Gleason Grade Migration:
Changes in Prostate Cancer Grade in the Contemporary Era

Daniel J. Luthringer, MD and Mitchell Gross, MD, PhD *Departments of Pathology and Medicine, Cedars-Sinai, Los Angeles*

Introduction

Tumor grade refers to the microscopic appearance of cancer tissue obtained after a biopsy or surgery as determined by a pathologist. For prostate cancer patients, tumor grade (along with clinical stage and PSA) is particularly important in determining prognosis and aids patients and physicians as they make important treatment decisions. The dominant grading system used for prostate cancers is named for its inventor, Dr. Donald Gleason.

In 1966, Dr. Gleason proposed a grading system for prostatic carcinoma that was based solely on architectural features of the tumor. The Gleason scoring system identifies five different patterns of cancer, (i.e. assigns a number from 1 to 5), based on how close to normal (differentiated) the cancer looks under the microscope. Gleason pattern 1 is the most differentiated (or benign appearing) pattern. Gleason pattern 5 is the most de-differentiated (or aggressive appearing) pattern. Prostate cancer is almost universally present in multiple parts of the gland and often has a different microscopic appearance (different Gleason patterns) in different areas of cancer. Therefore, the original description of the Gleason grading system included adding the numbers assigned to the most prevalent and second most prevalent patterns to result in a Gleason score (or Gleason sum). The Gleason score (ranging between 2 and 10) ultimately comprises the tumor grading used in prostate cancer. For example, if a pathologist observes a moderately well-differentiated area of cancer (Gleason 3 pattern) as both the most common and second-most common area in a specimen, the final Gleason score assigned would be 6; derived from 3 (most prevalent) + 3 (second most prevalent) = 6.

The Gleason grading scheme was widely adopted in North America through the 1980s and 1990s, after numerous studies firmly established that it served as a vital pathologic predictor for disease outcome. In 2003, recognizing the importance of the Gleason grading system, the World Health Organization (WHO) endorsed Gleason grading as the standard for prostate carcinoma. The Gleason grading system continues to play a critical role in the management and treatment stratification of patients with prostate cancer.

Gleason Grade Migration

Gleason grade migration refers to the observation that prostate cancers are today commonly graded higher, in the contemporary era, than in previous decades, resulting in a greater percentage of higher grade prostate cancers.[1] A number of studies have evaluated Gleason grade migration and its impact on important clinical measures such as the risk of the cancer recurrence and cancer-related deaths (prostate cancer specific mortality).

Albertsen et al[2] analyzed a group of 1858 cases of prostate cancer. The cases were drawn from a sample of all men diagnosed with prostate cancer between 1990 and 1992 in the state of Connecticut. With the patients' permission, clinical information was entered into a database, and microscopic slides from their original biopsy (obtained and read in 1990-92) were re-read in 2004 by a different, highly-experienced pathologist who was "blinded" to the original Gleason score. This study showed that the average Gleason score increased from 5.95 to 6.8 when comparing the original reading to the contemporary reading. Importantly, in 55% of the cases, the Gleason score was upgraded by one point or more. Therefore, this reassessment demonstrates a definite shift to higher grade prostate cancers, when a contemporary pathologist reads the same specimen that was read 10-15 years ago.

Ultimately, the importance of the Gleason score is to predict which patients have the most aggressive forms of prostate cancer. Therefore, it was important to determine if changing the Gleason score altered its ability to predict patient outcomes. When the contemporary Gleason scores were used and the patients grouped by Gleason scores, the authors reported that the every group of patients did significantly better with the contemporary over the original Gleason score. The prostate cancer outcomes for the entire group of patients were identical regardless of which Gleason grade ("contemporary" or "original"). Therefore, this study demonstrated an "inflation" or "upward migration" in Gleason scores occurring over time. When the effects of this reclassification were combined for all groups and standardized for differences in the number of patients with particular Gleason scores, the re-grading resulted in a 26% reduction in prostate cancer specific mortality compared with the same patients as graded by the original pathologists. Therefore, one important effect of Gleason grade inflation is to make patients diagnosed in the current era appear do better than historical controls when statistically adjusted for differences in Gleason scores.

Similar observations were made by Kondylis[3] et al who re-examined 100 cases of prostate cancers and compared this data with original grades and outcomes. A significant upward grade migration from the historic to the current grade was observed, causing deviations in the cancer-specific survival curves. In a study of 983 radiated prostate cancers, Chism et al[4] found a systemic Gleason score upgrading of cases in the 1990s that they attributed, at least partially, to an improved 5-year biochemical relapse-free survival. Smith et al[5] reassessed a series of patients treated by surgery, in which the Gleason scores, on review, proved to be significantly higher than a decade before. In a series of prostate cancers treated with brachytherapy, Schellhammer et al[6] also demonstrated a

significant upgrading of the Gleason scores over original scores of 15 years earlier.

Cedars-Sinai Experience

Anecdotally, and as unpublished observations, we have experienced a Gleason grade migration at our own institution. Looking at the biopsy diagnosis of prostate cancer incrementally in blocks of time from 1993 to1998 (n=264), 1999 to 2001 (n=292), and 2002 to 2005 (n=729), we observed a shift away from lower grade cancers diagnosed with Gleason score less than 6 (see Figure 1). In the 1993 to 1998 time period, these low score cases represented over 20% of all cases at the time of initial diagnosis. No cases of Gleason score less than 6 were diagnosed in the 2002 to 2005 time period. Similarly, the percentage of higher grade Gleason scores (scores 8, 9 or 10), shifted from about 3% to almost 10% of biopsies. Observations of the 2002 to 2005 time frame are important in the understanding of the grade shift. In 2002, prostate cancer was read by a small team of three pathologists primarily devoted to this part of the body. This was a dramatic change from upward of 16 inter-generational pathologists in previous years. The group of three focused significant attention on the contemporary understanding and application of the Gleason grading system, undoubtedly contributing to the observed grade migration.

In summary, our observations appear to confirm a trend to the upgrading of prostate cancers using the Gleason grading system and, as described in the studies above, may result in the appearance of improved outcomes for prostate cancer patients.

Factors Contributing to Gleason Grade Inflation

There are several factors that are thought to explain the phenomenon of Gleason grade inflation.

Pathologists may increasingly be swayed to incorporate a slight modification of the Gleason grading system itself. As initially described, pathologists were only supposed to include the two most common patterns in the Gleason score. However, there is increasing evidence suggesting that presence of a third (tertiary) Gleason grade higher than the primary or secondary component is important, and should be reported.[7,8] Pathologists may want to include a small amount of high-grade cancer in the Gleason score. As described below, new recommendations will actually mandate this change. Although not part of the classic grading system, this reinterpretation may explain some measure of grade migration.

Another explanation is the learned experience of pathologists with the system acquired over time. Many studies[9,10] have demonstrated that Gleason scores obtained from biopsies are frequently upgraded on prostatectomy specimens, most likely as the result of sampling error. This makes sense when you realize that only a very small portion of the prostate is analyzed by biopsy compared with the entire gland analyzed at the time of surgery. The idea is that through many years, the discrepancy between biopsy Gleason grade and surgical Gleason grade has pressured pathologists, in the case of borderline or questionable biopsy cases, to up-grade cancers, knowing that in a significant number of cases, the patient most likely has higher grade cancer lurking in his prostate gland.

Along with these factors which drive finding more higher grade cancers, there are also factors leading to a decreased incidence of lower grade cancers as well. The lowest Gleason grades (1 and 2) are generally found only in the central portion of the prostate. The central core of the prostate around the urethra, the "central zone," is generally not amenable to sampling using the current biopsy techniques. Hence, recommendations have been widely published[9,11] which strongly discourage pathologists from diagnosing lower grade cancers on transrectal biopsies. Further, modern pathologists often use more sophisticated techniques to examine specific proteins in cancer tissue (immuno-histochemistry). By using this technique, it is thought that many cases of Gleason 1 cancer were actually an abnormal benign growth in prostate tissue ("adenosis") which mimics cancer, but is not actually malignant (i.e. does not grow and spread outside of the prostate).

Changes to the Gleason Grading System

Much has changed since the Gleason grading system was developed 40 years ago. Based on changes in the way prostate cancer is diagnosed and treated, modifications to the Gleason grading system have

continued on page 9

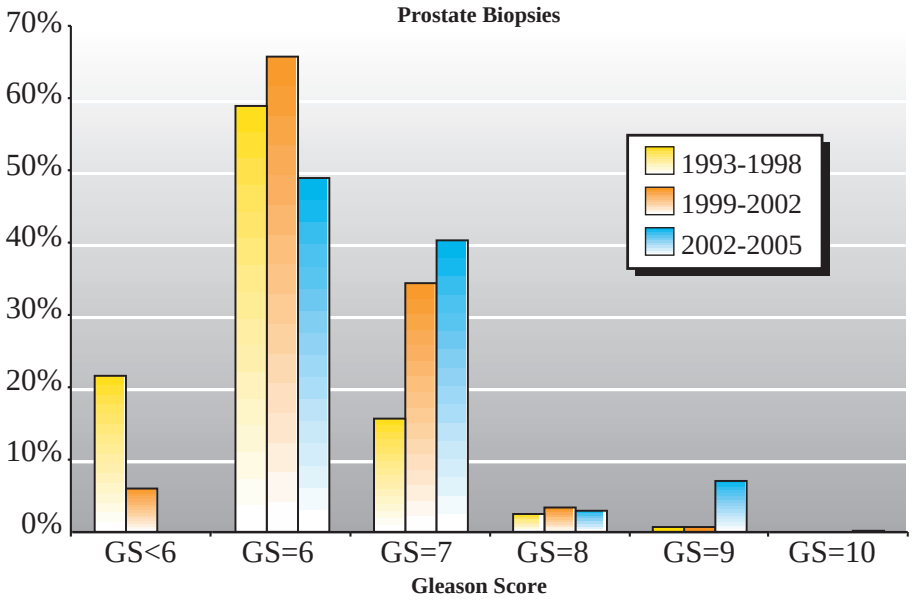

Figure 1. *Changes in Gleason scores observed at Cedars-Sinai Medical Center between 1993 and 2005.*

been proposed.

Up until recently, pathologists have been somewhat uncertain as to how to deal with the grading of prostate cancers in the face of evolving changes in prostate cancer detection. In late 2005, the International Society of Urologic Pathologists (ISUP) in conjunction with the WHO made a series of recommendations[10] for modification of the Gleason grading system to reflect contemporary knowledge, alleviate uncertainty and promote uniformity in its application. Amongst a broad series of proposals, one recommendation was for pathologists to report all higher tertiary grade components of the tumor as part of the Gleason score.

For example, suppose a pathologist observes three patterns of cancer in a single specimen: 60 % Gleason grade 3, 30 % Gleason grade 4 and 10% Gleason grade 5. Historically, this would be reported as Gleason score 3+4=7/10. With the revised system, it would instead be scored as Gleason score 3+5=8/10. Another recommendation was made for reporting of any higher grade cancer, no matter how small quantitatively. Previously, any secondary grade that occupied less than 5% of the specimen would not be reported. Currently, even a small percentage of Gleason 4 or 5 would be incorporated into the scoring system. These two modifications to the Gleason system are expected to further to contribute to Gleason grade inflation in the future.

What Does Grade inflation and Changes to the Gleason System Mean for Patients?

Patients and physicians must incorporate information from these studies to the care and follow-up of patients with prostate cancer. First, we must be careful how we compare information and clinical studies of contemporary series with older reports. Clinical outcomes (standardized for Gleason grade) may appear somewhat worse in older trials as an artifact of an older application of the Gleason grading system. Conversely, a patient diagnosed with a "modern" Gleason grade may be expected to do better than the historical controls. Therefore, comparing recent studies to "historical" or "retrospective" results may be even more suspect and problematic than previously thought. Second, we should be aware of which interpretation of the Gleason system ("classical" or "modern") is used depending on specific uses.

Note that most of the widely used clinical outcome prediction tools (such as the Kattan nomograms or the Partin tables) incorporated only the older interpretation of the Gleason system as read by the original pathologists 10-20 years ago. Therefore, the "classical" Gleason system read in a way more like the "original" pathologist should be used if we want to apply these nomograms to individual patients. However, the full description of the Gleason score (and potentially a different number) may still hold useful information. In particular, patients with minor components of high-grade cancer may need more aggressive monitoring or treatment compared with other patients of a similar grade. Further, reevaluation of the original biopsy material (especially by a highly experienced prostate pathologist) may provide new information to guide in patient management.

Summary

It is clear that an upward drift in the Gleason grades and scores of prostate cancers has been occurring over the past decades. Recent recommendations by the ISUP/WHO will most certainly cause further migration to higher grades and total Gleason scores. This is in turn affecting the apparent clinical outcomes in patient studies, and will most likely continue to do so for the foreseeable future. A greater understanding of this phenomenon is necessary, especially when interpreting comparative outcome data. ■

References

1. Thompson et al. Stage Migration and Grade Migration in Prostate Cancer: Will Rogers Meets Garrison Keillor. J Natl Cancer Inst 2005; 97:1236-1237.
2. Albertsen, PC et al. Prostate Cancer and the Will Rogers Phenomenon. J Natl Cancer Inst 2005; 97:1248-1253.
3. Kondylis, et al. Prostate Cancer Grade Assignments: The Effect of Chronological, Interpretive and Translation Bias. J Urol 2003; 170:1189-1193.
4. Chism et al. The Gleason score shift: Score for and seven years ago. Int J Radiat Oncol Bio Phys 2003; 56:1241-7.
5. Smith et al. Gleason Scores of prostate biopsy and radical prostatectomy specimens over the past 10 years. Cancer 2002; 94:2282-7.
6. Schellhammer et al. 15-year minimum follow-up of a prostate brachytherapy series: comparing and the past with the present. Urol 2000;56:436-9.
7. Stamey TA et al. Biological determinants of cancer progression in men with prostate cancer. JAMA1999;281:1395-1400.
8. Chin-Chen P et al. The prognostic significance of tertiary Gleason patterns of high grade in radical prostatectomy specimens. A proposal to modify the Gleason grading system A J Surg Pathol 2000;24:563-569.
9. Epstein et al. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy. Am J Surg Pathol 2000;24:477-8.
10. Epstein et al. The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005;29:1228-1242.

Selected Additional References

Feinstein et al. The Will Rogers Phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. New Engl J Med 1985; 312:1604-8.

Pan et al. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens, Am J Surg Pathol 2000;24:563-9.

Egevard et al. Current practice of Gleason grading among genitourinary pathologists. Hum Pathol 2005;36:5-9.

PCA3 References FROM PAGE 8

7. Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, van Balken B, Kiemeney LA, Witjes JA and Schalken JA: DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol. 44: 8-15; discussion 15-6, 2003.
8. Fradet Y, Saad F, Aprikian A, Dessureault J, Elhilali M, Trudel C, Masse B, Piche L and Chypre C: uPM3, a new molecular urine test for the detection of prostate cancer. Urology. 64: 311-5; discussion 315-6, 2004.
9. Tinzl M, Marberger M, Horvath S and Chypre C: DD3PCA3 RNA analysis in urine--a new perspective for detecting prostate cancer. Eur Urol. 46: 182-6; discussion 187, 2004.
10. Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, Brentano S, Mathis J, Pham J, Meyer T et al.: APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem. 52: 1089-95, 2006.
11. Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, Aubin SMJ, Cancio AT, Desaulniers M, Ellis WJ, Rittenhouse HG, Groskopf J: Prostate cancer specificity of PCA3 Urinary Gene Test. In Press, Urology, 2006.