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Background

Biochemical recurrence (BCR) after prostate radiotherapy is currently detected using static Prostate Specific Antigen (PSA) thresholds. This means failure is only identified after it has occurred., and the opportunity for early intervention is often missed.

PSA dynamics show potential for predicting long-term outcome. Current studies do not account for androgen deprivation therapy (ADT), only including patients who have not received ADT, or after recovery, limiting generalisability.

AIM: To determine whether PSA dynamic trajectories can characterise risk of BCR across heterogeneous radiotherapy techniques and ADT durations across three independent centres.

Methods

Clinical and repeat PSA data collected for patients treated with radical radiotherapy in one of three institutions (n=1,419) with or without ADT. Data formed one training cohort and five test cohorts (Figure 1).

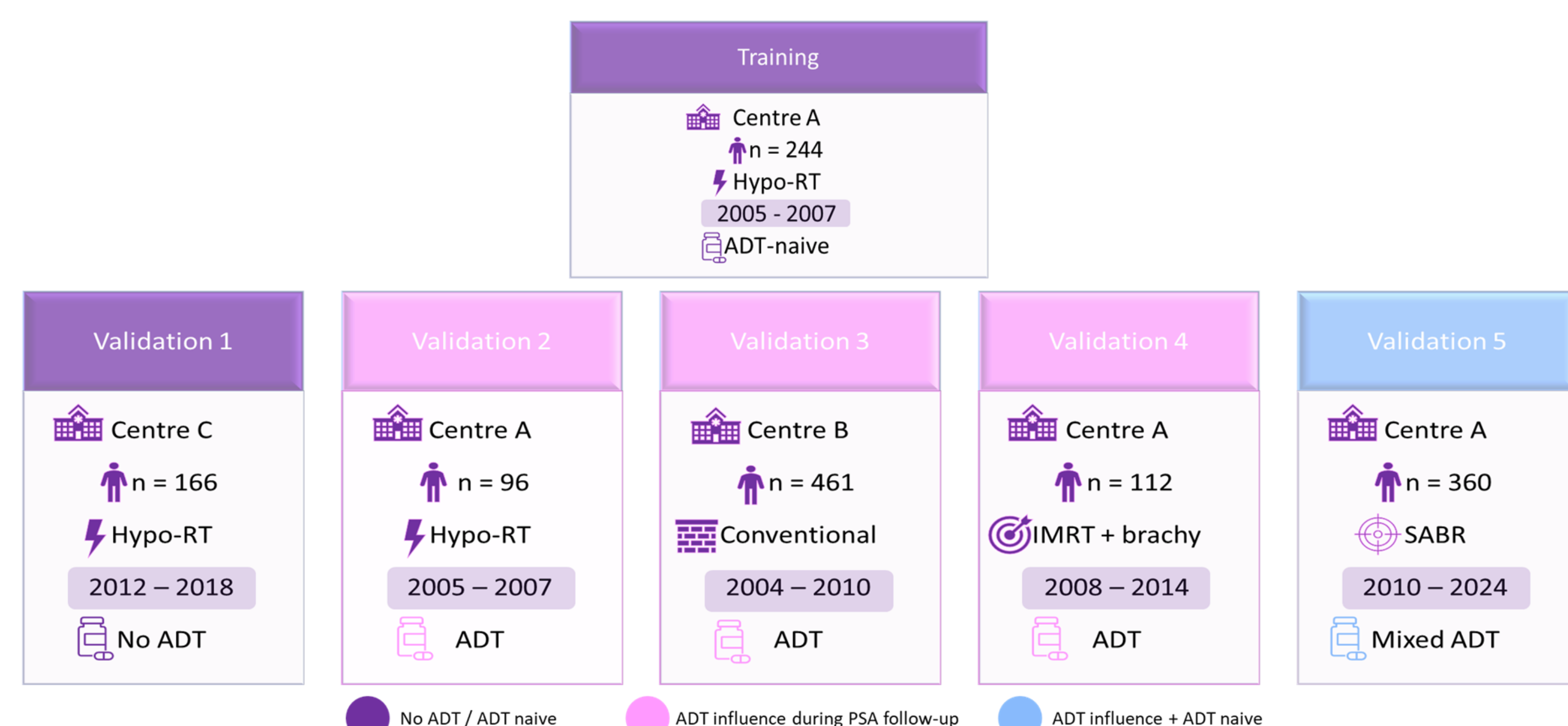


Figure 1: Summary of training and five validation cohorts. Validation cohorts were heterogeneous across treatment techniques, ADT exposures, and patients and disease characteristics.

Gaussian process model (MagmaClustR) trained to define clusters representing PSA trajectory phenotypes (Figure 2A).

Posterior mixture probabilities of each patient calculated to assign patients to a cluster (Figure 2B).

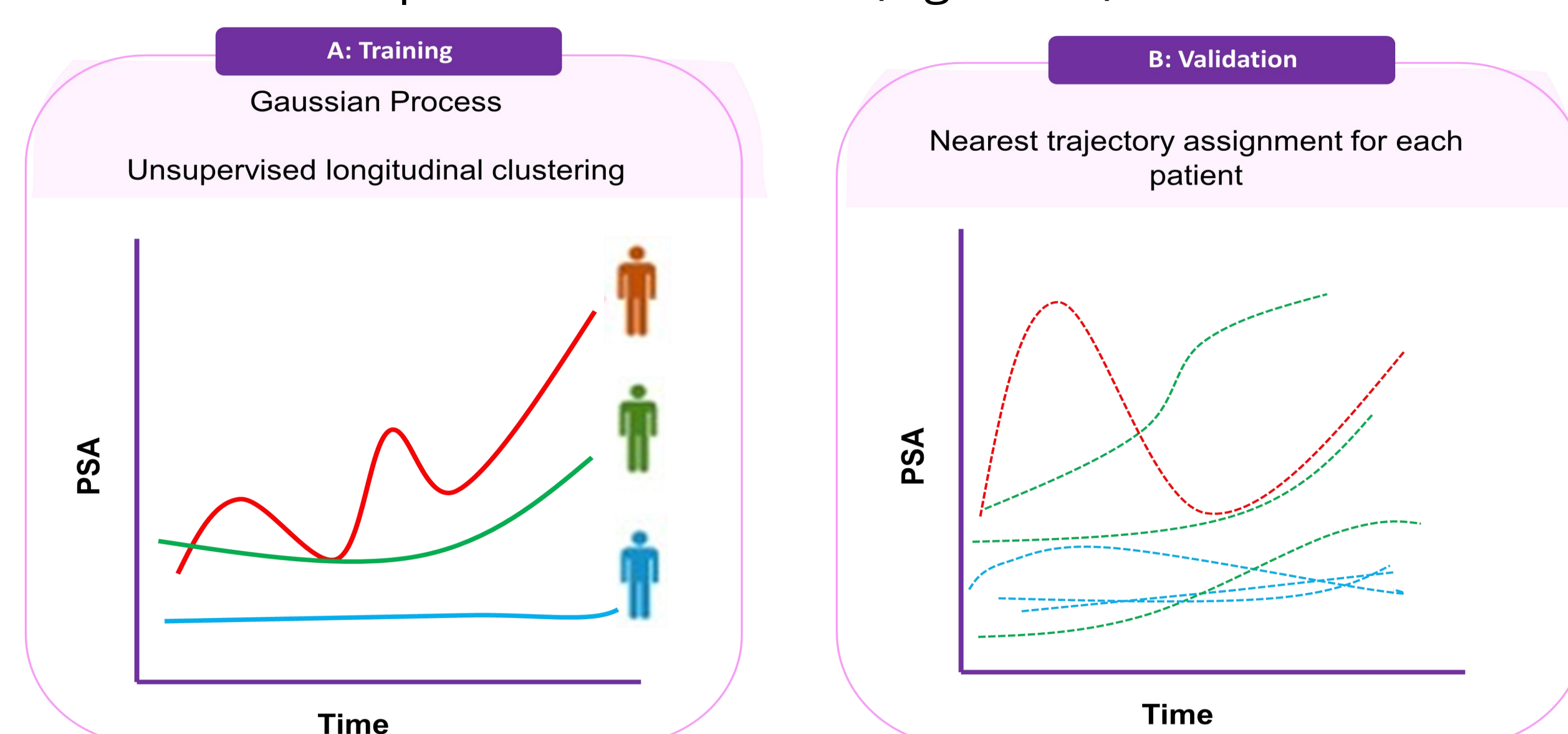


Figure 2: Proto-typical PSA trajectories were defined within the training data (A) and tested in three external datasets with different ADT status (B).

BCR-free survival assessed using Kaplan-Meier analysis, stratified by PSA phenotype. Multivariable Cox proportional hazard models with and without PSA phenotype compared. End-point: BCR (nadir+2ng/ml)

Results

Three reproducible PSA trajectory phenotypes identified: **unstable (K1)**, **low-stable (K2)**, **high-late rising (K3)**.

PSA trajectory phenotype was more prognostic than pre-treatment risk group or ADT prescription (p<0.001, Figure2).

In multi-variable cox regression (adjusted for baseline-risk, ADT, and baseline-PSA, and cohort stratification) PSA trajectory phenotype remained strongly associated with BCR, and improved model performance p<0.001, Figure 3).

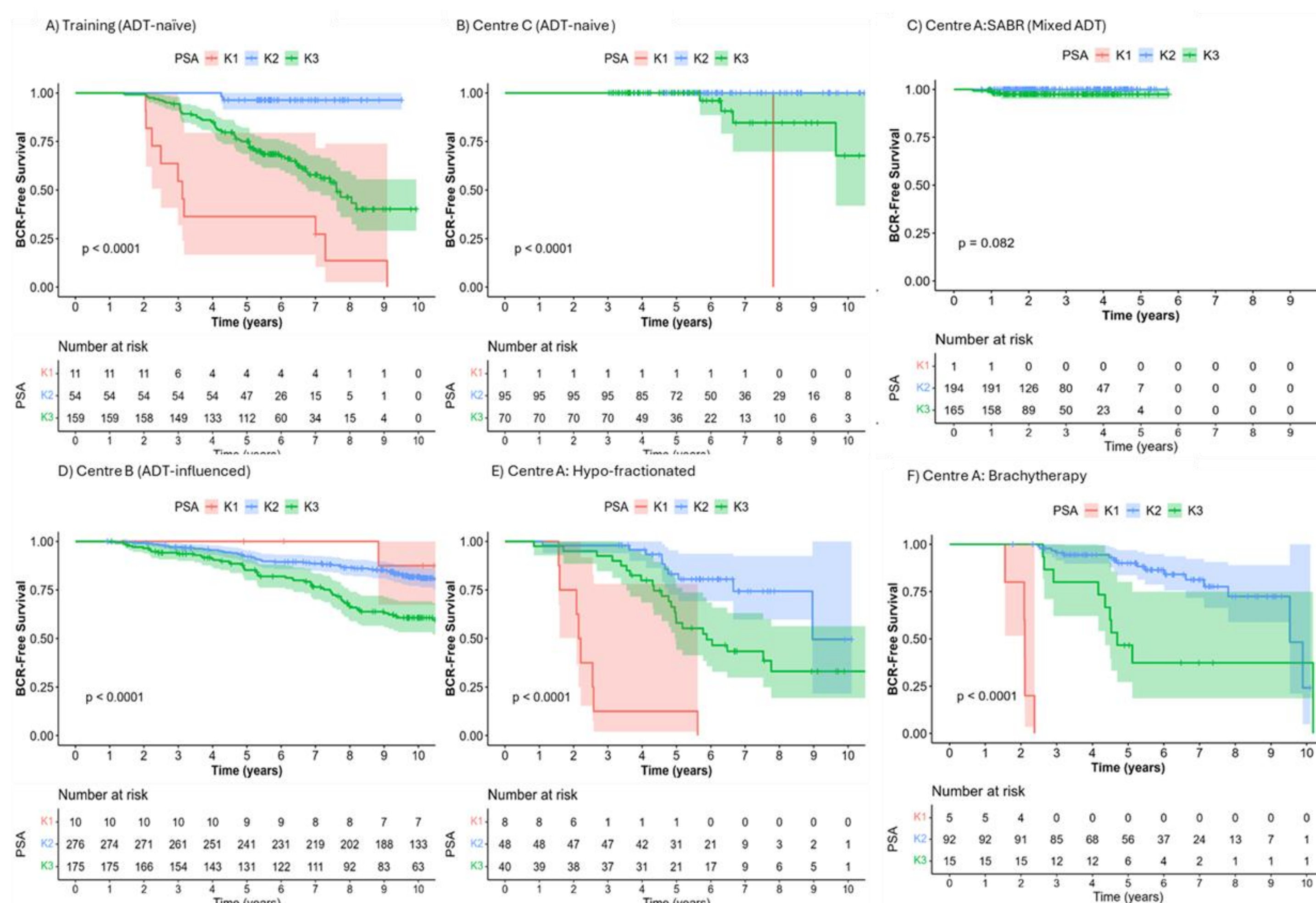


Figure 2: Kaplan-Meier curves showing significant differences in BCR when stratified by proto-typical PSA trajectory, for all ADT variations, radiotherapy techniques and schedules, and institutions.

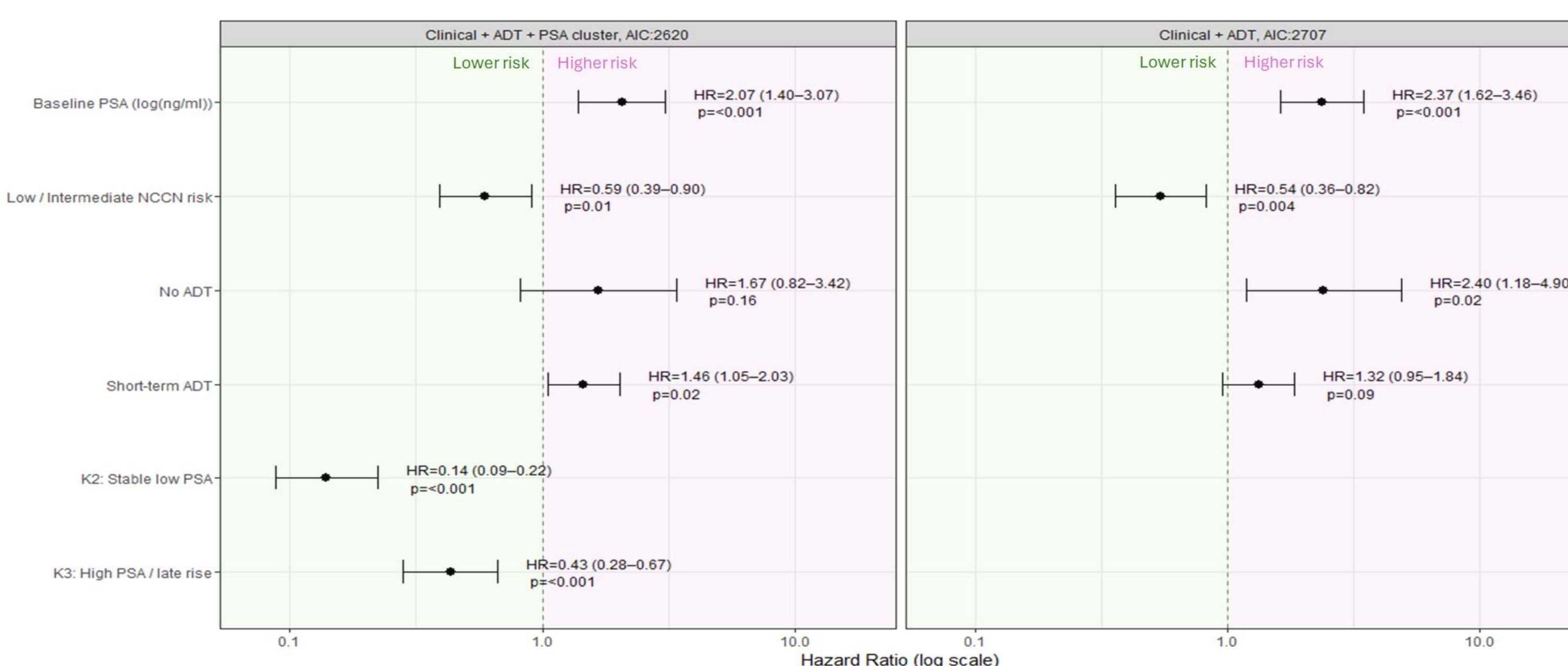


Figure 3: Forest plots for multivariable Cox proportional-hazards analysis for clinical prognostic covariates without and with the addition of follow-up proto-typical PSA trajectory

Take home message

PSA trajectories outperform static PSA thresholds and baseline risk groups in predicting BCR after radiotherapy, even in the presence of ADT.

Unstable PSA identifies patients at highest risk of early failure, while low-stable trajectories indicate excellent long-term control.

Routinely collected data can be used to re-stratify patients after treatment, enabling earlier, more personalised follow-up and salvage intervention.