Original Study

Penalized-Survival Nomogram Predicts 5-Year Metastasis-Free Survival After Salvage Radiotherapy for Postprostatectomy Patients: A Multicenter Study

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Abstract

We retrospectively analyzed 1,720 men from 15 European centers receiving salvage radiotherapy for biochemical recurrence after prostatectomy. Machine-learning generated a nomogram predicting 5-year distant-metastasis-free survival, achieving an external C-index of 0.70. Advanced pT stage, ISUP 4/5, and early SRT were independent risk factors. The model enables individualized surveillance and treatment intensification for high-risk patients.

Background/Aim: Salvage radiotherapy (SRT) is a key treatment for biochemical recurrence (BCR) after radical prostatectomy (RP), yet a significant proportion of patients progress to distant metastasis. This multicenter retrospective study aimed to analyze a series of patients who underwent SRT and to develop a predictive nomogram for 5-year-distant-metastasis-free survival (DMFS). **Material and Methods:** Data were collected from 15 European centers from June 1, 2022, to September 30, 2024. We included SRT patients due to BCR, following RP and no evidence of distant metastases on imaging. A penalized-survival nomogram was developed and internally validated; external validation was performed using data from the largest center. Patients were stratified into low-, intermediate-, and high-risk groups based on tertiles of the predicted risk score distribution. **Results:** Data from 1,720 SRT patients were analyzed. BCR after SRT occurred in 620 (37%) patients, while clinical recurrence in 494 (30%) patients. Distant metastases were

Abbreviation: ADT, androgen deprivation therapy; BCR, biochemical recurrence; BRFS, biochemical recurrence-free survival; CI, confidence interval; CRFS, clinical recurrence-free survival; CTCAE, common terminology criteria for adverse events; DMFS, distant metastasis-free survival; GI, gastrointestinal; GU, genitourinary; HR, hazard ratio; IQR, interquartile range; ISUP, international society of urological pathology; KM, Kaplan-Meier; MRI, magnetic resonance imaging; PET, positron emission tomography; PCa, prostate cancer; PD, progressive disease; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RTOG, radiation therapy oncology group; SRT, salvage radiotherapy; tAUC, time-dependent area under the curve; WB, whole body.

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diagnosed in 228 patients (13%). The 2- and 5- years DMFS rates were 93% (95% CI, 92%-95%) and 84% (95% CI, 81%-86%), respectively. Multivariate analysis identified pT3/pT4 stage (HR 1.54 [95% CI, 1.13-2.13], $P < .01$), ISUP grade group 4/5 (HR 1.75 [95% CI, 1.30-2.35], $P < .01$), and SRT <12 months from surgery (HR 1.49 [95% CI, 1.07-2.09], $P = .02$) as independent predictors of DM. The nomogram achieved a C-index of 0.70 in external validation. Stratification into risk groups showed significant differences in DMFS ($P < .01$). **Conclusions:** This externally validated nomogram provides a practical tool for predicting 5-year DMFS in patients undergoing SRT. It enables personalized risk assessment, guiding intensified surveillance and treatment for high-risk patients.

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Keywords: Adaptive elastic-net Cox, Distant metastasis, Machine-learning, Prostate cancer, Prognosis

Introduction

Prostate cancer (PCa) is the second most common malignancy affecting men worldwide,[1] significantly contributing to global morbidity and mortality. Radical prostatectomy (RP) is a fundamental curative treatment for localized PCa and, in recent decades, efforts have been made to advance the employed techniques.[2]

Nevertheless, a significant proportion of patients experience biochemical recurrence (BCR) at least 6 months following surgery.[3] While the timing of BCR does not markedly affect mortality in low-risk patients, those with unfavorable disease characteristics who exhibit early recurrence face an increased risk of mortality.[4] In this setting, clinicians must navigate the delicate balance between mitigating the risk of metastatic progression and avoiding overtreatment that could lead to unnecessary toxicity. The European Association of Urology (EAU) stratified the patients experiencing BCR leading to the development of 2 risk classes: low risk (Gleason score <8 and PSA doubling time [PSADT] >12 mo) versus high-risk (Gleason score ≥8 or PSADT ≤12 mo).[5] However, these factors may not sufficiently capture the complex biological behavior of prostate cancer, leading to suboptimal patient management.

More recently, advanced imaging techniques, such as prostate-specific membrane antigen positron emission tomography (PSMA PET) and whole-body magnetic resonance imaging (MRI), have demonstrated increased sensitivity in detecting recurrent disease even at low PSA levels[6,7]; however, the routine use of these modalities remains a topic of debate due to considerations regarding their cost-effectiveness, accessibility, and the potential for overdiagnosis.[8]

Metastasis-free survival has been validated as a surrogate endpoint for overall survival in localized prostate cancer,[9] as the development of distant metastases is associated with increased disease burden, need for systemic therapy, and deterioration of quality of life.[10] A comprehensive predictive model that integrates patient and tumor characteristics could aid in clinical decision-making, stratifying patients based on their risk of developing distant metastasis. The Decipher genomic classifier, which analyzes the expression of 22 genes associated with aggressive prostate cancer biology, has demonstrated utility in predicting metastatic progression and can guide treatment intensification decisions in the postprostatectomy setting.[11,12] However, while genomic classifiers like Decipher provide valuable prognostic information, simpler and more accessible clinical tools incorporating conventional pathologic and biochemical parameters remain essential for risk stratification in daily practice, particularly in healthcare settings with limited access to specialized diagnostics. Such patients could benefit from additional diagnostic workup (eg, PET PSMA scans) and tailored treatment approaches,[13] comprising treatment escalation strategies (eg, SRT combined with androgen deprivation therapy [ADT] and/or potential intensification with androgen receptor pathway inhibitors [ARPI]). Conversely, patients with a very low risk of distant metastasis, and therefore a minimal clinical impact on the prognosis of biochemical recurrence, might be managed with observation over time rather than immediate treatment.

Thus, the primary aim of this study is to analyze a multicentric retrospective series of patients who underwent RP and SRT for BCR and to develop a predictive model capable of identifying and stratifying patients at higher risk of distant metastasis at 5-year.

Material and Methods

This observational, multicenter study was conducted using data from 15 European Centers (14 Italian and 1 Polish), collected from June 1, 2022, to September 30, 2024. The study protocol received approval from the IEO-Monzino, Milan, Italy institutional review boards (UID 3576).

Patients included in the study met the following inclusion criteria: (1) histological diagnosis of PCa after prostatectomy; (2) BCR, defined following EAU guidelines,[14] treated with SRT including prostate bed ± pelvic irradiation; (3) concomitant ADT at the time of SRT was permitted (4) negative diagnostic work-up for distant (extra-pelvic) metastases with new generation or traditional imaging, when performed; (5) minimum follow-up period of at least 2 years.

Distant Metastasis-Free Survival (DMFS) was considered the primary endpoint and it was calculated as the time from the end of SRT to the occurrence of distant metastatic disease, identified using any diagnostic modality chosen by the investigator, or death.

Secondary endpoints were considered as follows:

(1) Biochemical Recurrence-Free Survival (BRFS): Time from the end of SRT to the date of biochemical recurrence, defined as 2 rising consecutive PSA values ≥0.2 ng/ml,[14] or death.
(2) Clinical Recurrence-Free Survival (CRFS): Time from the end of SRT to the date of clinical recurrence, determined by radiological evidence of disease, identified using any diagnostic modality chosen by the investigator, or death.

(3) Toxicity Assessment: Gastrointestinal (GI) and genitourinary (GU) toxicities were graded according to CTCAE v 5.0,[15] with chronic toxicities defined as those occurring or persisting beyond 90 days post-SRT. No central review was performed.

Statistical Analysis

Descriptive statistics were calculated for all variables. Missing data were handled using complete-case analysis. PSADT was not available for analysis due to insufficient serial PSA measurements in the retrospective dataset across participating centers. Survival analyses were performed using the Kaplan-Meier method. Differences between survival curves were evaluated using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were constructed to identify factors associated with survival outcomes. Centers were included as a stratification variable to account for potential institutional heterogeneity in treatment protocols and follow-up practices.[16] Since death from other causes could represent a competing risk, the Fine and Gray subdistribution hazards model was employed to account for competing risks.[17] Variables with a P-value $< .05$ in univariate analysis were included in the multivariate models. Subdistribution Hazard Ratios (sHRs) and 95% confidence intervals (CIs) were calculated for each variable. Proportional hazard assumptions were checked using Schoenfeld residuals. Statistical significance was set at $P < .05$.

Nomogram Development

A prognostic model for predicting 5-year DMFS was developed. Data from the highest populated center was set aside for external validation, while the remaining dataset was randomly divided into a training set (70%) and a testing set (30%). An elastic net Cox proportional hazards regression model was trained and optimal tuning parameters for the model were determined using 20-fold cross-validation with reproducibile seeds for hyperparameter optimization. The nomogram was constructed based on the final Cox model and internally by bootstrap resampling with 1000 iterations. The performance of the model was assessed using the concordance index (C-index) and Brier scores. Calibration was assessed using calibration plots, calibration slopes and intercepts. To improve model calibration, isotonic regression was applied, proving nonparametric recalibration while preserving the ranking of predictions. Patients were categorized into risk groups using tertile-based threshold: for each patient, a linear predictor value (ie, risk score) was calculated based on the coefficients of the final multivariable model used in the nomogram. The distribution of these risk scores was examined for normality and the presence of outliers, subsequently tertile boundaries were evaluated. Kaplan-Meier survival curves were plotted for these groups and log-rank test was used to compare risk cohorts.

Internal validation was performed using the held-out test set, while external validation used the independent dataset. Decision curve analysis (DCA) was conducted to evaluate the clinical utility of both original and isotonic regression-calibrated models across threshold probabilities from 1% to 60%. Bootstrap confidence intervals ($n = 1000$) were calculated for net benefit curves to assess the stability of clinical utility estimates.

Table 1 Patient Characteristics

Patient Characteristics	N
PSA Preprostatectomy	**8 [IQR 6-12] ng/ml**
Postoperative ISUP grade	
1	259 (15%)
2	487 (28%)
3	479 (28%)
4	268 (16%)
5	217 (13%)
pT	
2	739 (43.1%)
3	956 (56%)
4	10 (0.6%)
pN	
0	1109 (66%)
1	200 (12%)
x	381 (22%)
R	
0	829 (51%)
1	793 (49%)
Median PSA at BCR preSRT	0.26 [IQR 0.20-0.43] ng/ml
Median time from SRT to BCR	2.1 [IQR 0.7-4.9] years
SRT Dose (EQD2) at pelvic fossa	70 [66-74] Gy
SRT at pelvis	589 (34%)
SRT boost at positive nodal stations	128 (7.4%)
Concomitant ADT	358 (21%)
ADT duration	15 [IQR 9-24] months

All analysis were performed using R version 4.4.2.

Results

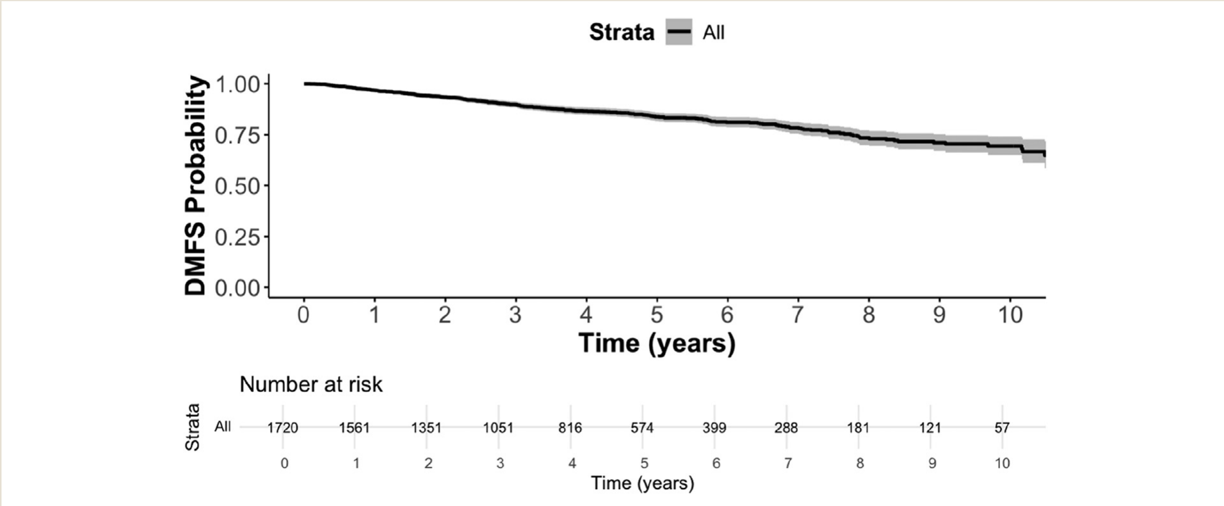
A total of 1,720 patients were retrospectively included in the study with a median follow-up of 4.21 [IQR 2.57-6.27] years from SRT. The median PSA value at first BCR was 0.26 [IQR 0.20-0.43] and 679 (39%) of patients underwent imaging before SRT. In the majority of the cases, the employed imaging was Choline PET (192 pts, 33%), followed by PSMA PET (137 pts, 23%) and WB MRI (71 pts, 12%) (Supplementary File 1). The study group and treatment characteristics are summarized in Table 1.

The median PSA 3 months after SRT was 0.07 [IQR 0.03-0.17] ng/ml, while the median nadir value was 0.02 [IQR 0.01-0.08] ng/ml. A total of 48 mortality events were recorded over the course of follow-up, including 13 that were attributable to prostate cancer.

Acute GI or GU toxicity $\geq$ G2 was observed in 86 patients (5.0%) and 124 patients (7.2%), respectively. Additionally, 39 patients (2.3%) developed chronic GI toxicity with a median onset of 4.13 (95% CI, 2.47-6.22) years, while 117 patients (6.8%) experienced chronic GU toxicity with a median onset of 3.97 (95% CI, 2.32-6.03) years. The cumulative incidence of GI and GU chronic toxicity over time is shown in eFigure 1.

Biochemical relapse occurred in 632 (37%) patients at a median time of 2.97 (95% CI, 1.49-4.89) years after SRT. The 2- and 5-years BRFS rates were 78% (95% CI, 76%-80%) and 58% (95%

Figure 1 **Kaplan–Meier curve for distant metastasis–free survival (DMFS) in the overall cohort (*n* = 1720). The plot shows the 10-year DMFS probability for all included patients treated with salvage radiotherapy (SRT) after radical prostatectomy (RP) for biochemical recurrence. The shaded area represents the 95% confidence interval. The number of patients at risk is reported at yearly intervals.** ***DMFS = distant metastasis–free survival; SRT = salvage radiotherapy; RP = radical prostatectomy.***



CI, 56%-61%), respectively. KM analysis is presented in Supplementary eFigure 2.

Clinical recurrence occurred in 506 (29%) patients with a median interval of 3.38 (95% CI, 1.85-5.25) years from SRT. The 2- and 5-years CRFS rates were 86% (95% CI, 84%-88%) and 67% (95% CI, 64%-69%), respectively. KM analysis is presented in Supplementary eFigure 3.

Distant metastases were diagnosed in 228 patients (13%) after a median time of 3.79 (95% CI, 2.23-5.81) years. The 2- and 5-years DMFS rates were 93% (95% CI, 92%-95%) and 84% (95% CI, 81%-86%), respectively. KM analysis is presented in Figure 1.

Multivariate Cox regression identified high ISUP grade (ISUP = 4-5 vs. 1-3; sHR, 1.75; 95% CI, 1.30-2.35; $p < 0.01$), advanced pathological tumor stage (pT = 3-4 vs. 1-2; sHR, 1.54; 95% CI, 1.11-2.13; $p < 0.01$), and shorter interval from surgery to SRT (< 12 months vs. ≥ 12 months; sHR, 1.49; 95% CI, 1.07-2.09; p = 0.02) as independent predictors of DMFS (Table 2).

A machine-learning based prognostic nomogram (Figure 2) was developed to predict the 5-year DMFS.

In the nomogram, a total of 33 points was assigned to pT stage 3 or 4, 100 points to ISUP grade 4 or 5, and 68 points to a time from surgery to SRT of < 12 months.

The predicted 5-year DMFS declined progressively with increasing total points. For example, a total score of 22 corresponded to an estimated 5-year DMFS of 90%, 138 points to 80%, and 211 points to 70%. This corresponds to an absolute 10% reduction in 5-year DMFS for approximately every 73-point increase in total score, or about 1% for every 7.3-point increase.

Patients were stratified into low-, intermediate-, and high-risk groups based on the total point score derived from the final nomogram. Risk group assignment showed a strong correlation with DMFS across all datasets. In the training cohort (*n* = 848), the event rates were 9.2% for low-risk (*n* = 476), 12.4% for intermediate-risk (n = 177), and 22.6% for high-risk patients (*n* = 195), with corresponding median DMFS times of 4.13, 3.76, and 3.38 years, respectively ($p < 0.0001$, Figure 3A). In the test cohort (*n* = 352), event rates were 7.6%, 10.3%, and 20.3% for the low- (*n* = 118), intermediate- (n = 155), and high-risk groups (*n* = 79), respectively, with median DMFS of 4.24, 3.82, and 4.01 years (*P* = .03, Figure 3B). In the external validation cohort (*n* = 497), the high-risk group demonstrated the worst prognosis, with an event rate of 29.2% (*n* = 35/120) and a median DMFS of 3.14 years, compared with 8.5% (*n* = 23/270) and 3.23 years for low-risk, and 16.8% (*n* = 18/107) and 3.66 years for intermediate-risk patients ($P <$ .0001, Figure 3C).

The nomogram demonstrated consistent predictive performance across internal and external validation cohorts. The Harrell's C-index was 0.68 in the training set, 0.62 in the test set, and 0.70 in the external validation cohort. The 5-year time-dependent AUC was 0.691, 0.633, and 0.656, respectively. Brier scores for the original uncalibrated model were 0.1109 (training), 0.1045 (test), and 0.3439 (external). After isotonic calibration, Brier scores improved to 0.092, 0.080, and 0.108. Calibration assessment showed that the original model tended to underestimate risk, as reflected by calibration slopes of 1.25, 1.02, and 1.37, and intercepts of –2.78, –2.83, and –4.44 across the training, test, and external datasets, respectively. Isotonic recalibration yielded markedly steeper slopes (8.47, 9.66, and 7.10) and better alignment between predicted and observed 5-year DMFS probabilities (eFigure 4). Finally, decision curve analysis (DCA) was plot for each subset of data (eFigure 5),

Figure 2 Nomogram for predicting 5-year distant metastasis–free survival (DMFS). The nomogram integrates 3 variables: pathological tumor stage (pT = 3 or 4 vs. 2), ISUP grade group (4 or 5 vs. 1–3), and time from surgery to SRT (<12 months vs. ≥12 months). Each variable contributes a specific number of points to the total score, which is converted into a linear predictor and corresponding 5-year DMFS probability. For example, patients with high ISUP grade or shorter time to SRT receive more points, indicating worse prognosis. Predicted 5-year DMFS probabilities decrease as total points increase. *ADT = androgen deprivation therapy; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; SRT = salvage radiotherapy; DMFS = distant metastasis–free survival.*

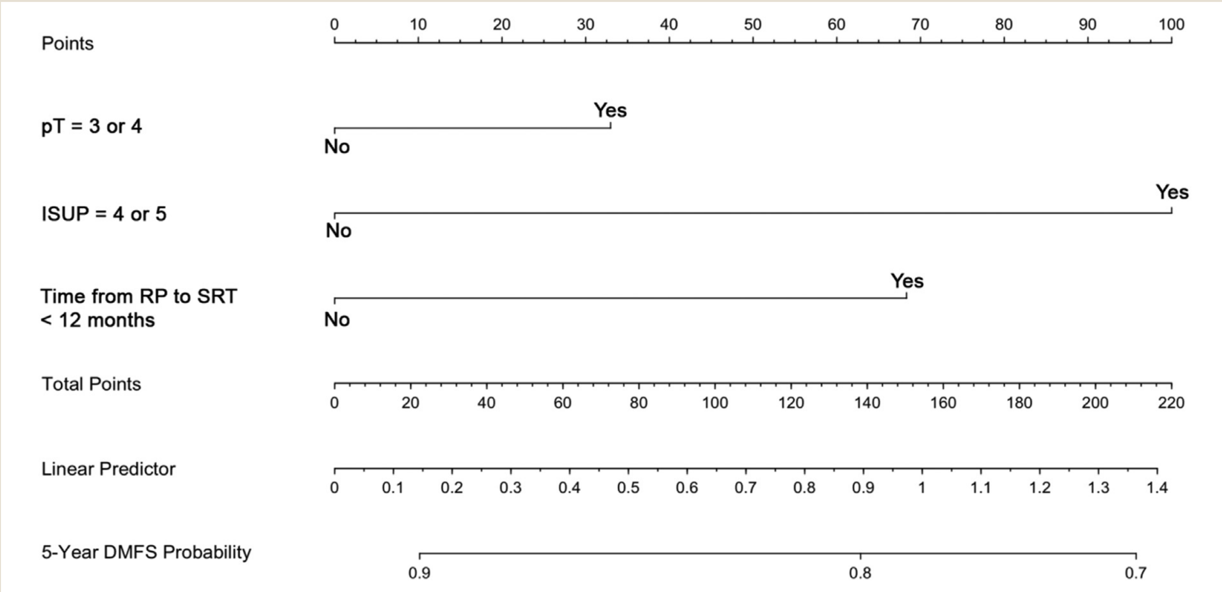


Figure 3 Kaplan–Meier survival curves by risk group across all datasets. Patients were stratified into low-, intermediate-, and high-risk groups based on tertiles of the total point scores from the final nomogram. Panels show distant metastasis–free survival (DMFS) for the (A) training dataset ($n = 848$), (B) test dataset ($n = 352$), and (C) external validation dataset ($n = 497$). Risk groups demonstrated significantly different DMFS in all cohorts (log-rank $P < .01$ for training and external datasets, and $P = .03$ for the test dataset). The number at risk is reported at yearly intervals up to 10 years for each group.

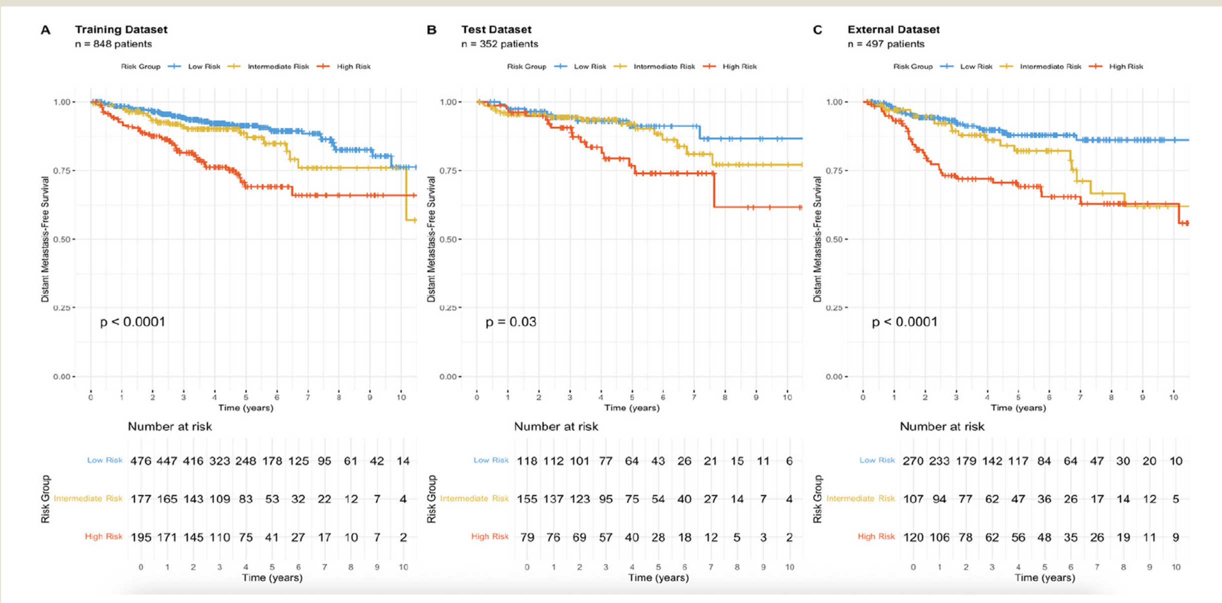


Table 2 Univariate and Multivariate Analysis of Cox-PH for Distant Metastasis Free Survival

Variable	Univ. sHR (95% CI)	Univ. *P*	Multiv. sHR (95% CI)	Multiv. *P*
ADT during SRT vs. no ADT during SRT	1.72 (1.29-2.27)	< .01[a]	1.12 (0.77-1.61)	.56
Imaging pre-SRT PET Choline vs. other	1.04 (0.71-1.52)	.86		
Imaging pre-SRT Conventional vs. other	1.00 (0.60-1.67)	.99		
Imaging pre-SRT MRI pelvis vs. other	0.74 (0.37-1.50)	.41		
Imaging pre-SRT PET PSMA vs. other	0.66 (0.36-1.20)	.17		
Imaging pre-SRT WB-MRI vs. other	0.88 (0.49-1.55)	.65		
ISUP = 4 or 5 vs. 1 or 2 or 3	2.27 (1.75-2.94)	< .01[a]	1.75 (1.30-2.35)	< .01[a]
Pelvis included in SRT vs. pelvis not included in SRT	1.63 (1.26-2.12)	< .01[a]	1.20 (0.88-1.63)	.25
pN = 0 or x vs. 1	2.00 (1.44-2.76)	< .01[a]	0.89 (0.57-1.37)	.59
PSA before RP	1.00 (1.00-1.00)	.047[a]	1.00 (0.999-1.001)	.75
PSA before SRT	1.14 (0.76-1.71)	.53		
pT = 3 or 4 vs. 2	2.02 (1.53-2.69)	< .01[a]	1.54 (1.11-2.13)	< .01[a]
Surgical margins (R) = 0 vs. 1	1.14 (0.88-1.49)	.33		
Time from surgery to SRT < 12 months vs. ≥12 months	2.25 (1.73-2.91)	< .01[a]	1.49 (1.07-2.09)	.02[a]

[a]Significant at $p < 0.05$. Abbreviations: ADT = androgen deprivation therapy, PET = positron emission tomography, RP = radical prostatectomy, SRT = salvage radiotherapy, WB-MRI = whole-body MRI.

Discussion

This study presents 1 of the largest cohorts of patients treated with SRT for BCR following radical prostatectomy available in the literature. The study shows favorable oncological outcomes, consistent with those documented in other large studies [18]. However, despite the overall success of SRT, a significant proportion of patients experience either biochemical (5-year BRFS: 58% [95% CI, 56%-61%]) or clinical recurrence (5-year CRFS: 67% [95% CI, 64%-69%]), resulting in a 2-year and 5-year DMFS rates of 93% (95% CI, 92%-95%) and 84% (95% CI, 81%-86%), respectively.

The study further identified several significant predictors of reduced DMFS. These included a higher pathological T stage (pT3 or pT4), a higher ISUP grade group (4 or 5), and an interval from surgery to SRT within 12 months. The importance of a shorter interval to SRT supports the notion that early BCR may reflect a more aggressive disease biology or the presence of occult metastases at primary treatment.[19,20] This observation is consistent with prior research showing that patients with a rapid PSA doubling time and early recurrence following surgery tend to have poorer outcomes.[21,22] However, in our study, PSA doubling time was not retrospectively collected and thus could not be included in our analysis. Despite the known-role of the PSA level at SRT,[23,24] no significant threshold resulted significant. Coming to ISUP grade, Spratt et al.[25] demonstrated a fundamental prognostic role of ISUP grade group 4 and 5 for DMFS, showing a markedly worse outcome. This data was also confirmed by Galla et al.,[26] who found similar results in their patient series, showing that higher ISUP and advanced pathological stages are significant predictors of poorer DMFS.

These clinical factors were incorporated into a nomogram designed to provide 5-year DMFS estimate, which showed not overly optimistic performance, with a promising external validation C-index (0.70). High-risk patients identified by the nomogram may benefit from intensified surveillance, early imaging with advanced modalities like PSMA PET,[27] or consideration of intensification in addition to SRT. Indeed, currently, the combined modality of prostate bed and pelvic radiotherapy with concomitant ADT is widely regarded for patients with BCR, as supported by the SPPORT trial.[28] Nevertheless, this approach is not universally applicable and must be individualized based on specific patient and tumor characteristics. Moreover, emerging evidence from the RADICALS-HD trial has renewed the debate regarding the optimal duration of ADT, leaving unresolved whether a short-term regimen (0-6 months) or a prolonged course (24 months) offers superior clinical benefit.[29]

Interestingly, no significant differences were observed between various imaging modalities employed before SRT, despite the heterogeneous distribution of conventional and advanced imaging techniques across participating centers. This finding likely reflects the institutional heterogeneity in imaging protocols and the relatively low median PSA values at SRT (0.26 ng/ml), which may limit the discriminative power of imaging modalities at very low PSA levels.[30,31]

Focusing on other nomograms available in the literature, the Stephenson nomogram, which includes variables such as pre-SRT PSA levels, Gleason grade, PSA doubling time, surgical margins, and lymph node metastasis, showed a 6-year progression-free probability of 32% (95% CI, 28%-35%) overall with concordance index of 0.69.[18] However, its performance varies, being more accurate at the extremes of risk.[32] Similarly to the present study, Miszczyk et al.[33] identified ISUP 4-5 vs. 1-3, PSA >0.2, and pT3 as adverse factors for disease-free survival in their nomogram. Notably, the Tendulkar nomogram,[24] updated in 2016, predicts progression in patients treated with SRT at lower PSA values with a time-dependent area under the curve (tAUC) of 0.60. Its recent machine-learning adaptation showed improved discrimination with a tAUC of 0.72 [34]. In this panorama, our nomogram achieved a concordance index of 0.70 in the external validation set, with fewer variables in comparison to the available ones, enhancing its practicality for daily clinical use. However, the external validation center, representing a highvolume academic institution with standardized treatment protocols and systematic follow-up procedures, may have contributed to the strong discriminative performance through consistent data quality and comprehensive outcome reporting.

Furthermore, our study highlights the favorable safety profile of modern SRT techniques, comprising one third of patients receiving elective pelvic irradiation, as evidenced by the low rates of both acute and chronic toxicities observed in the cohort, consistent with the toxicity profiles reported in other contemporary studies of SRT.[35,36] With the majority of patients experiencing minimal long-term side effects, the balance between efficacy and safety in SRT appears favorable, further supporting its role as a standard therapeutic approach in this patient population.[37]

Some limitations of this study should be acknowledged, as the retrospective design, the heterogeneity in imaging modalities and treatment protocols across the participating centers. Indeed, while patients with known distant metastases at the time of SRT were excluded from the analysis, differences in the sensitivity and specificity of the imaging methods employed may have led to inconsistencies in identifying undetected metastases, potentially impacting treatment outcomes. Furthermore, while the elastic net Cox regression approach employed in this study offers advantages in handling multicollinearity and feature selection, it is inherently limited to capturing linear relationships between variables and outcomes. Future iterations of prognostic models could benefit from exploring nonlinear machine learning approaches, such as random forests or gradient boosting methods, which may better capture complex interactions between clinical variables and improve predictive accuracy beyond the current C-index. Another limitation is that no biomarkers or other stratification methods (eg, Decipher score) were employed, however future models should incorporate genomic classifiers to potentially optimize risk stratification. Lastly, most patients in this cohort were treated before the publication of modern postoperative studies, so we anticipate a shift in the characteristics of the SRT population. Finally, to advance clinical implementation, this nomogram warrants prospective validation as stratification tools into trial design, potentially facilitating patient selection and optimizing treatment allocation.

Conclusions

This study presents a validated nomogram that utilizes pathological T stage, ISUP grade group, and time to SRT to predict the risk of distant metastasis in patients undergoing SRT for BCR after RP. By facilitating individualized risk assessment, the nomogram aids clinicians in making informed decisions regarding management strategies, potentially improving long-term outcomes by identifying patients who may benefit from additional diagnostic workup or treatment intensification. Prospective validation studies and real-world implementation research are essential to confirm the nomogram's clinical utility.

Clinical Practice Points

What is already known about this subject?

- Salvage radiotherapy (SRT) is the standard intervention for biochemical recurrence after radical prostatectomy, yet 15–20 % of patients still progress to distant metastasis. Existing prognostic nomograms are often single-institution, developed before widespread PSMA-PET use, and demonstrate only modest accuracy, limiting adoption in contemporary practice.

What are the new findings?

- In the largest modern multicenter cohort to date (1,720 men, 15 European centers, 2022-2024), an adaptive elastic-net Cox model created a nomogram using only 3 routinely available variables—pathologic stage, ISUP grade, and interval from surgery to SRT.
- External validation in the highest-volume center yielded a concordance index of 0.70 and showed a succesful stratification of 3 risk groups.
- Early SRT (<12 months), pT3/4 disease, and ISUP 4/5 independently increased metastatic risk, while modern SRT techniques produced low chronic ≥G2 toxicity rates (GI 2.3 %, GU 6.8 %).

How might it impact clinical practice in the foreseeable future?

- The nomogram delivers a fast, individualized 5-year metastatic-risk estimate that can be embedded in electronic records or mobile apps. High-risk patients can be triaged to intensified management—PSMA-PET staging, pelvic radiotherapy, longer-course or novel androgen suppression—while low-risk men may avoid unnecessary imaging or systemic therapy. Standardized risk stratification also supports patient selection and stratification in forthcoming precision-radiotherapy trials, advancing truly personalized postoperative prostate-cancer care.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

F. Mastroleo: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **R. Villa:** Data curation. **M. Zaffaroni:** Writing – review & editing, Investigation. **M.G. Vincini:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **C. Franzese:** Writing – review & editing, Data curation. **L. Nicosia:** Writing – review & editing, Data curation. **F. Matrone:** Writing – review & editing, Data curation, Conceptualization. **A. Donofrio:** Writing – review & editing, Data curation. **A. Magli:** Writing – review & editing, Data curation. **L. Triggiani:** Writing – review & editing, Data curation. **S. Barra:** Writing – review & editing, Data curation. **G. Timon:** Writing – review & editing, Data curation. **M. Augugliaro:** Writing – review & editing, Data curation. **V. Burgio:** Writing – review & editing, Data curation. **G. Francolini:** Writing – review & editing, Data curation. **M. Hasterok:** Writing – review & editing, Data curation. **M. Miszczyk:** Writing – review & editing, Data curation. **N. Simoni:** Writing – review & editing, Data curation. **C. Spatola:** Writing – review & editing, Data curation. **F. Alongi:** Writing – review & editing, Data curation. **S. Arcangeli:** Writing – review & editing, Data curation. **M. Scorsetti:** Writing – review & editing, Data curation. **G. Marvaso:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **B.A. Jereczek-Fossa:** Writing – review & editing, Supervision.

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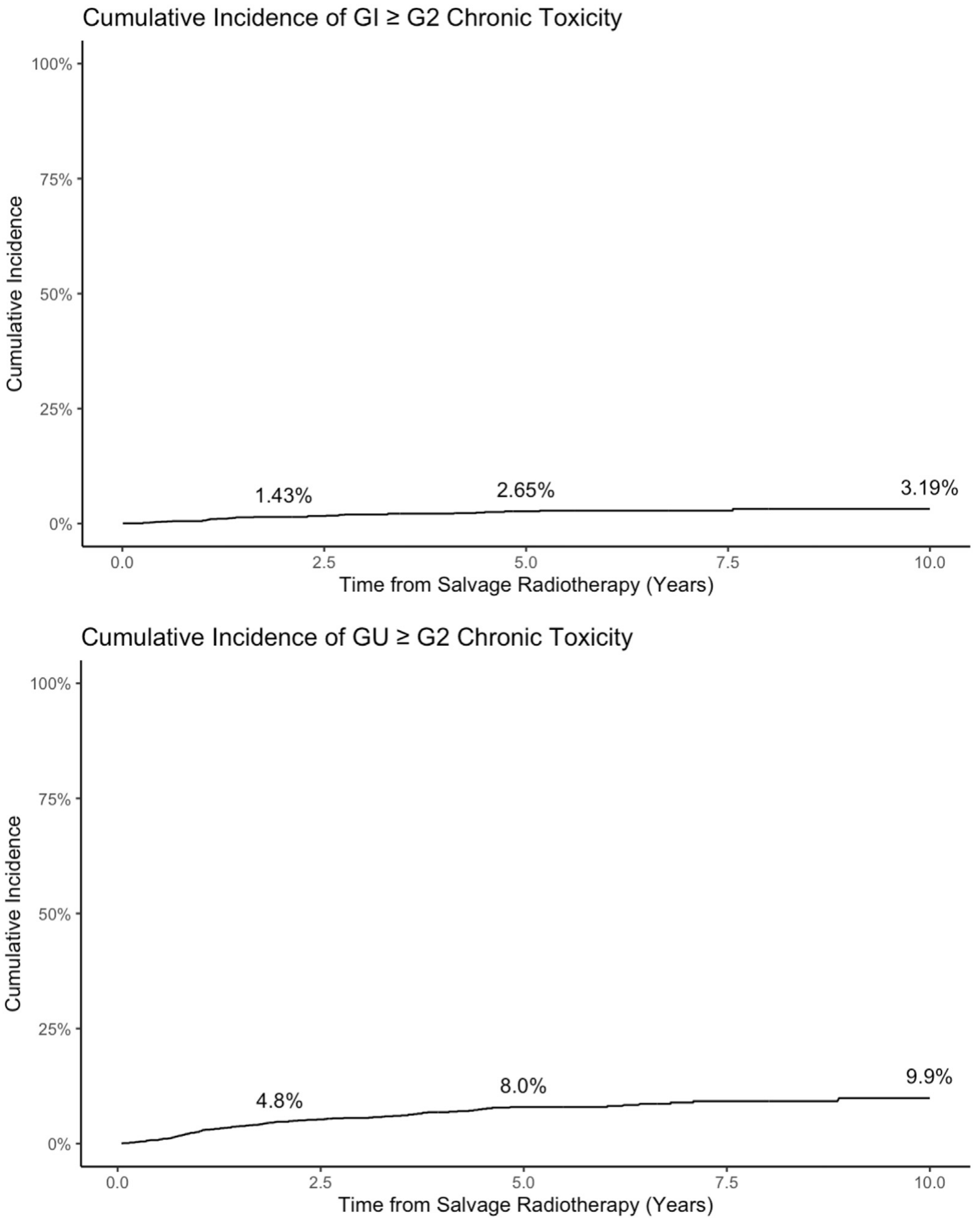
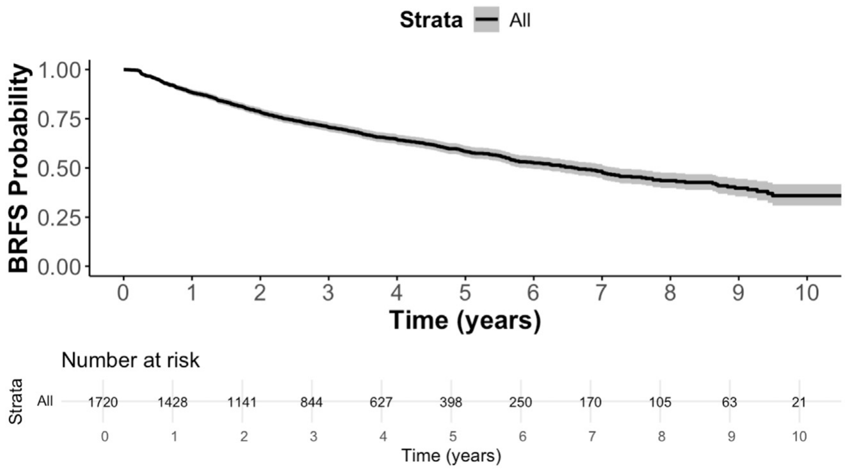
Appendix. Supplementary materials

eFigure 1, eFigure 2, eFigure 3, eFigure 4, eFigure 5, eTable 1.

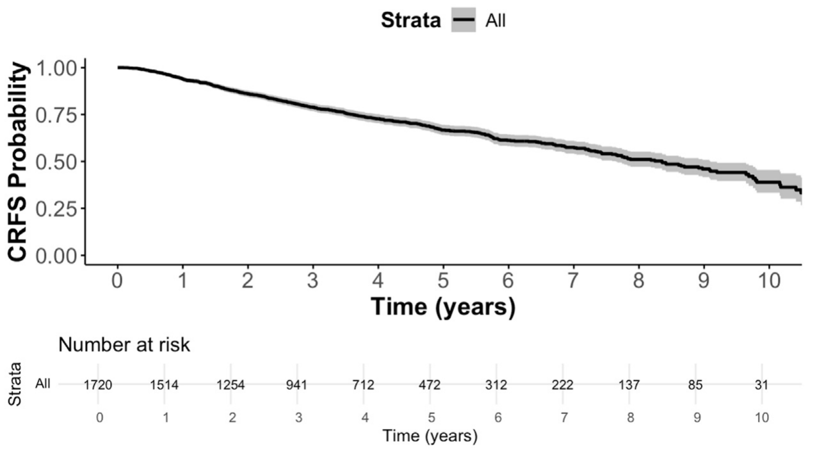
eFigure 1 Cumulative incidence of Grade ≥2 chronic gastrointestinal (GI) and genitourinary (GU) toxicity following salvage radiotherapy. (A) The cumulative incidence of GI Grade ≥2 chronic toxicity reached 1.43% at 2 years, 2.65% at 5 years, and 3.19% at 10 years. (B) The cumulative incidence of GU Grade ≥2 chronic toxicity was higher, with rates of 4.8% at 2 years, 8.0% at 5 years, and 9.9% at 10 years. Both curves were estimated from the time of salvage radiotherapy using the cumulative incidence function. *Abbreviations: GI, gastrointestinal; GU, genitourinary*



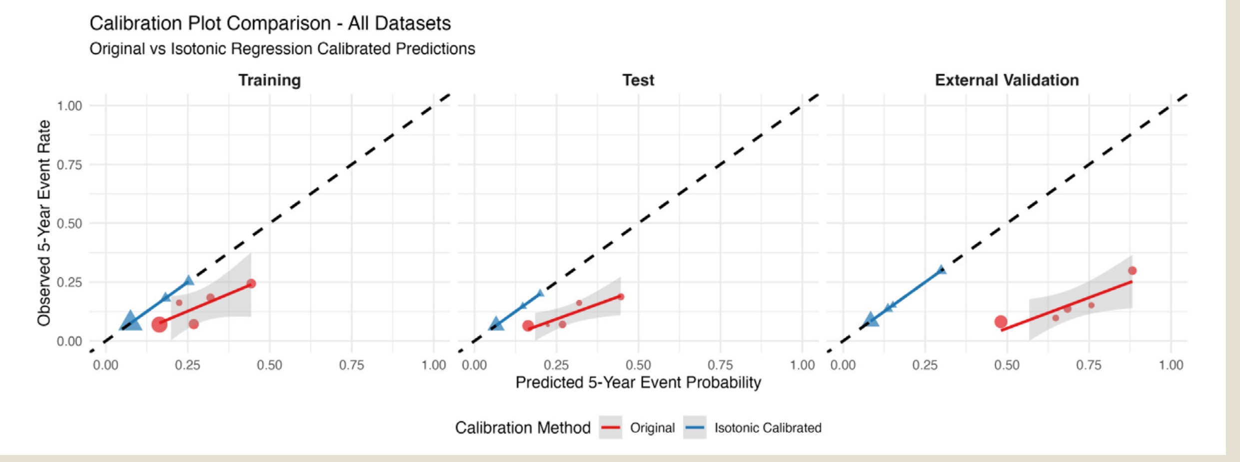
eFigure 2 Kaplan–Meier curve for biochemical recurrence–free survival (BRFS) in the overall cohort (n = 1,720). The plot depicts 10-year BRFS probability for all patients treated with salvage radiotherapy following radical prostatectomy for biochemical recurrence. The shaded area represents the 95% confidence interval. Numbers at risk are reported at yearly intervals. *Abbreviations: BRFS, biochemical recurrence–free survival.*



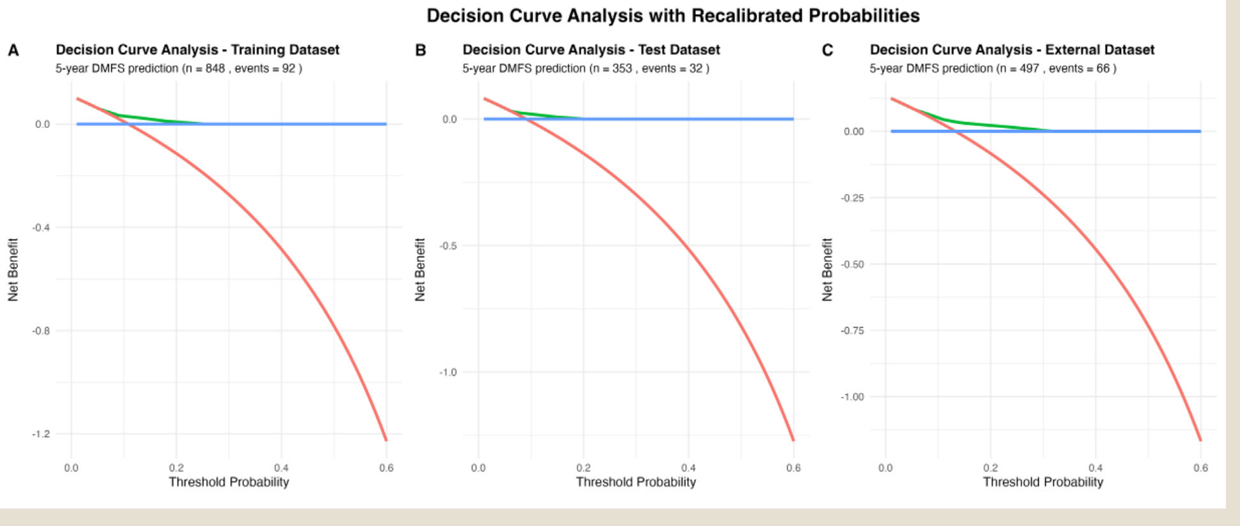
eFigure 3 Kaplan–Meier curve for clinical recurrence–free survival (CRFS) in the overall cohort (n = 1,720). The plot displays 10-year CRFS probability for all patients treated with salvage radiotherapy following radical prostatectomy for biochemical recurrence. The shaded area represents the 95% confidence interval. The number of patients at risk is shown at yearly intervals from baseline to 10 years. *Abbreviations: CRFS, clinical recurrence–free survival.*



eFigure 4 Calibration plots comparing original and isotonic-calibrated predictions of 5-year distant metastasis–free survival (DMFS). Plots show predicted vs. observed 5-year event probabilities in the (A) training, (B) test, and (C) external validation cohorts. Red lines indicate predictions from the original model, while blue lines represent isotonic regression–calibrated predictions. The diagonal dashed line indicates perfect calibration. Point size reflects bin sample size, and shaded areas denote 95% confidence intervals. Isotonic calibration consistently improved alignment between predicted and observed risk across all datasets. *Abbreviations: DMFS, distant metastasis–free survival.*



eFigure 5 Decision curve analysis (DCA) for 5-year distant metastasis–free survival (DMFS) prediction using recalibrated probabilities. Panels show the net clinical benefit of the nomogram across a range of threshold probabilities in the (A) training (n = 813), (B) test (n = 339), and (C) external validation (n = 464) cohorts. *Abbreviations: DCA, decision curve analysis; DMFS, distant metastasis–free survival.*



eTable 1 **Imaging modalities employed at first biochemical recurrence (BCR) prior to salvage radiotherapy. The table summarizes the distribution of imaging strategies used to assess patients at the time of first BCR following radical prostatectomy and prior to initiation of salvage radiotherapy. Modalities included conventional imaging (CT and bone scan), as well as advanced techniques such as choline-PET, PSMA-PET, pelvic MRI, and whole-body MRI (WB-MRI). Patients may have undergone more than one imaging modality.** ***Abbreviations: BCR, biochemical recurrence; CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; MRI, magnetic resonance imaging; WB-MRI, whole-body MRI.***

Imaging employed at BCR	Count (%)
Bone Scintigraphy	18 (3.1%)
Bone Scintigraphy + CT Thorax Abdomen Pelvis	14 (2.4%)
Bone Scintigraphy + CT Thorax Abdomen Pelvis + PET Choline + Pelvic MRI	1 (0.2%)
Bone Scintigraphy + CT Thorax Abdomen Pelvis + Pelvic MRI	4 (0.7%)
Bone Scintigraphy + PET Choline	1 (0.2%)
Bone Scintigraphy + PET Choline + Pelvic MRI	2 (0.3%)
Bone Scintigraphy + MRI Whole Body	4 (0.7%)
Bone Scintigraphy + Pelvic MRI	6 (1.0%)
CT Thorax Abdomen Pelvis	63 (11%)
CT Thorax Abdomen Pelvis + PET Choline	1 (0.2%)
CT Thorax Abdomen Pelvis + PET Choline + MRI Whole Body	1 (0.2%)
CT Thorax Abdomen Pelvis + MRI Whole Body	3 (0.5%)
CT Thorax Abdomen Pelvis + Pelvic MRI	1 (0.2%)
PET Choline	192 (33%)
PET Choline + MRI Whole Body	9 (1.5%)
PET Choline + Pelvic MRI	5 (0.9%)
PET PSMA	137 (23%)
PET PSMA + MRI Whole Body	16 (2.7%)
PET PSMA + Pelvic MRI	2 (0.3%)
MRI Whole Body	71 (12%)
Pelvic MRI	36 (6.1%)