

Current Status of Histologic Grading in Prostate Carcinoma and Renal Cell Carcinoma

Prostat Karsinomu ve Renal Hücreli Karsinoma Histolojik Derecelemesinde Son Durum

Duygu Kankaya

Ankara University Faculty of Medicine, Department of Pathology, Ankara, Türkiye

Introduction

Tumor grading is a fundamental component of histopathologic examination which is expected to provide prognostic information in addition to tumor stage and even contribute to making decision about the type of treatment. Gleason and Fuhrman gradings are widely used grading systems for prostate carcinoma and renal cell carcinoma (RCC), respectively (1,2). Despite of their widespread use, the purpose of increasing their prognostic significance has given rise to modifications several times. The International Society of Urological Pathology (ISUP) arranged consensus conferences in 2012 for RCC, and in 2014 for prostate carcinoma, in an attempt to enhance the efficiency of both these grading systems (3,4).

Prostate Cancer Grading

Gleason Grading: Development and Current State

The Gleason grading system, developed by Dr. Donald Gleason in 1966, has become the cornerstone in the management of prostate cancer (5). It has undergone revisions in 1974, 1977, and 1992 (1,6,7). Gleason's five-tier grading system is based on glandular architecture which is determined on low power examination, being the Gleason pattern 1 the most differentiated and Gleason pattern 5 the least differentiated (Figure 1). Nuclear atypia is not taken into consideration. As prostate carcinomas often show more than one architectural patterns, primary and secondary Gleason patterns (the most prevalent and the second most prevalent patterns, respectively) are defined and by taking sum of these primary and secondary Gleason patterns, a final grading score -Gleason score- is determined for each case which

range from 2 (1+1) to 10 (5+5) (Figure 2).

Needle biopsy Gleason score correlates with important pathological parameters at radical prostatectomy (e.g. pathologic stage, tumor volume, margin status, lymph node metastasis) and with prognosis after radical prostatectomy (recurrence and survival) or following radiotherapy (8,9). However, several studies investigating the correlation between Gleason scores in needle biopsies and corresponding radical prostatectomy specimens indicated that undergrading of carcinoma in needle biopsies is the most common problem, which were encountered in 42% of cases. This poor correlation and newly recognized entities of prostate carcinoma (i.e. pseudohyperplastic, foamy gland, mucinous, ductal) have given rise to a need for revision of the Gleason grading system and important modifications were performed by the conferences convened by the ISUP, firstly in 2005 and more recently in 2014 (Figure 1) (4,10).

On the current Gleason grading system, Gleason patterns 1 and 2 (Gleason score 2-5) have no longer been used in the grading of needle biopsies and only rarely on other specimens. Gleason score begins with 6, as the lowest score. As a result of numerous studies indicating the adverse prognosis of cribriform glands, they have not been allowed in Gleason pattern 3 anymore. Glomeruloid glands which is a variant of cribriform glands, the presence of poorly formed or fused glands have also been defined as Gleason pattern 4. The criteria for the pattern 5 have been remained unchanged since 1992 version of the Gleason grading.

Variants of prostate carcinoma (mucinous, foamy gland, pseudohyperplastic, atrophic, ductal variant etc.) are graded by considering their underlying architectural pattern, same as usual acinar prostate adenocarcinoma.

Correspondence: Duygu Kankaya MD, Ankara University Faculty of Medicine, Department of Pathology, Ankara, Türkiye

Phone: +90 532 551 29 03 **E-mail:** duygu.kankaya@gmail.com

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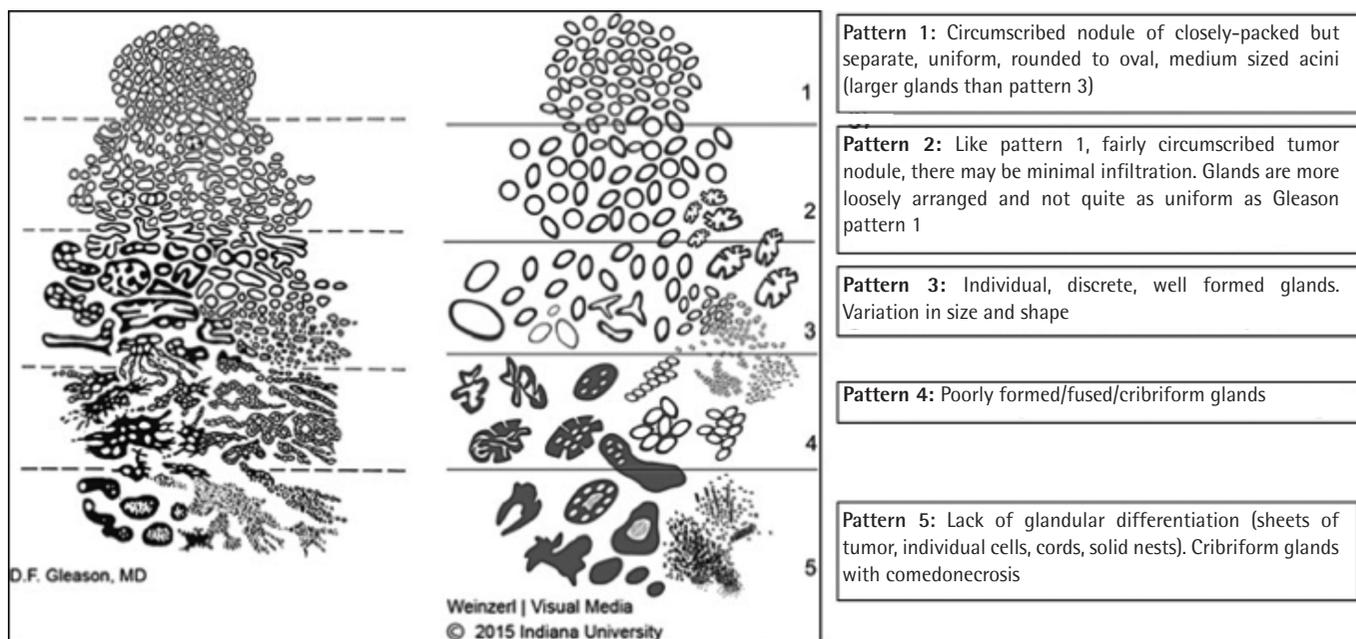


Figure 1. Prostatic adenocarcinoma histologic patterns: Original Gleason (left) and 2015 Modified International Society of Urological Pathology (right) schematic diagrams

Lower grade Gleason patterns which occupy <5% of the tumor should be ignored in needle biopsy, transurethral resection or radical prostatectomy. For instance, a needle biopsy with 97% Gleason pattern 4 and %3 Gleason pattern 3 should be diagnosed as Gleason score 8 (4+4). However, higher Gleason pattern in needle biopsy, irrespective of its quantity, should be involved in the Gleason score as secondary Gleason pattern, but in radical prostatectomies, only when it occupied >5% of the tumor.

When the highest score is Gleason score 7 in needle biopsies or radical prostatectomies, the percentage of Gleason pattern 4 is recommended to be reported as it may have an impact on patient management.

There are some problems with the clinical application of the Gleason system. Notification of the significant prognostic difference between prostate carcinomas with Gleason grade 3+4 and 4+3 revealed that treatment decisions using a single Gleason score misdirect the management of patients. Another limitation was that Gleason score 6, which was actually the lowest score, lead to an incorrect assumption on patients that their cancer was intermediate grade as falls into the middle of the scale of 2-10. A new prognostic grade grouping (1-5) has been defined (Table 1) (11) and provided more accurate grade stratification than the current Gleason system. It is recommended now to report both the new prognostic grouping system and the Gleason system together, until it becomes widely accepted and practiced.

The five-year biochemical recurrence-free progression probabilities for radical prostatectomy grade groups 1-5 are reported as 96%, 88%, 63%, 48%, and 26%, respectively. By this

Table 1. Gleason grade groups (12)

Grade group 1: Gleason score 6
Grade group 2: Gleason score 3+4=7
Grade group 3: Gleason score 4+3=7
Grade group 4: Gleason score 4+4=8, 3+5=8, 5+3=8
Grade group 5: Gleason scores 9-10

new prognostic grouping, Gleason score 6, as the lowest score, takes the lowest prognostic grade -prognostic grade 1- and this may reduce overtreatment of indolent prostate cancer.

Renal Cell Carcinoma Grading

Several grading systems based on architectural, cytoplasmic, and/or nuclear features for RCC have been proposed; of these, the most widely used one is Fuhrman classification (12). Four nuclear grades (1-4), increasing with nuclear size, irregularity and nucleolar prominence, were defined. Several problems regarding its application, validation and reproducibility have been identified. Some studies have shown that for clear cell and papillary RCC, assessment of nucleolar size alone for grading 1-3 tumors is a more powerful prognostic discriminator (13).

Recently, the ISUP held a consensus conference on many issues relevant to adult renal tumors and proposed a modified histological grading system based on nucleolar prominence in substitution for Fuhrman grading (3). It is a 4-tiered system in which nucleolar prominence define grades 1 to 3 and extreme nuclear pleomorphism or sarcomatoid and/or rhabdoid differentiation define grade 4 tumors (Table 2) (Figure 3).

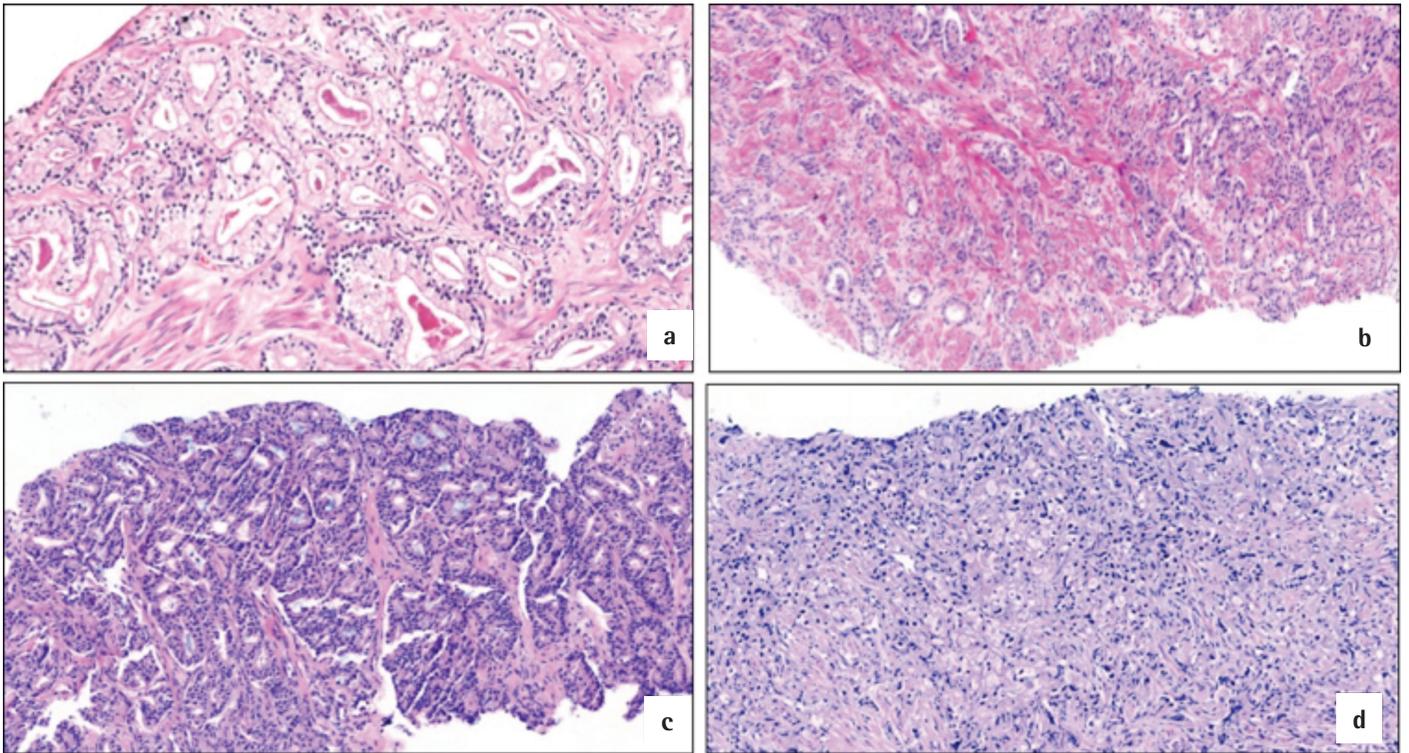


Figure 2. a) Prostate carcinomas with Gleason score 3+3=6 (grade group 1), b) Gleason score 4+3=7 (grade group 3), c) Gleason score 4+4=8 (grade group 4), d) Gleason score 5+5=10 (grade group 5)

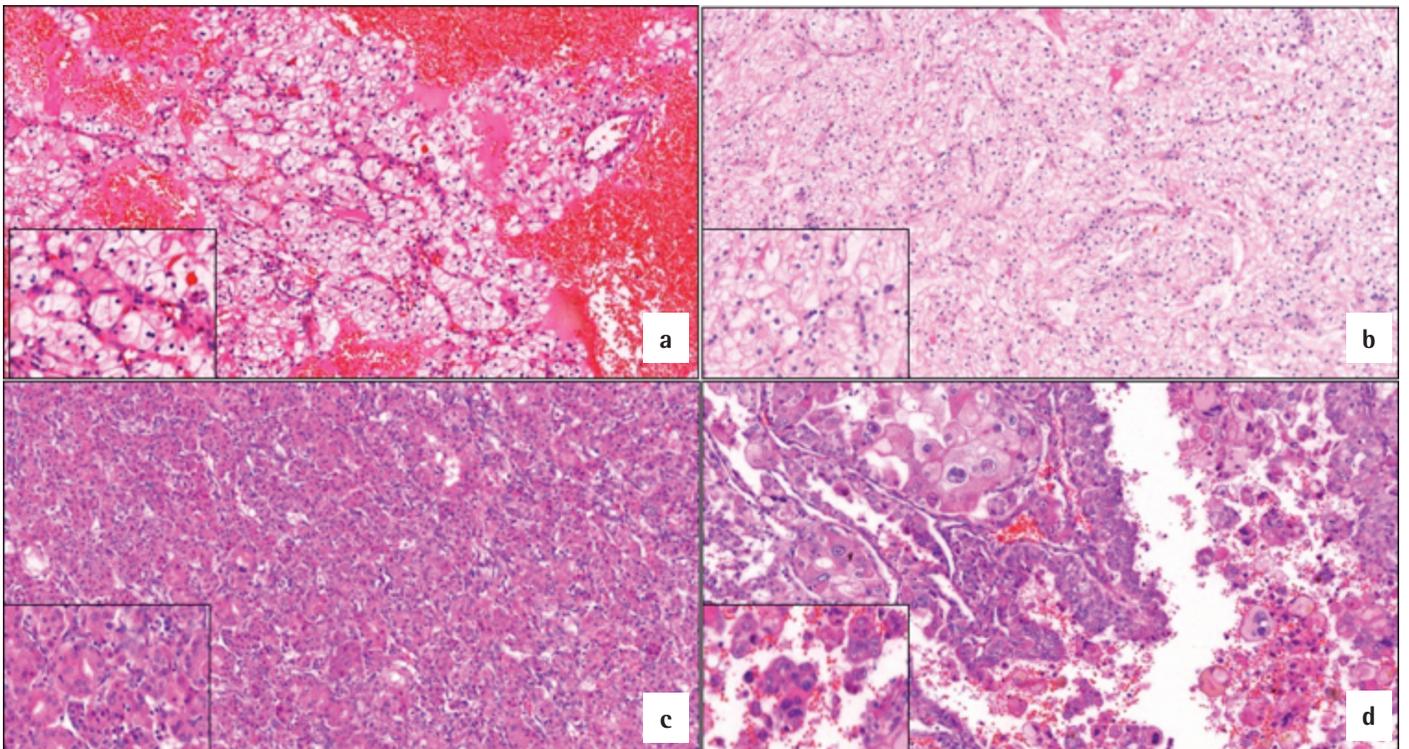


Figure 3. a, b, c, d) Grade 1, 2, 3 and 4 clear cell renal cell carcinomas graded by the World Health Organization/the International Society of Urological Pathology 2012

Table 2. The International Society of Urological Pathology grading system for clear cell and papillary renal cell carcinoma (3)

Grade	Description
1	Nucleoli absent or inconspicuous and basophilic at x400 magnification
2	Nucleoli conspicuous and eosinophilic at x400 magnification, and visible but not prominent at x100 magnification
3	Nucleoli conspicuous and eosinophilic at x100 magnification
4	Extreme nuclear pleomorphism and/or multinucleated tumor giant cells and/or rhabdoid and/or sarcomatoid differentiation

Grade should be determined within the single high power field showing the highest degree of nuclear pleomorphism.

There is consensus that this grading system is applicable to clear cell and papillary RCC, but not to chromophobe RCC, since none of the grading systems provides prognostic information for chromophobe RCC. There are several RCC entities currently defined and rarely seen. The ISUP grading system may be applied for these tumors for descriptive purposes, though prognostic significance is unknown.

Keywords: Renal cell carcinoma, prostate carcinoma, histological grading

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Ethics

Peer-review: Internally peer-reviewed.

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