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European Association of Urology

Prostate Cancer

Performance of a Prostate Cancer Genomic Classifier in Predicting Metastasis in Men with Prostate-specific Antigen Persistence Postprostatectomy

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Article info

Article history:
Accepted November 27, 2017

Associate Editor:
Giacomo Novara

Keywords:
Prostate cancer
Genomic classifier
Decipher
Detectable PSA
Persistent PSA
Prostatectomy
Biomarker
PSA

Abstract

Background: Prostate cancer patients who have a detectable prostate-specific antigen (PSA) postprostatectomy may harbor pre-existing metastatic disease. To our knowledge, none of the commercially available genomic biomarkers have been investigated in such men.
Objective: To evaluate if a 22-gene genomic classifier can independently predict development of metastasis in men with PSA persistence postoperatively.
Design, setting, and participants: A multi-institutional study of 477 men who underwent radical prostatectomy (RP) between 1990 and 2015 from three academic centers. Patients were categorized as detectable PSA (n = 150) or undetectable (n = 327) based on post-RP PSA nadir $\geq$0.1 ng/ml.
Outcome measurements and statisitical analysis: Cumulative incidence curves for metastasis were constructed using Fine-Gray competing risks analysis. Penalized Cox univariable and multivariable (MVA) proportional hazards models were performed to evaluate the association of the genomic classifier with metastasis.
Results and limitations: The median follow-up for censored patients was 57 mo. The median time from RP to first postoperative PSA was 1.4 mo. Detectable PSA patients were more likely to have higher adverse pathologic features compared with undetectable PSA patients. On MVA, only genomic high-risk (hazard ratio [HR]: 5.95, 95% confidence interval [CI]: 2.02–19.41, p = 0.001), detectable PSA (HR: 4.26, 95% CI: 1.16–21.8, p = 0.03),

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https://doi.org/10.1016/j.eururo.2017.11.024

and lymph node invasion (HR: 12.2, 95% CI: 2.46–70.7, $p = 0.003$) remained prognostic factors for metastasis. Among detectable PSA patients, the 5-yr metastasis rate was 0.90% for genomic low/intermediate and 18% for genomic high risk ($p < 0.001$). Genomic high risk remained independently prognostic on MVA (HR: 5.61, 95% CI: 1.48–22.7, $p = 0.01$) among detectable PSA patients. C-index for Cancer of the Prostate Risk Assessment Postsurgical score, Gandaglia nomogram, and the genomic classifier plus either Cancer of the Prostate Risk Assessment Postsurgical score or Gandaglia were 0.69, 0.68, and 0.82 or 0.81, respectively. Sample size was a limitation.

Conclusions: Despite patients with a detectable PSA harboring significantly higher rates of aggressive clinicopathologic features, Decipher independently predicts for metastasis. Prospective validation of these findings is warranted and will be collected as part of the ongoing randomized trial NRG GU-002.

Patient summary: Decipher independently predicted metastasis for patients with detectable prostate-specific antigen after prostatectomy.

1. Introduction

Prostate cancer is now the third most common malignancy in men in the USA, with an estimated 160 000 new cases diagnosed annually in 2017 [1]. Radical prostatectomy (RP) is a common form of radical treatment for localized prostate cancer [2]. However, men with high-risk features, including high-grade group, stage T3–4, lymph node (LN) invasion, or positive margins have a >40% chance of recurrence 5–10-yr postoperatively [3]. A subset of these patients will even have immediate evidence of persistent disease and their prostate-specific antigen (PSA) will never become undetectable after surgery. A detectable PSA after RP is a poor prognostic factor, and is often associated with more advanced disease and aggressive clinical course [4]. Functionally, it indicates either persistent local disease or potentially pre-existent metastatic disease. Therefore, treatment of these patients today often is both local (post-RP radiotherapy) and systemic (androgen deprivation therapy [ADT]) [5].

Multiple genomic classifiers have recently been developed and are commercially available to help prognosticate outcomes for men with prostate cancer [6,7]. Decipher, a 22-gene RNA-based genomic classifier, utilizes tissue from the RP specimens to help determine a patients risk of metastasis, independent of clinicopathologic variables [8,9]. However, none of the previous 40+ studies testing Decipher, including the recent individual patient meta-analysis of Decipher, included or specifically examined the genomic classifier in men with persistently detectable PSAs post-RP [10–14]. Given that a subset of men with detectable PSAs postoperatively likely already harbor metastatic disease, it is unclear if a tissue-based biomarker could help in this patient population.

Herein, we conducted the first study to examine the performance of a commonly used prognostic genomic classifier in men with persistently detectable PSAs post-RP to determine if it can independently add prognostic benefit to predict for metastases.

2. Materials and methods

2.1. Study cohort

Institutional Review Board approval was obtained from the participating institutions prior to initiating the current study [15,16]. Patients were included from three centers: MD Anderson Cancer Center, Durham VA Hospital, and Thomas Jefferson University. Patients were required to have undergone RP, sufficient tissue for genomic analysis, and serial PSA measurements post-RP to document undetectable versus persistently detectable PSAs postoperatively. Noedajuvant ADT was not allowed, and only 1% ($N = 4$) had ADT within 3 mo post-RP. A total of 477 men, who underwent RP between 1990 and 2015, met study inclusion criteria and formed the study cohort. None of the patients in the study received neoadjuvant treatment prior to RP. Patients whose PSA level fails to fall to undetectable levels (<0.1 ng/ml) within approximately 8 wk after RP were categorized as detectable PSA group.

2.2. Decipher score

Expression analysis of 22 biomarkers that comprise the commercial Decipher test were extracted and analyzed as previously described [8]. Analyses of the Decipher score were performed using two methods: (1) a continuous score between 0 and 1, and (2) previously established cutpoint scores of 0.45 and 0.60 to categorize patients into low-, intermediate-, and high-risk categories [10].

2.3. Covariables and endpoints

Analyzed variables included whether patients had a detectable or undetectable PSA post-RP (defined by a post-RP PSA within 8 wk of surgery), International Society of Urological Pathology (ISUP) grade (Gleason grade), pathologic T-stage, LN invasion, surgical margin status, Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) risk group, preoperative PSA, use of radiotherapy

Please cite this article in press as: Spratt DE, et al. Performance of a Prostate Cancer Genomic Classifier in Predicting Metastasis in Men with Prostate-specific Antigen Persistence Postprostatectomy. Eur Urol (2017), https://doi.org/10.1016/j.eururo.2017.11.024