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Prostate Cancer

A Biopsy-based 17-gene Genomic Prostate Score as a Predictor of Metastases and Prostate Cancer Death in Surgically Treated Men with Clinically Localized Disease

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Abstract

Background: A 17-gene biopsy-based reverse transcription polymerase chain reaction assay, which provides a Genomic Prostate Score (GPS—scale 0–100), has been validated as an independent predictor of adverse pathology and biochemical recurrence after radical prostatectomy (RP) in men with low- and intermediate-risk prostate cancer (PCa).
Objective: To evaluate GPS as a predictor of PCa metastasis and PCa-specific death (PCD) in a large cohort of men with localized PCa and long-term follow-up.
Design, setting, and participants: A retrospective study using a stratified cohort sampling design was performed in a cohort of men treated with RP within Kaiser Permanente Northern California. RNA from archival diagnostic biopsies was assayed to generate GPS results.
Outcome measurements and statistical analysis: We assessed the association between GPS and time to metastasis and PCD in prespecified uni- and multivariable statistical analyses, based on Cox proportional hazard models accounting for sampling weights.
Results and limitations: The final study population consisted of 279 men with low-, intermediate-, and high-risk PCa between 1995 and 2010 (median follow-up 9.8 yr), and included 64 PCD and 79 metastases. Valid GPS results were obtained for 259 (93%). In univariable analysis, GPS was strongly associated with time to PCD, hazard ratio (HR)/20 GPS units = 3.23 (95% confidence interval [CI] 1.84–5.65; $p < 0.001$), and time to metastasis, HR/20 units = 2.75 (95% CI 1.63–4.63; $p < 0.001$). The association between GPS and both end points remained significant after adjusting for National Comprehensive Cancer Network, American Urological Association, and Cancer of the Prostate Risk Assessment (CAPRA) risks ($p < 0.001$). No patient with low- or intermediate-risk disease and a GPS of < 20 developed metastases or PCD ($n = 31$). In receiver operating characteristic analysis of PCD at 10 yr, GPS improved the c-statistic from 0.78 (CAPRA alone) to 0.84 (GPS + CAPRA; $p < 0.001$). A limitation of the study was that patients were treated during an era when definitive treatment was standard of care with little adoption of active surveillance.
Conclusions: GPS is a strong independent predictor of long-term outcomes in clinically localized PCa in men treated with RP and may improve risk stratification for men with newly diagnosed disease.
Patient summary: Many prostate cancers are slow growing and unlikely to spread or threaten a man's life, while others are more aggressive and require treatment.

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Increasingly, doctors are using new molecular tests, such as the17-gene Genomic Prostate Score (GPS), which can be performed at the time of initial diagnosis to help determine how aggressive a given patient's cancer may be. In this study, performed in a large community-based healthcare network, GPS was shown to be a strong predictor as to whether a man's prostate cancer will spread and threaten his life after surgery, providing information that may help patients and their doctors decide on the best course of management of their disease.

1. Introduction

Prognostic molecular assays are increasingly bring used in practice to improve risk stratification for men with newly diagnosed prostate cancer (PCa) to inform treatment decisions such as whether to recommend immediate therapy or active surveillance (AS) or whether to administer adjuvant therapy [1,2]. National Comprehensive Cancer Network (NCCN) guidelines state that "men with clinically localized disease may consider the use of tumor-based molecular assays" [3]. For assays to be accepted for clinical care, there must be substantial evidence supporting and validating their ability to predict end points independent of conventional risk factors [4,5]. NCCN guidelines have noted the need for such assays to predict clinically relevant end points including adverse pathology (AP), biochemical recurrence (BCR), metastases, and disease-specific death [3].

The OncotypeDX Prostate Cancer assay is a biopsy-based reverse transcription polymerase chain reaction assay that has been analytically validated to measure the expression of 17 genes in RNA extracted from fixed tumor tissue from prostate needle biopsies [6]. The test provides a Genomic Prostate Score (GPS) result, scale 0–100, with increasing scores indicating more biologically aggressive disease. It has been clinically validated as a strong, independent predictor of (1) AP (defined as Gleason score [GS] $\geq$4 + 3 and/or non–organ-confined disease) [7,8] and (2) BCR after radical prostatectomy (RP) [8] in men with clinically very low–, low-, and intermediate-risk PCa. In addition, use of GPS has been associated with increased recommendation and utilization of AS in men with very low–, low-, and favorable intermediate–risk patients [9,10].

In this study, we assessed the ability of GPS to predict later, and arguably the most clinically relevant, outcomes—distant metastases and prostate cancer–specific death (PCD)—in a large cohort of surgically treated men managed in a community-based healthcare network with long-term follow-up.

2. Patients and methods

2.1. Study setting and population

This study was conducted among members of Kaiser Permanente Northern California (KPNC), an integrated healthcare system with over 4 million members in the greater northern California area. KPNC maintains a cancer registry for internal and external reporting and quality assurance requirements that uses strict Surveillance, Epidemiology and End Results (SEER) protocols [11]. The registry has been found to be essentially 100% complete in terms of new cancer ascertainment among KPNC members.

In the KPNC database, 6184 men were diagnosed with PCa between 1995 and 2010, and underwent RP within 12 mo of diagnosis. The clinical follow-up was standard of care, including regular prostate-specific antigen (PSA) assessments and imaging as clinically determined to assess recurrence or metastasis. For this study, all eligible men with adenocarcinoma were included without regard to postsurgical management. Clinical exclusion criteria for this study included <6 mo of follow-up after surgery, receipt of neoadjuvant therapy, and death within 6 mo of surgery.

2.2. Study design

The study design was collaboratively developed by Genomic Health, Inc. and KPNC researchers, and finalized prior to the initiation of the study protocol. Owing to a small number of PCD events as compared with the overall RP-treated cohort, this study employed a stratified cohort sampling design [12] within the study eligible cohort, with strata determined by treatment year, race, and NCCN risk groups. From the full cohort, all cases with documented PCD and available tissue were selected, along with non-PCD men sampled at a target ratio of 1:2 to 1:3. Non-PCD cases with missing tissue were replaced with additional non-PCD cases with tissue, resulting in a final ratio of 1:2.6. The protocol and statistical analysis plans were agreed upon by all investigators prior to study data collection. This study was approved by Kaiser Foundation Research Institute and Asentral, Inc. (Newburyport, MA, USA) institutional review boards and conformed to Reporting Recommendations for Tumor Marker Prognostic Studies guidelines [13]. Data were locked prior to analysis.

2.3. Outcome definitions

The investigators had access to all clinical, radiological, and laboratory data to identify and confirm the study end points. In addition, the KPNC Cancer Registry was used to ascertain key tumor data elements. PCD was determined by a review of Cancer Registry and KPNC mortality files with confirmation of the presence of metastasis or other supporting clinical evidence. Metastasis was defined as clinical evidence of disseminated PCa, such as a positive bone scan and/or CT scan, positive pathology of a metastatic site, or a combination of extremely elevated PSA levels and/or patient-reported symptoms indicative of prostate metastasis. BCR was defined as either two successive post-RP PSA levels of $\geq$0.2 ng/ml, or initiation of salvage therapy after a rising PSA of $\geq$0.1 ng/ml.

2.4. Pathological processing of diagnostic biopsies for molecular testing

Fixed paraffin-embedded diagnostic biopsy specimens were retrieved from the KPNC Pathology Specimen Repository and centrally reviewed by a single urological pathologist (J.S.H.), blinded to clinical outcomes and historical pathological data, using 2005 International Society of Urological Pathology consensus guidelines [14]. The tissue block with the

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