Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk

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OBJECTIVES To evaluate the ability of the Decipher genomic classifier in predicting metastasis from analysis of prostate needle biopsy diagnostic tumor tissue specimens.

MATERIALS AND METHODS Fifty-seven patients with available biopsy specimens were identified from a cohort of 169 men treated with radical prostatectomy in a previously reported Decipher validation study at Cleveland Clinic. A Cox multivariable proportional hazards model and survival C-index were used to evaluate the performance of Decipher.

RESULTS With a median follow up of 8 years, 8 patients metastasized and 3 died of prostate cancer. The Decipher plus National Comprehensive Cancer Network (NCCN) model had an improved C-index of 0.88 (95% confidence interval [CI] 0.77-0.96) compared to NCCN alone (C-index 0.75, 95% CI 0.64-0.87). On multivariable analysis, Decipher was the only significant predictor of metastasis when adjusting for age, preoperative prostate-specific antigen and biopsy Gleason score (Decipher hazard ratio per 10% increase 1.72, 95% CI 1.07-2.81, $P = .02$).

CONCLUSION Biopsy Decipher predicted the risk of metastasis at 10 years post radical prostatectomy. While further validation is required on larger cohorts, preoperative knowledge of Decipher risk derived from biopsy could indicate the need for multimodality therapy and help set patient expectations of therapeutic burden. UROLOGY 90: 148–152, 2016. © 2016 The Authors. Published by Elsevier Inc.

Accurate assessment of the biological potential of prostate cancer (PCa) at initial diagnosis is important for optimal treatment planning and decision making. Increased risk of metastasis is one factor that can influence the decision to not offer active surveillance, perform an extended lymph node dissection, or use adjuvant therapy. Decipher is an extensively validated genomic classifier that predicts metastasis and PCa mortality after radical prostatectomy (RP).[1-3] Prior validation studies evaluated the performance of Decipher using tumor tissue obtained from RP specimens. In the present study, we assessed the ability of the locked 22-biomarker signature, Decipher, measured on diagnostic needle biopsy specimens to predict the occurrence of metastasis at 10 years post RP, and compared its performance to tumor tissue obtained from the corresponding RP specimens.

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MATERIALS AND METHODS

Specimen Collection and Processing

Cases were selected based on availability of prostate needle biopsy specimens from a cohort of 169 patients treated with RP at Cleveland Clinic between 1987 and 2008, which were previously used to evaluate Decipher for prediction of metastasis within 5 years of RP.[4] In that study, patients were selected if they met at least one of the following criteria: (1) preoperative prostate-specific antigen (PSA) >20 ng/mL, (2) stage pT3 or margin positive, *or* (3) pathologic Gleason score ≥8. From this cohort, 57 patients who had both preoperative diagnostic needle biopsy specimens and matched RP specimens for genomic analysis were selected. The study was approved by the Cleveland Clinic Institutional Review Board.

All tissues used in the study were rereviewed by an expert genitourinary pathologist (CMG) and graded according to 2005 International Society of Urological Pathology criteria.[5] RNA was extracted from diagnostic biopsy specimens from the core with at least 1 mm of the highest Gleason pattern and linear length of tumor; for RP specimens, the block with the highest grade was used.[4] Twenty-five to 100 ng of RNA from each specimen was amplified for transcriptome-wide microarray expression analysis

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using an established platform.[4] Median RNA extracted from formalin-fixed paraffin embedded tissues from the 1980s and 1990s was 269.5 ng (interquartile range [IQR] 112.0-537.1 ng) and 214.5 ng (IQR 97.0-384.5 ng), respectively.

Calculation of Risk Models

The Stephenson post RP, Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) Score clinical models and Decipher scores were calculated as described previously.[4,6,7]

Statistical Analysis

The primary objective of the present study was to validate biopsy Decipher for prediction of metastasis within 10 years after RP. Secondary objectives included validation of Decipher for prediction of primary Gleason pattern 4 or greater on RP specimen, pT3 disease (extraprostatic extension or seminal vesicle invasion), and rapid metastasis (RM, metastasis within 5 years post RP). Statistical analyses were performed in R v3.1 (R Foundation for Statistical Computing, Vienna, Austria), with all tests of significance as 2-sided at the 0.05 level. Taking into account the small sample size and number of events, Firth's penalized likelihood Cox regression method was used to evaluate the performance of Decipher in univariable and multivariable analyses.[8] This method ensures the robustness of the analyses with a small number of events to avoid overestimation of the resulting estimates. Least absolute shrinkage and selection operation (LASSO) was also used to determine the most important variables in the multivariable analysis (MVA).[9] Time-dependent C-indices were constructed using the nearest neighbor estimator described by Heagerty et al.[10] with a span parameter of 0.001. The C-index of the combined models was estimated by subjecting the model to bootstrapping with 1000 resamples. For secondary end points, logistic regression analysis was used.

RESULTS

Demographic, clinical, and follow-up data of the patient cohort are provided in Table 1. The median year of surgery was 1998 (IQR 1994-2002) and the median patient age at RP was 62 years (IQR 58-67). The median preoperative PSA was 6.3 ng/mL (IQR 5.1-11.1); 63% had clinical stage T1c; and 61% had a biopsy Gleason score of 6, mirroring the demographic, clinical, and pathologic characteristics of our entire population of RP patients operated on in this era.[7] Based on National Comprehensive Cancer Network (NCCN) risk categories, 40%, 47%, and 7% of patients had low-, intermediate- and high-risk diseases, respectively. Of the 57 patients, 8 (14%) developed metastasis and 11 died, including 3 (5%) from PCa and 8 (14%) from non-PCa causes. The median follow-up of the censored patients was 8 years (IQR 6-11).

The median Decipher score on biopsy specimens was 0.38 (IQR 0.29-0.49). Based on previously established cutoffs, 38 (67%) had low (<0.45), 14 (25%) had intermediate (0.45-0.60), and 5 (9%) had high (>0.60) Decipher scores (Fig. 1). Overall, 46% of NCCN risk group patients were reclassified as lower or higher Decipher risk (Table 2). Pathologic details for the RP specimens are provided in Table 3. Twenty-five patients (44%) were upgraded to Gleason 3 + 4 or greater, 36 (63%) had extraprostatic extension, 6 (11%) had seminal vesicle invasion, and 44 (77%) were CAPRA-S intermediate- or high-risk. The median Decipher score on the RPs was 0.29 (IQR 0.18-0.44), and 75%, 11%, and 13% had low, intermediate, and high Decipher scores, respectively. Overall, Decipher scores on tumor derived from the RPs reclassified 62% of CAPRA-S risk groups into lower- or higher-risk categories (Supplementary Table S1).

Table 1. Patient demographic and clinical characteristics

Variables	Validation Cohort (N = 57)
Race, n (%)	
Caucasian	44 (77.2)
African-American	11 (19.3)
Asian	2 (3.5)
Patient age (y)	
Median (Q1, Q3)	62 (58, 67)
Year of surgery	
Median (Q1, Q3)	1998 (1994, 2002)
Preoperative PSA (ng/mL)	
Median (Q1, Q3)	6.3 (5.1, 11.1)
Clinical stage	
T1c	36 (63.1)
T2a	18 (31.6)
T2b	3 (5.3)
Biopsy Gleason score, n (%)	
≤6	35 (61.4)
7	14 (24.6)
≥8	4 (7.0)
Unknown	4 (7.0)
NCCN risk category, n (%)	
Low	23 (40.4)
Intermediate	27 (47.4)
High	4 (7.0)
Unknown	3 (5.3)
Follow-up of censored patients post RP (y)	
Median (Q1, Q3)	8 (6, 11)

NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; Q, quartile; RP, radical prostatectomy.

For the primary end point of the presence of metastasis within 10 years after RP, biopsy Decipher had a C-index of 0.80 (95% confidence interval [CI] 0.58-0.95) compared to 0.75 (95% CI 0.64-0.87) for the NCCN risk group (Fig. 2). A combined model of Decipher plus NCCN had an improved C-index of 0.88 (95% CI 0.76-0.96). In a sensitivity analysis, we determined the C-index at other time points (ie, 5-10 years post RP), which showed consistent C-index values (Supplementary Figure S1). On univariable analysis, only a biopsy Gleason score of ≥8 (hazard ratio [HR] = 8.6, 95% CI 1.42-55.98, P = .02) and biopsy Decipher (HR = 1.85 per 10% increase, 95% CI 1.22-2.87, P = .004) were significant predictors of metastasis (Table 4). On MVA with clinical risk factors, biopsy Decipher remained a significant predictor of metastasis (HR = 1.72 per 10% increase, 95% CI 1.07-2.81, P = .02). LASSO regression showed that biopsy Decipher and biopsy Gleason score were the remaining variables in the model when the penalty parameter was optimized (Supplementary Figure S2). Similar results were observed when we modeled Decipher with the rereviewed biopsy Gleason score (Supplementary Table S2). Biopsy Decipher remained significant when modeled with