Leading Article

The Evolution of Gleason Grading of Prostate Cancer

Hemamali Samaratunga\textsuperscript{1, 2}, Brett Delahunt\textsuperscript{1, 3}, Lars Egevad\textsuperscript{4}, John R Srigley\textsuperscript{5} and John Yaxley\textsuperscript{6}

\textsuperscript{1}Aquesta Pathology, Brisbane, Queensland, Australia, \textsuperscript{2}University of Queensland Faculty of Medicine, Brisbane, Queensland, Australia, \textsuperscript{3}Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand, \textsuperscript{4}Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden, \textsuperscript{5}Trillium Health Partners and University of Toronto, Mississauga, ON, Canada and \textsuperscript{6}Wesley Hospital, Brisbane, Queensland, Australia,

Submitted on 26.01.2017 \hspace{1em} Accepted for publication on 30.03.2017

DOI: http://doi.org/10.4038/jdp.v12i1.7733

Summary

One of the most important prognostic indicators of prostate cancer is tumour grading and the system that has been accepted worldwide for more than half a century was that developed by Donald Gleason. From the time of the publication of Gleason’s original report, the prognostic significance of Gleason scores (GS) has been confirmed. This system was established in the pre-prostate specific antigen (PSA) era when the diagnosis and management of prostate cancer were quite different from current practice. While Gleason grading fulfilled the role of a powerful prognostic indicator for many years, it became evident that, for the grading system to remain relevant in modern practice, certain modifications were required. The initial changes were made by Dr Gleason himself and in 2005, the International Society of Urological Pathology (ISUP), introduced significant improvements through a consensus conference attended by 52 International Urological Pathology experts. Since the 2005 ISUP conference Gleason scores 2-5 have effectively been abandoned for needle biopsies and as a consequence the lowest score found on a needle biopsy is now 6. The ISUP, through a further consensus conference in 2014, introduced ISUP grading consisting of 5 grades: Grade 1 (GS 3+3), grade 2 (GS 3+4), grade 3 (GS 4+3), grade 4 (4+4, 3+5, 5+3) and grade 5 (GS 9-10). Other changes introduced were to consider all cribriform cancers and tumours with glomerular patterns as grade 4, and to grade mucinous adenocarcinoma based on the underlying architecture. Given the significant new information in the literature, primarily relating to the prognostic significance of percentage of grade 4, it is likely that ISUP grading will evolve further.

Keywords: prostate adenocarcinoma, grade, Gleason, International Society of Urological Pathology
More than 50 years ago, Dr Donald Floyd Gleason created a unique system for the grading of prostate cancer. This grading system was based on histological findings from needle biopsies, transurethral resections and radical prostatectomy specimens of 270 patients enrolled in a study conducted by the Veterans Administration Co-operative Urological Research Group (VACURG). The majority of patients presented with extra-prostatic (stage 3) disease, while almost 40% had metastatic disease.

A unique feature of the criteria proposed by Gleason was that grading was based entirely upon tumour architecture. In contrast to systems for grading many other cancers, as well as those for prostate cancer grading then currently in use, cytological atypia was not considered to be a component of grading. Another aspect of the Gleason system that differed from other systems was that, rather than focusing upon the highest grade, the grade representing the largest area of cancer and the second largest area were added to give a score upon which patient management was based.

Five grading patterns were proposed. Grade 1 was defined as closely packed uniform glands forming well-circumscribed nodules. Grade 2 tumours were similar but the nodules were less well circumscribed, consisting of well differentiated glands with variability of size and shape, while some cribriform patterns were permitted. Grade 3 was composed of infiltrating well-differentiated glands; however, this could also include cribriform glands, single cells and cords, and masses of cells. Grade 4 was defined as a diffuse growth of large polygonal cells resembling clear cell carcinoma of the kidney, while grade 5 tumours consisted of undifferentiated carcinoma with little or no glandular differentiation.

The Gleason system has been validated using cancer specific mortality as the end point. This early study found that both the primary and secondary patterns were important, with survival of patients having two tumour patterns falling between that expected for each individual pattern.

Changes to Gleason grading by Gleason

In 1974 Gleason made several changes to his grading system based on a larger study population of 1032 patients. While no changes were made to grade 1 criteria, those for grades 2-5 were significantly amended. Specifically the presence of cribriform glands was now considered a feature of grade 3, rather than grade 2 tumours. Cribriform patterns in grade 3 were described as variable in size and could be large and infiltrating. In addition to this, papillary architecture was added to the features of grade 3 tumours. Pattern 4 was expanded to include raggedly infiltrating fused glands as well as coalescing and branching glands. Single cells were no longer included in the features of grade 3 tumours, but were now classified as grade 5. Grade 5 tumours also included carcinomas with comedonecrosis, signet ring cells and nests and sheets of cells without a glandular architecture.

Using these improved criteria, and following recommendations that grading be performed at low magnification using a x4 or x10 objective, Gleason found that lower grade tumours were commonly lower stage and that higher grade tumours were commonly high stage at presentation. Interobserver reproducibility was found to be 50% and within +/- 1 grade in approximately 85%.

Gleason score groups (lumping/ grouping of scores)

The establishment of 5 grades and 9 scores in the Gleason system was considered necessary to accommodate the heterogeneity and the variety architectural patterns characteristic of prostate cancer. It became clear over time, that the complexity of the grading system hindered survival analysis. In particular it was considered, for the purposes of research, that a smaller number of
prognostic groups should be established. In order to reduce the number of grading/scoring categories, groupings designated low, intermediate and high-grade were often utilized, although the challenge for most researchers was to decide which scores belonged to each category. In 1977 Gleason commented on the “common practice” by research groups of “lumping” of Gleason scores in an attempt to increase statistical significance in their studies. He criticized the use of score groups 2-4, 5-7 and 8-10 as he considered that this resulted in loss of useful clinical information, and that the middle group of scores had significantly different outcomes. He suggested that separating the groups according to Gleason scores 2-5, 6, 7 and 8-10 would be a clinically valid alternative. It was considered that score groups 2-6 and 7-10 were also useful in distinguishing between prognostic groups.\[^8\] \[^9\] Subsequently, others have used different combinations of Gleason scores as prognostic groups for the purpose of determining appropriate treatment options.\[^10\] - \[^18\] Some of these score groupings consisted of two categories representing low and high grade tumours. In other studies three categories, representing low, intermediate and high-grade, and 4 as well as 5 categories were investigated for prognostic significance.

**Why change a “perfectly good” grading system?**

Despite the attempted establishment of numerous other grading systems for prostate cancer, Gleason grading is the only system that has achieved worldwide acceptance and has remained in usage for more than fifty years. Despite this longevity it is evident that the system has problems. The diagnosis and management of prostate cancer has changed significantly over the last 50 years. In particular, prostate specific antigen (PSA) testing and screening has become available, resulting in early detection of prostate cancer. The method of taking prostate needle biopsies has also changed. Whereas previously one or two thick gauge needle biopsies were used to sample a palpable abnormality, more recently sampling of multiple areas is performed using thin core biopsies. In addition, different methods are now used to optimize cancer detection, including multiparametric magnetic resonance imaging (MRI)/transrectal ultrasound (TRUS) guided biopsies and transperineal biopsies. The methods of treatment have also changed dramatically, with a high proportion of patients receiving either curative treatment or active surveillance.

In addition to changes to the diagnosis and management of prostate cancer over recent years, it became clear that significant amendments to Gleason grading criteria were necessary. In particular the appropriateness of including cribriform glands as a feature of Gleason pattern 3 has been questioned. During this period it also became apparent that some pathologists were not strictly adhering to Gleason’s grading rules. In view of these developments it was widely considered that some evolution of Gleason grading was necessary for it to remain relevant to current practice. The necessity to amend Gleason grading and to adapt it to modern usage was embraced by The International Society of Urological pathology (ISUP). In 2005 the ISUP convened a consensus conference in San Antonio, Texas, USA in order to re-formulate prostate cancer grading.

**2005 modifications to Gleason grading**

The 2005 ISUP Consensus Conference was attended by 52 invited international urological pathology experts, with decisions being attained through discussion and voting.\[^19\] As a result of the meeting, major changes were agreed upon, although the resulting 2005 Modified Gleason System (MGS) classification was still largely based upon Gleason’s original recommendations. It was agreed that Grade 1 cancers either represented non-malignant conditions or inadequately sampled tumours of higher grade and as a consequence there was consensus that this grade should not be used. It was also agreed that while Grade 2 cancer may be found in the transition zone in
resection specimens, this grading should not be applied to needle biopsies. The consequence of this is that GS 1+1, 1+2, 2+1 and 2+2 cancers should not be diagnosed in these specimens. It was decided that cribriform glands, other than those that are small round and uniform with regular round lumens, should be classified as grade 4. An additional pattern, that of poorly formed glands, was added to the criteria of grade 4. The method of Gleason scoring in needle biopsies was significantly altered. Instead of summing the most common and the second most common grade to derive a score, the most common grade and the highest grade, no matter how small, were added to give the GS. In contrast, if the secondary pattern of a lower grade was <5%, it was excluded from the GS.

In contrast to the conventional Gleason classification, grading of variants was recommended and for most variants it was agreed that this should be based upon tumour architecture, ignoring cytologic changes. One exception to this was mucinous adenocarcinoma in which consensus was not achieved regarding a preferred grading method. The MGS has been validated in several studies which have shown a better correlation between needle biopsy and radical prostatectomy GS, as well as with pT staging category and biochemical recurrence free survival, than the conventional GS.20-22 Despite this, one study with nadir PSA as the clinical end point, found that both GS and MGS were of prognostic significance and that conventional GS out performed MGS in needle biopsies.23

2014 ISUP grading

By 2014, it became clear, due to the availability of new scientific knowledge, that further amendments to the MGS of 2005 were necessary. It was apparent that, while the amendments would be minor, it was important that they should be undertaken. Timing for this was crucial in view of the imminent updating of the World Health Organisation (WHO) Classification of Tumours of the Urinary System and Male Genital Organs, which was due to be published in early 2016. A further consensus conference was convened under the auspices of the ISUP. In order to facilitate this an organising committee of 6 expert uropathologists were appointed and the resulting meeting consisted of 65 uropathologists and 17 urologists and oncologists, from 19 countries.24 The organising committee members presented evidence relating to various questions and these were later voted upon at the conference.

Recent studies have shown that prostate cancer with cribriform morphology behaves as an aggressive cancer.25,26 It has also been shown that rounded cribriform cancers, previously classified as Gleason grade 3, are extremely rare without associated irregular cribriform glands or other patterns of grade 4.27 Further, distinguishing these tumours from cribriform grade 4 tumours has been shown to be subjective, with little interobserver reproducibility even amongst experts.28 From this it was decided that any cribriform cancer would be better designated Gleason grade 4 and this recommendation achieved consensus at the meeting. Similarly, it was agreed that all glomeruloid structures should be considered grade 4 as they were basically cribriform in architecture. The other important modification that achieved consensus at the meeting was that mucinous adenocarcinoma should be graded on the morphology of the underlying architecture and not uniformly considered to be grade 4.

A major feature of the conference was the development of a 5 tier grading system based upon Gleason grading. The necessity for this was a result of the recommendations of 2005 MGS where it was decided that Gleason patterns 1 and 2 should not be diagnosed on needle biopsy, which meant that the lowest GS diagnosable on needle biopsy would be 6. Given that 6 is in the middle of the range of scores 2-10, some patients were left thinking that they had intermediate grade cancer with
an intermediate risk of aggressive behavior. Recent studies had indicated that GS 6 tumours were indolent cancers with one study even showing that these tumours have no metastatic potential. Following on from Gleason's earlier prognostic group concept, it was suggested that this could be solved through the establishment of groupings of MGS. It was proposed that as score 6 is the lowest possible score this would be designated grade 1 with GS 3+4 as Grade 2, GS 4+3 as Grade 3, GS 4+4, 3+5 or 5+3 as Grade 4 and GS 9-10 as Grade 5. The naming of this "new" grading system was the subject of much discussion. The organizing committee had agreed that this would be ISUP Grade since the consensus meeting was convened under the auspices of the ISUP. However, without the prior knowledge of the other organizing committee members, one committee member floated the idea that this system should be named after himself. This did not achieve consensus despite two separate votes and subsequently, there was unanimous agreement by the ISUP Council that the term ISUP Grade should be applied.

Recent investigations have been undertaken to validate ISUP grading as a prognostic parameter for prostate cancer. Separate from and prior to the 2014 ISUP consensus conference, a large multi-institutional study was performed in an attempt to validate the newly proposed prognostic groups. Unfortunately, as the cases in this study were accessioned between 2005 and 2014 there can be no certainty as to which grading criteria were used. This is of particular importance as the cases in this study were not subjected to central review. Subsequent studies; however, have validated the new ISUP grading system with grading categories being shown to be significantly associated with death or biochemical failure.

**The future of ISUP grading**

It is now evident that improvements can be made to the 2014 ISUP grading to better predict patient outcome and to select treatment options. Specific features of the grading system in need of revision relate to ISUP grades containing Gleason pattern 4 carcinoma. An ISUP grade 2 tumour can have < 5% to 50% of Gleason grade 4 tumour, with a risk of metastasis and cancer-related death proportionate to the amount of grade 4 tumour present. A consequence of this is that the amount of grade 4 tumour present can influence treatment and in particular, can be a factor influencing the decision between active surveillance and definitive treatment. Gleason score 4+3 cancer can have 50-95% of Gleason grade 4 and again the higher the proportion of grade 4 the worse the prognosis. From these data it is evident that the percentage of Gleason pattern 4 present in needle biopsies should be factored into prostate cancer grading in order to maximize the prognostic information that is available to the clinician. Unfortunately there is currently no evidence to suggest which method should be used to assess the amount of pattern 4 present, and in particular whether this should be core or case based. Further, it is undecided whether the percentage of a pattern present should be assessed as the area of tumour or the length of tumour within a core. There have also been suggestions that the presence of cribriform cancer be reported separately and distinct from other patterns of grade 4, as this may be associated with a worse outcome.

A further issue that requires addressing relates to the score groups that constitute the ISUP system. In the current system ISUP grade 4 consists of 4+4, 3+5 and 5+3 tumours. It has been demonstrated that these three categories are different prognostically, with 5+3 cancers, in some cases, appearing to be as aggressive as ISUP grade 5 cancer.

In conclusion, ISUP grading, based upon 2005 MGS-based grouped Gleason scores is already in widespread usage. The terminology here is of some importance and is inappropriate to label these as grade groups as they are not grade, but rather score groups.
Clearly, this system in its current form requires further evolution so as to maximize

References

1. Gleason DF. Classification of prostatic carcinomas. Cancer Chemotherapy Reports 1966;50:125–8.
2. Delahunt B, Srigley JR, Lamb DS. Gleason grading: consensus and controversy. Pathology 2009;41:613–14.
3. Graham JB. Histologic grading of cancer of the uterine cervix. Surgery Gynecology and Obstetrics. 1953;96:331-7.
4. Pugh RC. The grading and staging of bladder tumours: the Institute of Urology classification. British Journal of Urology. 1957;29:222-5.
5. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. British Journal of Cancer. 1957;11:359-77.
6. Bailar JC 3rd, Mellinger GT, Gleason DF. Survival rates of patients with prostatic cancer, tumor stage, and differentiation – preliminary report. Cancer Chemotherapy Reports 1966;5:129–36.
7. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. Journal of Urology. 1974;111:58-64.
8. Gleason DF. Histological grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. Urologic Pathology: The Prostate. Philadelphia: Lea & Febiger; 1977:171–98.
9. Gleason DF. Histologic grading of prostate cancer: a perspective. Human Pathology 1992;23:273–9.
10. Banerjee M, Biswas D, Sakr W, Wood DP Jr. Recursive partitioning for prognostic grouping of patients with clinically localized prostate carcinoma. Cancer 2000;89:404–11.
11. McLean M, Srigley J, Banerjee D, Warde P, Hao Y. Interobserver variation in prostate cancer Gleason scoring: are there implications for the design of clinical trials and treatment strategies? Clinical Oncology 1997;9:222–225.
12. Glass TR, Tangen CM, Crawford ED, Thompson I. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. Journal of Urology 2003;169:164-169.
13. Shipley WU, Thames HD, Sandler HM, et al. Prognostic information that will more appropriately inform treatment.
14. Partin AW, Kattan MW, Subom ENP, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. JAMA 1997;277:1445–1451.
15. Donohue JF, Bianco FJ Jr, Kuroiwa K, et al. Poorly differentiated prostate cancer treated with radical prostatectomy: long-term outcome and incidence of pathological downgrading. Journal of Urology 2006;176:991–995.
16. Tolonen TT, Kujala PM, Tammela TLJ, et al. Overall and worst Gleason scores are equally good predictors of prostate cancer progression. BMC Urology 2011;11:21.
17. Eifler JB, Feng Z, Lin BM, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU International 2013;111:22–29.
18. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU International 2013;111:753–760.
19. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad L. ISUP Grading Committee. The 2005 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. American Journal of Surgical Pathology 2005;29:1228–1242.
20. Uemura H, Hoshino K, Sasaki T, et al. Usefulness of the 2005 International Society of Urological Pathology Gleason grading system in prostate biopsy and radical prostatectomy specimens. BJU International 2009; 103: 1190–1194.
21. Billis A, Guimaraes MS, Freitas LL, et al. The impact of the 2005 International Society of Urological Pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. Journal of Urology 2008;180:548–552.
22. Helpap B, Egevad L. The significance of modified Gleason grading of prostatic carcinoma in biopsy and radical prostatectomy specimens. Virchows Archiv 2006; 449:622–627.
23. Delahunt B, Lamb DS, Srigley JR, et al. Gleason scoring: a comparison of classical and modified...
Evolution of Gleason grading criteria using nadir PSA as a clinical end point. Pathology 2010; 42:339–343.

24. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, The Grading Committee. 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. American Journal of Surgical Pathology 2016; 40:244–252.

25. Sarbay BC, Kir G, Topal CS, Gumus E. Significance of the cribriform pattern in prostatic adenocarcinomas. Pathology Research and Practice 2014;210:554–557.

26. Kir G, Sarbay BC, Gumus E, Topal CS. The association of the cribriform pattern with outcome for prostatic adenocarcinomas. Pathology Research and Practice 2014;210:640–644.

27. Latour M, Amin MB, Billis A, et al. Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology. American Journal of Surgical Pathology 2008;32:1532–1539.

28. Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, van Leenders GJ. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Modern Pathology 2015;28:457–464.

29. Ross HM, Kryvenko ON, Cowan JE, et al. Do adenocarcinomas of the prostate with Gleason score (GS) ≤6 have the potential to metastasize to lymph nodes? American Journal of Surgical Pathology. 2012; 36:1346-1352.

30. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. European Urology 2016; 69:428–435.

31. Delahunt B, Egevad L, Srigley JR, et al. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 ‘RADAR’ trial clinical data. Pathology 2015; 47:520–525.

32. Berney DM, Beltran L, Fisher G, et al. Validation of a contemporary prostate cancer grading system using cancer death as outcome. British Journal of Cancer 2016;114:1078–1083.

33. He J, Albertsen PC, Moore D, et al. Validation of a contemporary five-tiered Gleason grade grouping using population-based data. European Urology 2016;http://dx.doi.org/10.1016/j.eururo.2016.11.031.

34. Samaratunga H, Delahunt B, Gianduzzo T, et al The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer. Pathology 2015;47:515–519.

35. Spratt DE, Cole Al, Palapattu GS, et al. Independent surgical validation of the new prostate cancer grade-grouping system. BJU International 2016;118:763–9.

36. Loeb S, Folklajlon Y, Robinson D, et al. Evaluation of the 2015 Gleason grade groups in a nationwide population-based cohort. European Urology 2016;69:1135–41.

37. Mathieu R, Moschini M, Beyer B et al. Prostate Prognostic value of the new grade groups in prostate cancer: a multi-institutional European validation study. Cancer and Prostatic Diseases advance online publication, 10 January 2017; doi:10.1038/pcan.2016.66.

38. Kir G, Seneldir H, Gumus E. Outcomes of Gleason score 3+4=7 prostate cancer with minimal amounts (<6%) vs >6% of Gleason pattern 4 tissue in needle biopsy specimens. Annals of Diagnostic Pathology 2015;20:48–51.

39. Sauter G, Steurer S, Clauditz TS, et al Clinical utility of quantitative Gleason grading in prostate biopsies and prostatectomy specimens. European Urology 2016;69:592–598.

40. Egevad L, Delahunt B, Evans A et al. International Society of Urological Pathology (ISUP) grading of prostate cancer American Journal of Surgical Pathology 2016;40:858-861.