Molecular signature to risk-stratify prostate cancer of intermediate risk

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Running title: Molecular signature of intermediate risk prostate cancer

Funding: J.H. is supported by grants from the National Cancer Institute (1R01CA205001, 1R01CA181242, 1R01CA172603), Department of Defense Prostate Cancer Research Program (PC150382, PC150382) and Stand Up To Cancer-Prostate Cancer Foundation Prostate Dream Team Translational Cancer Research Grant SU2C-AACR-DT0812. This research grant is made possible by the generous support of the Movember Foundation. Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. Y.H. was supported by the National Comprehensive Cancer Network Young Investigator Award and Circle of Service Foundation.

Disclosure: The authors declare no conflict of interest
Summary

A new 30-gene signature has been described that separates prostate cancers of Gleason score $\leq 6$ from those of Gleason score $\geq 8$. It provides independent prognostic information for prostate cancers of intermediate risk (Gleason score of 7) which has the potential to stratify these patients into different risk groups.
In this issue of Clinical Cancer Research, Sinnott and colleagues describe a gene expression signature that has the potential to stratify prostate cancer (PCa) of intermediate risks (Gleason score 7) into high risk and low risk groups(1). 

PCa is a heterogeneous disease with highly variable outcomes. While most patients have indolent diseases that do not impact quality of life or life expectancy, some patients will die of the cancer. Many clinical and pathologic factors, such as serum PSA level, pathology stage, tumor grade, margin status in the prostatectomy specimen and presence or absence of lymph node metastasis, are associated with prognosis. Among these, Gleason grading is one of the most powerful prognostic factors. This grading system was developed by Dr. Donald Gleason who described 5 histologic patterns of PCa. Tumors with Gleason pattern 1 are the best differentiated while those with pattern 5 show poorest differentiation. Gleason score is the sum of the primary pattern and the secondary pattern ranging theoretically from 2 to 10 with higher scores associated with poorer disease outcome. In clinical practice, Gleason score of 5 and under are rarely diagnosed as such tumors always follow a benign course. In an earlier study, using a Swedish Watchful Waiting Cohort and the Physicians' Health Study (PHS) cohort, this group discovered a 157 gene signature that distinguished tumors with Gleason score $\leq 6$ from those with Gleason score $\geq 8$ (2). Although a gene signature that distinguishes Gleason score $\leq 6$ from Gleason score $\geq 8$ tumors is interesting and important, the two disease groups can be more readily distinguished by histologic evaluation. In the current study, this group of investigators built a new gene expression signature using similar approaches with the PHS and the Health Professionals Follow-up Study (HPFS) cohorts. The 30-gene signature (only 5 were in the original signature) similarly distinguished Gleason score $\leq 6$ from Gleason score $\geq 8$ tumors. The authors then applied the new signature to Gleason score 7 tumors which are histologically divided into Gleason 3+4 and 4+3 for risk stratification. With the HPFS cohort, the model of 3+4/4+3 status alone had an Area Under the Curve (AUC) for lethal PCa of 0.68. The new signature alone had an AUC for lethal PCa of 0.73, which was better than 3+4/4+3 status although the difference was not statistically significant. The model combining the signature and 3+4/4+3 status had an AUC for lethality of 0.76 which was a statistically significant improvement over 3+4/4+3 status alone. The signature is predictive of 4+3 versus 3+4 status (AUC=0.74). There are higher signature values for lethal cases compared to the indolent cases within each subcategory of Gleason score 7. Therefore, for patients who have received prostatectomy, this 30-gene signature can potentially improve upon Gleason grading, particularly for Gleason 7 tumors, for the prediction of long term outcome including the probability of biochemical recurrence, metastasis and death from PCa.

Future studies should decide whether the same gene signature can be used in biopsy tissue for patients with newly diagnosed PCa for management. Many studies have demonstrated that tumors with Gleason score 6 and under are almost never life-threatening, while those with Gleason score 8 and above are of high risk. The field has achieved a consensus that active surveillance is most appropriate for patients in the former group while patients in the latter group should be managed aggressively. Tumors with Gleason score 7 (3+4 and 4+3) pose a significant challenge since many of them will follow an indolent course but some will be aggressive. While it has been shown that Gleason 4+3 tumors are more aggressive than Gleason 3+4 tumors as mentioned above, sampling error, subjectivity in assigning Gleason patterns, and inter-observer variability are well known confounding factors, particularly for biopsy specimens. Therefore, a molecular signature that can independently stratify these tumors into different risk groups will have significant clinical value in patient management. The original Epstein
criteria for active surveillance do not allow any component of Gleason 4 (3). Recent studies have shown that many patients with PCa of intermediate risk including a component of Gleason 4 can still be conservatively managed (4). Unfortunately deciding who can stay on active surveillance vs who should be treated remains a difficult decision. In addition to subcategorizing tumors into 3+4 vs 4+3, more and more pathologists have started the practice of describing the percentage of Gleason 3 and 4 components, respectively, which provides more information for management decisions but uncertainties still remain. The field thus may benefit from molecular signatures such as the one published here that provides independent prognostic information that can help to create the most appropriate management plan for each individual patient with a biopsy diagnosis of Gleason 7 PCa.

Many similar studies have been reported, some of which have been developed into commercial tests. The Decipher Prostate Cancer Test, based on the expression pattern of 22 RNA markers in prostatectomy specimen, allows post-surgery risk stratification to predict likelihood of metastases and cancer-specific mortality (5). As a result, this test can help to determine the need for adjuvant versus salvage therapy. It may also help treatment decisions in patients who have already had a biochemical recurrence. It has been reported that transcriptomic features detected in prostatectomy specimens, including the Decipher prognostic test, were detectable in biopsy tissues with a high correlation(6). Consequently, biopsy-based Decipher results will likely be a valuable instrument in the pretreatment setting to predict adverse pathology and lymph node metastasis. Prolaris test is a 46-gene signature that assesses the aggressiveness of an individual patient’s cancer based on quantification of cell cycle progression (CCP). CCP is calculated as a function of gene expression of 31 CCP marker genes relative to 15 housekeeping control genes(7). Although it was originally developed with prostatectomy specimens, Prolaris test may also apply to biopsy tissue from PCa patients conservatively managed with active surveillance since the test scores are highly predictive of disease-specific mortality. A study has shown that the test results changed management in a significant proportion of patients (8). Oncotype DX® is a commercially available test used in biopsy tissue based on reverse transcription polymerase chain reaction quantification of a panel of 17 PCa-associated genes to assess the probability of high risk disease. The genomic prostate score (GPS) produced by this test has been used to improve patient selection for active surveillance(9).

In conclusion, due to the heterogeneous nature of PCa, and the inability of the currently available parameters to accurately predict the clinical course in many patients, particularly those with PCa of intermediate risk, gene expression-based biomarkers may give us additional tools for better management decisions. Although management of PCa patients continue to improve with better understanding of the disease, uncertainty still remains for many individual patients. Going forward, risk assessment and appropriate management will likely include a combination of clinical and pathologic parameters, gene signature, pre-operative radiologic evaluation such as multi-parametric MRI and improved biopsy technology (10). Figure 1 depicts our view of how the available tools may be integrated for the management of PCa patients. With the availability of multiple useful molecular tests, it will be important for the field to decide on the most appropriate molecular test(s) for the various clinical settings and for individual patients.
Figure Legend

Figure 1. Integration of clinical, pathological, radiological and molecular tools for the management of patients with suspected and confirmed prostate cancer.

REFERENCES

Figure 1:

Elevated PSA

Radiologic evaluation (e.g., multiparametric MRI)

No target

Template biopsy

Benign

Follow up

Low risk

Conservative management

Intermediate risk

Molecular test

High risk

Aggressive treatment

Target present

Target + template biopsy

Benign

Follow up

Low risk

High risk