although not discussed at the 2014 Consensus Meeting, an option preferred by the majority of the authors of this manuscript is that in these unusual discordant cases merely list the separate tumor nodules as Tumor Nodule #1, Tumor Nodule #2, etc. and give the separate grade, and stage for each nodule without designating any nodule as dominant. Although one could question the following process based on tumor biology, what is typically done in these discordant cases for the purposes of recording the staging and grade of the overall tumor is to take the highest grade and highest stage, even though they may not be from the same tumor nodule.

TABLE 3. Summary of Recommendations From the 2014 Consensus Meeting

- (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
- (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
- (5) Support for reporting grade using the new Grade Groups 1-5, initially in parallel to reporting Gleason score
- (6) Report percentage pattern 4 in Gleason score 7 on biopsy, TURP, and RP
- (7) A preferred term for tertiary-grade pattern on RP is minor high-grade pattern, which indicates tertiary should not merely be just the third most common pattern but that it should be minor or limited in extent. The only quantification of minor high-grade pattern that has been used in the literature with evidence-based data correlating with outcome has been the 5% cutoff
- (8) On needle biopsy, the Gleason score is based on the predominant pattern + the highest grade pattern
- (9) Minor high-grade patterns do not change the Grade Groups. For example, Gleason score 3 + 4 = 7 (Grade Group 2) with minor high-grade (tertiary) pattern 5
- (10) Assign individual Gleason scores to separate cores as long as the cores are submitted in separate containers or the cores are in the same container yet specified by the urologist as to their location (ie, by different color inks)
- (11) In cases where there are different undesignated cores with different grades in the same specimen container, it is optional whether to assign individual grades to different cores or a global grade for the specimen container
- (12) 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
- (13) In cases with multiple fragmented cores in a jar, give a global Gleason score for that jar
- (14) On RP, each major tumor nodule should be graded separately

TURP indicates transurethral resection of the prostate.

EMERGING TOPICS DISCUSSED AT THE 2014 CONSENSUS MEETING

Data were presented in the 2014 Consensus Conference that cribriform pattern 4 was associated with an adverse prognosis to justify that all cribriform glands should be graded as Gleason pattern 4. An emerging issue in the studies and those published subsequent to the meeting was that cribriform morphology is associated with a worse prognosis than poorly formed or fused glands.^{22,46-54} It was not discussed at the meeting, but cribriform glands may in the future be specifically incorporated into grading practice.

CONCLUSIONS

Over 2 years have passed after the first reporting of the 2014 Consensus Conference on prostate cancer grading. The recommendations of the meeting are summarized in Table 3. It is recognized that even though major changes and advances have occurred with grading of prostate cancer driven by the 2005 and 2014 Consensus conferences, the field is still evolving. We believe that the results from the 2014 Consensus Conference and the updates provided in this paper are vitally important to our specialty to promote uniformity in reporting of prostate cancer grade and in the contemporary management of prostate cancer.

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