

Gleason Grade, Defined by Systematic Review and mRNA Signature, as a predictor of Lethal Prostate Cancer



Kathryn Penney*, Jennifer Sinnott*, Jennifer Stark, Katja Fall, Yudi Pawitan, Yujin Hoshida, Michelangelo Fiorentino, Peter Kraft, Neil Martin, Sven Perner, Stephen Finn, Stefano Calza, Richard Flavin, Swen-Olof Andersson, Edward Giovannucci, Philip Kantoff, Jan-Erik Johansson, Hans-Olov Adami, Massimo Loda, Todd Golub, Mark Rubin, Ove Andrén, Meir Stampfer, Lorelei Mucci
 Prostate Cancer Program, Dana Farber/Harvard Cancer Center, Boston MA; Harvard School of Public Health, Boston, MA; Channing Laboratory, Brigham and Women's Hospital; University of Örebro, Örebro, Sweden; Karolinska Institutet, Stockholm, Sweden; Cancer Program, Broad Institute; Cambridge, MA

Contact Email: lmucci@hsph.harvard.edu



Background:

Gleason score

- Morphologic measure of loss of normal tissue structure
- One of strongest clinical predictors of prostate cancer survival

mRNA Signatures of Gleason score

- Distinct set of genes and pathways may affect the de-differentiation
- Understanding gene signatures of Gleason pattern may give insight into prostate cancer progression
- Prior studies identified mRNA signatures for Gleason pattern → results across studies not validated, likely due to small sample sizes

AIM. To examine Gleason grade, defined histopathologically and by mRNA signature, to elucidate pathways of de-differentiation and test ability of Gleason grade to discriminate lethal outcomes

Materials & Methods:

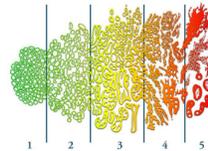
Patients

- 650 TURP samples from a Swedish Watchful Waiting Cohort (1977-1999)
- 950 prostatectomy samples from the US Physicians' Health Study and Health Professionals Follow-up Study cohorts (1983-2004)

Gleason grading

- Original Gleason score data from medical records
- Standardized re-review Gleason score from histopathological review by study pathologists

Figure 1: Schematic of Gleason grading system



Gene expression profiling

- Illumina DASL platform: ~6100 genes
- Available for 388 Swedish men and 116 US men from PHS

Statistical methods

- Calculated hazard ratios (95% CI) and c-statistics to examine predictive ability of standardized Gleason grading to predict lethal prostate cancer
- Prediction Analysis in Microarrays to build mRNA signature of high and low grade prostate cancer in Swedish cohort → applied to PHS cohort
- Used Gene Set Enrichment to explore pathways distinguishing grade

Results:

Histo-pathological review

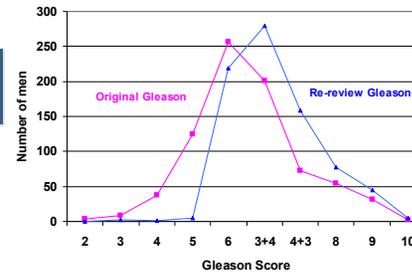


Figure 2: Distribution of Gleason scores comparing original score vs. standardized re-review Gleason

mRNA signature

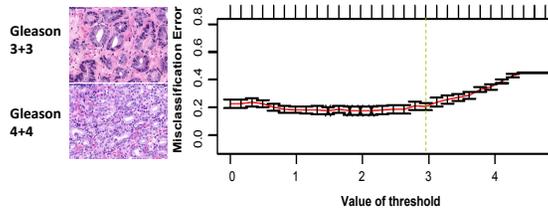


Figure 4: Identification of 157-gene signature of high vs. low grade prostate cancer through Prediction Analysis of Microarray

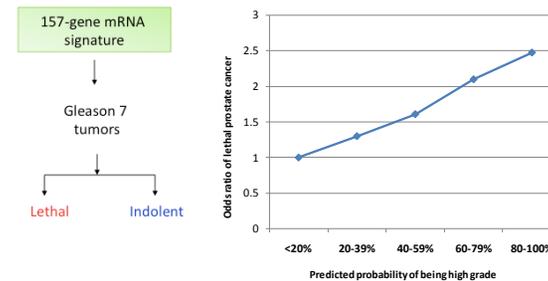


Figure 6: 157-gene signature significantly improves prediction of lethal outcomes in men with Gleason 7, beyond the Gleason score was 4+3 or 3+4

Gleason grade and Lethal PCa

Gleason	Hazard Ratio (95% CI) [†]
2-6	0 deaths
3+4	1.00 (Ref)
4+3	2.6 (1.1, 5.9)
8	5.6 (2.4, 12.9)
9-10	13.2 (6.0, 29.2)

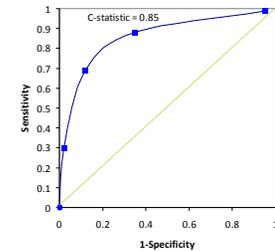
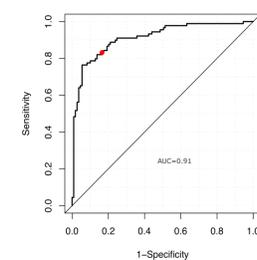


Table 1 and Figure 3: Ability of a re-reviewed Gleason score to predict lethal prostate cancer. In standardized review, 4+3 vs. 3+4 added prognostic value

Model Built on Swedish, Tested on Swedish



Model Built on Swedish, Tested in PHS

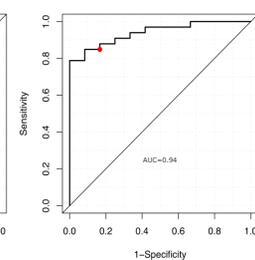


Figure 5: Ability of re-reviewed Gleason to predict lethal prostate cancer. In standardized review, 4+3 vs. 3+4 added prognostic value

Conclusions:

- Ignoring predominance of Gleason pattern 4 in Gleason 7 cancers may conceal prognostic information.
- Standardized review of Gleason can improve prediction of prostate cancer survival.
- mRNA expression signature may enhance understanding of the de-differentiation process of prostate tumors
- Gene set enrichment analysis identified pathways involved in cell cycle, PI3K/AKT pathway, pyrimidine metabolism, and one-carbon folate
- Signature may have clinical application for men with Gleason 7, improving classification of a high or low risk of dying from cancer

Acknowledgements:

LAM is a Young Investigator Award from the Prostate Cancer Foundation. This project was supported by US Army Prostate Cancer Program W81XWH-05-1-0562, the Dana Farber/Harvard Cancer Center Prostate Cancer SPORE, and NIH/NCI.