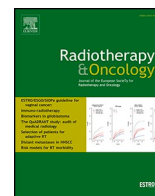




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Original Article



Refining prognostic stratification in salvage radiotherapy for prostate cancer: a retrospective multicenter cohort study using PSMA-PET and machine learning

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ABSTRACT

Background: Salvage radiotherapy (SRT) is the standard treatment for biochemical recurrence (bREC) after radical prostatectomy (RP), yet optimal radiation dose, field size, and the role of advanced imaging like PSMA-PET remain unclear. This study assessed the impact of SRT dose and the prognostic role of PSMA-PET on 2-year biochemical relapse-free survival (bRFS) in patients with localized disease.

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PSMA-PET
 Salvage radiotherapy
 ISUP grade
 Pathological T stage
 Radiotherapy dosing
 Androgen deprivation therapy
 Prognostic factors
 Biochemical relapse-free survival
 Metastasis-free survival
 Therapeutic intensification
 Prophylactic lymph node irradiation

Methods: In this retrospective multicenter study, 255 patients treated with SRT across 11 centers were selected from a database of 1,201 cases. Inclusion criteria included PSA persistence/recurrence (≥ 0.1 ng/mL) post-RP and negative PSMA-PET for nodal or distant metastases. Patients receiving androgen deprivation therapy or with PSA > 0.5 ng/mL pre-SRT were excluded. Prognostic factors were identified using LASSO analysis and modeled with CART analysis. The primary endpoint was 2-year bRFS.

Results: With a median follow-up of 33 months, 2-year bRFS was 88.2 %. Lower pre-SRT PSA (< 0.2 ng/mL), PSMA-PET negativity, longer PSA doubling time, older age, favorable ISUP grades (1–2), and shorter intervals from surgery to bREC were associated with improved bRFS. CART analysis demonstrated that PSMA-PET findings significantly influenced prognosis in patients with PSA levels below 0.2 ng/mL, while PSA-doubling time was predictive in patients with PSA 0.2–0.5 ng/mL. SRT dose and elective nodal irradiation did not significantly affect bRFS.

Conclusions: This study underscores the complexity of prognostic modeling in SRT for prostate cancer, highlighting the value of PSMA-PET and CART for refined risk stratification.

Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies worldwide, posing significant risks of morbidity and mortality [1]. Radical prostatectomy (RP) remains a cornerstone treatment for localized PCa, offering the potential for cure. However, despite its efficacy, approximately 20–40 % of patients experience biochemical recurrence (bREC) during follow-up, underscoring the need for effective post-operative interventions [2].

Salvage radiotherapy (SRT) is the primary treatment for patients with bREC, offering a targeted approach to managing recurrence while minimizing unnecessary radiation exposure [3,4]. Early SRT at low PSA levels < 0.5 ng/ml has largely replaced adjuvant radiotherapy for most patients due to its ability to address recurrence without overtreatment. However, unlike the well-established guidelines for definitive radiotherapy in PCa [5], significant uncertainties persist in the optimal management of SRT. These include questions regarding the ideal radiation dose, the role of concomitant or adjuvant androgen deprivation therapy (ADT), and the need of prophylactic pelvic lymph node irradiation.

Prostate-specific membrane antigen positron emission tomography (PSMA-PET) has emerged as a valuable imaging modality in staging patients with bREC, even at low prostate-specific antigen (PSA) levels [6,7]. PSMA-PET not only detects extra-pelvic disease recurrence, helping identify patients unsuitable for SRT, but also identifies local macroscopic recurrences in the prostatic bed. These findings have implications for optimizing SRT dose escalation strategies in such patients [7].

Despite its clinical utility, there are no standardized guidelines for determining the optimal SRT dose in patients with positive or negative PSMA-PET findings in the prostatic bed. For example, the NCCN guidelines recommend a wide dose range of 64–72 Gy for post-RP radiotherapy in the absence of macroscopic disease [5]. Similarly, the European Society for Radiotherapy and Oncology (ESTRO) guidelines propose doses ranging from 70 to 76 Gy for macroscopic local relapses [8]. This variability highlights the need for further research to define effective and individualized dose regimens.

This study hypothesizes that integrating PSMA-PET imaging into the stratification of patients undergoing SRT after bREC of PCa will enhance prognostic accuracy and inform personalized treatment planning. Specifically, we hypothesized that patients with lower pre-SRT PSA levels (< 0.2 ng/mL) and PSMA-PET negativity will demonstrate superior 2-year biochemical relapse-free survival (bRFS) compared to those with higher PSA levels or PSMA-PET positivity. Additionally, we hypothesize that machine learning models, such as Least Absolute Shrinkage and Selection Operator (LASSO) and classification and regression tree (CART), will identify nuanced interactions among key predictors, such as PSA doubling time (PSA-DT), International Society of Urological Pathology (ISUP) grade, that traditional additive models may overlook.

More specifically, the present study aims to evaluate the impact of

SRT dose on biochemical relapse-free survival (bRFS) in two distinct populations: those with positive and those with negative PSMA-PET findings in the prostatic bed. Additionally, we assess the prognostic significance of PSMA-PET results to develop more precise and effective treatment strategies for managing PCa recurrence.

Materials and methods

Study design and aims

This retrospective multicenter cohort study aims to evaluate the role of PSMA-PET imaging in predicting 2-year bRFS in patients with bREC of PCa treated with SRT. We hypothesize that PSMA-PET imaging will improve prognostic stratification, particularly in patients with lower pre-SRT PSA levels (< 0.5 ng/mL). Additionally, we aim to explore the predictive interactions of clinical and imaging variables using machine learning techniques, hypothesizing that these methods will uncover complex relationships that contribute to more accurate and personalized risk stratification.

Study setting and participants

This study is part of an international project that collected data from 1201 patients treated with SRT across 11 medical centers in 5 countries between August 2013 and June 2020. For this specific analysis a refined cohort of patients was selected based on predefined inclusion and exclusion criteria. Institutional review board approvals were obtained from all participating centers. Patients included in the study had PSA persistence or recurrence (≥ 0.1 ng/mL) following RP. In every included case, a PSMA-PET/CT was performed at the time of bREC or PSA persistence (PSA ≥ 0.1 ng/mL) and prior to radiotherapy planning; this imaging step was a mandatory criterion for study entry. Patients with histologically confirmed lymph node metastases (pN1), PSA levels > 0.5 ng/mL prior to SRT, or nodal or distant disease on PSMA-PET/CT were excluded. Additionally, patients who received ADT either before, during, and after SRT were not included in the analysis.

PSMA-PET Imaging, treatment, and follow-up

Imaging was conducted using standardized protocols with tracers such as ^{68}Ga -PSMA-11 and ^{18}F -PSMA-1007, based on institutional availability. PSMA-PET images were independently reviewed by two experienced nuclear medicine specialists at each participating center to ensure consistency in the interpretation of findings. Discrepancies in interpretation were resolved through consensus discussion. However, formal measures of inter-rater reliability, such as Cohen's kappa or intraclass correlation coefficients, were not assessed. Treatment decisions, including the radiotherapy technique, SRT dose to the prostatic fossa, and the use of elective pelvic lymphatic irradiation, were made at the discretion of treating radiation oncologists, guided by contemporary

standards and PSMA-PET findings. Patients underwent regular follow-up with serum PSA assessments according to institutional protocols. Restaging was performed for patients with suspected bREC based on rising PSA levels after SRT. PSMA-PET imaging, SRT, and follow-up protocols at different centers have been previously reported in detail [9].

Study variables

The analysis considered a comprehensive set of clinical and pathological variables as potential predictors of bRFS, including patient age at bREC, PSA levels before RP and at the start of SRT, PSA persistence after surgery (post-operative PSA > 0.1 ng/mL), surgical resection status (R0 vs R1), pathological tumor stage (pT stage), ISUP grade, PSMA-PET findings, PSA-doubling time (PSA-DT), the interval between RP and bREC, elective nodal irradiation, SRT dose, and the time interval between PSMA-PET and SRT. Because the LASSO analysis requires dichotomized data, we dichotomized the variables as detailed in Table 1. All categorical variables were converted in binary format using the one hot encoding method, where each category is represented by a separate column. Variables with $p < 0.20$ on univariable screening were entered into a LASSO model with five-fold cross-validation to identify the optimal multivariable set. The composite EAU risk classification was deliberately excluded because it is constructed from initial PSA, pT stage and ISUP grade, all of which were analyzed individually; adding the composite alongside its components would have introduced collinearity and jeopardized model stability. Final statistical significance was defined as two-sided $p < 0.05$. bRFS was defined as the time from completion of SRT to documented bREC, defined as 2 consecutive PSA rises > 0.2 ng/mL after SRT.

Variable selection and machine learning modeling

Significant predictors of bRFS were identified using the LASSO method, a supervised algorithm designed to manage multicollinearity and select meaningful variables. These variables were subsequently used to construct a CART model, a decision tree-based machine learning technique capable of identifying conditional relationships and interactions within complex datasets.

In order to improve the generalization ability and avoid overfitting, the model was developed using five-fold cross-validation. The original data was split into five groups, with each subset acting as a test set and the remaining four data subsets acting as training set. Five models were produced, and the classifier's performance index under fivefold cross-validation was determined by averaging the final validation set's classification accuracy. Model performance was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC), providing a robust evaluation of predictive accuracy. All hypothesis tests were two-sided, and a p -value < 0.05 was considered statistically significant. All statistical analyses were performed using the XLSTAT statistical software, version 2024.2.2 (Addinsoft, New York, USA).

Results

After applying the inclusion and exclusion criteria, a cohort of 255 patients was selected and is the subject of this analysis (Fig. 1). During follow-up, no patients died, and 13 developed metastases.

The demographic and clinical characteristics of the study population are summarized in Table 1. The median age at bREC was 69 years (range: 48–87 years). Most patients (87.5 %) did not experience PSA persistence after prostatectomy, while 12.5 % showed PSA levels > 0.1 ng/mL after RP. The majority of patients had pathological stages pT2 (54.1 %) or pT3a (33.7 %), and 40.8 % had ISUP grade group 1–2 disease. The median follow-up duration was 33 months (range: 24–86 months). Elective nodal irradiation was performed in 20.8 % of patients,

Table 1
Patients characteristics.

Characteristic	Number	Percentage
Patients	255	100 %
Age at bREC (years)	Median 69, range 48–87	
Initial PSA (ng/mL)		
0–10	121	47.5 %
10.1–20	43	16.9 %
>20	14	5.5 %
– Unknown	77	30.2 %
PSA level (ng/mL) at the start of salvage RT		
0.1–0.2	105	41.2 %
≥0.21	150	58.8 %
Pathological stage		
pT2	138	54.1 %
pT3a	86	33.7 %
pT3b	27	10.6 %
pT4	1	0.4 %
– Unknown	3	1.2 %
Resection status		
R0	184	72.2 %
R1	71	27.8 %
ISUP grade group		
1–2	104	40.8 %
3	96	37.6 %
4	29	11.4 %
5	26	10.2 %
PSA persistence after prostatectomy (PSA > 0.1)		
No	223	87.5 %
Yes	27	10.6 %
Unknown	5	2.0 %
Follow-up (months)		
Median (range)	33 (24–86)	
Metastases during follow-up		
No	228	89.4 %
Yes	27	10.6 %
bREC during follow-up		
No	186	72.9 %
Yes	69	27.1 %
bREC before 2 years from salvage RT	30	11.8 %
Elective nodal irradiation		
No	184	72.2 %
Yes	53	20.8 %
Unknown	18	7.0 %
Salvage RT dose (Gy)		
<66	26	10.2 %
66–70	119	46.7 %
>70	98	38.4 %
Unknown	12	4.7 %
Time gap PSMA-PET to salvage RT (months)		
<3	114	44.7 %
3–6	25	9.8 %
>6	23	9.0 %
Unknown	63	24.7 %
PSMA-PET findings in prostatic bed		
Negative	131	51.4 %
Positive	124	48.6 %
PSA doubling time (months)		
0–6	67	26.3 %
6.1–12	37	14.5 %
>12	57	22.4 %
Unknown	94	36.9 %
Time gap prostatectomy to bREC (years)		
0–1	102	40.0 %
>1	144	56.5 %
Unknown	9	3.5 %

bREC: Biochemical recurrence; ISUP: International Society of Urological Pathology grade group; PSA: Prostate-Specific Antigen; PSMA-PET: Prostate-Specific Membrane Antigen Positron Emission Tomography; RT: Radiotherapy.

and the median SRT dose was 70 Gy. Positive PSMA-PET findings in the prostatic bed only were recorded in 48.6 % of patients.

Patients with PET positive findings had the following dose stratification: 6.7 %, 40.0 % and 53.3 % of patients were treated with salvage

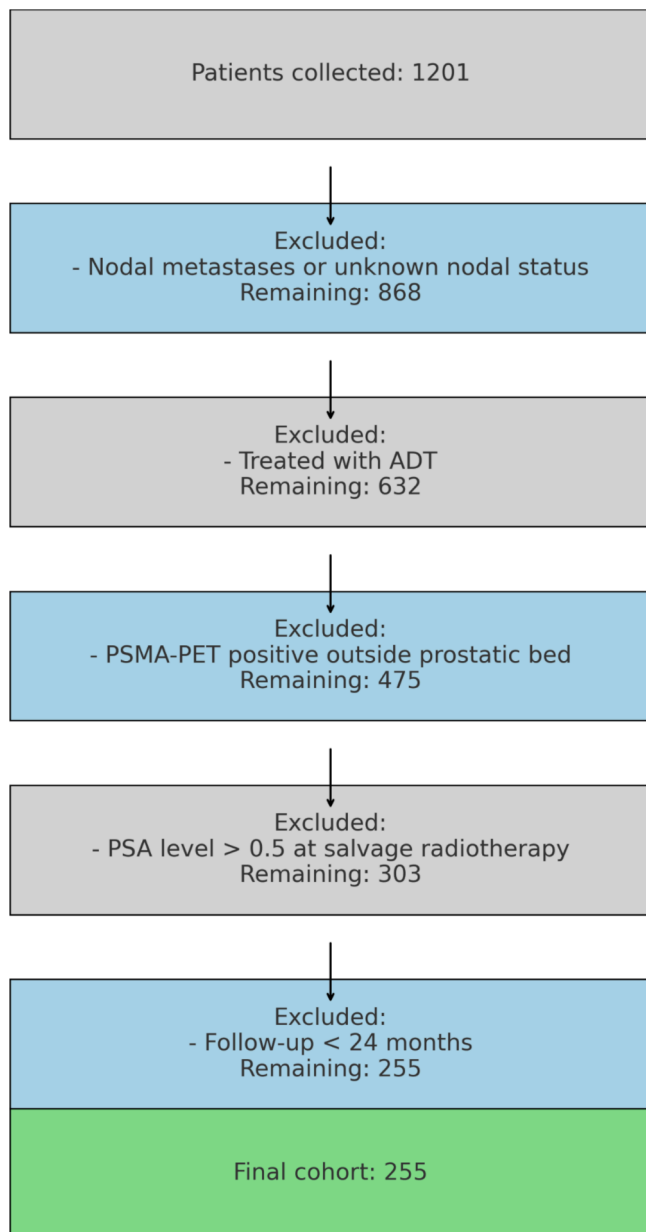


Fig. 1. Flow diagram of patient selection (ADT: Androgen Deprivation Therapy; PSA: prostate specific antigen; PSMA-PET: Prostate-Specific Membrane Antigen Positron Emission Tomography).

RT doses < 66 Gy, 66–70 Gy and > 70 Gy, respectively. On the other side, patients with PET negative findings had the following dose stratification: 14.6 %, 57.7 % and 27.6 % of patients were treated with salvage RT doses < 66 Gy, 66–70 Gy and > 70 Gy, respectively. The differences were statistically significant with $p < 0.001$. The overall 2-year bRFS for the cohort was 88.2 %.

Using the LASSO algorithm, six variables were identified as significantly associated with 2-year bRFS: pre-SRT PSA levels, PSMA-PET findings in the prostatic bed, PSA-DT, time from RP to bREC, ISUP grade, and patient age. The positive or negative association of the six variables with 2y-bRFS was reported in [appendix \(Fig. A1\)](#). These variables were incorporated into a CART model to construct a predictive model. The five-fold cross-validation ROC curve for the training/validation set is shown in [Fig. 2](#), with a mean AUC of 0.823.

The predictive model stratified outcomes based on PSA levels before SRT. Patients with PSA levels of 0.1–0.2 ng/mL had a 2-year bRFS of 96.2 %. Within this group, PSMA-PET findings further stratified

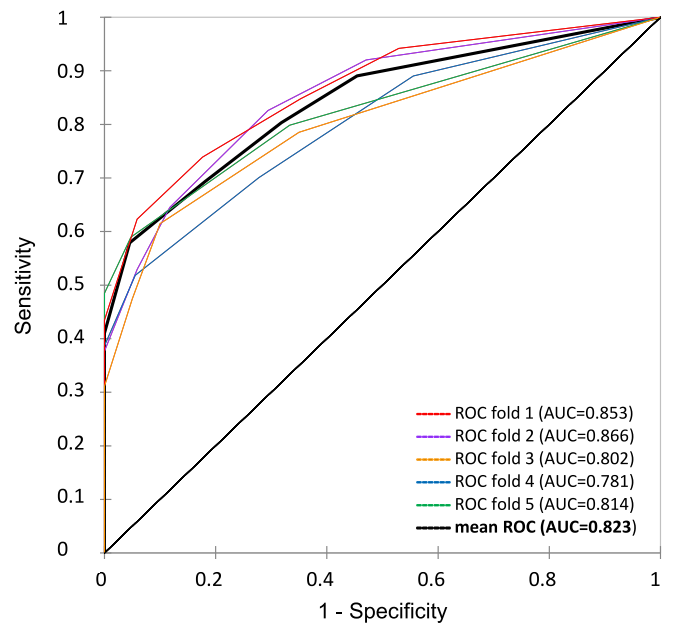


Fig. 2. Five-fold cross-validation receiver operating characteristic (ROC) curves for the training/validation set for 2-year biochemical relapse-free survival (AUC: area under the curve).

outcomes:

- Patients with PSMA-PET positivity in the prostatic bed had a slightly lower 2-year bRFS of 90.5 %. Among these patients, those with a time from RP to bREC < 1 year achieved a 2-year bRFS of 100 %, while those with a longer interval (>1 year) had a reduced 2-year bRFS of 83.3 %.
- Patients with PSMA-PET negativity in the prostatic bed had a 2-year bRFS of 100 %.

In patients with PSA levels of 0.21–0.5 ng/mL, the overall 2-year bRFS was lower, at 82.7 %. PSA-DT was a critical determinant in this subgroup:

- Patients with PSA-DT < 1 year had a 2-year bRFS of 78.1 %. Further stratification by ISUP grade revealed a 2-year bRFS of 86.7 % for ISUP grades 1–2 and 72.5 % for ISUP grades 3–5.
- Patients with PSA-DT > 1 year exhibited improved outcomes, with a 2-year bRFS of 97.2 %. In this subgroup, age further stratified results, with patients aged < 70 years achieving a 2-year bRFS of 93.8 %, while those aged > 70 years reached 100 %.

These findings are visually represented in [Fig. 3](#), highlighting the complex interactions between prognostic factors identified by the CART model.

Discussion

This study evaluated the prognostic role of PSMA-PET and its integration into predictive modeling for bRFS following SRT in PCa patients. Due to the small number of patients who developed metastases (5.1 %), it was not possible to create a predictive model for metastasis-free survival. Using the LASSO algorithm, six key factors influencing 2-year bRFS were identified: pre-SRT PSA levels, PSMA-PET findings, PSA-DT, time from surgery to recurrence, ISUP grade, and patient age. Machine learning models, specifically CART analysis, stratified bRFS based on conditional relationships between these variables, revealing nuanced interactions not captured by traditional prognostic tools. The five-fold cross-validation ROC curve for the training/validation set showed a

PSA level before salvage RT							
0.1-0.2 ng/ml (105 pts)			0.21-0.5 ng/ml (150 pts)				
96.2%			82.7%				
PSMA-PET positivity in the prostate bed			PSA doubling time > 12 months				
No (63 pts)		Yes (42 pts)	No (114 pts)		Yes (36 pts)		
100.0%		90.5%	78.1%		97.2%		
		Time surgery-bREC		ISUP		Age at salvage RT	
		< 1 year (18 pts)	≥ 1 year (24 pts)	1-2 (45 pts)	3-5 (69 pts)	≤ 70 years (16 pts)	> 70 years (20 pts)
		100.0%	83.3%	86.7%	72.5%	93.8%	100.0%

Fig. 3. Predictive model of 2-year biochemical relapse free survival (bREC: biochemical recurrence; ISUP: International Society of Urological Pathology; PSA: prostate specific antigen; PSMA-PET: Prostate-Specific Membrane Antigen Positron Emission Tomography; pts: patients; RT: radiotherapy).

mean AUC of 0.823, demonstrating robust predictive accuracy. This suggests the model potential utility in stratifying patients based on risk, though further validation in independent cohorts is warranted.

Comparison with prior evidence

Uncertainties in the management of SRT persist, particularly regarding optimal radiation dose, treatment field size, and the integration of ADT and advanced imaging techniques such as PSMA-PET. Dose escalation studies, including SAKK-09/10 [10] and the Qi’s et al. trial [11], have demonstrated no significant improvement in bRFS with higher doses (70–72 Gy) compared to conventional dosing (64–66 Gy), while higher doses were associated with increased late toxicity. Our findings, consistent with these trials, revealed no dose-dependent differences in bRFS. However, whether patients with PSMA-PET or multiparametric magnetic resonance imaging-detected macroscopic recurrence could benefit from dose escalation warrants further exploration.

Similarly, the role of elective nodal irradiation remains debated. The SPPORT trial (NRG/RTOG-0534) [12] reported modest benefits of pelvic nodal irradiation combined with ADT, including improved progression-free survival but no significant impact on distant metastases or overall survival. In our study, which included patients with PSA < 0.5 ng/mL and negative PSMA-PET lymph node findings, no significant differences in bRFS were observed between those receiving or not receiving elective nodal irradiation. This may reflect the low risk of lymph node metastases in this carefully selected cohort.

Alignment and contrasts with existing evidence

Many of our findings align with established prognostic factors. High ISUP grades [13], shorter PSA-DT [14], and higher PSA levels at recurrence [14] remain well-documented predictors of poor outcomes. However, our analysis yielded two unexpected findings.

First, patients with a shorter interval (<1 year) between RP and bREC demonstrated better bRFS compared to previously reported trends [15]. This result was observed in a small subgroup of 42 patients with unique characteristics: PSA < 0.2 ng/mL and positive PSMA-PET

findings in the prostatic bed. These findings highlight the potential for unique biological or clinical characteristics that differentiate this uncommon subgroup, underscoring the need for further investigation.

Second, older patients with PSA levels of 0.2–0.5 ng/mL and a PSA-DT > 12 months experienced better outcomes, contrasting with studies that associate older age with worse prognosis [16]. This discrepancy may be attributed to the standardized treatment across age groups in our study, specifically the absence of ADT, whereas older patients in other cohorts often receive less aggressive therapy, likely influenced by comorbidities or reduced functional status. [16].

A key finding of this study was the significant impact of pre-SRT PSA levels on bRFS. Patients with PSA < 0.2 ng/mL exhibited a 13.5 % improvement in 2y-bRFS compared to those with PSA 0.2–0.5 ng/mL. These results support current guidelines advocating for the initiation of SRT at early PSA elevations, without waiting for the traditionally used specific cut-off of 0.2 ng/mL to define recurrence [15].

Strengths and unique insights

Compared to earlier studies published by our group, this analysis focused on a more homogeneous cohort of patients with PSA ≤ 0.5 ng/mL, negative nodal/distant findings, and, if recurrences were present, they were confined to the prostatic bed as identified by PSMA-PET. Previous studies employing a random survival forest (RSF) model [17] or nomogram-based approaches [9] included broader populations with more heterogeneous characteristics, such as nodal or distant recurrences. The inclusion of such variability may mask nuanced prognostic relationships, which our focused approach effectively uncovered.

Additionally, while earlier studies suggested potential benefits of higher SRT doses [18] or nodal irradiation [12], our findings did not replicate these associations, likely reflecting the low-risk nature of our cohort. CART analysis further highlighted unique interactions, such as the influence of PSMA-PET positivity being significant only in patients with PSA < 0.2 ng/mL and the impact of PSA-DT being confined to patients with PSA levels of 0.2–0.5 ng/mL. These findings underscore the limitations of traditional additive prognostic models, emphasizing the need for tailored approaches to prognostic stratification.

Limitations and future directions

This study has several limitations. The small sample size restricted the scope of analyses, particularly subgroup analyses, as the LASSO model requirement for dichotomous endpoints further narrowed the cohort to patients with > 2 years of follow-up. In addition, in the subgroup with pre-SRT PSA < 0.2 ng/mL only 4 of 105 patients experienced bREC within 24 months; consequently, the corresponding risk estimates should be interpreted with extreme caution, as they may reflect random variation rather than true biological differences. These exploratory findings therefore require confirmation in larger, prospectively accrued cohorts with longer follow-up. Missing data for variables such as initial PSA levels, pathological stage, and PSA doubling time, categorized as 'unknown' may have introduced bias or reduced analytical power. The analysis was also limited to biochemical outcomes due to the low incidence of metastasis or survival-related events, underscoring the need for longer follow-up and larger cohorts.

The study design and inclusion criteria may have introduced selection bias, as excluding patients with pre-SRT PSA > 0.5 ng/mL or those receiving ADT likely overrepresented low-risk patients with favorable prognoses, potentially inflating bRFS rates. Variability in PSMA-PET imaging protocols and interpretation across institutions, without formal inter-rater reliability assessments, may have affected reproducibility. Moreover, the physiological excretion of PSMA-ligands within the urine is a well-known limitation for PSMA PET imaging of prostatic bed. Additionally, the retrospective, multicenter design introduces inherent biases, including variability in data collection, treatment approaches, and reliance on historical records, which could influence outcomes.

Furthermore, while our findings support early initiation of SRT at PSA levels below 0.2 ng/mL, it is important to contextualize this in light of the very low event rate (<4%) observed in this subgroup. Although none of the included patients received treatment at PSA < 0.1 ng/mL, the risk of overtreatment remains a concern when intervening at such early stages, particularly in patients with favorable disease biology. The use of 2-year bRFS as an endpoint, while useful for early prognostication, may not fully reflect clinically meaningful outcomes such as metastasis-free or overall survival. As such, these results should not be extrapolated to broader clinical practice without caution. Extended follow-up and independent validation will be essential to determine whether early bRFS reliably predicts long-term benefits and to refine treatment thresholds that avoid unnecessary interventions.

Finally, the short follow-up period limits the generalizability of the predictive model to long-term bRFS. While sensitivity analyses could provide insights, the small sample size and complexity of subgroups precluded their feasibility, as such analyses risk overfitting or unreliable results due to insufficient statistical power.

Despite these limitations, efforts were made to minimize bias by applying uniform inclusion criteria across all centers and using objective machine learning methods to analyze prognostic variables. Particularly, the robustness of the findings is supported by the use of LASSO and CART methodologies, which inherently minimize overfitting and optimize variable selection.

Future studies with larger, prospective cohorts are needed to validate these findings and explore the stability of subgroup-specific outcomes through robust sensitivity analyses. Furthermore, other analyses should integrate genomic classifiers, such as Decipher, with pre-SRT PSA levels to further refine patient selection for ADT and intensified treatments [19]. Additionally, combining molecular imaging insights with novel fractionation techniques and long-term follow-up could optimize SRT strategies while balancing oncologic efficacy with toxicity [20,21].

Conclusion

This study highlights the prognostic significance of PSMA-PET imaging and key clinical factors, including pre-SRT PSA levels, PSA-DT,

and ISUP grade, in predicting bRFS following SRT for PCa. Patients with lower PSA levels (<0.2 ng/mL), PSMA-PET negativity, longer PSA-DT, and favorable tumor characteristics demonstrated superior outcomes, emphasizing the importance of early intervention and tailored patient selection.

While no dose-dependent differences in bRFS were observed, our findings reinforce the complexity of prognostic modeling in SRT. The integration of PSMA-PET findings into machine learning models allowed for nuanced risk stratification, underscoring the limitations of traditional additive prognostic tools. These results suggest that a personalized approach to SRT planning, accounting for the conditional interplay between clinical and imaging variables, may optimize outcomes. Although our analysis did not show a statistically significant benefit from dose escalation, we recognize that the study population was at relatively low risk and that 2-year bRFS is an early surrogate endpoint. Consistent with the ESTRO-ACROP consensus guidance, a focal boost (≥ 74 Gy EQD₂ or SBRT) to PSMA-PET-positive macroscopic disease in the prostatic bed remains a reasonable option provided organ-at-risk constraints are respected (8). Conversely, our CART analysis delineated a subset with pre-SRT PSA 0.21–0.50 ng/mL, PSA-DT < 12 months and ISUP 3–5 who carry a > 25 % risk of early biochemical failure. For these men, short-course ADT concomitant with SRT, or inclusion in trials evaluating systemic or radiotherapy intensification, should be considered.

Finally, the study retrospective design, small sample size, and short follow-up period limit the generalizability of the findings, particularly for long-term outcomes. Larger, prospective studies with longer follow-up are needed to validate these observations and explore the potential benefits of integrating genomic classifiers, advanced imaging modalities, and novel radiotherapy techniques into SRT strategies.

Institutional Review Board Statement: the study was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethics Committee of the participating institutions.

Informed Consent Statement: informed consent was obtained from all subjects involved in the study.

Data Availability Statement: data supporting the reported results will be made available on reasonable request.

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CRedit authorship contribution statement

Federica Medici: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization. **Daniel M. Aebersold:** Writing – review & editing, Validation, Data curation. **Jozefina Casuscelli:** Writing – review & editing, Validation, Data curation. **Louise Emmett:** Writing – review & editing, Validation, Data curation. **Stefano Fanti:** Writing – review & editing, Validation, Data curation. **Andrea Farolfi:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Matthias Guckenberger:** Writing – review & editing, Validation, Data curation. **George Hruby:** Writing – review & editing, Validation, Data curation. **Stefan A. Koerber:** Writing – review & editing, Validation, Data curation. **Stephanie A. Thoma:** Writing – review & editing, Validation, Data curation. **Jan C. Peeken:** Writing – review & editing, Validation, Data curation. **Paul Rogowski:** Writing – review & editing, Validation, Data curation. **Sophia Scharl:** Writing – review & editing, Validation, Data curation. **Mohamed Shelan:** Writing – review & editing, Validation, Data curation. **Simon K.B. Spohn:** Writing – review & editing, Visualization, Data curation. **Iosif Strouthos:** Writing – review & editing, Visualization, Data curation. **Marco Vogel:** Writing – review & editing, Validation, Data curation. **Thomas Wiegel:** Writing – review & editing, Validation, Data curation. **Constantinos Zamboglou:** Writing – review & editing, Writing – original draft, Validation, Supervision,

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2025.111113>.

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