Modified Gleason system and its prognostic importance

Rodolfo Montironi, MD, FRCPath, IFCAP
Polytechnic University of Marche Region (Ancona)
School of Medicine, Ancona, Italy
and
Arizona Cancer Center, Tucson, AZ, USA
Gleason grading system

• **Quintessential prognostic factor in predicting**
  1. findings in radical prostatectomy
  2. biochemical failure
  3. local recurrences
  4. lymph node or distant metastasis

• **in patients receiving**
  • radical prostatectomy, radiation therapy and other therapies, including AS

• **All predictive models incorporate the GS**
Gleason grading system

1966: Donald F. Gleason created a unique grading system for PCa:

- sum of the two most common architectural patterns and reported as the “Gleason score”
1977: Gleason provided comments on the application of the Gleason system

1. Grading is performed under low magnification
2. An occasional small area of fused glands does not change a pattern 3 tumour to pattern 4
3. The cribriform tumour under Gleason pattern 3 is described as having a “smooth and usually rounded edge”
4. Occasionally, small areas of a third pattern are observed
PCa has changed dramatically since the late 1960s (type of patients)

• In 1966 there was no screening for PCa other than by DRE, as serum PSA had not yet been discovered

• In Gleason’s studies, the vast majority of men had advanced disease with either local extension out of the prostate on DRE or distant metastases
PCa has changed dramatically since the late 1960s (type of specimens)

- The method of obtaining prostate tissue was also different from today’s practice
- In the 1960s, radical prostatectomy was relatively uncommon
- The Gleason system also predated the use of immunohistochemistry
The GS remains one of the most powerful prognostic factors in PCa

1. Certain aspects of the original GS interpreted differently in today’s practice

2. Variations in applying the GS amongst pathologists with some differences regional in nature and others dependent on other demographic factors
International Society of Urological Pathology (ISUP)

2005 ISUP Modified Gleason System

ISUP consensus conference in San Antonio, TX, in 2005

1. A Gleason score of 1+1=2 should not be diagnosed, regardless of the type of specimen, with extremely rare exception

2. The diagnosis of Gleason score 2-4 should not be made on needle biopsies

3. “Individual cells” would not be allowed within Gleason pattern 3

4. The vast majority of cribriform patterns are diagnosed as Gleason pattern 4 with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3C
Reasons for not assigning Gleason score 2–4 on needle biopsy

1. Extraordinarily rare in needle biopsies as compared to transurethral resection specimens
2. Poor reproducibility among experts for lower grade tumours
3. Poor correlation with the prostatectomy score for Gleason 2-4 tumours
4. May misguide clinicians and patients into believing that there is an indolent tumour
Cribriform Gleason pattern 3 PCa

- Resembles cribriform HGPIN, yet shows diagnostic features of infiltrating carcinoma such as:
  1. glands negative for basal cell markers
  2. back-to-back glands, ruling out high-grade prostatic intraepithelial neoplasia or
  3. glands exhibiting pathognomonic features of carcinoma such as perineural invasion or EPE
2005 ISUP Modified Gleason System

- **Tertiary Gleason pattern**

1. On needle biopsies with patterns 3, 4, and 5, both the *primary pattern and the highest grade should be recorded*

2. For a radical prostatectomy specimen one assigns the Gleason score based on the *primary and secondary patterns with a comment as to the tertiary pattern*
Impact of the modified Gleason grading system

- The most immediate result of limiting the definition of Gleason pattern 3 and expanding the definition of pattern 4 has been Gleason grade migration or *up-grading*

  - *Gleason score 6 cancers decreased from 48% to 22% of cases, whereas Gleason score 7 increased from 25% to 68%*
Impact of the modified Gleason grading system

- An important effect of modifying Gleason grading has been to improve the agreement between Gleason scores on needle biopsy and radical prostatectomy

  - Prior to the 2005 ISUP modification, the agreement ranged between 28 to 68%
  - ISUP modified Gleason system:
    - Exact agreement between needle biopsy and radical prostatectomy specimens increased from 58% to 72% when using the modified system (Helpap et al, 2006)
    - Zareba et al (2009) showed no significant impact on the biopsy-radical prostatectomy Gleason agreement (63.4% and 65.5%, respectively)
Impact of the modified Gleason grading system

- An important consequence of changes to the definition of Gleason pattern 4 has been *an improvement in observer reproducibility*

  1. Gleason wrote that he duplicated exactly his previous histological scores approximately 50% of times

  2. Most studies using the modified Gleason system have shown that overall observer reproducibility hovers around 80%
Clinical implications of the modified Gleason grading system

- There are clinical consequences with the up-grading in the Gleason score, for instance, *in the type of therapy offered to an individual patient with PCa*

- Patients with high grade tumours may be discouraged:
  - from undergoing RP because of the high likelihood of non-organ confined and even systemic disease at presentation
  - from undergoing AS
Clinical implications of the modified Gleason grading system

- The true test of the validity of the 2005 ISUP Modified Gleason System is its correlation with patient outcome.
- Studies by Uemura et al. (2009) and Billis et al. (2008) demonstrated that the Gleason scores on needle biopsies using the modified but not the original Gleason system correlated with progression after radical prostatectomy.
Clinical implications of the modified Gleason grading system

- The true test of the validity of the 2005 ISUP Modified Gleason System is its *correlation with patient outcome*

- Delahunt et al. (2010) reported that the original Gleason grading system outperformed the modified system in predicting PSA nadir following external beam radiotherapy and hormone therapy
Subsequent (2010) proposals for slight modifications of the ISUP grading system

- **All cribriform patterns** are diagnosed as Gleason pattern 4 rather than pattern 3
- **Glomerulations** most likely represent an early stage of cribriform pattern 4 cancer and should likely be graded as pattern 4
Conclusions

• The GS has remained timely by gradual adaptations of the system to accommodate the changing practice of medicine

• 2005 ISUP Modified Gleason System

• The oncologists, urologists and pathologists have to be aware of the impact on patient’s prognosis and treatment of the GS used