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Gleason 6 Prostate Cancer: Translating Biology into Population Health

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Abstract

Purpose—Gleason 6 (3+3) is the most commonly diagnosed prostate cancer among men with prostate specific antigen screening, the most histologically well differentiated and is associated with the most favorable prognosis. Despite its prevalence, considerable debate exists regarding the genetic features, clinical significance, natural history, metastatic potential and optimal management.

Materials and Methods—Members of the Young Urologic Oncologists in the Society of Urologic Oncology cooperated in a comprehensive search of the peer reviewed English medical literature on Gleason 6 prostate cancer, specifically focusing on the history of the Gleason scoring system, histological features, clinical characteristics, practice patterns and outcomes.

Results—The Gleason scoring system was devised in the early 1960s, widely adopted by 1987 and revised in 2005 with a more restrictive definition of Gleason 6 disease. There is near consensus that Gleason 6 meets pathological definitions of cancer, but controversy about whether it meets commonly accepted molecular and genetic criteria of cancer. Multiple clinical series suggest that the metastatic potential of contemporary Gleason 6 disease is negligible but not zero. Population based studies in the U.S. suggest that more than 90% of men newly diagnosed with prostate cancer undergo treatment and are exposed to the risk of morbidity for a cancer unlikely to cause symptoms or decrease life expectancy. Efforts have been proposed to minimize the number of men diagnosed with or treated for Gleason 6 prostate cancer. These include modifications to prostate specific antigen based screening strategies such as targeting high risk populations, decreasing the frequency of screening, recommending screening cessation, incorporating

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remaining life expectancy estimates, using shared decision making and novel biomarkers, and eliminating prostate specific antigen screening entirely. Large nonrandomized and randomized studies have shown that active surveillance is an effective management strategy for men with Gleason 6 disease. Active surveillance dramatically reduces the number of men undergoing treatment without apparent compromise of cancer related outcomes.

Conclusions—The definition and clinical relevance of Gleason 6 prostate cancer have changed substantially since its introduction nearly 50 years ago. A high proportion of screen detected cancers are Gleason 6 and the metastatic potential is negligible. Dramatically reducing the diagnosis and treatment of Gleason 6 disease is likely to have a favorable impact on the net benefit of prostate cancer screening.

Keywords

prostatic neoplasms; neoplasm grading; early detection of cancer; watchful waiting; prostatectomy

OVERVIEW OF GLEASON SYSTEM

During the first half of the 20th century the absence of a standardized method to distinguish the diverse pathological spectrum of prostate cancer limited clinicians' prognostic abilities and hampered emerging treatment and research efforts. Dr. George Mellinger, Chair of Urology at the Minneapolis Veteran's Hospital, recognized this deficiency. He recruited Dr. Donald Gleason to the newly established Veteran's Administration Cooperative Urological Research Group to develop a uniform prostate cancer grading system.

Gleason reviewed material from 270 consecutive patients with prostate cancer, including 80% with clinical stage III–IV disease. In 1966 Gleason reported 9 patterns of gland formation ranging from organized and uniform to disordered and infiltrative. The clinical outcomes of patients led him to consolidate these findings into 5 distinct patterns.[1] Notably Gleason found many cases harbored more than 1 histological pattern and the overall prognosis was between that predicted by the primary and secondary patterns. Therefore, the group combined the 2 distinct patterns to obtain a histological score. In the earliest versions of the system a final point was attributed for clinical stage.[2]

In 1978 the American Cancer Society sponsored a series of workshops to evaluate the various pathological approaches to prostate cancer.[3] While several approaches were found to have advantages, the Gleason system was recognized as "definable, simple, reproducible, and had compelling clinical relevance". Therefore, the recommendation was for the Gleason system to be adopted, validating what subsequently became the contemporary standard grading system for prostate cancer (see figure).

GLEASON SCORING CHANGES

Following Gleason's initial description, the pathological assessment of prostate tissue remained relatively unchanged for decades. Widespread adoption of PSA based screening, systematic transrectal biopsies, increasing number of biopsy cores and modifications to the Gleason scoring system all contributed to a downward stage and grade migration for prostate cancer. The development of immunohistochemical staining led to the identification of

patterns that appeared misclassified in Gleason's original drawings, and a clearer distinction between mimickers of cancer (adenosis, prostatic intraepithelial neoplasia) and cancer.[4] In 2005 the ISUP Consensus Conference essentially eliminated Gleason pattern 1–2 and total Gleason scores 5 or less as they were no longer considered adenocarcinoma, they lacked reproducibility and the distinctions among lower Gleason scores had no prognostic value.[5]

In addition to essentially eliminating Gleason grade 1–2 disease from the assessment of biopsy tissue, the ISUP proposed a more restrictive definition of the Gleason 3 pattern. Many features characterized as Gleason 3 in the original system were now considered pattern 4 or 5 due to reclassification of cribriform morphology and poorly formed glands. Thus, approximately 34% of cases of Gleason 6 prostate cancer in the pre-2005 system were up graded to Gleason 7 or higher. Modifications associated with the 2005 ISUP Consensus Conference changed the epidemiological landscape of prostate cancer, with the proportion of patients with low grade prostate cancer decreasing from 68% using the pre-2005 Gleason system to 49% using the 2005 ISUP consensus system.[6]

The ISUP held another Consensus Conference in November 2014 and formally proposed further modifications. Details have yet to be published, but the primary recommendation is for a new grading system of ISUP with grade 1—Gleason 6 or less, ISUP grade 2—Gleason 3+4, ISUP grade 3—Gleason 4+3, ISUP grade 4—Gleason 8 and ISUP grade 5—Gleason grade 9 or 10.

DOES GLEASON 6 MEET HISTOLOGICAL, MOLECULAR AND GENETIC CRITERIA FOR CANCER?

From a histological standpoint prostate cancer distinguishes itself from high grade prostatic intraepithelial neoplasia and benign prostate by infiltrative growth and the absence of a basal cell layer. Gleason 6 prostate cancer meets these criteria with extension between benign glands, perineural invasion and extension beyond the prostate.[7,8]

Gleason 6 meets the histological criteria for adenocarcinoma, although some argue it does not meet the 6 hallmarks of cancer, namely sustained proliferative signaling, evasion of growth suppressors, resistance of apoptosis, replicative immortality, induction of angiogenesis and invasion/metastasis.[9,10] Central to all 6 hallmarks is genetic instability, which can be routinely identified in Gleason 6 cancer and is often concordant with higher grade cancers. TMPRSS2-ERG fusion is the most intensely studied genetic alteration in prostate cancer. While present in the majority of metastases and approximately 50% of low volume Gleason 6, TMPRSS2 rearrangement rates do not differ substantially based on Gleason score.[11,12] Overlapping expression patterns (eg RNA based cell cycle progression genes[13]) and molecular alterations (eg alpha-methylacyl-CoA racemase [AMACR][14]), glutathione S-transferase [GST],[15] loss of PTEN[16]) are observed in Gleason6andhigher grade cancers. Additionally, heritable risk factors (eg BRCA, HOXB13) predispose to low and high grade cancers to a similar extent. The frequent overlap in histological, genetic and molecular alterations suggests that the designation of Gleason 6 as cancer is appropriate.

DOES GLEASON 6 MEET CLINICAL CRITERIA FOR CANCER?

The term “cancer” encompasses a wide range of clinical conditions, from uniformly lethal to indolent lesions with an extremely low potential for metastatic progression. Some have suggested “clinical” cancer should be differentiated from pathological definitions, and instead based on growth characteristics, likelihood of clinical symptoms, and risk of progression or outcome. The use of an alternative term, IDLE (indolent lesion of epithelial origin), has been proposed for those histological changes unlikely to cause harm if initially untreated and monitored.[17]

Arguments supporting the use of alternate terminology include the lack of metastatic potential of Gleason 6 in radical prostatectomy specimens. After a contemporary rereview of 14,000 totally embedded radical prostatectomy specimens using the updated Gleason grading system, no lymph node metastases were identified in men with Gleason 6 confirmed on prostatectomy.[18] Additionally, after standardized review of prostatectomy specimens from the Physicians’ Health Study, no man with confirmed Gleason 6 disease had lethal prostate cancer during more than 2,200 person-years of followup.[19] However, the presence of Gleason 6 disease on biopsy may be a surrogate for other areas of higher grade cancer in the prostate. Of men with a microfocus of Gleason 6 disease on biopsy 22% have a higher grade or stage present at prostatectomy.[20]

SCREENING, DETECTION AND OVER TREATMENT OF GLEASON 6 PROSTATE CANCER

The introduction and rapid uptake of PSA screening in the early 1990s were associated with a marked increase in prostate cancer incidence. Subsequently the last 20 years has witnessed a 45% age adjusted decrease in prostate cancer mortality, with much of this reduction attributable to effective screening and improvements in primary treatment.[21] However, autopsy data have demonstrated a high prevalence of Gleason 6 prostate cancer in men older than age 50, and widespread, indiscriminate screening has led to the over detection of histological changes in the prostate that are of questionable clinical significance.[22]

Intensity of screening is often misaligned with a man’s predicted life expectancy and the risk of harboring life threatening prostate cancer. The coexistence of these factors has led to unfavorable benefit-to-harm ratios. For example, African-American men are at higher risk for a prostate cancer diagnosis (60% higher) and mortality (140% higher) compared to white men,[23] yet they are less likely to undergo PSA based screening.[24,25] Conversely, approximately 45% of men in their 70s undergo PSA based screening, even those at high risk for other cause mortality, exposing these patients to the risks of detection and treatment without measurable survival benefit.[26]

One method to quantify over detection is to calculate the number needed to screen or diagnose to prevent a single death, figures which are highly influenced by length of followup. With up to 15-year followup in the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Göteborg trials,[27,28] the NNS has decreased from 1,410 to 1,055 and from 293 to 200, respectively, while the NND has decreased from 48 to 37 and 12

to 9, respectively. Other approaches involving complex modeling of large populations have suggested even lower estimates of NNS and NND and, consequently, lower estimates of over detection.[21] Regardless of the exact long-term NNS and NND, there are likely mortality benefits associated with prostate cancer screening. However, a majority of patients diagnosed with prostate cancer will not derive a meaningful clinical benefit.

After a diagnosis of prostate cancer, management is often discordant with the likelihood of an adverse oncologic outcome if left untreated. While the general consensus is currently that Gleason 6 prostate cancer has historically been over treated, treatment rates of patients with low risk cancer are widely variable and there is no agreement on what constitutes over treatment. Low rates of cancer specific mortality in active surveillance studies suggest that AS is a safe strategy in appropriately selected individuals. For example, a simulation model using Johns Hopkins and CaPSURE® (Cancer of the Prostate Strategic Urologic Research Endeavor) low risk cohorts suggested only a 1% improvement in cancer specific mortality at 20 years for patients treated with immediate surgery vs AS.[29]

Despite data demonstrating low rates of metastasis or death associated with Gleason 6 prostate cancer managed by AS, contemporary treatment rates range from 55% to 96%,[30] including 96% of men age 55 years or younger with very low risk prostate cancer, 54% of U.S. veterans with low risk disease and multiple comorbidities, and 62% of men older than 70 years with low risk disease. In a CaPSURE study through 2004 only 9% of very low risk and 7% of low risk patients elected AS.[31] Furthermore, using SEER (Surveillance, Epidemiology and End Results) data from 1986 to 2005 Welch and Albertsen estimated an additional 1,305,600 men have been diagnosed with prostate cancer due to opportunistic PSA screening, 1,004,800 (77%) of whom were definitively treated with an estimate of 56,500 (4%) deaths averted and a NND of 23.[32]

Over treatment is a particularly important issue since radical prostatectomy and radiotherapy may adversely impact long-term urinary, bowel and sexual function. Studying a large prospective cohort Resnick et al reported that prostatectomy and radiotherapy were associated with erectile dysfunction rates of 87% and 94%, urinary incontinence rates of 14% and 7%, and bowel urgency rates of 22% and 36%, respectively.[33] While single center studies generally report considerably better rates of sexual and urinary function, there are clear changes in quality of life that occur as a result of treatment, even at high volume centers.[34]

THE WAY FORWARD: IMPROVED RISK STRATIFICATION AND ACTIVE SURVEILLANCE

A significant opportunity exists to refine and improve clinical care for men being screened or treated for prostate cancer. Several groups have identified strategies to screen smarter for prostate cancer. These methods involve selecting more appropriate populations for screening, using PSA data more effectively and incorporating novel screening tools.

Smarter Screening

Men most likely to benefit from prostate cancer screening are those who harbor prostate cancer destined to become clinically evident and those with limited competing risks of death. Men with a limited remaining life expectancy are unlikely to benefit from PSA screening. Tools such as the Social Security Administration Life Expectancy Calculator can be used to estimate average RLE, emphasized in the NCCN guidelines.[35,36] RLE can then be adjusted based on patient overall health by adding or subtracting by 50% for the best and worst quartile of health, respectively.[37] Since randomized screening studies showing a survival benefit began to reveal divergence of the 2 arms at 8 to 10 years,[27,28] it is generally discouraged to perform PSA screening on men with a shorter RLE.

Future efforts to improve screening will incorporate RLE, comorbidity and shared decision making. The 2013 AUA guidelines specifically incorporate shared decision making with a discussion of options for an increased PSA, inaccuracies of testing, 2-year screening intervals for men at average risk, downstream implications, potential harms and a mortality benefit.[38] It is also sensible to use earlier or more intensive screening strategies for men at higher risk based on African-American race or family history. The NCCN guidelines for the early detection of prostate cancer recommend an initial PSA at age 45 that can then be used to stratify screening intensity.[39]

In the process of shared decision making some patients will opt for PSA screening. For these men several previously common practices have fallen out of favor. Specifically, empiric treatment of an increased PSA with antibiotics is not of clinical benefit and is discouraged.[40] In addition, PSA velocity has been shown to have no value for biopsy decision making.[41]

Discontinuation of Screening

More than 50% of men dying of prostate cancer are diagnosed at age 75 or older.[42] Large numbers of older men undergo PSA screening with a low likelihood of benefit[26] and determining who can safely stop screening is important. Among a large cohort of men from Sweden it has been demonstrated that men with a PSA less than 1 ng/ml at age 60 have a risk of prostate cancer death by age 85 of 0.2%.[43] Compared to an unscreened population, screened men with a PSA less than 2 ng/ml at age 60 had an increased incidence of cancer but no change in metastatic rates or mortality. However, screened men with a PSA of 2 ng/ml or greater at age 60 had lower mortality rates with a NND of 6 to save a life at 15 years.[43] In the Baltimore Longitudinal Study of Aging no participants between age 75 and 80 with a PSA less than 3.0 ng/ml died of prostate cancer, suggesting a safe age for discontinuation in this elderly population.[44] These data based recommendations incorporate age and PSA to consider minimizing the frequency or eliminating PSA screening in certain populations.

Predictive Models and Novel Screening Tools

Despite its poor specificity PSA remains an integral component of statistical models combining assorted patient specific variables.[45] Validated models, such as the Prostate Cancer Prevention Trial (PCPT) Risk Calculator 2.0, are clinically useful but remain imperfect, as they can never account for all factors impacting risk.[46] Studies evaluating

novel biomarkers (eg Prostate Health Index,[47] 4K,[48] PCA3[49]) have shown improvement in the prediction of prostate cancer compared to PSA alone. Additionally, clinical trials are ongoing to incorporate MRI into the screening paradigm by limiting random sampling or obviating biopsies (see supplementary references on jurology.com).[50,51]

Post-Diagnostic Prognostic Biomarkers

A one size fits all strategy for localized prostate cancer is anachronistic. Characterizing the cancer, understanding competing medical conditions and patient wishes, and fairly presenting all management options will maximize the benefits of treatment while reducing patient exposure to potential treatment related morbidity.[52]

Recent advances have allowed for improvement in cancer characterization, particularly among men with biopsy Gleason 6 cancers. For example, MP-MRI was used in 60 men who met AS criteria (T1c–T2a, Gleason 6, PSA 10 ng/ml or less) on initial biopsy.[53] At re-staging biopsy the rates of up grading were 9%, 25% and 77% if the MRI showed no lesion, a less than 1 cm lesion, or a greater than 1 cm lesion, respectively. Similarly, among 298 patients meeting criteria for AS who had MP-MRI followed by radical prostatectomy, the presence of a lesion on MRI was associated with a higher likelihood of up grading (50% vs 14%) and independently predicted adverse pathological features.[54] A similar study evaluated 85 men who met strict criteria for AS and underwent MRI-ultrasound fusion guided prostate biopsy.[55] Based on imaging features and re-staging biopsy 25 (29%) cases were reclassified and were no longer candidates for AS based on number of lesions, lesion suspicion and lesion density. Emerging data suggest the value of MP-MRI for men with low risk prostate cancer but further study is required to assess cost-effectiveness, standardize techniques and interpretation, and accurately define those who may benefit.

Biomarker development, validation and clinical utility have the potential to dramatically improve the care of men with prostate cancer. However, value, cost- effectiveness and comparative effectiveness need to be addressed in future studies. Recently data have become available on biopsy based tissue biomarkers for men with newly diagnosed prostate cancer.

Oncotype Dx (Genomic Health) is a 17-gene realtime polymerase chain reaction assay estimating the rates of nonorgan confined disease and/or primary pattern Gleason 4 or greater. The genes span multiple pathways including androgen signaling, stromal response, cell cycle and cellular organization. Oncotype Dx targets men considering AS based on NCCN risk criteria.[56]

Prolaris® (Myriad Genetics) is an RNA based genomic classifier using the cell cycle proliferation pathway to estimate the risk of biochemical recurrence, metastases or cancer specific death after treatment or conservative management.[57–61] Among men diagnosed with low risk Gleason 6 cancer it provides independent prognostic value.[58] Ki67 is also a CCP gene and a marker of cell proliferation whose expression in biopsy tissue has been independently associated with CSS after radical prostatectomy.[62] However, when combined in a model with CCP score it no longer retains prognostic value.

ProMark™ (Metamark Genetics) is a quantitative protein based immunofluorescence assay targeting men with biopsy Gleason 3+4 or less disease and appears to provide independent value for the prediction of adverse pathological features at prostatectomy.[63–65]

ProstaVysion™ (Bostwick Laboratories) provides biopsy based ERG gene fusion and PTEN deletion status, which are both potentially important events in prostate cancer progression.[16,66,67]

While these new genomic markers are highly promising and will likely improve the risk stratification of men with prostate cancer, they have not yet been studied in a prospective fashion. It remains uncertain whether these molecular markers will direct care in an appropriate fashion and positively impact outcomes.

Observation or Active Surveillance

Two prospective randomized trials included men with Gleason 6 prostate cancer and examined treatment vs observation. SPCG-4 was conducted during the pre-PSA era on European men with up to 23 years of followup (median 13). Among all men radical prostatectomy reduced the risk of metastatic disease by 43%, death from prostate cancer by 44% and death from any cause by 29%.[68] In men with low risk cancers the risk reduction was 10%, 3% (nonsignificant) and 15%, respectively. In contrast, the PSA era PIVOT (Prostate Cancer Intervention Versus Observation Trial) in U.S. Veterans with a median followup of 10 years showed no overall differences in metastases or cancer specific mortality,[69] mirrored in the subset of men with low risk cancers, although there was a suggestion of treatment benefit in higher risk men. Notably the study inclusion criteria involved estimated life expectancy greater than 10 years but approximately 40% of the men died by 10 years and the study failed to meet accrual goals, thereby hampering the quality and generalizability of the study.

Both of these studies compared radical prostatectomy to observation (or watchful waiting), a strategy typically undertaken in elderly men or those with substantial comorbidities. Alternatively AS involves monitoring the patient through PSA, examination, imaging and biopsies, with the dual goals of 1) avoiding unnecessary treatment along with associated risk of decline in quality of life and 2) close monitoring to allow for curative treatment if disease progression occurs without compromising long-term oncologic outcomes. AS is an evidence-based strategy endorsed by several prominent professional organizations.[36,70,71] For example, the NCCN recommends surveillance for men with low risk prostate cancer and a RLE less than 10 years, and for men with very low risk prostate cancer and a RLE less than 20 years.[36] While only approximately 20% of eligible patients in the U.S. in 2011 proceeded with AS, a collaborative project from Michigan recently reported 48% use of AS among 682 men with low risk cancers.[72,73] The ProtecT trial in the United Kingdom randomized 1,600 men between 2001 and 2009 to active surveillance vs radiation therapy vs surgery, and will soon provide further data to inform the management of newly diagnosed patients.[74]

Several prospective observational AS cohorts are informative (see table).[75–80] Inclusion criteria vary slightly, as do the frequency, intensity and methods of surveillance. Progression

to curative intent treatment occurs in approximately 30% to 40% of men at 5 to 10 years. In the series with longest median followup (6.4 years), 10-year and 15-year CSS was 98% and 94%, respectively (cohort of low and intermediate risk patients).[81] In most other reports CSS is 100%, albeit with more restrictive inclusion criteria and a shorter followup.

Despite encouraging data on AS, multiple challenges remain such as defining the ideal inclusion criteria, and monitoring the regimen and triggers for intervention. As rates of over diagnosis vary dramatically based on age, Gleason score and PSA, nomograms have been constructed to individualize the estimates of over detection to inform decisions about whether to proceed with active surveillance.[82]

Data suggest that most up grading (progression) occurs in the first few years as a result of sampling error at biopsy rather than true progression.[75] Imperative to the success of AS is accurate initial and ongoing characterization of the cancer. Newer tools such as MP-MRI with or without targeted biopsy and serum/tissue biomarkers are beginning to be reported in AS cohorts.[55,83] Despite earlier studies showing limited uptake of AS,[31] emerging data point to the increasing use of this strategy,[72,84] and its use can be encouraged through education and other quality improvement efforts (Appendix 2).[73]

CONCLUSIONS

Gleason 6 is the most commonly diagnosed prostate cancer histological grade and is of questionable clinical significance. Intensive PSA based screening strategies coupled with high rates of treatment, regardless of histological grade and remaining life expectancy, have led many to question the benefit-to-harm ratio for PSA testing and prostate cancer treatment. Limiting the diagnosis and treatment of Gleason 6 disease should dramatically improve the net benefit. Specific screening modifications (targeting high risk populations; decreasing the frequency of screening [particularly for those with a low age adjusted baseline PSA]; restricting screening in older men or those with limited life expectancy; incorporating remaining life expectancy estimates, imaging and biomarkers) are intended to minimize the detection and treatment of Gleason 6 cancers while maintaining the identification of higher grade cancers. Data from large series suggest that most men with Gleason 6 cancer detected on biopsy can undergo active surveillance with minimal metastatic risk. Our group of young urologic oncologists with expertise in prostate cancer believes modifying the contemporary treatment of men with Gleason 6 disease is an important public health issue. Dramatically reducing the diagnosis and treatment of Gleason 6 prostate cancer is likely to have a favorable impact on the net benefit of PSA screening and, as a result, improve men’s health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

AS	active surveillance
CSS	cancer specific survival

ISUP	International Society of Urologic Pathology
MP	multiparametric
MRI	magnetic resonance imaging
NCCN®	National Comprehensive Cancer Network
NND	number needed to diagnose
NNS	number needed to screen
PSA	prostate specific antigen
RLE	remaining life expectancy

APPENDIX 1

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APPENDIX 2

Recommendations to minimize over detection and over treatment of prostate cancer

Smarter Screening

- Consider screening only if estimated remaining life expectancy (RLE) greater than 8–10 years
- Utilize shared decision making with patient

- If mutual decision to screen:
  - be aware of American Urological Association (AUA) 2013 Early Detection Guideline[38]
  - predictive models such as PCPT calculator[45,46] may be useful
  - consider novel biomarkers such as Prostate Health Index (PHI),[47] 4K[48] or PCA3[49]
- Consider less frequent screening interval if PSA less than 2 ng/ml at age 60[43]
- Consider discontinuation of screening if:
  - RLE less than 8–10 years
  - PSA less than 1 ng/ml at age 60[43] or PSA less than 3 ng/ml at age 75[44]

Minimizing Over Treatment

- Active surveillance recommended for:
  - Men with low-risk cancer and RLE less than 10 years[36]
  - Men with very low-risk cancer and RLE less than 20 years[36]
- Active surveillance as a management option for:
  - Any man with very low-risk or low-risk cancer[75–81]
  - Select men with intermediate-risk cancer[84]
- Prognostic markers following diagnosis may be helpful:
  - MRI of the prostate[53–55]
  - Biopsy-based biomarkers:
    - Oncotype Dx[56]
    - Prolaris[13,57,58,60,61]
    - Ki67[62]
    - ProMark[63–65]
    - ProstaVysion[16,66,67]

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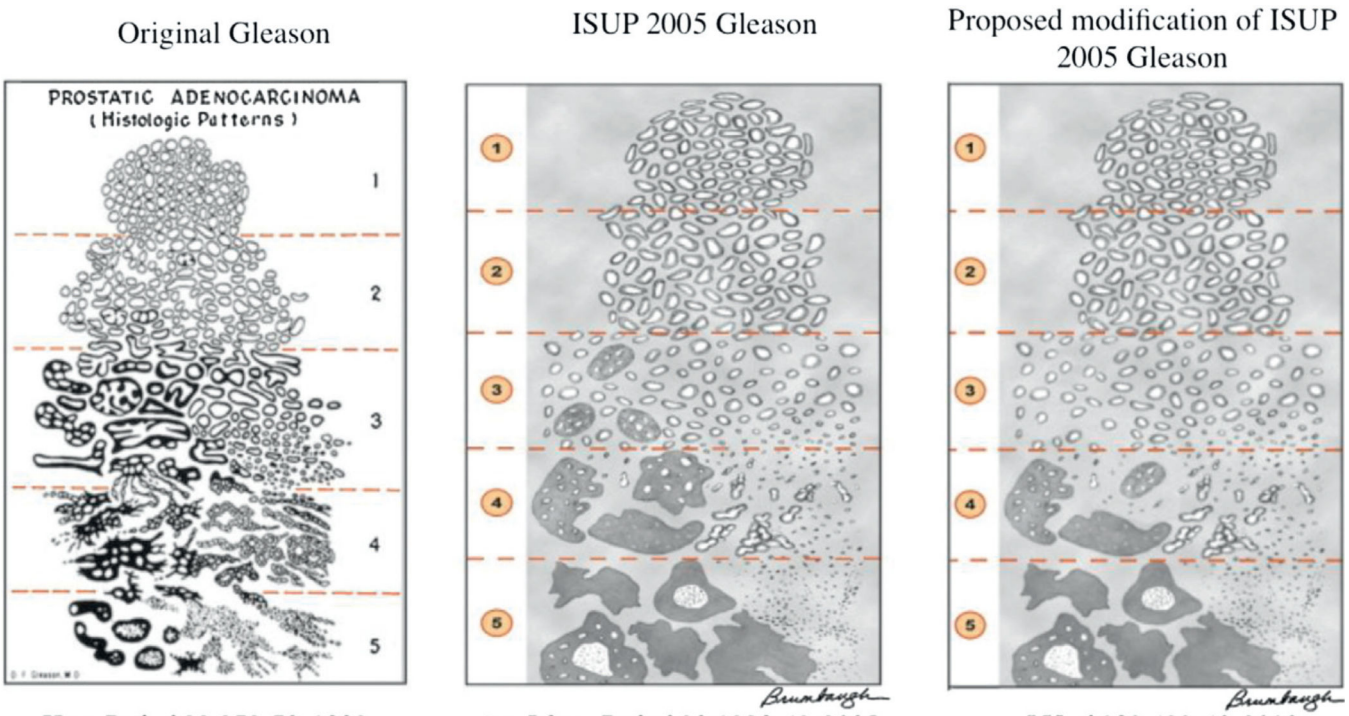

Gleason grading system

Summary of active surveillance data

	Johns Hopkins[78]	UCSF[75]	ERSPC[79]	Royal Marsden[77]	Toronto[76]	Sweden[80]
No. pts	769	649	616	471	450	6,849
Inclusion criteria:						
Clinical stage	T1c	T1–T2a	T1c–T2	T1–T2	None	T1–T2
PSA (ng/ml)	–	Less than 10	10 or Less	Less than 15	10 or Less	20 or Less
PSA density (ng/ml/cm^3)	Less than 0.15	–	Less than 0.2	–	–	–
Gleason score	3+3 or Less	3+3 or Less	3+3 or Less	3+3 or Less, 3+4 if older than 65 yrs	3+3 or Less*	7 or Less
Total pos cores	Less than 3	33% or Less	Less than 3	50% or Less	Not applicable	Not applicable
% of Core	Less than 50	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Median age	66	62	66	66	70.3	64.7
Followup (yrs)	2.7	3.9	3.91	5.7	6.8	8.2
Biopsy schedule (mos)	12	12–24	12, 48, 84	18–24	6–12, 36–48	Not applicable
Progression/treatment-free survival (%)	59 at 60 Mos	54 at 47 Mos	43 at 120 Mos	70 at 60 Mos†	72 at 60 Mos	34 at 48 Mos
Overall survival (%)	98	97	77	98	68	80 at 10 Yrs
CSS (%)	100	100	100	99	97.2	97.6 at 10 Yrs

*Before 2000, men older than 70 years with Gleason 3+4 or less and PSA 15 ng/ml or less were included in study.

†At 5 years adverse pathology was 22% and treatment-free probability was 70%.