One is the new six: The International Society of Urological Pathology (ISUP) patient-focused approach to Gleason grading

John R. Srigley, MD;[1] Brett Delahunt, MD;[2] Lars Egevad, MD;[3] Hemamali Samaratunga, MD;[4] John Yaxley, MD;[5] Andrew J. Evans, MD[6]

[1]Trillium Health Partners and University of Toronto, Mississauga, ON, Canada; [2]Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand; [3]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [4]Aquesta Uropathology and University of Queensland, Brisbane, Queensland, Australia; [5]Department of Urology, Royal Brisbane Hospital and University of Queensland, Brisbane, Queensland, Australia; [6]University Health Network and University of Toronto, Toronto, ON, Canada

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Fifty years ago, Donald Gleason published his eponymous grading system and demonstrated its prognostic utility in clinical trials designed to investigate hormonal therapies for prostate cancer.[1] Over the ensuing decades, the Gleason system has been widely used in clinical practice and research, and has been endorsed as the global grading standard for prostate cancer by numerous organizations, including the World Health Organization (WHO) and the Union for International Cancer Control (UICC).[2,3]

The diagnosis and treatment of prostate cancer has changed dramatically in recent decades and as the new millennium dawned, a modernization of the Gleason system commenced. In 2005, the International Society of Urological Pathology (ISUP) convened a consensus conference at which the patterns comprising the various Gleason grades were clarified, along with the practical rules for their application.[4] There was emphasis on how the grading system should be employed in biopsy practice. It was agreed that Gleason grades 1 and 2 should not be used in biopsy reporting. The consensus was that these uncommon patterns should be restricted to occasional tumours, usually originating in the transition zone, that were only diagnosable in transurethral resections or radical prostatectomy specimens. As a consequence of this, the Gleason scale for biopsies started at Gleason score six. Cribriform patterns, with the exception of the uncommon small, round, and regular cribriform structures, and so-called poorly formed glands (without well-formed lumens) were included as features of Gleason pattern (grade) 4. Additionally, it was decided that in biopsies where three Gleason patterns are present, the dominant pattern and worst remaining one, irrespective of its extent should comprise the Gleason score.

Over the following decade, the changes endorsed by ISUP in 2005 resulted in an upgrading of prostate cancer, with a greater proportion of patients being classified within high-risk categories.[5-7] Additionally, the recalibration of the Gleason scale resulted in practical problems for both urologists and oncologists, who had to explain to patients that Gleason 6 cancer was a low-grade tumour and that active surveillance, in many cases, was the treatment of choice. With the availability of information from the web and other sources, patients were often left confused by the concept of Gleason 6 being considered the most favourable grade on biopsy, when the Gleason system spanned scores 2–10. They were asking, "Wouldn't my Gleason 6 cancer be considered intermediate grade?" Even for stratification of patients into a high-profile clinical trial, Gleason 6 was considered intermediate-grade rather than low-grade.[8] Additionally, there was a suggestion by some clinicians, epidemiologists, and public health physicians to re-name Gleason 6 adenocarcinoma as "indolent lesion of epithelial origin (IDLE)."[9]

Because of these and other unresolved issues from the 2005 consensus conference, the ISUP convened a second meeting in 2014 to further clarify details of prostate cancer grading based on evidence generated since 2005 wherever possible. This conference was attended by 65 pathologists and 17 clinicians from 19 countries.[10] At the meeting it was agreed that all cribriform and glomeruloid patterns should be classified as Gleason grade 4. It was further agreed that grading for mucinous tumours should be based upon the underlying architectural pattern and not be influenced by the mucin component. Finally, intraductal carcinoma of prostate, which has come to prominence as an important adverse prognostic factor in the last decade, would not be graded and only the associated invasive component would be assigned a Gleason score.

A major focus of the 2014 meeting was the refinement and endorsement of a prognostic grouping system initially proposed by Eifler et al in 2012.[11] Over the years, numerous grade grouping systems have been proposed and the current system is a natural progression of this (Table 1).[12-25] The ISUP grades, which are based on the grouping of Gleason scores and patterns, are shown in Table 2. Arguably, the

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Table 1. Chronological evolution of the Gleason score/ grade groupings*

Year	Gleason groupings	Reference
1977	2-3 v 4-5 v 6 v 7-8 v 9-10	Gleason[12]
1987	2-5 v 6-7 v 8-10	Pilepich[13]
1990	2-5 v 6 v 7 v 8-10	Bagshaw[14]
1991	2-4 v 5-7 v 8-10	Russell[15]
1993	2-6 v 7-10	Epstein[16]
1994	2-4 v 5-6 v 7 v 8-10	Ohori[17]
1995	2-3 v 4-6 v 7 v 8-10	Zagars[18]
1997	2-4 v 5 v 6 v 7 v 8-10	Partin[19]
1998	2-6 v 7 v 8-10	D'Amico[20]
2000	2-4 v 5-6 v 7-10	Freedland[21]
2006	<6 v 3+4 v 4+3 v 8-10	Donohue[22]
2007	2-6 v 3+4 v 4+3 v 8-10	Makarov[23]
2011	≤3+4 v 4+3 v 8 v 9-10	Tolonen[24]
2012	2-6 v 3+4 v 4+3 v 8 v 9-10**	Eifler[11]

*Modified from Egevad et al[25]; **refined and endorsed at International Society of Urological Pathology consensus conference (2014).

Table 2. The International Society of Urological Pathology (ISUP) grading system

ISUP grade	Gleason scores	Definition
Grade 1	2–6	Only individual discrete well-formed glands
Grade 2	3+4=7	Predominantly well-formed glands with lesser component of poorly formed/fused/ cribriform glands
Grade 3	4+3=7	Predominantly poorly formed/fused/ cribriform glands with lesser component of well-formed glands
Grade 4	4+4=8	Only poorly formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component of well-formed glands
Grade 5	9–10	Lacking gland formation (or with necrosis) with or without poorly formed/fused/ cribriform glands

most significant element of the new system is the grouping of all cases with Gleason scores ≤6 as grade 1. The identification of this very low-risk category helps alleviate patients' concerns regarding the intermediate placement of Gleason score 6 tumours on the 2–10 Gleason scale. Many patients with these low-grade tumours can be followed by active surveillance and the reclassification of these as ISUP grade 1 emphasizes their indolent nature.

ISUP grades 2 and 3 stratify Gleason 7 into two categories based on whether well-formed glands or poorly formed/ fused/cribriform glands predominate. These two categories have long been known to have different prognostic significance and in fact, Gleason scores 7 (3 + 4) and 7 (4 + 3) have been incorporated into nomograms and risk calculators for many years.[26-28] Subsequent to the 2014 consensus meeting, it was decided by the ISUP working group that the percentage pattern 4 should be documented in all Gleason 7 tumours, with agreement for this decision being obtained from participants by web-polling. The documentation of percentage pattern 4 is particularly important in ISUP grade 2 cancers, as the active surveillance guideline published by Cancer Care Ontario and subsequently endorsed by the American Society of Clinical Oncology, indicates that selected patients with Gleason 7 tumours who have ≤10% pattern 4 tumour, can be considered for active surveillance protocols.[29,30] The documentation of percent pattern 4 in Gleason 7 cancers is also recently recommended by the WHO.[31]

The grade 4 category of the ISUP grading system is heterogeneous and consists predominantly of tumours with Gleason score 4 + 4 = 8, with less common Gleason patterns 3 + 5 and 5 + 3 also being included. These tumours behave in a significantly more aggressive manner than ISUP grade 3.[32-34] Grade 5 is the highest ISUP grade and consists of Gleason scores 9 and 10. These latter tumours are associated with poor prognosis.[32-34] From a practical perspective, it is recommended that the ISUP grade be reported in all needle biopsies, along with the corresponding Gleason patterns and scores.[10]

While ISUP grading represents a significant advance in prostate pathology, future modifications will likely be required. In particular, ISUP grade 4 tumours consisting of Gleason patterns 5 + 3 have been shown to have the worst prognosis compared to those with only pattern 4 or 3 + 5 and may be more appropriately included in ISUP grade 5.[35] Other problem areas include the level (individual core, specimen, case) at which ISUP grading should apply, the handling of grade diversity across specimens, and whether ISUP grade should be based on the worst or composite Gleason score. A further major unresolved issue is the lack of consensus as to how tertiary patterns should be handled in radical prostatectomy specimens.

Despite these issues, the ISUP grading system addresses several of the criticisms faced by urological pathologists related to the inaccuracy of Gleason scale and perceived over-diagnosis of cancer. Furthermore, and most importantly, it provides patients with low-risk disease the lowest possible grade. Indeed, one is the new six.

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Correspondence: Dr. John R. Srigley, Trillium Health Partners and University of Toronto, Mississauga, ON, Canada; john.srigley@trilliumhealthpartners.ca