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Comment

Prostate cancer grading, time to go back to the future

In November 2014, the International Society of Urological Pathology (ISUP) convened a consensus meeting in Chicago, Illinois, USA to consider grading criteria for prostatic adenocarcinoma [1]. The primary purpose and main outcome of this meeting was a recommendation that, not only should the Gleason score of prostate cancer be reported, but that grading should also incorporate a five-tier grade based on a grouping of Gleason scores. The outcome of the conference has resulted in widespread confusion as to the grading nomenclature. This has weighed heavily on the prostate cancer literature to the extent that the time has now come to question the scientific value of the score grouping.

The Chicago conference was held as a stand-alone 1-day meeting and was rushed to enable a consensus decision to be achieved to inform the editorial meeting of the WHO Classification of Tumours of the Urinary System and Male Genital Organs in March 2015. Unfortunately, this consensus was never generated. At the WHO meeting, it was agreed that the WHO Bluebook should not endorse any of the proposed names for the grading scheme and the Bluebook instead adopted the descriptive and provisional term 'grade groups' [2]. An important issue is that while the term 'grade group' is catchy, it is factually incorrect as the system is not a grouping of Gleason grades, but a grouping of Gleason scores. A further major problem is that 'grade groups' are usually abbreviated to GG which has for decades been the acronym for Gleason grade, i.e. Gleason pattern. The issue has been compounded by the plethora of terms and abbreviations that have flooded the literature, with the grading system being referred to as: GG (grade group) [3]; GrG (grade group) [4]; PGG (prognostic grade group [5]; prostate cancer grade group [6]); GGG (Gleason grade group) [7]; ISUP grade [8]; WHO grade group [9]; ISUP grade group [10]; ISUP score [11]; and others. The problems resulting from the use of 'GG' as an acronym are not confined to the confusion as to whether it refers to 'grade group' or Gleason grade (i.e. Gleason pattern) as it is also unclear what is meant by 'grade' in this context. Does this refer to Gleason score, Gleason pattern or 'grade group'? The pathology community has spent considerable energy on this dispute over the last 5 years [12–15].

It has been claimed that the main advantage of grouping of Gleason scores is that it assists clinicians in their discussions with patients over the likely behaviour and outcome of their prostate cancer. Understandably, a diagnosis of a grade 1 cancer may indeed sound more reassuring than that of a Gleason score 6 cancer. However, we question the cost–benefit ratio of the putative pedagogical advantage vs the confusion that has been caused by the plethora of new terms. It has been shown that there is indeed a need to explain the grading information to the patients as fewer than 50% in one study were found to have adequate understanding of the current nomenclature [16]. Yet, an increasing number of patients are well informed as they have access to a wealth of information on the Internet. Even if pathologists did cease to refer to the ISUP 2014 score grouping in the scientific literature, clinicians would still be free to translate a Gleason score 6 to grade 1, if that was more understandable in communications with the patient.

There may have been a hope among some pathologists that 'grade groups' would replace Gleason grading entirely, but it is now apparent that this is a very unlikely scenario. Grading of prostate cancer is based on architectural patterns and pathologists need to specify these patterns to describe their findings. The wordy description of the morphology of the ISUP 2014 scheme in the consensus document is clearly insufficient for the discussion of individual architectural patterns [1]. It is clear from this that the so-called groupings and the definitive Gleason scores would always need to be reported simultaneously and thus continue to provide redundant information. Pathology reports tend to become increasingly extensive with an increasing amount of prognostic information. Even if synoptic reporting is used, all this information will risk obscuring the important diagnostic and prognostic elements. Any duplicate information should therefore be avoided.

Prostate cancer grading has gone through uninterrupted change over the past two decades. Few other areas of tumour pathology have seen such a landslide of variation in reporting recommendations. Some of this development reflects an increased understanding of the biology of the disease, such as the notion that the presence of invasive cribriform cancer and intraductal carcinoma of the prostate conveys a poor prognosis [17,18]. While cribriform cancer used to be included in either Gleason pattern 3 or 4, depending on the size and shape of the glands, the ISUP 2014 revision considers all cribriform cancer to be Gleason pattern 4, or even 5 if comedonecrosis is present [19]. The recognition of the prognostic impact of intraductal carcinoma of the prostate has led to the recommendation that this lesion be assigned a Gleason pattern 4 or 5 using the same criteria as for prostatic carcinoma with stromal invasion [18,20]. Other decisions have been much less well founded and have led to confusion among general pathologists. The first major revision of the Gleason system resulted from the ISUP consensus conference in 2005 [21]. Here a re-definition of the significance of the components of the Gleason scores in needle biopsies was proposed. This has resulted in a

significant Gleason inflation, which was confirmed in a registry study of almost 100 000 men with newly diagnosed cancer on needle biopsy in 1998–2011 [22]. A gradual shift towards the upgrading of tumours has been observed over a prolonged period, but this has been particularly evident after 2005. After an adjustment for stage shift, the proportion of tumours diagnosed as Gleason scores 7–10 increased from 59% to 72% when cancers reported before and after 2005 were compared. It has also been shown that, following the publication of the 2005 ISUP revision of the Gleason classification, the grading of general pathologists has become more aggressive than that of uropathology experts [23]. This has had a negative impact on the management of prostate cancer, with the perception that the Gleason score has become fluid rather than finite. This is unfortunate as the development of well-established reporting systems must be based on strong scientific evidence and a high level of consensus in the uropathology community.

The correlation between Gleason score in needle biopsies and radical prostatectomy specimens has been claimed to be improved after the ISUP 2005 revision of the Gleason grading system [24]. This conclusion was supported by an often-cited early report [25]; however, that particular study did not take into account the differences in grade distribution when comparing grading undertaken before and after 2005. If the number of grade categories that are actually used is reduced by new recommendations, there will be a spurious improvement of prediction accuracy of prostatectomy grade. In a later registry study of more than 15 000 men, it was found that, when grade distribution and other confounders were taken into account, there was actually a decreased grade concordance after 2005 [26]. When the scores were grouped according to ISUP 2014 the concordance fell even further, suggesting that even the ISUP 2014 revision may have done more harm than good in this respect.

The percentage of Gleason pattern 4/5 present in biopsies was introduced as a prognostic marker by Stamey et al. two decades ago [27]. Despite validation of the prognostic value and assessment of the reproducibility of this marker [28,29], assessment of percentage of Gleason pattern 4/5 present in tumours did not gain widespread traction in clinical practice. More recently the reporting of percentage of pattern 4/5 present in cancers has become more prevalent [8]. An explanation for this increasing interest may be that the Gleason inflation that was fueled by the ISUP 2005 consensus recommendations has pushed a considerable number of cancers from Gleason score 6 to 7 [21]. There is now a need for the identification of additional descriptors that will permit the triaging of Gleason score 7 tumours into categories that will provide guidance in the management of patients. This incremental reporting of percentage of Gleason pattern 4 further reduces interest in the reporting of broad categories of Gleason patterns 3 vs 4 involvement as grades 2, 3 and 4 (1–49%, 50–95% and >95% Gleason pattern 4), especially since pure Gleason score 8 (4 + 4) in radical prostatectomy specimens is apparently rare, contributing to only 0.6–3.9% cases in tumour series [30,31]. Furthermore, several studies have demonstrated overlapping outcome curves for ISUP grades 3 and 4 [30,32–34]. This makes it even more questionable whether it is worth assigning a separate grade category to the unusual pure Gleason score 4 + 4 = 8 cancers, while other steps in the continuous scale of percentages of Gleason pattern 4 are ignored. In some active surveillance programmes, 10% is a limit for allowing active surveillance [35]. Stamey et al. emphasized that, if biopsies contained at least 20% Gleason pattern 4/5, the prostatectomy specimen also contained at least 20% of these patterns in 90% of men, indicating that this threshold may be of clinical interest [27]. None of these thresholds is accounted for by 'grade groups' 2–4.

Yet another problem with the suggested grouping of grades is the unsettled definition of ISUP grade 4 [36]. At the ISUP consensus conference in 2014, this grade category was defined as Gleason score 8 (4 + 4, 3 + 5 and 5 + 3), while Pierorazio et al. [5] defined prognostic grade group 4 as Gleason score 8 based on investigations of the outcome of Gleason score 4 + 4 cancer alone. Thus, ISUP 2014 grading departs from the Pierorazio et al. grouping, both in the grouping of scores and in the interpretation of morphology. Several studies have indicated a possible heterogeneity in Gleason score 8 tumours. Some have found a higher prostate cancer-specific mortality in Gleason score 5 + 3 than in 3 + 5 and 4 + 4 [37] or in 3 + 5 and 5 + 3 than in 4 + 4 [38], while others have found a lower biochemical [31] or clinical recurrence rate [39] in cancers of Gleason score 3 + 5 than in other Gleason score 8 tumours. A further issue is that 'grade groups' lack the granularity of Gleason scoring. The clearest example of this relates to 'grade group' 4. Here it is unknown if this refers to Gleason score 3 + 5=8, 4 + 4=8 or 5 + 3 = 8. There is increasing evidence that the percentage of pattern 4 tumour present has an impact on outcome and, as such, it seems bizarre that 'grade group' 4 tumours have either 100% pattern 4 or 0% pattern 4 and yet are classified as an identical grade.

It has also been suggested that Gleason score 5 + 4 cancers may have a higher risk of lymph node involvement and a worse outcome after radical prostatectomy than Gleason score 4 + 5 tumours [40]. In addition, we may at present be unaware of details that now escape us such as the distinction of very low-grade patterns detected by MRI-targeted biopsies from the anterior prostate, as all low-grade tumours are currently lumped together on needle biopsy.

All of these examples illustrate that collapsing the Gleason grading system to five groups simplifies the complexity of prostate cancer morphology, with resulting loss of detail of information. Few revisions of a histopathological grading system have contributed as little as the ISUP grading

recommendations of 2014. The notion that this would be a novel grading system is a misconception as it is a mere translation of the Gleason scores into an alternative terminology at the expense of loss of information. It is time to realize that the introduction of this grouping was a mistake and reclaim the universally understood Gleason nomenclature for grading of prostate cancer. The future development of prostate cancer prognostication should rather be based on the integration of novel knowledge of the role of genetics of prostate carcinogenesis [41,42] and classical morphology, possibly assisted by artificial intelligence [20,43].

Conflict of Interest

None declared.

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References

1 **Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA.** 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. *Am J Surg Pathol* 2016; 40: 244–52.

2 **Moch H, Humphrey PA, Ulbright TM, Reuter VR.** *WHO Classification of Tumours of the Urinary System and Male Genital Organs*, 4th edn, Lyon: WHO Press: 2016

3 **Berney DM, Beltran L, Sandu H et al.** The percentage of high-grade prostatic adenocarcinoma in prostate biopsies significantly improves on Grade Groups in the prediction of prostate cancer death. *Histopathology* 2019; 75: 589–97

4 **Chen-Maxwell D, Prendeville S.** Grading of prostate cancer: the impact of including intraductal carcinoma on the overall grade group assigned in diagnostic biopsies. *Histopathology* 2020; 77: 503–7.

5 **Pierorazio PM, Walsh PC, Partin AW, Epstein JI.** Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int* 2013; 111: 753–60

6 **Sze C, Tsivian E, Tay KJ et al.** Anterior gland focal cryoablation: proof-of-concept primary prostate cancer treatment in select men with localized anterior cancers detected by multi-parametric magnetic resonance imaging. *BMC Urol* 2019; 19: 127

7 **Loeb S, Folkvaljon Y, Robinson D, Lissbrant IF, Egevad L, Stattin P.** Evaluation of the 2015 Gleason Grade Groups in a Nationwide Population-based Cohort. *Eur Urol* 2016; 69: 1135–41

8 **Egevad L, Judge M, Delahunt B et al.** Dataset for the reporting of prostate carcinoma in core needle biopsy and transurethral resection and enucleation specimens: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Pathology* 2019; 51: 11–20

9 **Raspollini MR, Montagnani I, Cirri P et al.** PreImplantation Factor immunohistochemical expression correlates with prostate cancer aggressiveness. *Int J Biol Markers* 2020; 35: 82–90

10 **Lu TC, Collins L, Cohen P, Jay A, Campbell JM, O'Callaghan M.** Prognostic differences in ISUP Grade Group 4: a systematic review and meta-analysis. *Pathol Oncol Res* 2020; 26: 1367–75

11 **Takeuchi N, Sakamoto S, Nishiyama A et al.** Biparametric prostate imaging reporting and data system version2 and international society of urological pathology grade predict biochemical recurrence after radical prostatectomy. *Clin Genitourin Cancer* 2018; 16: e817–29

12 **Delahunt B, Grignon DJ, Samaratunga H et al.** Prostate cancer grading: a decade after the 2005 modified Gleason grading system. *Arch Pathol Lab Med* 2017; 141: 182–3

13 **Egevad L, Delahunt B, Evans AJ et al.** International Society of Urological Pathology (ISUP) Grading of Prostate Cancer. *Am J Surg Pathol* 2016; 40: 858–61

14 **Epstein JI.** International Society of Urological Pathology (ISUP) grading of prostate cancer: Author's Reply. *Am J Surg Pathol* 2016; 40: 862–4

15 **Epstein JI, Kryvenko ON.** In Reply. *Arch Pathol Lab Med* 2017; 141: 183–4

16 **Tagai EK, Miller SM, Kutikov A et al.** Prostate cancer patients' understanding of the Gleason Scoring System: Implications for Shared Decision-Making. *J Cancer Educ* 2019; 34: 441–5

17 **Kweldam CF, Kummerlin IP, Nieboer D et al.** Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. *Mod Pathol* 2016; 29: 630–6

18 **Samaratunga H, Delahunt B, Egevad L et al.** Intraductal carcinoma of the prostate is an aggressive form of invasive carcinoma and should be graded. *Pathology* 2020; 52: 192–6

19 **Epstein JI, Egevad L, Amin MB et al.** 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. *Am J Surg Pathol* 2016; 40: 244–52.

20 **van Leenders G, van der Kwast TH, Grignon DJ et al.** The 2019 International Society of Urological Pathology (ISUP) Consensus

Conference on Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2020; 44: e87–99.

21 **Epstein JI**, **Allsbrook WC Jr**, **Amin MB**, **Egevad L**. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2005; 29: 1228–42.

22 **Danneman D**, **Drevin L**, **Robinson D**, **Stattin P**, **Egevad L**. Gleason inflation 1998–2011: a registry study of 97,168 men. *BJU Int* 2015; 115: 248–55

23 **Egevad L**, **Ahmad AS**, **Algaba F et al.** Standardization of Gleason grading among 337 European pathologists. *Histopathology* 2013; 62: 247–56

24 **Delahunt B**, **Miller RJ**, **Srigley JR**, **Evans AJ**, **Samaratunga H**. Gleason grading: past, present and future. *Histopathology* 2012; 60: 75–86

25 **Helpap B**, **Egevad L**. The significance of modified Gleason grading of prostatic carcinoma in biopsy and radical prostatectomy specimens. *Virchows Arch* 2006; 449: 622–7

26 **Danneman D**, **Drevin L**, **Delahunt B et al.** Accuracy of prostate biopsies for predicting Gleason score in radical prostatectomy specimens: nationwide trends 2000–2012. *BJU Int* 2017; 119: 50–6

27 **Stamey TA**, **McNeal JE**, **Yemoto CM**, **Sigal BM**, **Johnstone IM**. Biological determinants of cancer progression in men with prostate cancer. *JAMA* 1999; 281: 1395–400

28 **Glaessgen A**, **Hamberg H**, **Pihl CG**, **Sundelin B**, **Nilsson B**, **Egevad L**. Interobserver reproducibility of percent Gleason grade 4/5 in total prostatectomy specimens. *J Urol* 2002; 168: 2006–10

29 **Glaessgen A**, **Hamberg H**, **Pihl CG**, **Sundelin B**, **Nilsson B**, **Egevad L**. Interobserver reproducibility of percent Gleason grade 4/5 in prostate biopsies. *J Urol* 2004; 171: 664–7

30 **Sauter G**, **Steurer S**, **Clauditz TS et al.** Clinical utility of quantitative Gleason grading in prostate biopsies and prostatectomy specimens. *Eur Urol* 2016; 69: 592–8

31 **van den Bergh RC**, **van der Kwast TH**, **de Jong J et al.** Validation of the novel International Society of Urological Pathology 2014 five-tier Gleason grade grouping: biochemical recurrence rates for 3+5 disease may be overestimated. *BJU Int* 2016; 118: 502–5

32 **Berney DM**, **Beltran L**, **Fisher G et al.** Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. *Br J Cancer* 2016; 114: 1078–83

33 **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: 520–5

34 **Grogan J**, **Gupta R**, **Mahon KL et al.** Predictive value of the 2014 International Society of Urological Pathology grading system for prostate cancer in patients undergoing radical prostatectomy with long-term follow-up. *BJU Int* 2017; 120: 651–8

35 **Morash C**, **Tey R**, **Agbassi C et al.** Active surveillance for the management of localized prostate cancer: guideline recommendations. *Can Urol Assoc J* 2015; 9: 171–8

36 **Delahunt B**, **Egevad L**, **Grignon DJ**, **Srigley JR**, **Samaratunga H**. Prostate cancer grading: recent developments and future directions. *BJU Int* 2016; 117(Suppl 4): 7–8

37 **Mahal BA**, **Muralidhar V**, **Chen YW et al.** Gleason score 5 + 3 = 8 prostate cancer: much more like Gleason score 9? *BJU Int* 2016; 118: 95–101

38 **Huynh MA**, **Chen MH**, **Wu J**, **Braccioforte MH**, **Moran BJ**, **D'Amico AV**. Gleason Score 3 + 5 or 5 + 3 versus 4 + 4 prostate cancer: the risk of death. *Eur Urol* 2016; 69: 976–9

39 **Gandaglia G**, **Karnes RJ**, **Sivaraman A et al.** Are all grade group 4 prostate cancers created equal? Implications for the applicability of the novel grade grouping. *Urol Oncol* 2017; 35: e7–14

40 **Lim SK**, **Kim KH**, **Shin TY et al.** Gleason 5+4 has worse oncological and pathological outcomes compared with Gleason 4+5: significance of Gleason 5 pattern. *Ann Surg Oncol* 2013; 20: 3127–32

41 **Cucchiara V**, **Cooperberg MR**, **Dall'Era M et al.** Genomic markers in prostate cancer decision making. *Eur Urol* 2018; 73: 572–82

42 **Sluka P**, **Pezaro C**, **Wardan H**, **Sengupta S**, **Davis ID**. Identification of novel oncogenic events occurring early in prostate carcinogenesis using purified autologous malignant and non-malignant prostate epithelial cells. *BJU Int* 2019; 123(Suppl 5): 27–35

43 **Egevad L**, **Strom P**, **Kartasalo K et al.** The utility of artificial intelligence in the assessment of prostate pathology. *Histopathology* 2020; 76: 790–2

Abbreviation: ISUP, International Society of Urological Pathology.