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Original Research Article

The value of post radiotherapy prostate specific antigen dynamics for prostate cancer risk stratification models

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ABSTRACT

Background and purpose: Risk-stratification at diagnosis of prostate cancer does not always predict risk of biochemical recurrence (BCR). Fully utilizing post-radiotherapy follow-up Prostate Specific Antigen (PSA) data could offer earlier and higher prognostic value than pre-treatment risk-stratification.
We investigate whether PSA dynamics in the first three-years of follow-up can re-stratify risk of treatment failure after radical radiotherapy, allowing for targeted intervention.
Materials and methods: Retrospective analysis of repeat follow-up PSA measurements from men with mixed-risk prostate cancer treated in two separate radical radiotherapy techniques (n = 446, 2005–2007). PSA trajectories were modelled between zero and three-years follow-up using Gaussian Process regression. Models were sampled and clustered using hierarchical clustering to define characteristic post-radiotherapy PSA trajectories.
Kaplan-Meier analysis compared dichotomising by pre-treatment risk-group and characteristic PSA trajectory. Cox proportional-hazard models with and without follow-up PSA information compared using Akaike Information Criterion (AIC).
Results: PSA trajectories were characterized as stable, steady-rise, and unstable. Kaplan-Meier analysis showed that pre-treatment risk-group was not prognostic of BCR ($p > 0.05$), however characteristic PSA trajectory was ($p < 0.001$). PSA trajectory improved multivariable model performance when added to baseline prognostic variables. Unstable PSA had highest BCR.
Results were validated across two cohorts and sensitivity analysis, suggesting results were robust. However, analysis excluded patients with BCR within three-years follow-up due to lack of data.
Conclusion: PSA dynamics within the first three-years of post-radiotherapy follow-up for prostate cancer were more prognostic of BCR than pre-treatment risk-groups, suggesting PSA dynamics could be used to re-stratify BCR risk during early follow-up.

1. Introduction

At diagnosis, prostate cancer patients are stratified into risk-groups according to National Comprehensive Cancer Network (NCCN) guidelines [1], which consider baseline tumour characteristics. Although useful for initial management decisions, they do not always accurately predict the risk of treatment failure, or biochemical recurrence (BCR), after radiotherapy, and around 20 % of patients are misclassified [2].

Early identification that a patient may be at risk of treatment failure is important for disease control and survival. Current routine follow-up for prostate radiotherapy consists of six-monthly prostate specific antigen (PSA) monitoring, regardless of pre-treatment risk-group. Despite regular collection of data, BCR is detected via rises in PSA of ≥2 ng/ml above nadir, which is a patient-defined PSA threshold that can only be detected after the event [3]. Consequently, recurrence can go undetected between PSA tests, and intervention can be delayed by months.

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Fully utilizing routine longitudinal follow-up PSA data may offer additional prognostic value and help re-categorize risk of treatment failure earlier than current methods, allowing for more appropriate follow-up or intervention with salvage treatment. Studies are emerging suggesting that various follow-up PSA parameters, such as PSA doubling time, are associated with treatment outcome [4–8], and that PSA dynamic prediction models offer improved prognostic performance compared to baseline clinical variables alone [4,5]. However, there remains a need for a universal and accessible mechanism that captures dynamic information without any restrictive or arbitrary thresholds to alert clinicians of higher or lower risk of treatment failure earlier than current methods.

We investigated whether short-term follow-up PSA dynamics can re-characterise risk of treatment failure for prostate cancer patients treated with radical radiotherapy.

2. Materials and methods

2.1. Study design

Patient and tumour characteristics, including repeat post-radiotherapy PSA, were collected for 446 mixed risk prostate cancer patients treated with radical radiotherapy at a single academic centre between 2005 and 2007 (research ethics committee reference: 17/NW/0060).

Patients received either 3D-conformal hypo-fractionated radiotherapy (50 Gy in 16 fractions, n = 327), or Intensity Modulated Radiotherapy (IMRT) (37.5 Gy to the prostate in 15 fractions) plus a 15 Gy single fraction High Dose Rate (HDR) brachytherapy boost (n = 119). All patients were treated to a small volume prostate and no prophylactic nodal radiotherapy was given. Treatment schedules and hormone therapy were assigned according to local practice.

To investigate whether BCR could be predicted during early follow-up, only patients who did not experience BCR within three-years follow-up were included. This was chosen as a pragmatic and appropriate balance between the small number of patients who are expected to recur within this period, and the number of patients with sufficient PSA data available[4,5]. All patients had at least two readings. Inclusion criteria is shown in the consort diagram in Supplementary Fig. S1.

Fractionation cohorts were analysed separately. End-point: BCR (PSA nadir + 2 ng/ml) [7].

2.2. PSA modelling and clustering

Log-transformed PSA trajectories were modelled using Gaussian Process regression (python v3.6.5, GPy). Hyper-parameter length-scale was set according to the average time between PSA readings for each patient, and variance reflected PSA measurement error (1 ng/ml)[8]. The model mean, 95 % confidence band, and log-likelihood were calculated, and models were visually inspected to assure a good fit.

To characterize PSA dynamics, mean-centered model means were sampled at regular intervals between zero and three-years (0.1 years) and compared pairwise using the root mean square of the Euclidian distance. The standard deviation (sd) of the Euclidian distance was used to characterize the trajectories by shape [9,10]. First follow-up PSA was included in analysis separately to account for absolute PSA value. Time between end of radiotherapy and first follow-up PSA, which depended on local practice, was also calculated and included in analysis to account for variation between patients.

Hierarchical agglomerative clustering with Ward linkage (python v3.6.5, scikit-learn) was then used to cluster PSA trajectories. Clustering was performed with no prior number of clusters or distance threshold defined, and the optimum number of clusters determined using visual inspection of dendrogram. This method is illustrated in Fig. 1.

2.3. Statistical analysis

Kaplan-Meier analysis was performed, dichotomizing by: (1) pre-treatment risk-group, (2) characteristic PSA trajectory within the first three-years of follow-up.

Multivariable Cox proportional-hazard models with baseline prognostic factors only (age, T-stage, Gleason Grade, ADT duration, baseline-PSA), and then including post-radiotherapy characteristic PSA trajectory, first follow-up PSA, and time between end of radiotherapy and first follow-up PSA, were produced and statistically significant model improvements, defined by the Akaike-information-criterion (AIC), assessed.

To ensure analysis was robust against number of PSA readings during the first three-years of follow-up, analysis was repeated, where number of PSA readings was significantly associated with BCR, using a reduced number of time-points.

All statistical analysis was performed using R (version4.0.2) in RStudio (desktop version 1.3.1073).

3. Results

118/446 patients were excluded due to insufficient PSA follow-up (56/118) or BCR recorded within three-years of follow-up (62/118). Approximately 80 % (94/118) of these patients were high-risk (Supplementary Table 1S, Fig. 2S, $p < 0.001$).

Patient demographics (n = 328) are presented in Table 1. Despite similar BCR between cohorts ($p = 0.47$, Supplementary Fig. 3S), patients treated with brachytherapy boost were higher pre-treatment risk ($p < 0.001$, hypo-fractionated high-risk: 51 %, brachytherapy high-risk: 82 %) and received ADT for approximately four-months longer than hypo-fractionated patients ($p < 0.001$, hypo-fractionated: four-months, brachytherapy: nine-months).

Patients treated with hypo-fractionated radiotherapy had a median of five [2–10] PSA measurements during the three-year period, and brachytherapy patients had a median of six [2–9] (Supplementary Fig. 4S, cohorts: $p < 0.001$, Chi-square).

First follow-up PSA was recorded an average of six-months earlier for

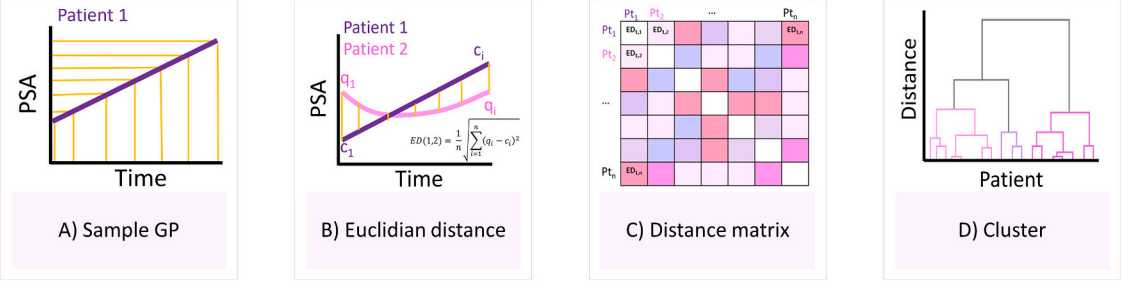

Fig. 1. Flow diagram illustrating the method used to characterise PSA dynamic information. Gaussian Process model means are sampled at regular intervals (A), and compared pairwise using the standard deviation of the Euclidian distance (B). Each distance is entered into a distance matrix (C), which is then used to perform hierarchical clustering (D).

Table 1
Demographics of patients included in analysis.

	Hypo-fractionated (N = 277)	IMRT + Brachytherapy (N = 51)	P-value
Risk			**<0.001**
High	141 (50.9 %)	42 (82.4 %)	
Intermediate or low	136 (49.1 %)	9 (17.6 %)	
Age (years)			
Mean (SD)	68.1 (6.20)	68.8 (5.59)	0.401
T-Stage			**<0.001**
1	107 (38.6 %)	3 (5.9 %)	
2	94 (33.9 %)	25 (49.0 %)	
3	74 (26.7 %)	23 (45.1 %)	
4	1 (0.4 %)	0 (0 %)	
Missing	1 (0.4 %)	0 (0 %)	
Gleason grade			**<0.001**
6	96 (34.7 %)	4 (7.8 %)	
7	135 (48.7 %)	27 (52.9 %)	
8	29 (10.5 %)	9 (17.6 %)	
9	15 (5.4 %)	11 (21.6 %)	
10	1 (0.4 %)	0 (0 %)	
Missing	1 (0.4 %)	0 (0 %)	
ADT duration (months)			
Median [Min, Max]	5.00 [0, 27.0]	9.00 [3.00, 24.0]	**<0.001**
Missing	4 (1.4 %)	1 (2.0 %)	
Base PSA (ng/ml)			
Mean (SD)	18.3 (19.4)	22.4 (18.4)	0.143
BCR	77 (28 %)	13 (25 %)	0.733
Time to Recurrence (years)			
Mean (SD)	6.15 (1.46)	6.33 (2.03)	0.550
Followup time (years)			
Mean (SD)	6.92 (1.68)	7.12 (2.29)	0.563

brachytherapy patients (three-months vs nine-months, $p < 0.001$, Supplementary Fig. 4S). To account for this, time to first PSA was included as an adjustment variable in statistical models. Both cohorts had PSA readings that were, on average, approximately 13-months apart ($p = 0.15$).

Kaplan-Meier analysis in Fig. 2, dichotomized by pre-treatment risk-group, shows no significant difference in recurrence between high- and intermediate/low-risk patients ($p \geq 0.041$).

3.1. PSA trajectories

Trajectories were successfully modelled (log-likelihood [−4.7–5.6], mean: −2.6, sd: 2.3) and clustered (Supplementary Fig. 5S). Three characteristic trajectories were observed: stable, steady-rise, and unstable; Fig. 3, Supplementary Figs. 6-7S.

Unstable PSA fluctuated in both positive and negative directions, and varied the most both over time and between patients (Supplementary Figs. 6S-7S, mean (sd) (log(ng/ml)/year): hypo-fractionated: stable: $3x10^{-4}$(0.1), steady-rise: 0.2(0.1), unstable 0.2(0.3). Brachytherapy: stable $-1x10^{-2}$($-1x10^{-2}$), steady-rise: $-8x10^{-4}$(0.2), unstable: 0.1 (0.01). This was significant for hypo-fractionated patients ($p < 0.001$).

Although higher Gleason grade and longer ADT was correlated with unstable PSA for hypo-fractionated patients ($p \leq 0.001$, Supplementary Fig. 8S), there was no correlation between any baseline demographic and PSA trajectory for those treated with brachytherapy ($p \geq 0.047$, Supplementary 9S). Results show no consistent correlation between any baseline demographic and PSA trajectory.

47/277 hypo-fractionated patients, and 32/51 brachytherapy patients received ADT during some of PSA follow-up (Supplementary Figs. 10S-11S). The number of PSA measurements during ADT was similar across clusters for brachytherapy patients ($p = 0.51$, Supplementary Fig. 10S) (readings during ADT: 0 (n = 19), 1 (n = 16), 2 (n = 10), 3 (n = 3), 4 (n = 2), 5 (n = 1)). However, hypo-fractionated patients with unstable PSA had significantly more measurements during ADT than those with stable or steadily-rising PSA ($p = 0.001$, Supplementary Fig. 11S) (readings during ADT: 0 (n = 230), 1 (n = 31), 2 (n = 10), 3 (n = 4), 4 (n = 2)). All PSA measurements taken during ADT were taken within the first 18-months of follow-up.

Patient numbers and pre-treatment risk in each cluster are summarized in Fig. 3. 167/277 (hypo-fractionated) and 29/51 (brachytherapy) patients had a stable PSA. Of these, 60 (36 %, hypo-fractionated) and 25 (86 %, brachytherapy) were high-risk. Two low-risk patients in each

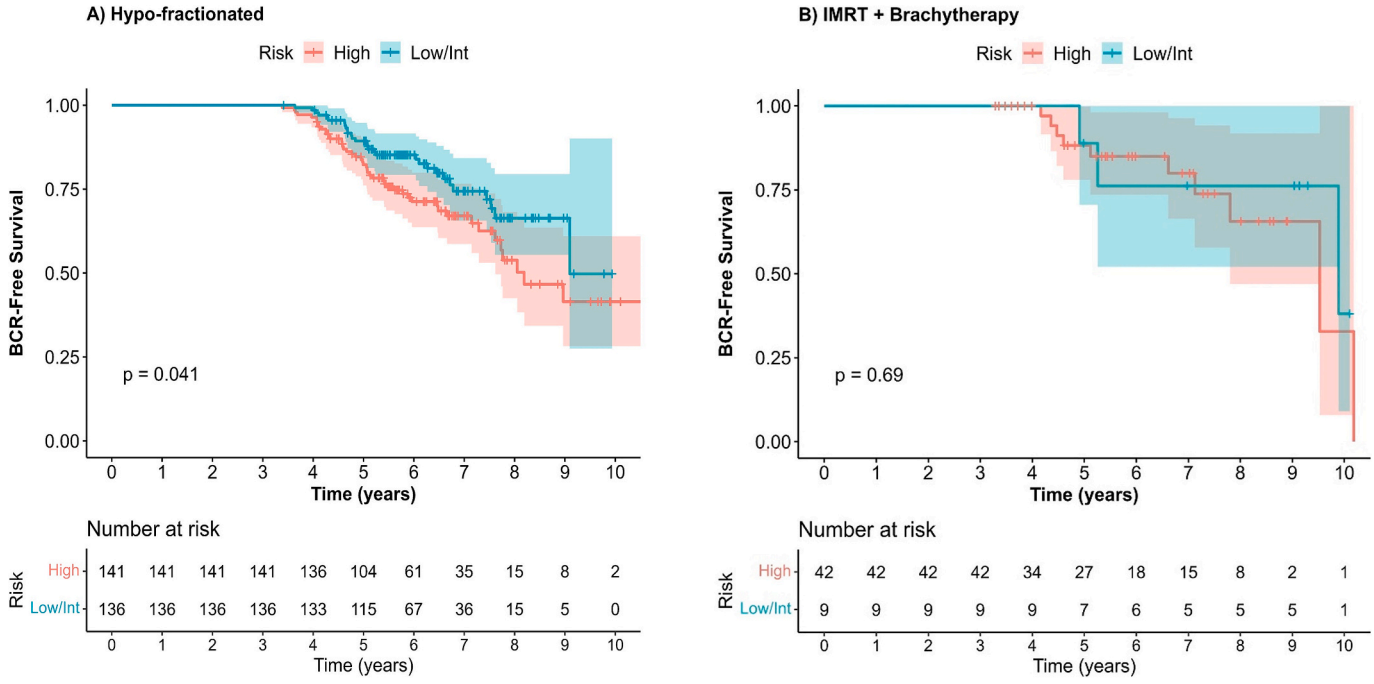

Fig. 2. Kaplan-Meier survival curves for patients treated with (A) conformal hypo-fractionated radiotherapy and (B) IMRT plus a single HDR brachytherapy boost, dichotomised on pre-treatment risk. There was borderline or no difference in recurrence between risk-groups.

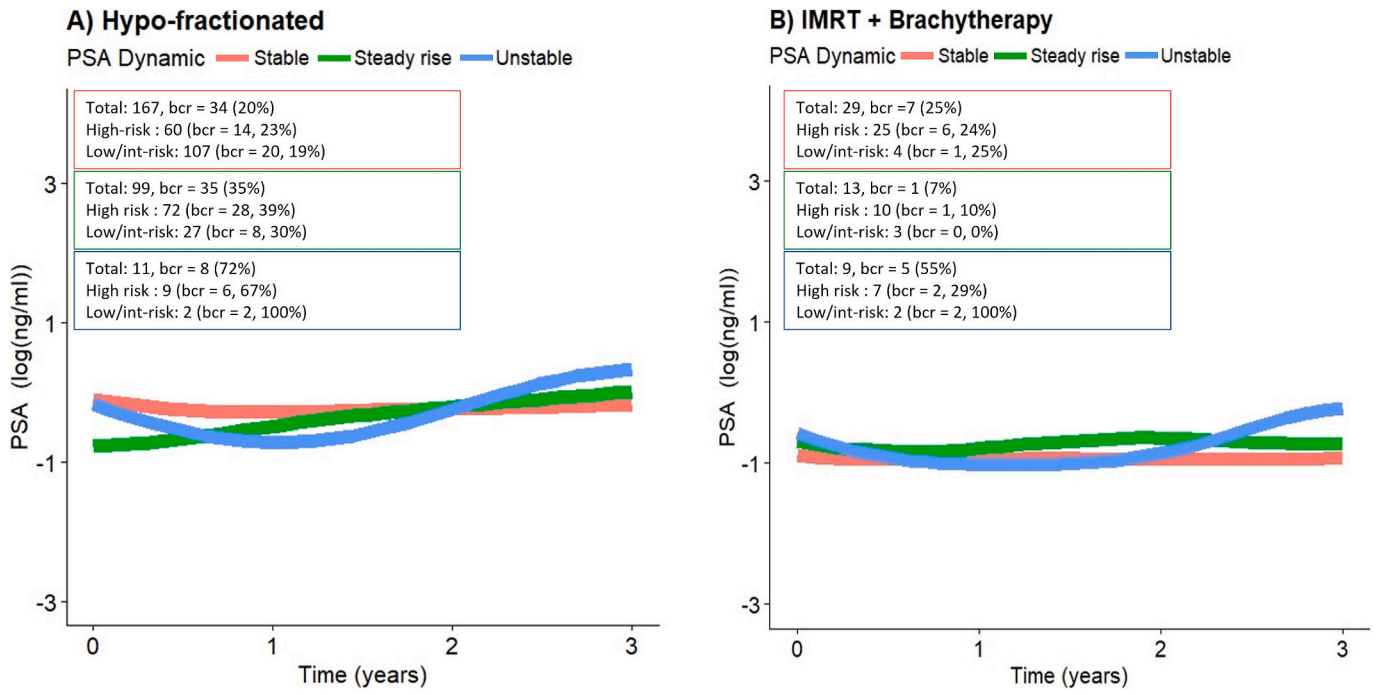

Fig. 3. The average proto-typical PSA trajectory for patients treated with (A) conformal hypo-fractionated radiotherapy and (B) IMRT plus a single HDR brachytherapy boost. A stable and flat, stead rise, and unstable trajectory was observed in both cohorts.

cohort had an unstable PSA, all of which recurred.

For both cohorts, Kaplan-Meier analysis showed significant difference in BCR between PSA trajectories ($p < 0.001$, Fig. 4), with patients with unstable PSA having highest BCR risk regardless of pre-treatment risk. Risk of BCR at five-years was 34–55 % for those with unstable PSA; significantly higher than those with steadily-rising or stable PSA, who had 11–21 % and 2–6 % risk respectively (smaller percentages: brachytherapy cohort).

Hypo-fractionated patients with unstable PSA had more measurements (median: 5 [4 –8]) than patients with stable or steadily-rising PSA. All patients in this cluster had a minimum of four readings, compared to other clusters who had a minimum of two ($p = 0.002$, Supplementary Figs. 10-11S). Most patients in this cohort had at least an annual PSA measurement (Supplementary figure 12S A). To test robustness of results and reflect generalized practice within our dataset, PSA measurements at or closest to the zero-, one-, two-, and three-year time-points were selected for a reduced dataset (Supplementary figure 12S B). Repeating analysis using a reduced data set showed no significant impact on results, indicating that our results are robust against number of PSA measurements (Supplementary Fig. 12S C).

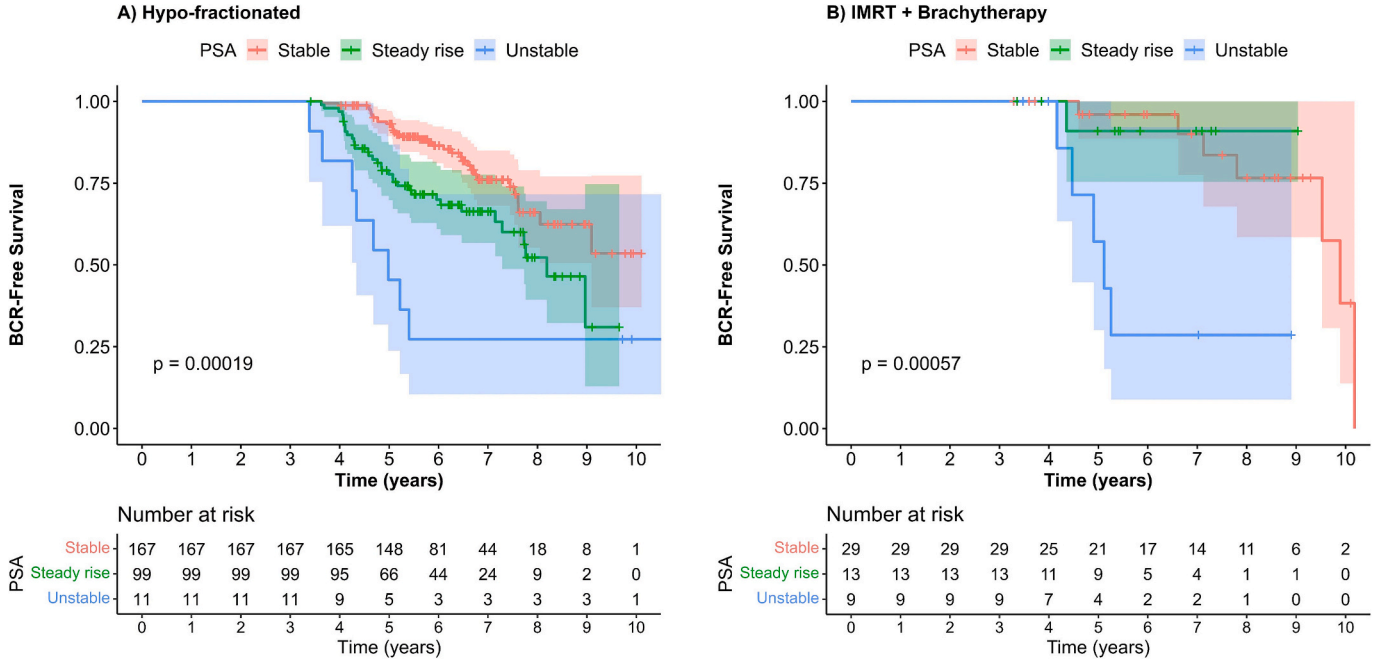

Fig. 4. Kaplan-Meier survival curves for patients treated with (A) conformal hypo-fractionated radiotherapy and (B) IMRT plus a single HDR brachytherapy boost, dichotomised by proto-typical PSA trajectory in the first three years of follow-up. There was significant difference in recurrence between trajectories for both cohorts.

3.2. Predictive risk performance

Table 2 shows multivariable analysis, including baseline prognostic factors only (age, T-stage, Gleason grade, ADT duration, baseline-PSA), and then post-radiotherapy PSA information (first follow-up PSA, time to first follow-up PSA, PSA trajectory). For both cohorts, PSA trajectory was significantly associated with BCR, with a steadily-rising or unstable PSA resulting in worse outcome than stable PSA ($p \leq 0.002$). Higher first follow-up PSA was also significantly associated with BCR for hypo-fractionated patients (HR: 3.44 [1.83, 6.47], $p < 0.001$). Time to first follow-up PSA was not significant for either cohort ($p \geq 0.3$).

For both cohorts the AIC value reduced, indicating improved performance, when follow-up PSA information was included, compared with clinical baseline variables alone ($\Delta AIC \geq 10$, $p < 0.001$). Including first follow-up PSA information improved model performance the most for hypo-fractionated patients (clinical: AIC = 750, first PSA: AIC = 631, PSA trajectory: AIC = 639, all PSA information: AIC = 730, Table 2, Supplementary Table 2S). For brachytherapy patients, including PSA trajectory alone improved model performance the most (clinical: AIC = 77, first PSA: AIC = 80, PSA trajectory: AIC = 66, all PSA information: AIC = 69, Table 2, Supplementary Table 3S).

Univariable analysis, which shows significant association between PSA characteristic and BCR in both cohorts, is presented in Supplementary Table 2S and 3S (Hypo-fractionated: HR: 4.03, $p < 0.001$, IMRT + brachytherapy: HR: 7.6, $p = 0.003$).

4. Discussion

Routine six-monthly PSA monitoring after prostate radiotherapy can miss early signs of failure. We show that short-term PSA dynamics can offer earlier and stronger prediction of long-term prognosis than baseline risk-groups. This is, to the best of our knowledge, the first time that PSA dynamics have been used to re-characterize risk-groups in this way.

Three characteristic PSA trajectories were consistently identified in two cohorts treated at a single center: stable, steady-rise, and unstable (Fig. 3). Rate of change and standard deviation of change was substantially larger for those with unstable PSA, with large fluctuations in both positive and negative directions (Supplementary Fig. 6S and 7S). Regardless of pre-treatment risk, five-year BCR was almost ten-fold higher for these patients than it was for those with stable PSA (34–55 % vs 2–6 %), and three-times higher than those with steadily-rising PSA (11–21 %). All intermediate/low-risk patients with unstable PSA recurred.

Our results suggest that dynamic short-term follow-up PSA could be used to redefine risk-groupings for patients after radiotherapy independently of baseline risk. Given the long timelines needed to assess prostate cancer treatment efficacy, early markers of success or failure are essential. Rather than proposing a PSA cut-off, our findings highlight how post-treatment PSA patterns could inform early physician management decisions. If validated externally and across treatment types, unstable PSA in low/intermediate-risk patients could prompt earlier intervention (e.g. salvage radiotherapy), while stable PSA in high-risk patients may offer reassurance of low failure risk.

As our results were consistent across two cohorts, and robust against number of PSA measurements, which could be due to clinical or non-clinical reasons, we are confident the identified PSA characteristics provide prognostic information compared to current methods. Further validation in external datasets is needed, however, our approach shows promise as a clinical tool to re-stratify risk-groupings and alert clinicians earlier than current methods. This could be further paired with a mechanistic, patient specific, model to forecast the trajectory during early follow-up [4]. Additionally, this methodology could be applied across other treatment modalities (watchful waiting, surgery, chemotherapy, hormone therapy).

Six patients (one hypo-fractionated, five brachytherapy) had two PSA readings. Although this is insufficient to distinguish between a stable and unstable PSA, the aim of this work is to demonstrate how all routinely collected post-radiotherapy PSA data could be utilized differently for prognostic value. Although our results were robust when using a maximum of four readings in our reduced dataset (Supplementary Fig. 12S), less patients are assigned to the steady-rise cluster, and more to the stable or unstable clusters. This could suggest that, whilst the extreme differences are being captured with less readings, more readings are required to pick up on subtleties between trajectories.

We note that BCR risk for brachytherapy patients with steadily-rising PSA was not significant, compared to stable PSA in univariable or multivariable analysis ($p \geq 0.7$, Table 2, Supplementary Table 3S), likely due to limited cohort size. Although all results strongly demonstrate the prognostic value of unstable PSA, the more subtle prognostic impact of a steadily-rising PSA, and the optimum number of PSA measurements required to accurately assign patients to proto-typical PSA trajectories, should be investigated in larger, more regular, cohorts.

We consider PSA over a three-year period. Perhaps a more prevalent question is how quickly a patient can be categorized into a PSA trajectory. Ideally a dynamic model that can be updated as PSA measurements become available, which would allow post-treatment risk to be

Table 2
Multivariable Cox proportional-hazards analysis for clinical prognostic covariates included in the study (age, T-stage, Gleason grade, ADT duration, baseline PSA), and with the addition of follow-up PSA information, for both fractionation cohorts. Characteristic PSA trajectory was significantly associated with BCR for both cohorts. Including dynamic PSA information improved model performance.

	Hypo-fractionated				**IMRT + HDR brachytherapy boost**			
	Multivariable Clinical		**Multivariable Clinical + PSA Dynamics**		**Multivariable Clinical**		**Multivariable Clinical + PSA Dynamics**	
	HR (CI)	**p-value**	**HR (CI)**	**p-value**	**HR (CI)**	**p-value**	**HR (CI)**	**p-value**
Age (years)	0.96 (0.93, 1.00)	**0.050**	0.98 (0.94, 1.03)	0.400	1.00 (0.88, 1.14)	>0.900	0.88 (0.73, 1.07)	0.200
T-stage (≥ T3 reference)								
< T3	0.90 (0.54, 1.50)	>0.700	0.71 (0.42, 1.23)	0.200	0.22 (0.06, 0.83)	**0.025**	0.07 (0.01, 0.44)	**0.004**
Gleason grade (≥ 8 reference)								
< 8	0.69 (0.36, 1.30)	0.300	0.68 (0.33, 1.42)	0.300	0.94 (0.26, 3.47)	>0.900	0.31 (0.05, 2.06)	0.200
ADT duration (months, (≥ 18 months reference))								
< 18 months	1.53 (0.67, 3.49)	0.300	0.80 (0.33, 1.95)	0.600	0.90 (0.19, 4.32)	0.900	0.35 (0.04, 3.01)	0.300
Baseline PSA (log(ng/ml))	3.73 (1.97, 7.10)	**<0.001**	2.93 (1.49, 5.80)	**0.002**	1.22 (0.54, 2.80)	0.600	0.88 (0.31 2.55)	0.800
First post-RT PSA (log(ng/ml))	—	—	3.44 (1.83, 6.47)	**<0.001**	—	—	0.44 (0.07, 2.78)	0.400
Time to first post-RT PSA (years)	—	—	0.75 (0.41, 1.37)	0.300	—	—	1.39 (0.05, 41.4)	0.900
PSA characteristic (Stable reference)								
Steady rise	—	—	3.88 (1.94, 7.73)	**<0.001**	—	—	1.64 (0.10, 27.9)	0.700
Unstable	—	—	1.94 (0.74, 5.08)	0.200	—	—	53.1 (4.54, 620)	**0.002**
[1] HR = Hazard Ratio, CI = Confidence Interval	**AIC = 749.7633**		**AIC = 730.468**		**AIC = 76.51752**		**AIC = 69.40291**	

dynamically updated and personalized follow-up schedules to be defined, should be developed. Parr *et al.* [6] and Roy *et al.* [5] both demonstrate that dynamic PSA information up to two- to three-years could be useful in predicting recurrence, overall survival and prostate cancer-related survival via dynamic prediction joint models. Although robust analysis, this method is complex to interpret and computationally expensive to effectively apply clinically. Our study uses clustering techniques to define sub-groups of patients, observing consistent results in two demographically different cohorts treated with different radiotherapy techniques, where PSA values and dynamics would be expected to differ [11]. Some thought should be given to the clinical accessibility of these models.

More holistically, and of potentially significant clinical impact, would be to determine the earliest timepoint of reliable prediction. Our results indicated that the first PSA after radiotherapy was prognostic. The largest impact on model performance was observed when first follow-up PSA and time to first follow-up PSA was included for hypo-fractionated patients (Table 2, Supplementary Table 2S). No correlations between time to first follow-up PSA and BCR (Table 2), any baseline variable, or risk-group, were observed, perhaps suggesting that follow-up PSA is more prognostic than pre-radiotherapy characteristics, regardless of time since treatment. A recent study reported that PSA six-months after radiotherapy offers prognostic value [12]. As only 64 (23 %) of our patients began follow-up within six-months, we were unable to determine the optimum timepoint for this measurement. To answer this, larger data sets should be acquired, or a prospective study, where more regular PSA measurements are collected earlier during follow-up, should be implemented.

Due to irregular measurements, we could not apply our methodology with follow-up shorter than three-years, leading to the exclusion of 118 patients with significantly higher risk and BCR ($p < 0.001$, Supplementary Table 4S, Fig. 13S). As over half (52 %) experienced BCR within three-years, our findings underscore the importance of routine PSA monitoring in early follow-up. A dynamic model providing prognostic insight within six months of radiotherapy and forecasting future PSA trends [4] would be highly beneficial.

It is important to determine the cause of unstable PSA, and the optimum salvage treatment. Although hypo-fractionated patients with unstable PSA received ADT for longer, and were of higher Gleason grade, which could suggest a pathological connection, we did not observe any correlation between PSA dynamic and baseline characteristic in brachytherapy patients. Our results indicate that PSA dynamic was not acting as a surrogate for pre-treatment demographic or risk stratification, and could not have been predicted based on pre-treatment characteristics.

Unstable PSA was not representative of PSA bounce in our data (whose prognostic value is inconclusive) [13–15]. Tumor heterogeneity, where different regions respond differently to radiotherapy, and inflammation or infection (e.g. prostatitis), could be linked to unstable PSA [16]. We did not have access to toxicity data for the cohorts included in this study, and so could not determine whether radiation-induced side effects could be associated with PSA patterns. Both, however, could be linked to response to radiotherapy dose–response relationship.

Recent studies suggest incidental dose outside of the prostate is related to outcome for some patients [17–19]. These studies employ a method called image-based data mining, or voxel-based analysis, whereby dose in each voxel is linked to an outcome. Risk maps showing the risk of treatment failure (e.g. hazard ratio maps) in different parts of the anatomy, and regions of significant association are determined [20]. We recommend that this method be applied to assess if an association exists between radiotherapy dose and PSA dynamic to identify anatomical regions where under-dosage is associated with unstable PSA, and should be given further consideration during radical or salvage radiotherapy.

Finally, there is strong evidence that hormone therapy affects PSA dynamics up to 12–18 months post-ADT [20]. Unlike other studies that exclude ADT patients or wait for PSA recovery [4–8], we included all PSA data regardless of ADT duration. We found no clear impact of concurrent ADT on PSA trends (Supplementary Figs. 6S–7S, 10S–11S) and ADT duration was not prognostic (Table 2). This suggests PSA during ADT may still be informative. However, without data from cohorts with controlled ADT duration, the impact remains uncertain. Further study across diverse cohorts is needed to clarify this relationship.

In conclusion, PSA dynamics within the first three-years of follow-up were prognostic of treatment failure for patients treated with curative intent radiotherapy treated with two independent fractionation schedules. Further, post radiotherapy PSA dynamics improved performance of predictive models compared with pre-treatment prognostic variables. These results demonstrate the value of short-term follow-up PSA information for re-stratifying risk of treatment failure and provide a mechanism for better targeted follow-up.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2025.100787.

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