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

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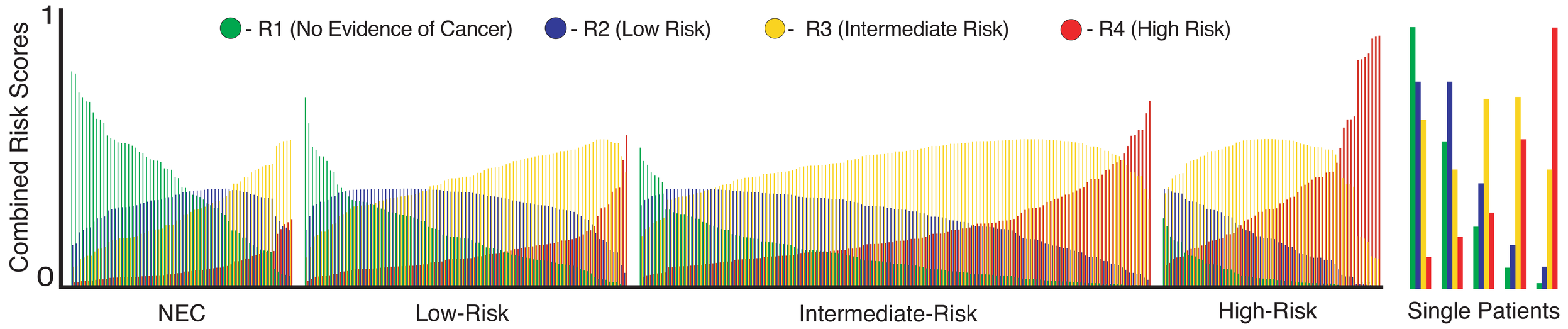

Figure 1: Combined risk profiles of the entire Movember cohort, grouped by D'Amico risk category and ordered by ascending R4 score. Each individual patient has four signatures associated with their sample, detailing the membership probability of their sample to normal tissue (R1 - green), D'Amico Low-risk (R2 - blue), Intermediate-risk (R3 - yellow), and High-risk (R4 - red). Example profiles of individual patients are shown on the right.

Quick Read

Question: Can a non-invasive single-sample urine test reveal **both diagnostic & 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**) & predicted initial biopsy outcome (**AUC = 0.81**)

Impact: Clinical implementation of this model has the potential to **avoid the unnecessary initial biopsy of men** & 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

Clinical problem: To combat the over-treatment of men with indolent prostate cancer, men with D'Amico Low & favourable Intermediate risk cancers are often offered active surveillance (AS) as an option[1]. Involving regular assessment for signs of disease progression, AS has proven successful in reducing unnecessary treatment.But invasive and repeated assessment means elective treatment rates can be higher than 30%[2] and there is no formal method for patients to exit AS.

Rationale: Previous studies established urine as a suitable medium for non-invasive sampling of the prostate[3–6]. In this vein, we have developed a risk prediction model, using NanoString quantified RNA expression from urinary extracellular vesicles, with the aim to discriminate accurately between men with, and without, clinically significant cancers.

The Movember Cohort

Patients & Samples: Post-DRE urine from 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. Extracellular vesicle RNA profiles derived with NanoString. Biopsy information from trans-rectal ultrasound guided needle biopsy.

AS Eligibility & Progression: 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 was defined as 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

Model: Continuation-ratio LASSO regression trained on 67% of the data & treating D'Amico risk status as an ordinal variable. Four risk signatures generated predicted probabilities of normal tissue (R1), D'Amico Low-risk (R2), Intermediate-risk (R3), and High-risk (R4) PCa in a given sample.

Testing: ROC-AUC analysis tested prediction of biopsy outcome in the remaining 33% test dataset. Survival analyses assessed prognostication of disease progression of patient in an AS sub-cohort with long follow-up(n = 87, >5 years).

Results

Prediction of D'Amico Risk & biopsy outcome: There was a strong association with clinical category, appearing to recategorise approximately 15% of samples at either end of each D'Amico risk group (Figure 1). AUC of a clinically significant initial biopsy outcome of D'Amico Intermediate- or High-Risk: **0.813 (95% CI: 0.779 - 0.847, Figure 2)**.

AS Prognostication Two groups, dichotomised by a robust R4 threshold had large differences in time to progression; 60% of those deemed high risk progressed whilst only 10% of low risk patients progressed 5 years from urine sample collection: (Figure 3, median progression 26%). Cox models detailed significant differences in progression; **R4 HR = 3.71 (95% CI: 1.53 to 5.89)**, and **R1 HR =-7.03 (95% CI: -12.29 to -1.77)**.

Conclusion

Clinical implementation of our model for biopsy prediction could reduce the rate of unnecessary initial biopsy, performing similarly to previously published urine tests for clinically significant cancers. However, no other test currently exists to prognosticate AS patients as we have shown. The model has the potential identify men at particular risk of progression, or, more importantly, those who may be safely left alone for up to five years.

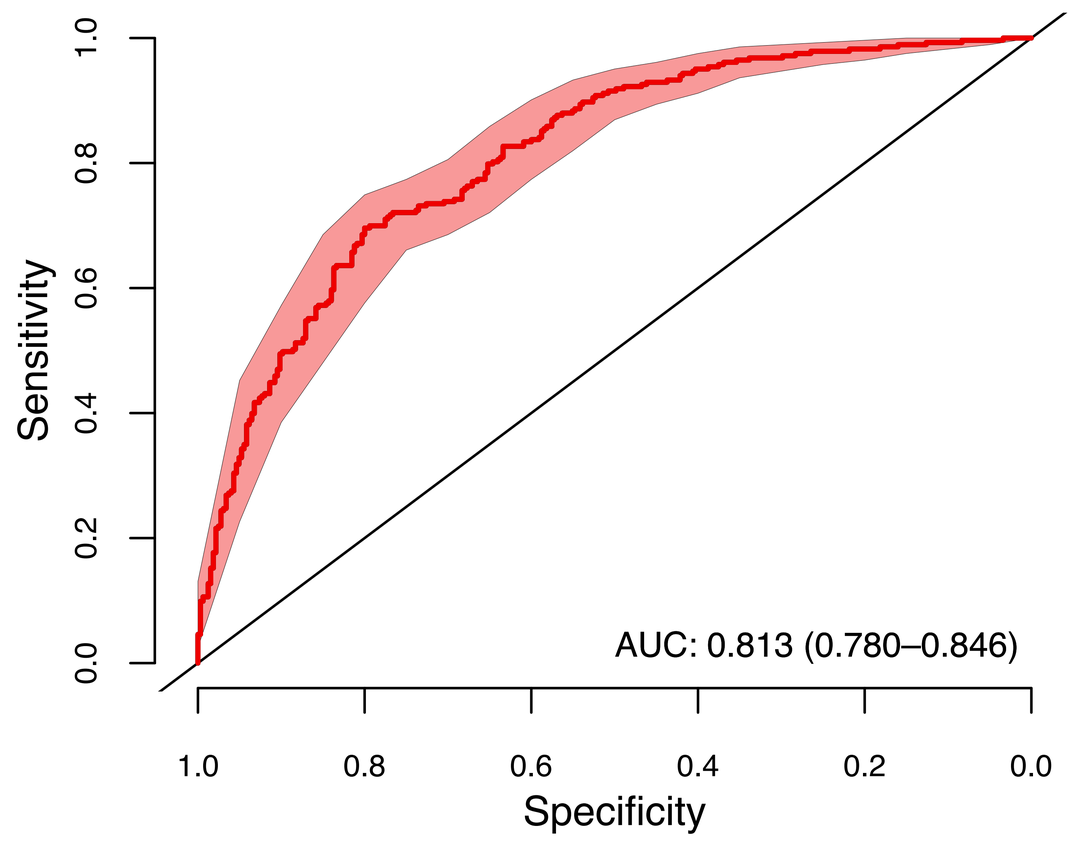

Figure 2: ROC-AUC plot of the ability of R4 to predict the presence of D'Amico Intermediate or High risk cancer on initial biopsy. Shaded region indicates 95% confidence intervals from 2000 bootstrap resamples.

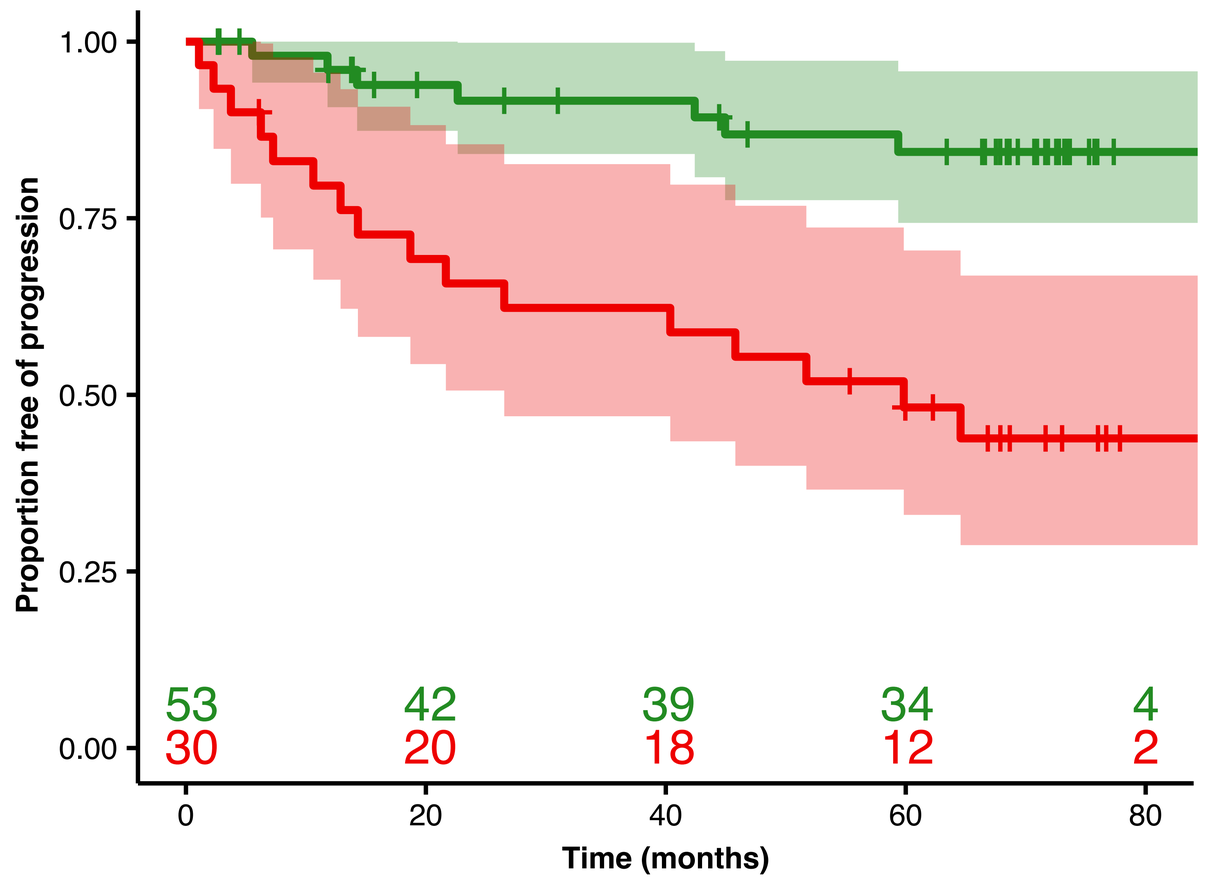

Figure 3: Kaplan-Meier plot of time to disease progression in months from initial urine collection. Colours indicate the dichotomised model thresholds, Green – Low R4, Red – High R4. Numbers above the x-axis indicate the number of patients in each group at risk at the given time intervals. Shaded regions indicate 95% confidence intervals.

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All analyses presented were undertaken in R, with the poster produced through the 'posterdown' package. All of the code & data needed to reproduce this poster exactly as seen can be found at **https://github.com/Shedimus/EACR-Tracking-Cancer**