The Gleason grading system: where are we now?

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Abstract

The most commonly used pathologic grading system for prostatic carcinoma (PCa) was first described by Donald F. Gleason in 1966. It is remarkable that, more than 40 years after the inception of the Gleason grading system, it remains one of the most powerful prognostic factors in prostate cancer. In part, this system has remained timely by gradual adaptations of the system to accommodate the changing practice of medicine. The 2005 International Society of Urological Pathology (ISUP) conference helped to codify these adaptations as well as gain consensus in areas where there was divergence in practice. The consensus conference and subsequent articles proposing further modifications help pathologists adapt the Gleason grading system to current day practice in a more uniform manner. In particular, narrowing the scope of pattern 3 carcinoma and widening the scope of pattern 4 carcinoma have played an important role in improving the prognostic value and inter-observer reproducibility of Gleason's system. Whether these changes have a significant impact on the clinical treatment of the disease remains to be seen. The differences between the original Gleason grading system and the 2005 ISUP modified Gleason system make difficult to compare data sets assessing patient outcomes in PCa over time.

Keywords Gleason; Gleason grading; International Society of Urological Pathology; 2005 ISUP Gleason system; prostate cancer

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Introduction

The Gleason grading system of prostatic carcinoma is the quintessential prognostic factor in predicting findings in radical prostatectomy, biochemical failure, local recurrences, lymph node or distant metastasis in patients receiving no treatment, radiation therapy, radical prostatectomy and other therapies, including cryotherapy and high intensity focal ultrasound therapy. Clinicians use various tools, such as Partin tables or Kattan nomograms, to predict outcomes, including the pathological stage or prognosis following radical prostatectomy or radiotherapy. All of these tools incorporate the Gleason score.[1]

Original Gleason grading system

Donald F. Gleason in 1966 created a unique grading system for PCa based solely on the architectural pattern of the tumour, using a five-point scale, where patterns 1–3 represent tumours which most closely resemble normal prostatic glands and patterns 4 and 5 tumours show increasingly abnormal glandular architecture (Box 1).[2,3] An innovative aspect of this system, based on a study of 270 patients from the Minneapolis Veterans Administration Hospital, was that, rather than assigning the worst grade as the grade of the carcinoma, the grade was defined as the sum of the two most common patterns and reported as the "*Gleason score*".

Gleason's modifications

By 1974, Gleason and the Veterans Administration Cooperative Urological Research Group expanded their study of the original Gleason system to 1032 men.[4] Gleason pattern 4 was described in a figure legend as "*raggedly infiltrating, fused-glandular tumour, frequently with pale cells, may resemble hypernephroma of kidney.*" The Gleason system was further refined by Mellinger in 1977 when the papillary and cribriform tumour under Gleason pattern 3 was described as having a "*smooth and usually rounded edge*".[5] In describing the breakdown of Gleason patterns amongst 2911 cases, Gleason pattern 1 was seen in 3.5%; pattern

The five patterns according to the original Gleason five[13]

1 Very well differentiated, small, closely-packed, uniform, glands in essentially circumscribed masses.
2 Similar (to pattern 1) but with moderate variation in size and shape of glands and more atypia in the individual cells; cribriform pattern may be present, still essentially circumscribed, but more loosely arranged.
3 Similar to pattern 2 but marked irregularity in size and shape of glands, with tiny glands or individual cells invading stroma away from circumscribed masses, or solid cords and masses with easily identifiable glandular differentiation within most of them.
4 Large clear cells growing in a diffuse pattern resembling hypernephroma; may show gland formation.
5 Very poorly differentiated tumours; usually solid masses or diffuse growth with little or no differentiation into glands.

Box 1

2 in 24.4%; pattern 3 in 87.7%; pattern 4 in 12.1%; and pattern 5 in 22.6%.[5] These percentages added up to approximately 150%, since 50% of the tumours showed at least two different patterns.

In 1977, Gleason provided additional comments concerning the application of the Gleason system: "*Grading is performed under low magnification*".[6] He also stated "*an occasional small area of fused glands did not change a pattern 3 tumour to pattern 4. A small focus of disorganized cells did not change a pattern 3 or 4 tumour to pattern 5.*" The only comment relating to tertiary patterns was "*occasionally, small areas of a third pattern were observed*".

Changes of prostate carcinoma since the late 1960s

PCa has changed dramatically since the late 1960s, when the Gleason grading system was described. In the 1960s, there was no screening for PCa other than by digital rectal examination (DRE), as serum PSA had not yet been discovered. In Gleason's 1974 study, the vast majority of men had advanced disease with either local extension out of the prostate on DRE or distant metastases. Only 6% of patients had non-palpable tumour diagnosed by transurethral resection and 8% of patients were diagnosed with a localized nodule on DRE.[7]

The method of obtaining prostate tissue was also different from today's practice. Typically, only a couple of thick gauge needle biopsies were directed into an area of palpable abnormality, usually through the perineum. The use of 18-gauge thin biopsy needles and the concept of sextant needle biopsies to more extensively sample the prostate were not developed until the 1980s. Consequently, the grading of prostate cancer in thin cores and in multiple cores from different sites of the prostate were not issues in Gleason's era.

In the 1960s, radical prostatectomy was relatively uncommon, prostates were not as often removed intact, and glands were not processed in their entirety or as extensively and systematically to the degree currently seen. Further issues relating to radical prostatectomy specimens, such as the grading of multiple nodules within the same prostate as well as variants and variations of PCa or dealing with tertiary patterns were not addressed within the original Gleason system.

The Gleason system also predated the use of immunohistochemistry. It is likely that, with immunostaining for basal cells, many of Gleason's original 1 + 1 = 2 PCa would today be regarded as adenosis (atypical adenomatous hyperplasia), i.e., a benign lesion.[8] Similarly, many of the cases in 1966 diagnosed as cribriform Gleason pattern 3 carcinoma would probably be currently referred to as cribriform high-grade prostatic intraepithelial neoplasia, if labelled with basal cell markers.[9]

Forty years after the inception of the Gleason system

It is remarkable that nearly 40 years after the inception of the Gleason system it remains one of the most powerful prognostic factors in PCa. In part, this system has remained timely by minor adaptations to accommodate the changing practice of medicine.[10–12] However, certain aspects of the original Gleason system are interpreted differently in today's practice. With such changes have come variations in applying the Gleason system amongst pathologists with some differences regional in nature and others dependent on other demographic factors. For example, it was demonstrated that pathologists over 50 years of age tended to diagnose Gleason score ≤4 on needle biopsy to a statistically significantly higher frequency than younger pathologists, who were trained to do so rarely if ever. The assigning of an overall score to needle biopsy specimens with different grades on different cores is more of a phenomenon practiced in Europe as compared to the USA.

2005 ISUP modified Gleason system

The *International Society of Urological Pathology* convened a conference in 2005 in San Antonio, TX, USA, in an attempt to achieve consensus in controversial areas relating to the Gleason system (Boxes 2 and 3). This has lead to what is called "*2005 ISUP modified Gleason System*".[13] This conference was preceded by an international consensus meeting on ''International Consultation on Predictors of Patient Outcome in Prostate Cancer" sponsored by the World Health Organization took place in 2004 in Stockholm, Sweden.[10] National groups, independently of the ISUP activities, had already undertaken a work of revision of the Gleason system with proposals that preceded those included in the 2005 ISUP modified Gleason system.[14–16]

It is outside the scope of this review to describe individually all the features included in the 2005 ISUP modified Gleason System. Interested readers are referred to the full paper.[13] The differences between the original Gleason system and the 2005 ISUP modified Gleason System are reported in Table 1 (Figure 1). Here is a brief summary of the ISUP modified Gleason grading system.

- The Gleason score is the sum of the primary (most predominant) Gleason grade and the secondary (second most predominant) Gleason grade.
- A Gleason score of 1 + 1 = 2 is a grade that should not be diagnosed regardless of the type of specimen, with extremely rare exception. The diagnosis of Gleason 2–4 should not be made on needle biopsies (Box 4) (Figures 2 and 3).

The *International Society of Urological Pathology* (ISUP) conference held in 2005 in San Antonio, TX, USA, in an attempt to achieve consensus in controversial areas relating to the Gleason system[13]

1 General applications of the Gleason grading system.
2 Gleason patterns.
3 Grading variants and variations of acinar adenocarcinoma of the prostate.
4 Reporting secondary patterns of lower grade when present to a limited extent.
5 Reporting secondary patterns of higher grade when present to a limited extent.
6 Tertiary Gleason patterns.
7 Percent pattern 4–5.
8 Radical prostatectomy specimens with separate tumour nodules.
9 Needle biopsy with different cores showing different grades.

Box 2