Impact of the Cell Cycle Progression Test on Physician and Patient Treatment Selection for Localized Prostate Cancer

Neal D. Shore,*,† Naveen Kella,† Brian Moran,† Judd Boczko,† Fernando J. Bianco,† E. David Crawford,† Thaylon Davis,‡ Kirstin M. Roundy,‡ Kristen Rushton,‡ Charles Grier,‡ Rajesh Kaldate,‡ Michael K. Brawer‡ and Mark L. Gonzalgo†

From the Carolina Urologic Research Center, Myrtle Beach, South Carolina (NDS), The Urology and Prostate Institute, San Antonio, Texas (NK), Prostate Cancer Foundation of Chicago, Westmont, Illinois (BM); WESTMED Medical Group, Woodmere, New York (JB), Urological Research Network, Miami Lakes (FJB), and University of Miami Miller School of Medicine, Miami (MLG), Florida, University of Colorado at Denver, Aurora, Colorado (EDC), and Myriad Genetic Laboratories, Inc., Salt Lake City, Utah (TD, KMR, KR, CG, RK, MKB)

Abbreviations and Acronyms

ADT = androgen deprivation therapy

AUA = American Urological Association

CCP = cell cycle progression

EBRT = external beam radiation therapy

PSA = prostate specific antigen

VAS = visual analog scale

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* Correspondence: Carolina Urologic Research Center, 823 82nd Parkway, Myrtle Beach, South Carolina 29572 (telephone: 843-449-1010; e-mail: nshore@gsuro.com).

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Purpose: The cell cycle progression test is a validated molecular assay that assesses prostate cancer specific disease progression and mortality risk when combined with clinicopathological parameters. We present the results from PROCEDE-1000, a large, prospective registry designed to evaluate the impact of the cell cycle progression test on shared treatment decision making for patients newly diagnosed with prostate cancer.

Materials and Methods: Untreated patients with newly diagnosed prostate adenocarcinoma were enrolled in the study and the cell cycle progression test was performed on the initial prostate biopsy tissue. A set of 4 sequential surveys tracked changes relative to initial therapy recommendations (before cell cycle progression) based on clinicopathological parameters following physician review of the cell cycle progression test result, physician/patient review of the cell cycle progression test results and a minimum of 3 months of clinical followup (actual treatment).

Results: Of the 1,596 patients enrolled in this registry 1,206 were eligible for analysis. There was a significant reduction in the treatment burden recorded at each successive evaluation ($p < 0.0001$), with the mean number of treatments per patient decreasing from 1.72 before the cell cycle progression test to 1.16 in actual followup. The cell cycle progression test caused a change in actual treatment in 47.8% of patients. Of these changes 72.1% were reductions and 26.9% were increases in treatment. For each clinical risk category there was a significant change in treatment modality (intervention vs nonintervention) before vs after cell cycle progression testing ($p=0.0002$).

Conclusions: The cell cycle progression test has a significant impact in assisting physicians and patients reach personalized treatment decisions.

Key Words: biological markers, evaluation studies, data collection, prostatic neoplasms

PROSTATE specific antigen screening for prostate cancer has contributed to a decrease in disease specific mortality.[1] However, it is widely accepted that PSA testing has also resulted in the over detection of indolent cancer due its inability to discriminate between low risk and aggressive

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malignancies.[2,3] Furthermore, clinical and pathological features are limited in their ability to distinguish between low risk and aggressive prostate cancers.[4–6] Consequently nearly 90% of men will receive treatment despite the fact that only 15% to 30% of prostate cancers will exhibit oncologic progression.[7–11] For these over diagnosed and/or overtreated patients the risk of treatment related complications and morbidity may outweigh their prostate cancer risk.[10,12] The limitations in prostate cancer risk assessment also result in the under treatment of men with more aggressive cancers, contributing to the approximately 30,000 annual deaths from prostate cancer.[13] Ultimately this demonstrates the need for a prognostic test to distinguish low vs high risk patients with prostate cancer to facilitate appropriate medical management decisions.[14]

The CCP test (Myriad Genetic Laboratories, Inc.) is a commercially available molecular diagnostic test that assesses the risk of prostate cancer progression in patients with clinically localized prostate cancer. The test is based on the relative gene expression levels of 31 cell cycle progression genes that show increased expression in aggressive tumors. The CCP report provides patients with an individual CCP score and placement of this score within a distribution of other patient CCP scores in the U.S. population.[15] The purpose of the CCP test in the prostate cancer treatment pathway is to provide more precise prognostic information to enhance patient-physician decision making before a final treatment selection. The CCP assay has been validated in 6 studies consisting of 8 unique patient cohorts, demonstrating its utility as a predictor of prostate cancer specific mortality, biochemical recurrence and metastasis.[16–21] In addition, an independent meta-analysis of 5 clinical validity studies suggested that use of the CCP test improved patient prognosis and can be a valuable tool for clinicians.[22]

In this report we present the CCP test effect and results from PROCEDE-1000, the largest prospective registry to date, to our knowledge, of a genomic biomarker on therapeutic decisions and patient management. Changes in treatment recommendations were tracked at 4 sequential points in the decision making process, including a minimum of 3 months after receipt of the CCP test results. This allowed changes in treatment recommendations to be evaluated in a stepwise process, including actual treatment based on clinical followup.

METHODS

Study Design

This study was a prospective open registry to measure the impact of the CCP test on therapeutic decisions in patients with newly diagnosed prostate cancer (Clinical Trials.gov, NCT01954004). This study was approved for each study site through a centralized (Western Institutional Review Board, Puyallup, Washington) or an academic/medical group institutional review board. Study site selection was based on previous investigator experience with the CCP test to ensure that samples would meet laboratory specifications[15] and to avoid any selection bias related to first test ordering. Patients were identified by the physician or designated research staff and were included in the registry if they were newly diagnosed (6 months or less); had histologically proven, presumed clinically localized prostate cancer; had not received any treatment and had sufficient biopsy tissue.[15] Patients with a known history of hypogonadism or those who had been treated with hormonal therapy were excluded from the registry.

Physicians were encouraged to enroll consecutive eligible patients to minimize any selection bias from a physician selected population. Any potential bias from patients missing from the analysis due to loss to followup was mitigated by including these patients in sensitivity analyses. For sample size calculation purposes it was assumed that this registry study would be able to show a magnitude of change of at least 10% with regard to any of the end points. For an estimation study this required that the lower limit of a 95% CI on the proportion representing the primary end point be 10% or greater. Sample sizes were computed using NCSS PASS 2008 (version 08.0.13).

Study Questionnaires

The clinical utility of the CCP test was evaluated based on patient management in 4 sequential questionnaires/parts. Patient management was used in lieu of outcomes data due to the high prostate cancer specific survival rates and the resultant length of time (10 to 20 years) to definitive outcomes. Using standard clinicopathological parameters (PSA, Gleason score, clinical stage and percent positive cores), physicians completed questionnaire A (part A—before CCP test treatment recommendation) to record the initial treatment modality recommendation (intervention vs nonintervention) and treatment options within that modality (supplementary fig. 1, http://jurology.com/). These treatment options included potential interventional options (RP, EBRT primary, EBRT adjuvant, CyberKnife®, proton beam radiation, brachytherapy interstitial, brachytherapy high dose rate, ADT primary, ADT neoadjuvant, ADT adjuvant, ADT concurrent, pelvic lymph node dissection, cryosurgery, high intensity focused ultrasound and other [remaining catchall category]) and noninterventional options (watchful waiting [waiting for clinical progression] or active surveillance [active monitoring for progression]).

They also recorded their likelihood of recommending a noninterventional therapy approach on a VAS. The VAS recording was then calibrated to a VAS score based on a range of 0 to 100. A series of surveys (supplementary fig. 1, http://jurology.com/) tracked changes in treatment relative to subsequent stages of the decision making process (supplementary fig. 2, http://jurology.com/). Physicians completed questionnaire B (part B—after CCP test, before patient consult treatment recommendation) after