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INVITED REVIEW

Prostate Cancer

Contemporary grading of prostate cancer: 2017 update for pathologists and clinicians

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The Gleason grading system for prostate cancer (PCa) was developed in the 1960s by DF Gleason. Due to changes in PCa detection and treatment, the application of the Gleason grading system has changed considerably in pathology routine practice. Two consensus conferences were held in 2005 and in 2014 to update PCa Gleason grading. This review provides a summary of the changes in the grading of PCa from the original Gleason grading system to the prognostic grade grouping, as well as a discussion of the clinical significance of the percentage of Gleason patterns 4 and 5.

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INTRODUCTION

Treatment of prostate cancer (PCa) is based on the clinical and pathological features that predict the course of the disease. The risk of local or systemic recurrence is usually based on data obtained from prostate needle biopsy or radical prostatectomy (RP) specimens. The Gleason grading system is one of the most important prognostic factors.[1–3]

In 1966, DF Gleason created a grading system for PCa based on tumor architectural patterns.[4] Dr. Gleason recognized the heterogeneity of PCa by assigning two grades to the two most common architectural patterns, reported as the Gleason score (GS).[4] Dr. Gleason reported that the presence of more than two architectural patterns was quite rare to allow for an accurate evaluation of the prognostic role of the third most prevalent pattern (i.e., the tertiary pattern).[5]

The management of PCa has changed since the original system was proposed. In particular, patients in the 1960s and 1970s were not treated with RP because they presented with advanced disease and because of the greater morbidity associated with surgery; therefore, grading of RPs with multiple tumor foci and tertiary patterns was not fully investigated by Dr. Gleason. With the PSA screening and 18-gauge needle biopsies, pathologists faced new issues, such as how to report multiple cores with PCa of different GSs and how to grade small amounts of PCa. Pathologists needed guidance for applying the grade to newly described histological patterns and variants of PCa, and modifications of the original Gleason system were needed to reflect the modern practice. The Gleason grading system has undergone changes as a result of two International Society of Urological Pathology (ISUP) consensus conferences held in 2005 and 2014.[4,6]

A summary of the changes to PCa grading from the original Gleason grading system to the latest prognostic grade grouping is presented. This review also includes a discussion of the clinical significance of the percentage of Gleason patterns 4 and 5.

THE 2005 AND 2014 MODIFIED GLEASON GRADING SYSTEMS

One of the biggest changes to the Gleason grading system was the classification of Grades 1 and 2. Grade 1 tumors are generally benign, and Grade 2 tumors do not appear to differ from those classified as Grade 3. In 2005, Grade 2 was recommended to be used "rarely, if ever," and in the 2014 modified Gleason grading system, grading started from 3. This modification accounted for some of the observed rises in Gleason scores. A second change causing an increase in Gleason scores was the narrowing of the definition of Gleason 3 and concomitant expansion of Gleason 4.

From the 2005 to the 2014 consensus conferences, the histologic criteria for Gleason patterns 3 and 4 changed, resulting in the reduction of pattern 3 and expansion of pattern 4.[2] In the original system, pattern 3 included some cribriform as well as poorly formed glands.[5] Only well-formed discrete glands are included in pattern 3 in the 2014 modified Gleason grading system. In particular, cribriform glands lacking basal cells, independently of their morphology and size, are considered as pattern 4 in the 2014 modified Gleason system.[1,2,6–15] Fused, poorly formed, and glomeruloid glands are part of the morphologic spectrum of the current Gleason pattern 4.

As some patterns that were previously included in Gleason pattern 3 are now considered pattern 4, PCas with a GS of 3 + 3 = 6 based on the ISUP 2014 modified system have a far better prognosis than PCas

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with a GS 6 based on the original Gleason system.[16] The concordance between biopsy and RP grades has also improved.[17–19]

A further modification to the grading system in 2005 with regard to needle biopsy was that for high-grade tumors, the lower grade or pattern should not be included in the GS if it is <5% of the tumor. In needle biopsy findings with three distinct patterns, the most prevalent pattern is combined with the highest grade to form the GS, thus discarding to the second most common pattern.[4] Grading is based on the "first plus the worst," that is, the most prevalent pattern plus the highest grade, such that if patterns 3, 4, and 5 are present in that order of prevalence, the grade is 3 + 5 = 8.

A recommendation from the 2014 consensus conference was that the percentage of pattern 4 is recorded in all GS 7 (3 + 4, 4 + 3) tumors.[6,20] This further stratifies GS 7 and allows for identification of tumors with a limited (i.e., ≤10%) or extensive (i.e., >75%) amount of pattern 4.[21] The practical value is that selected patients with GS 7 (3 + 4) and a small amount of pattern 4 (such as ≤10%) may be still enrolled in active surveillance programs.[22–24]

Main limitations of the 2005 and 2014 modified Gleason scoring systems

From a clinical perspective, the 2005 and 2014 modified Gleason systems are suboptimal due to several reasons as follows:[2,25–29]

1. Patients with GS 3 + 3 = 6 are considered to have intermediate-risk cancer, even though GS 6 is the lowest score used on prostate biopsies
2. The category of GS 7 includes tumors with 3 + 4 = 7 and 4 + 3 = 7, with studies showing better outcome for GS 7 with primary pattern 3 versus 4
3. GS 9–10 tumors have a poorer prognosis than that seen with GS 4 + 4 = 8 tumors[30,31]
4. Different grouping systems have been used to combine tumors with different GSs for treatment as well as for estimated prognosis.

GRADE GROUPS

A novel grading system for PCa was adopted in 2014 to address some of the above limitations, which included five distinct Grade Groups (GGs), from 1 to 5 (**Table 1**).[28] The clinical importance of the GGs has been shown in clinical studies (**Table 2**).[28,32–43] However, it has been suggested that the GG system should be used in parallel with the 2014 Gleason grading system.[44,45]

Genomics and grade group

A genomic study using whole exome and genome sequencing data from 426 localized PCas treated by RP supports the clinical significance of the prognostic GGs.[46] This study showed an increase in the frequency of both genomic deletions and amplifications associated with an increasing risk strata and of nonsynonymous point mutations. Low-risk GG 1 tumors were haploid, whereas GG 2–5 tumors showed an increasing frequency of polyploidy. Distinct genomic profiles among the five GGs were seen with Principal Component Analysis, giving support to GG 1 through GG 3 being distinct categories; however, there is genomic similarity between GG 4 and GG 5.[46]

Excellent prognosis for GG 1

PCa with GS 6 is not considered to be a lethal cancer, even though tumor progression and/or lymph node deposits have been documented in a small number of patients.[47,48] In a study of 395 RPs, where 151 patients were GG 1 (i.e., GS 3 + 3 = 6), four of the patients with GG 1 (2.6%) showed disease recurrence and progression, three were alive after a mean follow-up of 82 months, and one died after 108 months.[40] A histologic review of the slides of these four patients resulted in an upgrade of three cases to GG 2 (i.e., GS 3 + 4 = 7), while the fourth case was still considered as a GG 1 (i.e., GS 3 + 3 = 6) albeit with positive surgical margins. Aside from the three patients with a minor component of pattern 4 (two cribriform and one glomeruloid) and one patient with positive surgical margins, the other 147 patients were GG 1 (i.e., GS 3 + 3 = 6) and remained alive without tumor relapse or recurrence after a follow-up period of 8–10 years.

Such observations are in agreement with another study, in which no disease-specific death or metastasis was observed in patients with GS ≤6 PCa at RP.[49] Similarly, an earlier study concluded that lymph node metastases do not occur with GS ≤6 tumors, and Gleason patterns 4 or 5 are needed for metastatic PCa.[50] It should be noted that GS 6 tumors have cancerous morphology and exist on a molecular continuum with higher GSs.[51]

Future studies

Additional studies are needed to investigate the clinical utility of the new GG system in prospective clinical trials. Studies correlating current PCa diagnosis methods with multiparametric magnetic resonance imaging (mpMRI) and PCa GG are yet to be conducted. It is hoped that information will be derived on whether mpMRI can also be used to determine the proportion of high-grade cancer and GGs.[52,53] This will have a great importance in the multidisciplinary management of patients with PCa, including treatment by urologists, oncologists, uropathologists, and radiation oncologists.[1]

CLINICAL SIGNIFICANCE OF THE PERCENTAGE OF GLEASON PATTERNS 4 AND 5

In tumors with GS >7, the percentage of Gleason patterns 4 and 5 has clinical significance from a prognostic perspective.[21] In particular, the presence of even a smaller amount of Gleason pattern 5 (tertiary) is associated with a greater risk of biochemical recurrence. Therefore, the presence of Gleason patterns with unfavorable prognosis in localized PCa, such as Gleason pattern 5, is known to be associated with an

Table 1: Prognostic grade groups

Grade group	*Description*
GG 1 (GS ≤6)	PCa composed only of well-formed and separated glands
GG 2 (GS 3+4=7)	PCa with predominantly well-formed and separated glands and a lesser component of poorly formed/fused/glomeruloid/cribriform elements
GG 3 (GS 4+3=7)	PCa with predominantly poorly formed/fused/glomeruloid/cribriform elements with a minor component of well-formed and separated glands
GG 4 (GS 4+4=8, 3+5=8, or 5+3=8)	PCa with poorly formed/fused/glomeruloid/cribriform glands or tumors with well-formed and separated glands and lesser component without glands, or tumor predominantly without glands with a lesser component of well-formed and separated glands
GG 5 (GS 9 or 10)	PCa without gland/lumen or with necrosis, with or without poorly formed/fused/glomeruloid/cribriform elements

GG: grade group; GS: Gleason score; PCa: prostate cancer

Table 2: Studies showing the clinical significance of the grade groups system

Study	*Patient (n)*	*Type of specimens*	*Median follow-up*	*Prognosis (end point of the study)*
Pierorazio *et al.*[28]	7869	Biopsy (preprostatectomy), RP	2 years	Biochemical recurrence-free survival
Epstein *et al.*[32]	26 346 (20 845 RP + 5501 bx)	Biopsy (preprostatectomy), RP, Biopsy (preradiation therapy)	3 years	Biochemical risk-free survival
Spratt *et al.*[33]	3694	Biopsy (preprostatectomy), RP	52.7 months	Biochemical recurrence-free survival
Spratt *et al.*[34]	847	Biopsy (preradiation therapy)	88 months	Biochemical recurrence-free survival, DMFS, PCSS
Berney *et al.*[35]	988	Biopsy (preprostatectomy), biopsy (preradiation therapy)	10 years	PCa-specific death
Samaratunga *et al.*[36]	2079	Biopsy (preprostatectomy)	44 months	Biochemical recurrence-free survival
Delahunt *et al.*[37]	496	Biopsy (preradiation therapy and androgen ablation)	6.5 years (minimum)	DMFS, PCSS, biochemical recurrence-free survival
Loeb *et al.*[38]	5880	RP, biopsy (preradiation therapy)	4.6 years	Biochemical recurrence-free survival
Minardi *et al.*[39]	395	RP	8–10 years	Biochemical recurrence-free survival
Leapman *et al.*[40]	10 529	Biopsy (preprostatectomy), RP, biopsy (preradiation therapy)	81 months	PCa-specific mortality and bone metastasis
He *et al.*[41]	331 320	Biopsy (preprostatectomy), RP, biopsy (preradiation therapy)	38 months	PCa-specific mortality
Dell'Oglio *et al.*[42]	9728	Biopsy (preprostatectomy), RP	5.8 years	Clinical recurrence
Ham *et al.*[43]	1768 (721 biopsy + 1047 RP)	Biopsy (preprostatectomy), RP	3 years for biopsy, 4 years for RP	PCa-specific mortality

CR: clinical recurrence (defined as local and/or nodal recurrence [recurrence in prostatic bed and/or pelvic lymph nodes], retroperitoneal recurrence, or systemic recurrence [skeletal and/or visceral relapse]); DMFS: distant metastasis-free survival; PCa: prostate cancer; RP: radical prostatectomy; PCSS: prostate cancer-specific survival

increased risk of tumor recurrence and metastasis after primary treatment with RP, external beam radiation therapy, or brachytherapy.[54] According to one study, one of the most accurate predictors of patient outcome is the combined percentage of Gleason patterns 4 and 5, with this method having apparent superiority over GS for identification of patients with an increased risk of disease progression.[55] Evaluation of the combined percentage of Gleason patterns 4 and 5 in RP specimens is recommended, and the percentage of high-grade cancer in a RP specimen should be considered during assessment of patient prognosis and the selection of potential treatment options.[55]

There is evidence to support the clinical utility of including the percentage of high-grade tumor component in the pathology report.[21,56] However, there is no agreement on how the percentage of Gleason patterns 4 and 5 is to be recorded. For instance, it could be in intervals of 10% or of <5%, 5%–10%, 10%–25%, 25%–50%, 50%–75%, and >75%.[24]

Tertiary pattern 5, grade groups, and integrated quantitative Gleason score

Several studies have evaluated the prognostic significance of tertiary Gleason pattern 5 both in biopsy and in RP.[57–75] The method for reporting the presence of tertiary Gleason pattern 5 on RP specimens has been controversial.[2] The 2005 ISUP consensus conference recommended the inclusion of Gleason pattern 5 in the final GS if it is >5% of the tumor, or to consider it as a tertiary pattern if it is <5% of the tumor.[4] According to the 2014 ISUP consensus conference, tertiary patterns should only be recorded in RP specimens with either 3 + 4 = 7 or 4 + 3 = 7.[2]

It is unclear how to integrate small Gleason pattern 5 components into GG classification. Concerning the tertiary pattern 5 on RP specimens with GS 3 + 4 = 7 and 4 + 3 = 7 tumors, these would be considered to be GG 2 and GG 3, respectively, with a minor higher grade component, or as GGs >2 or >3.[2,76,77] Following the 2014 ISUP consensus conference, publication of a separate report was planned, with recommendations relating to special scenarios, such as patients with a small percentage of high-grade tumor, tertiary grade patterns, utilization of pattern 4 percentage, and case- versus core-level reporting.[6] Gleason 3 + 5 = 8 cancer is a type of special case, and this biopsy finding predicts an outcome similar to 4 + 4 = 8 tumors, suggesting that 3 + 5 = 8 belongs to GG 4.[78]

Detection of cribriform glands confers a 6-fold odds ratio of PSA failure and an increased risk of metastasis or death. An ongoing shortcoming of the GG grading system is that large gland spaces with cribriform-to-papillary-to-almost-solid cell arrangements (without basal cells, or intraductal carcinoma if basal cells are present) are graded as Gleason pattern 4, which is identical to the fused small gland pattern, yet the outcome for cribriform/intraductal glands is demonstrably more adverse.[8,15,78]

Since 2011, more than a dozen studies have confirmed the uniquely adverse implications of the cribriform pattern.[1] As a result, urologic pathology reports are required to specify whenever a cribriform growth pattern is present. One of the main practical implications of cribriform/intraductal growth is preclusion of the patient's treatment choice of active surveillance. Ultimately, the presence of these growth patterns will need to be incorporated in the GG system.

An analysis of the role of the percentage of Gleason patterns 4 and 5 in a large cohort of more than 10 000 patients has demonstrated the importance of the percentage of these Gleason patterns in predicting PCa aggressiveness.[79] A Gleason 5 component correlated with cancer progression and predicted, independently of its amount, further deterioration in the clinical course.[79] A system for integration of both patterns into a continuous numerical scale or score, i.e., integrated quantitative (IQ) – Gleason score, was developed that provides a method for combining quantitative Gleason grading and tertiary Gleason patterns into a single prognostic value.[79] This approach may enable clinicians to utilize the minor component of high-grade tumors and tertiary grade patterns in association with the PCa Gleason grading system, including the GGs.

CONCLUSIONS

The proposed GG system reduces PCa grades to the lowest number of grades, each being associated with a unique prognosis. This simplified grading system of five groups allows for more accurate stratification of patients than Gleason systems, with the potential for reducing overtreatment of PCa. The shift from a lowest value of 6 to 1 has a

positive impact from a psychological perspective on patients' disease awareness, thus facilitating patients' choice of treatment, including prostatectomy, targeted cryoablation, radiotherapy, hormonal therapy, and active surveillance. In particular, GS 6 cancer is characterized by indolent growth with an excellent prognosis. However, it should still be considered potentially metastatic since it is rarely localized so as not to mislead patients seeking a cure.[80] The GG system has been considered by the international community to be a new grading system, although most urologic pathologists consider it to be a novel grouping of the 2014 ISUP modified Gleason system.

AUTHOR CONTRIBUTIONS

R Montironi and MS were involved in conception and design of the manuscript, R Mazzucchelli was involved in acquisition of data, FM was involved in analysis and interpretation of data, SG and AC were involved in preparation of drafting manuscript, ALB and LC were involved in critical revision of the manuscript for intellectual content, AD provided technical and material support, and RM (Rodolfo Montironi) supervised the preparation of the manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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