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Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy

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Abstract

Background: Despite salvage radiation therapy (SRT) for recurrent prostate cancer (PCa) after radical prostatectomy (RP), some patients still progress to metastases. Identifying these men would allow them to undergo systemic therapy including testing novel therapies to reduce metastases risk.
Objective: To test whether the genomic classifier (GC) predicts development of metastatic disease.
Design, setting, and participants: Retrospective multi-center and multi-ethnic cohort study from two academic centers and one Veterans Affairs Medical Center in the United States involving 170 men receiving SRT for recurrent PCa post-RP.
Outcome measurements and statistical analysis: Time from SRT to development of metastatic disease tested using Cox regression, survival c-index, and decision curve analysis. Performance of GC was compared to the Cancer of the Prostate Risk Assessment Score and Briganti risk models based on these metrics.
Results and limitations: With a median 5.7 yr follow-up after SRT, 20 patients (12%) developed metastases. On multivariable analysis, for each 0.1 unit increase in GC (scaled from 0 to 1), the hazard ratio for metastasis was 1.58 (95% confidence interval 1.16–2.17; $p = 0.002$). Adjusting for androgen deprivation therapy did not materially change the results. The c-index for GC was 0.85 (95% confidence interval 0.73–0.88) versus 0.63–0.65 for published clinico-pathologic risk models. The 5-yr cumulative incidence of metastasis post-SRT in patients with low, intermediate, and high GC scores was 2.7%, 8.4%, and 33.1%, respectively ($p < 0.001$).
Conclusions: While validation in larger, prospectively collected cohorts is required, these data suggest GC is a strong predictor of metastases among men receiving SRT for recurrent PCa post-RP, accurately identifying men who are excellent candidates for systemic therapy due to their very high-risk of metastases.
Patient summary: Genomic classifier and two clinico-pathologic risk models were evaluated on their ability to predict metastases among men receiving salvage radiation therapy for recurrent prostate cancer. Genomic classifier was able to identify candidates for further therapies due to their very high-risk of metastases.

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1. Introduction

Our ability to predict outcomes following salvage radiation (SRT) for recurrent disease after radical prostatectomy (RP) is poor. A prior study evaluated 1540 men treated with SRT at multiple academic centers [1]. The best nomogram predicted 6-yr prostate specific antigen (PSA) control with 69% accuracy. This compares poorly to other prostate cancer (PCa) nomograms, which predict PCa death (a more definitive endpoint) with 80% accuracy or higher at diagnosis [2], post-RP [1,3], or at initial rising PSA post-RP [4]. While intermediate endpoints (eg, rising PSA) are important, assessment of risk factors for hard endpoints such as metastasis are needed.

Advancements in genetics and high throughput "omics" coupled with a robust biomarker discovery program have resulted in several commercially available tissue-based molecular markers for PCa prognosis [5]. While these markers have been evaluated in multiple populations, only one has been examined on patients receiving radiation as primary curative therapy [6] and none in men all receiving SRT. Based upon performance in other populations, a promising test is the Decipher genomic classifier (GC) [7–9]. Unlike other tests that examined a limited number of genes in their discovery [5], GC examined the whole tumor gene expression profile. Thus, GC has the theoretical advantage of capturing the entire tumor biology in one signature. GC was developed among men undergoing RP at the Mayo Clinic to predict metastases using a nested case-control study design [7]. It has subsequently been evaluated in multiple independent populations receiving varying degrees of postoperative radiation [8,10,11], but never in men who all received SRT. Importantly, these prior studies all included men who received adjuvant radiation, some of whom were cured with surgery alone. As such, it is impossible to assess whether GC predicted response to radiation or the likelihood of the surgery being curative, which invariably would also relate to metastases risk. Therefore, it is crucial to assess the ability of GC to identify metastases risk in a more homogenous group of men who all recurred and all received SRT to address whether GC predicts outcomes after SRT.

To test whether GC predicts metastases after SRT, we performed a multi-center study of men undergoing SRT post-RP. Our population included men from two tertiary-care referral centers and a Veterans Affairs (VA) hospital, which contained nearly 50% African-American men. Importantly, no man in this study cohort was included in the GC development. Thus, this study is an independent evaluation of GC's ability to predict metastases in men undergoing SRT. We hypothesized GC would predict metastases with high accuracy, especially compared with standard clinico-pathologic variables and two clinico-pathologic risk models: the Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) model [12] and the Briganti risk model [13], which was developed for predicting biochemical recurrence following early SRT. Neither of these clinico-pathologic risk models were initially designed to predict metastasis. The Briganti model, however, represents a recent and relevant risk model for post-SRT patients while CAPRA-S has been externally validated on a European cohort to predict metastasis [14].

2. Materials and methods

2.1. Study cohort

A total of 170 RP patients who received postoperative SRT without prior neoadjuvant or adjuvant therapy and without lymph node invasion were included. Lymph node invasion was defined by the presence of at least one node with a tumor. Seventy prostatectomy patients treated at Durham VA between 1991 and 2010 with postoperative SRT were obtained for analysis (Supplementary Fig. 1). Patients analyzed from Thomas Jefferson University ($n = 61$; yr of RP 1991–2009) and Mayo Clinic ($n = 39$; yr of RP 2000–2006) were obtained from a prior validation study wherein GC had been performed using RP tumor tissue testing GC for predicting metastases in men undergoing postoperative radiation (adjuvant and salvage) [11]. Of the 188 patients in this prior study, only 100 received radiation with PSA > 0.2 ng/ml (ie, SRT), and were thus included in the current study. Importantly, no patient in the current study was included in the GC development [7,11]. Radiation therapy regimens were as previously described where patients were treated to a median dose of 66.6 Gy [11,15]. At all three institutions, only the prostatic fossa is typically radiated for node negative patients. The primary endpoint for the current study was metastasis (regional or distant) detected using computed tomography and/or a bone scan. SRT was defined as radiation for PSA > 0.2 ng/ml or by radiation following salvage androgen deprivation therapy (ADT). Concurrent ADT with SRT was defined as ADT administered within 3 mo of SRT [16–18]. ADT was delivered at the discretion of the providing physician at each institution with a median administration time of 12 mo post-RP. The study met the REporting recommendations for tumor MARKer prognostic studies criteria for evaluation of prognostic biomarkers [19]. The Institutional Review Boards at Durham VA, Thomas Jefferson University, and Mayo Clinic approved this study.

2.2. Tumor tissue sampling, RNA extraction, and testing

RP tumor specimens from Durham VA patients were selected after restaging and regrading from the original hematoxylin and eosin slides. Formalin-fixed paraffin embedded tumor blocks with the highest Gleason grade, and if present, extraprostatic extension or seminal vesicle invasion were selected. Using a hematoxylin and eosin slide freshly prepared from the formalin-fixed paraffin embedded block, the target region of tumor was selected to additionally have >80% tumor by area to minimize presence of benign glands. The tumor was sampled using a single 1.0-mm diameter disposable biopsy punch tool (Miltex, York, PA, USA). RNA extraction, Affymetrix Human Exon 1.0 ST oligonucleotide microarray (Affymetrix, Santa Clara, CA, USA) data generation and preprocessing were as previously described [11]. The approach for tissue selection and analysis was identical at the other sites, as we have previously described [11].

2.3. Calculation of GC, clinico-pathologic risk models, and combined models

GC is a locked risk model developed on a nested case-control data set consisting of 545 patients from the Mayo Clinic [7] which is independent of the cohorts involved in the current study and thus there are no overlapping patients. The expression values for the 22 prespecified biomarkers constituting GC were extracted from the normalized data matrix and entered into the random forest algorithm that was locked

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