Published OnlineFirst November 1, 2016; DOI: 10.1158/1078-0432.CCR-16-2400

CCR Translations

Clinical Cancer Research

Molecular Signature to Risk-Stratify Prostate Cancer of Intermediate Risk

Yu Yin[1,2], Qingfu Zhang[2,3], Hong Zhang[2], Yiping He[2], and Jiaoti Huang[2]

A new 30-gene signature has been described that separates prostate cancers of Gleason score ≤6 from those of Gleason score ≥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. *Clin Cancer Res; 23(1); 6–8. ©2016 AACR.*

See related article by Sinnott et al., p. 81

In this issue of *Clinical Cancer Research*, Sinnott and colleagues describe a gene expression signature that has the potential to stratify prostate cancer of intermediate risks (Gleason score 7) into high-risk and low-risk groups (1).

Prostate cancer is a heterogeneous disease with highly variable outcomes. Although most patients have indolent diseases that do not impact quality of life or life expectancy, some patients will die of 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 five histologic patterns of prostate cancer. Tumors with Gleason pattern 1 are the best differentiated, whereas those with pattern 5 show the 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, a Gleason score of 5 and under is rarely diagnosed, as such tumors always follow a benign course. In an earlier study using the Swedish Watchful Waiting Cohort and the Physicians' Health Study (PHS), a group that included Sinnott and colleagues discovered a 157-gene signature that distinguished tumors with Gleason score ≤6 from those with Gleason score ≥8 (2). Although a gene signature that distinguishes Gleason score ≤6 from Gleason score ≥8 tumors is interesting and important, the two disease groups can be more readily distinguished by histologic evaluation. In the study in this issue of *Clinical Cancer Research*, Sinnott and colleagues built a new gene expression signature using similar approaches with the PHS and the Health Professionals Follow-Up Study (HPFS) cohorts (1). The 30-gene signature (only five were in the original signature) similarly distinguished Gleason score ≤6 from Gleason score ≥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 AUC for lethal prostate cancer of 0.68. The new signature alone had an AUC for lethal prostate cancer 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 with 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 prostate cancer.

Future studies should decide whether the same gene signature can be used in biopsy tissue for patients with newly diagnosed prostate cancer for management. Many studies have demonstrated that tumors with Gleason score 6 and under are almost never life-threatening, whereas those with Gleason score 8 and above are high risk. The field has achieved a consensus that active surveillance is the most appropriate course of action for patients in the former group, whereas patients in the latter group should be managed aggressively. Tumors with Gleason score 7 (3 + 4 and 4 + 3) pose a significant challenge, as many of them will follow an indolent course, but some will be aggressive. Although 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 interobserver 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 a 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 prostate cancer of intermediate risk, including a component of Gleason 4, can still be conservatively managed (4). Unfortunately, deciding who can stay on active surveillance versus who should be treated remains a difficult decision. In addition to subcategorizing tumors into 3 + 4 versus 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; however, uncertainties still remain. The field thus may benefit from molecular signatures, such as the one published by

[1]Department of Pathology, Anhui Medical University, Hefei, China. [2]Department of Pathology, Duke University School of Medicine, Durham, North Carolina. [3]Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang, China.

Note: Y. Yin and Q. Zhang contributed equally to this article.

Corresponding Author: Jiaoti Huang, Department of Pathology, Duke University School of Medicine, 40 Duke Medicine Circle, Durham, NC 27710. Phone: 919-668-3712; Fax: 919-681-0778; E-mail: Jiaoti.huang@duke.edu

doi: 10.1158/1078-0432.CCR-16-2400

Published OnlineFirst November 1, 2016; DOI: 10.1158/1078-0432.CCR-16-2400

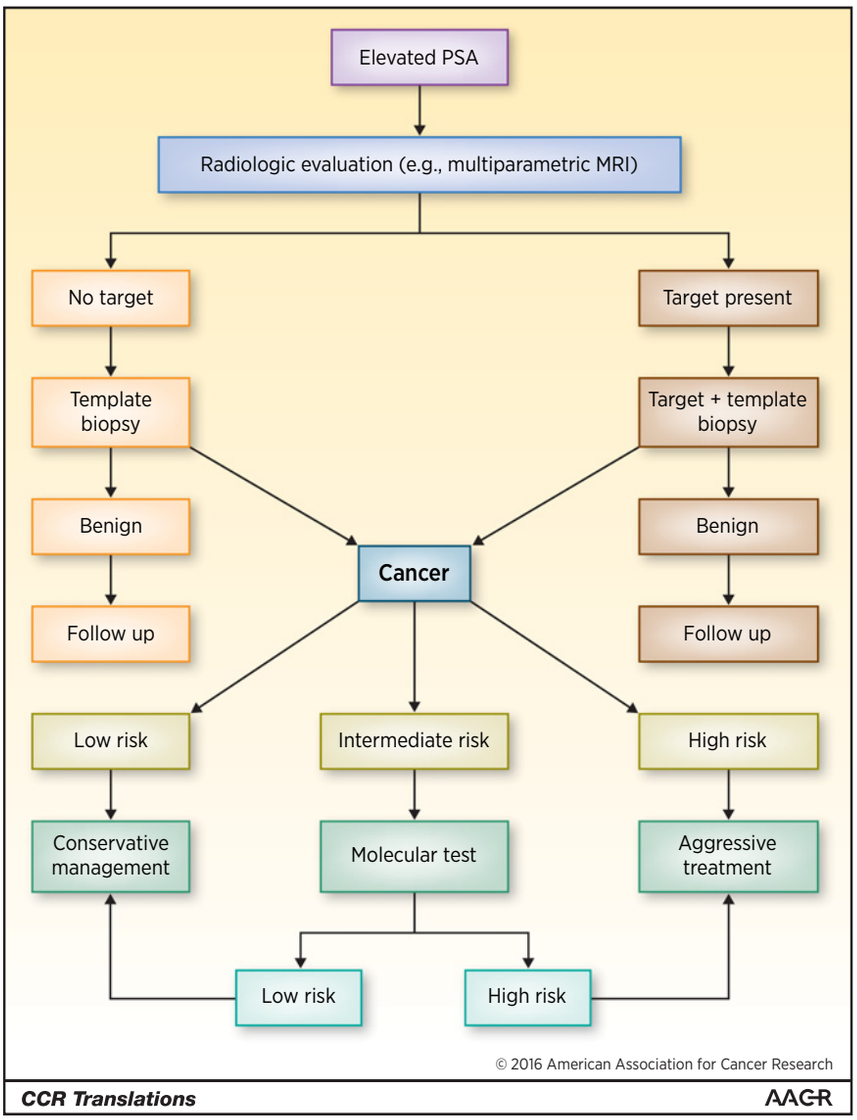

Figure 1.
Integration of clinical, pathologic, radiologic, and molecular tools for the management of patients with suspected and confirmed prostate cancer.

Sinnott and colleagues (1), which 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 prostate cancer.

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 specimens, allows postsurgery risk stratification to predict the 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 to make 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 is a 46-gene signature test 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, the Prolaris test may also apply to biopsy tissue from prostate cancer patients conservatively managed with active surveillance, as the test scores are highly predictive of disease-specific mortality. One study showed 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 RT-PCR quantification of a panel of 17 prostate cancer–associated genes to assess the probability of high-risk disease. The genomic prostate score produced by this test has been used to improve patient selection for active surveillance (9).

In conclusion, due to the heterogeneous nature of prostate cancer and the inability of the currently available parameters to accurately predict the clinical course in many patients, particularly those with prostate cancer of intermediate risk, gene

Published OnlineFirst November 1, 2016; DOI: 10.1158/1078-0432.CCR-16-2400

expression–based biomarkers may give us additional tools for better management decisions. Although the management of patients with prostate cancer continues 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; preoperative radiologic evaluation, such as multiparametric MRI; and improved biopsy technology (10). Figure 1 depicts our view of how the available tools may be integrated for the management of patients with prostate cancer. With the availability of multiple useful molecular tests, it will be important for the field to decide on the most appropriate molecular test(s) within various clinical settings and for individual patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: H. Zhang, J. Huang
Development of methodology: H. Zhang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Zhang
Writing, review, and/or revision of the manuscript: Y. Yin, Q. Zhang, H. Zhang, Y. He, J. Huang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Huang
Study supervision: J. Huang

Grant Support

Y. He was supported by the National Comprehensive Cancer Network Young Investigator Award and Circle of Service Foundation. J. Huang is supported by grants from the NCI (1R01CA205001, 1R01CA181242, 1R01CA172603), Department of Defense Prostate Cancer Research Program (PC150382, W81XWH-16-1-0291), 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.

Received October 6, 2016; accepted October 13, 2016; published OnlineFirst November 1, 2016.

References

1. Sinnott JA, Peisch SF, Tyekucheva S, Gerke T, Lis R, Rider JR, et al. Prognostic utility of a new mRNA expression signature of Gleason score. Clin Cancer Res 2017;23:81–7.
2. Penney KL, Sinnott JA, Fall K, Pawitan Y, Hoshida Y, Kraft P, et al. mRNA expression signature of Gleason grade predicts lethal prostate cancer. J Clin Oncol 2011;29:2391–6.
3. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976–83.
4. Cooperberg MR, Cowan JE, Hilton JF, Reese AC, Zaid HB, Porten SP, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J Clin Oncol 2011;29:228–34.
5. Karnes RJ, Bergstralh EJ, Davicioni E, Ghadessi M, Buerki C, Mitra AP, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047–53.
6. Knudsen BS, Kim HL, Erho N, Shin H, Alshalalfa M, Lam LL, et al. Application of a clinical whole-transcriptome assay for staging and prognosis of prostate cancer diagnosed in needle core biopsy specimens. J Mol Diagn 2016;18:395–406.
7. Cuzick J, Swanson GP, Fisher G, Brothman AR, Berney DM, Reid JE, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245–55.
8. Crawford ED, Scholz MC, Kar AJ, Fegan JE, Haregewoin A, Kaldate RR, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. Curr Med Res Opin 2014;30:1025–31.
9. Klein EA, Cooperberg MR, Magi-Galluzzi C, Simko JP, Falzarano SM, Maddala T, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66:550–60.
10. Le JD, Stephenson S, Brugger M, Lu DY, Lieu P, Sonn GA, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. J Urol 2014;192:1367–73.

Published OnlineFirst November 1, 2016; DOI: 10.1158/1078-0432.CCR-16-2400

Clinical Cancer Research

Molecular Signature to Risk-Stratify Prostate Cancer of Intermediate Risk

Yu Yin, Qingfu Zhang, Hong Zhang, et al.

Clin Cancer Res 2017;23:6-8. Published OnlineFirst November 1, 2016.