Predicting outcome in prostate cancer patients using a multi-signature risk classifier, derived from urinary extracellular vesicles

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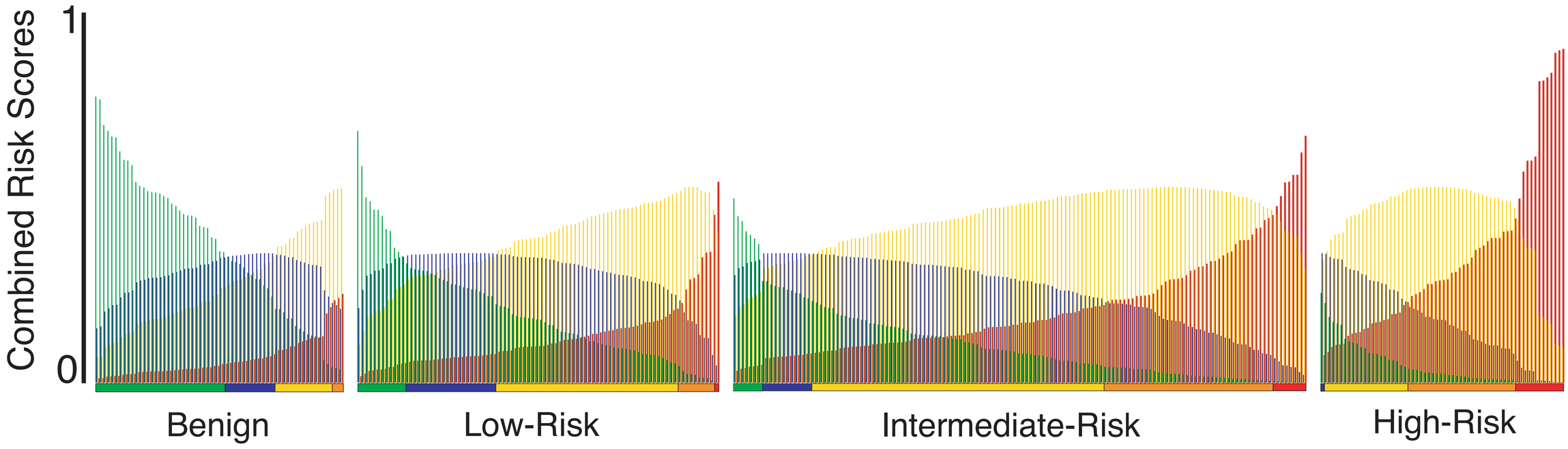

Quick Read:

Question: Can a non-invasive single-sample urine test reveal **both diagnostic and prognostic information** about 537 prostate cancer patients, utilising extracellular vesicle-derived RNA expression patterns?

Findings: A robust, four-risk-signature model identified two groups with differing rates of treatment intervention in active surveillance use (**High Risk HR = 3.7, Low Risk HR = -7.0**) and predicted initial biopsy outcome (**AUC = 0.81**)

Impact: Clinical implementation of this model has the potential to avoid the unnecessary initial biopsy of men and the repeated, invasive follow-up of men on active surveillance with indolent prostate cancer could be drastically reduced, or provide a means for exiting surveillance altogether.

Introduction

Prostate cancer is estimated to be diagnosed in 12% of men, the most commonly diagnosed cancer in men in the UK[1]. However, 5-year survival of men with prostate cancer is very high, and treatment of indolent, clinically "irrelevant" disease has significant side-effects, including incontinence and impotence.

Men diagnosed with lower risk cancer are often placed on active surveillance (AS) programmes, which have proven successful in improving survival rates. Regardless, there is still no formal method for patients on AS to exit these programmes.

Urine represents a suitable medium for non-invasively sampling the prostate[2, 3, 4]. In this vain, we have developed a risk prediction model based on NanoString quantified RNA expression in urinary extracellular vesicles, with the aim to discriminate accurately between men with, and without, clinically significant cancers.

The Movember Cohort:

Patients: 537 men with and without histologically proven cancer with a PSA < 100 ng/mL, collected from urology clinics in the UK, Ireland and USA between 2009 and 2015.

Samples: NanoString extracellular vesicular RNA expression profiles of 167 gene-probes, derived from first-catch post-digital rectal examination urine.

AS Eligibility: Age 50–80, clinical stage T1/T2, PSA < 15 ng/mL, Gs <7 (Gs < 4+3 if age >65), and <50% percent positive biopsy cores.

Progression: PSA velocity >1 ng/mL per year or adverse histology on repeat biopsy, defined as primary G >3 or >50% biopsy cores positive for cancer

Methods:

A continuation-ratio LASSO model was trained on 67% of the data, using D'Amico risk status as an ordinal variable, producing four risk signatures for predicting the probability of normal tissue (R1), D'Amico Low-risk (R2), Intermediate-risk (R3), and High-risk (R4) PCa in a given sample.

This model was applied to the test dataset and to an AS sub-cohort (n = 87) for diagnostic and prognostic evaluation, respectively. ROC-AUC analysis was used to test predicting biopsy outcome, and survival analyses used to prognosticate the progression of patient in the AS cohort.

Results

R4 was able to determine a clinically significant biopsy outcome of D'Amico Intermediate- or High-Risk from a single urine sample, with an **AUC = 0.813 (95% CI: 0.779 - 0.847, Figure 1)**.

A robust R1 threshold dichotomised AS patients in to groups at low and high risk of progression. The two groups had a large difference in time to progression: 60% progression within 5 years of urine sample collection in the poor prognosis group compared to 10% in the good prognosis group ($p < 0.001$, log-rank test, Figure 2).

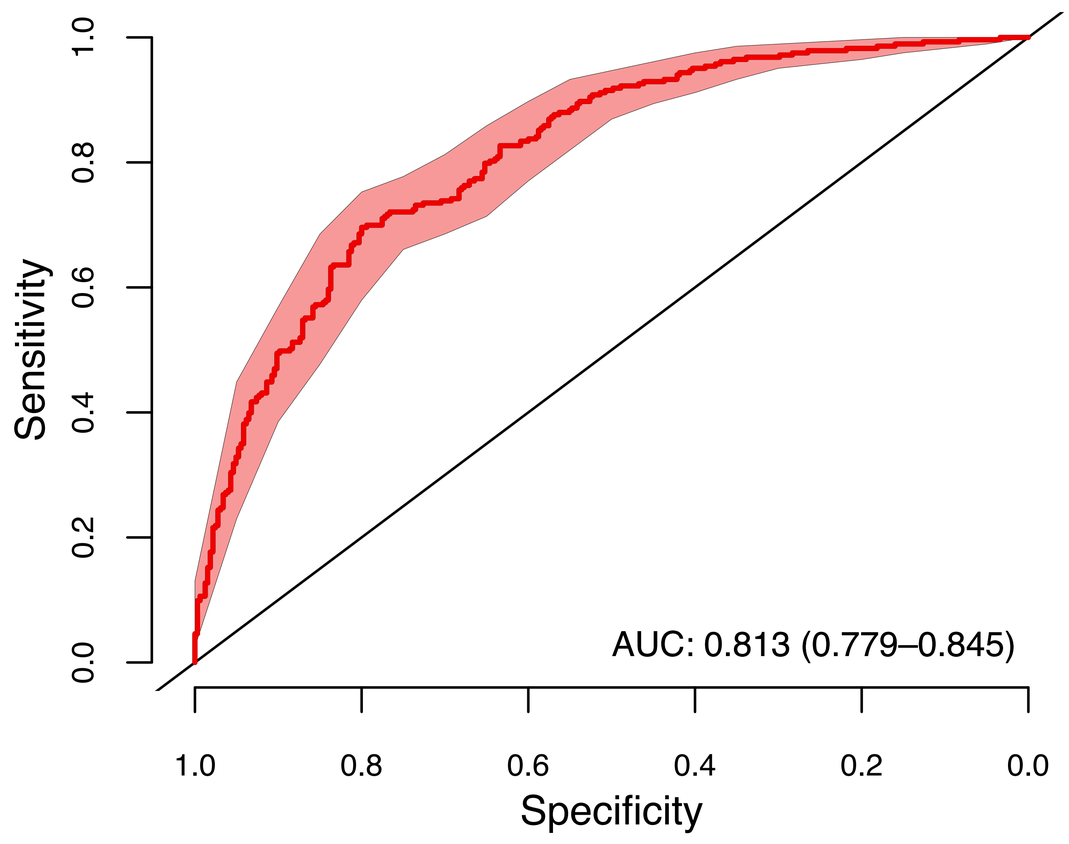

Figure 1: ROC-AUC plot of the ability of R4 to predict the presence of D'Amico Intermediate or High risk cancer on initial biopsy.

Cox proportional hazards models showed significant differences in clinical outcome based on R1 or R4 of patients. The hazard ratio associated with R4 was **3.71 (95% CI: 1.53 to 5.89)**, with the **HR of R1 =-7.03 (95% CI: -12.29 to -1.77)**.

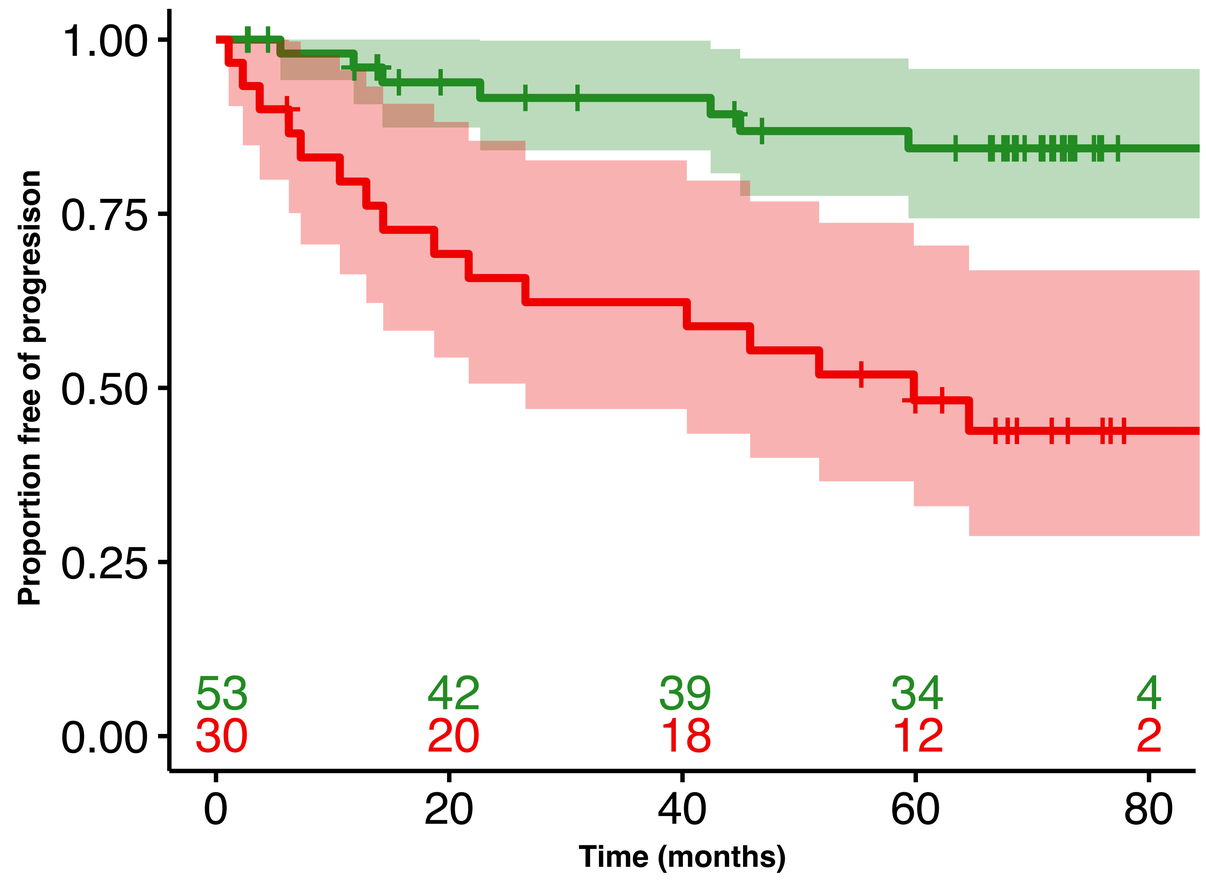

Figure 2: Kaplan-Meier plot of time to disease progression in months from initial urine collection. Colours indicate the dichotomised model thresholds, Green – High R1, Red – Low R1. Numbers above the x-axis indicate the number of patients in each group at risk at the given time intervals.

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