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Development and Validation of a Multi-institutional Nomogram of Outcomes for PSMA-PET–Based Salvage Radiotherapy for Recurrent Prostate Cancer

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Abstract

IMPORTANCE Prostate-specific antigen membrane positron-emission tomography (PSMA-PET) is increasingly used to guide salvage radiotherapy (sRT) after radical prostatectomy for patients with recurrent or persistent prostate cancer.

OBJECTIVE To develop and validate a nomogram for prediction of freedom from biochemical failure (FFBF) after PSMA-PET–based sRT.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included 1029 patients with prostate cancer treated between July 1, 2013, and June 30, 2020, at 11 centers from 5 countries. The initial database consisted of 1221 patients. All patients had a PSMA-PET scan prior to sRT. Data were analyzed in November 2022.

EXPOSURES Patients with a detectable post–radical prostatectomy prostate-specific antigen (PSA) level treated with sRT to the prostatic fossa with or without additional sRT to pelvic lymphatics or concurrent androgen deprivation therapy (ADT) were eligible.

MAIN OUTCOMES AND MEASURES The FFBF rate was estimated, and a predictive nomogram was generated and validated. Biochemical relapse was defined as a PSA nadir of 0.2 ng/mL after sRT.

RESULTS In the nomogram creation and validation process, 1029 patients (median age at sRT, 70 years [IQR, 64-74 years]) were included and further divided into a training set (n = 708), internal validation set (n = 271), and external outlier validation set (n = 50). The median follow-up was 32 months (IQR, 21-45 months). Based on the PSMA-PET scan prior to sRT, 437 patients (42.5%) had local recurrences and 313 patients (30.4%) had nodal recurrences. Pelvic lymphatics were electively irradiated for 395 patients (38.4%). All patients received sRT to the prostatic fossa: 103 (10.0%) received a dose of less than 66 Gy, 551 (53.5%) received a dose of 66 to 70 Gy, and 375 (36.5%) received a dose of more than 70 Gy. Androgen deprivation therapy was given to 325 (31.6%) patients. On multivariable Cox proportional hazards regression analysis, pre-sRT PSA level (hazard ratio [HR], 1.80 [95% CI, 1.41-2.31]), International Society of Urological Pathology grade in surgery specimen (grade 5 vs 1+2: HR, 2.39 [95% CI, 1.63-3.50], pT stage (pT3b+pT4 vs pT2: HR, 1.91 [95% CI, 1.39-2.67]), surgical margins (R0 vs R1+R2+Rx: HR, 0.60 [95% CI, 0.48-0.78]), ADT use (HR, 0.49 [95% CI, 0.37-0.65]), sRT dose (>70 vs ≤66 Gy: HR, 0.44 [95% CI, 0.29-0.67]), and nodal recurrence detected on PSMA-PET scans (HR, 1.42 [95% CI, 1.09-1.85]) were associated with FFBF. The mean (SD) nomogram concordance index for FFBF was 0.72 (0.06) for the internal validation cohort and 0.67 (0.11) in the external outlier validation cohort.

(continued)

Key Points

Question Is it possible to create and validate a nomogram for prediction of freedom from biochemical failure (FFBF) among patients with prostate cancer after prostate-specific membrane antigen positron-emission tomography (PSMA-PET)–guided salvage radiotherapy after prostatectomy?

Findings This cohort study included 1029 patients (training set, 708; internal validation set, 271; external outlier validation set, 50) with a median follow-up of 32 months from a retrospective multicenter cohort. The nomogram concordance index was 0.72 for FFBF in the internal validation set and 0.67 for FFBF in the external outlier validation set.

Meaning This study suggests that a nomogram can be created and validated for FFBF prediction among patients with prostate cancer after PSMA-PET–guided salvage radiotherapy.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE This cohort study of patients with prostate cancer presents an internally and externally validated nomogram that estimated individual patient outcomes after PSMA-PET–guided sRT.

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Introduction

Approximately 30% to 50% of patients with prostate cancer develop a biochemical relapse or prostate-specific antigen (PSA) persistence within the first 5 years after primary radical prostatectomy.[1,2] Current international guidelines[3] recommend early salvage radiotherapy (sRT) directed to the prostate bed with or without androgen deprivation therapy (ADT) in this disease setting; predictive nomograms are widely used to provide individualized estimates of biochemical relapse after sRT.[4] However, prostate-specific membrane antigen positron-emission tomography (PSMA-PET) is increasingly used for staging patients with biochemical relapse or PSA persistence after radical prostatectomy,[5] which affects the treatment decision process prior to delivery of sRT.[6,7]

To our knowledge, no predictive tools for biochemical relapse estimation among this patient population currently exist. In addition, a multicenter study by Emmett et al[8] suggested that PSMA-PET findings are associated with treatment response to sRT and stratify men into a favorable treatment response (negative or confined to the fossa) vs men with poor response (nodes or distant disease). Consequently, the aim of this multicenter retrospective cohort study was to establish a contemporary nomogram to estimate biochemical relapse after PSMA-PET–based sRT after radical prostatectomy for patients with recurrent or persistent prostate cancer. The nomogram was validated internally and within an external outlier validation cohort.

Methods

Patients

Eleven medical centers from 5 countries submitted data for analysis and nomogram construction and evaluation. The multicenter case series followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and received institutional review board approval from all institutions (University of Freiburg, Freiburg, Germany; University of Munich, Munich, Germany; Technical University of Munich, Munich, Germany; University of Bologna, Bologna, Italy; University of Ulm, Ulm, Germany; Ethics Committee Zuerich, Zuerich, Switzerland; University of New South Wales, Sydney, Australia; University of Heidelberg, Heidelberg, Germany; Cyprus National Bioethics Committee, Nicosia, Cyprus; and Cantonal Ethics Commission Bern, Bern, Switzerland). Written informed consent was waived due to the retrospective character of the study in accordance with all respective review boards. All study centers were asked to collect patients who underwent open or laparoscopic radical prostatectomy and were subsequently managed with PSMA-PET–based sRT for a PSA persistence or recurrence (PSA level after prostatectomy, ≥0.1 ng/mL [to convert to micrograms per liter, multiply by 1.0] for both). Patients were excluded if distant metastases were detected on PSMA-PET scan or computed tomography (CT) scan or if ADT was commenced prior to PSMA-PET scan or CT scan.

In total, 1221 patients who received sRT between July 1, 2013, and June 30, 2020, met the inclusion criteria. Overall, 192 patients were excluded: 141 due to missing clinical data, 47 for exclusion of the prostatic fossa from the sRT field, and 4 because PSMA-PET avid lesions were not covered by the sRT field. Consequently, 1029 patients were included in the nomogram creation and validation process.

PSMA-PET Scans or CT Scans Prior to sRT

PET-CT or PET–magnetic resonance imaging prior to sRT were performed with the following radiotracers: ^{68}Ga-labeled PSMA-11 (n = 723), ^{68}Ga-labeled PSMA-I&T (n = 61), ^{18}F-labeled PSMA-1007 (n = 117), ^{18}F-labeled PSMA-DCFPyL, ^{18}F-labeled siPSMA-14, or ^{18}F-labeled PSMA-rhPSMA-7/-7.3 (n = 128). All scans were performed according to local practice and images were locally interpreted by 2 experienced readers. See eTable 1 in Supplement 1 for PET protocols.

Treatment and Follow-up

Clinical decisions were made at the discretion of the treating physicians based on standards of care at the time of sRT and based on PSMA-PET findings. All patients received intensity-modulated and image-guided sRT to the prostatic fossa, and, in some cases, a simultaneous integrated boost to local recurrence depending on institutional clinical practice. Additional irradiation of the pelvic lymphatics (elective) and ADT were administered according to each individual patient's risk factors. See eTable 2 in Supplement 1 for sRT protocols. Follow-up assessments including serum PSA testing at regular intervals as well as restaging in case of biochemical relapse after sRT was performed according to the institutional clinical practice (eTable 3 in Supplement 1).

Statistical Analysis

Prior to data collection, the study team decided via online conferences and a majority vote on the inclusion of the clinical variables for nomogram creation. Analogous to the article by Tendulkar et al,[4] International Society of Urological Pathology (ISUP) grade in surgery specimen, pT stage, resection status, PSA serum values before sRT, ADT use, and dose to the prostatic fossa were included in the modeling. The dose to the prostatic fossa was defined as the maximum prescribed dose to the fossa or, if present, to the local recurrence on PSMA-PET. Persistence of PSA after surgery was also considered, based on the findings of Bartkowiak et al.[9] In addition, 2 PET-derived variables were included: pelvic lymph nodes (PLN-PETs) or local recurrences prior to sRT. The biochemical disease-free interval between surgery and sRT, the presence of pelvic lymph nodes in the surgical specimen, PSA doubling time, and preoperative PSA were not included in the analysis due to limited predictive values in previous studies.[4,10]

The primary study end point was freedom from biochemical failure (FFBF), which was defined as time from completion of sRT to documented biochemical relapse, which was defined as a PSA nadir after sRT of 0.2 ng/mL. The 3-year FFBF rate of the participants was estimated with 95% CIs by the Kaplan-Meier method. A second study end point was freedom from distant metastases (FFDM), which was defined as time from completion of sRT to documented distant metastases based on imaging examinations (PSMA-PET scan or CT scan or conventional imaging with bone scintigraphy and CT scan). Due to unknown metastatic status in 106 patients (10.3%) and the use of different imaging modalities in case of biochemical relapse after sRT, no separate nomogram for FFDM was created.

For nomogram creation, the data set was separated into an external outlier validation data set (center 3; n = 50) and a learning (n = 979) data set. The external outlier validation data set was chosen based on the dissimilarity of the centers; the most dissimilar center was chosen. To study the dissimilarity between the centers, a principal component analysis[11] was built by excluding the center variable and was used to project the center as an illustrative variable. The visual interpretation enabled us to select the most dissimilar center for the outlier validation set (eFigure in Supplement 1).

A set of 30 seed values between 1 and 10 000 was chosen by uniform drawing. For each seed, the learning data set was split 30 times into a training set (708 of 979 [72.3%]) and an internal validation (271 of 979 [27.7%]) set based on stratification by all significant variables determined by a preliminary multivariate Cox proportional hazards regression model applied to the whole data set (eTable 4 in Supplement 1).

A multivariate Cox proportional hazards regression model was fitted on each training data set using stepwise variable selection based on the Akaike information criterion (AIC). The best model for

FFPF prediction was selected based on the AIC and Brier score from all 900 models. The proportional hazards assumption was verified using Schoenfeld residuals plot and appropriate tests for each covariate and for global model. The nomogram model was derived from the coefficients obtained in the Cox proportional hazards regression model and created to predict FFBF at 12, 24, and 30 months and tested on both validation sets. Results were presented with the Harrell concordance index (C index). The Greenwood-Nam-D'Agostino (GND) test was used to assess the performance of the calibration. The Fisher exact or χ^2 tests for categorial variables were used to compare clinical and treatment characteristics between the different data sets. The created nomogram was also tested for FFDM prediction.

Finally, the internal validation set was divided into 2 groups (low risk vs high risk) based on a threshold defined by the median of the number of points given by the nomogram in the training set. A Kaplan-Meier plot was used for the graphical representation of FFBF and FFDM in the 2 groups and was accompanied by the log-rank test.

In an exploratory analysis, we added the center as an additional variable or as a mixed-effect variable to evaluate its association with outcomes. We compared the models using the likelihood ratio test.

A 2-sided $P < .05$ was considered as statistically significant. All statistical analysis was performed using R statistical software, version 4.1.0 (R Group for Statistical Computing).

Results

Baseline Patient and Treatment Characteristics

The baseline patient and treatment characteristics of the total cohort (n = 1029; median age at sRT, 70 years [IQR, 64-74 years]) and the training set (n = 708), internal validation set (n = 271), and external outlier data set (n = 50) are listed in the **Table**. For the learning cohort (training + internal validation sets; n = 979), 610 patients (62.3%) had PSA serum values before sRT of 0.5 ng/mL or less, 430 (43.9%) had PET scan–detected locally recurrent disease, and 266 (27.2%) had at least 1 PLN-PET. Androgen deprivation therapy was prescribed for 315 of 979 patients (32.2%). None of the patients in this study received an escalation of systemic therapy beyond ADT. The most frequently applied equivalent dose in 2 Gy per fraction (EQD2, α/β = 1.6 Gy) to the prostatic fossa or to local recurrent disease was 66 to 70 Gy (547 of 979 [55.9%]). On results of PSMA-PET scan prior to sRT, 430 of 979 patients (43.9%) had local recurrences and 266 of 979 patients (27.2%) had nodal recurrences. Salvage radiotherapy to elective pelvic lymphatics was delivered to 349 of 979 patients (35.6%). All PLN-PETs received dose-escalated sRT; the most frequent dose (149 of 266 [56.0%]) was 50 to 60 Gy (EQD2, α/β = 1.6 Gy). No significant differences in clinical and treatment characteristics were observed between the training and the internal validation cohort (eTables 5 and 6 in Supplement 1). The external outlier cohort had no patients with negative PSMA-PET scans, significantly more patients with complete resection (44 of 50 [88.0%]; $P = .001$), and significantly more patients with positive pelvic lymph nodes (47 of 50 [94.0%]; $P < .001$). The delivered dose to the prostatic fossa was significantly lower at less than 66 Gy for 46 of 50 patients (92.0%; $P < .001$). Androgen deprivation therapy was administered to 10 of 50 patients (20.0%) and 37 patients with positive lymph nodes detected on PET scans received no ADT. No significant differences in the distributions of the ISUP grade and the pT stage were observed (eTable 6 in Supplement 1).

FFBF Analysis

Overall, 303 patients (29.4%) had biochemical relapse after a median follow-up time of 32 months (IQR, 21-45 months); the median time to relapse was 26 months (IQR, 15-40 months). The estimated 3-year FFBF rate was 73% (95% CI, 69%-77%). Four patients died during follow-up; all deaths were due to progressive prostate cancer. The best Cox proportional hazards regression model (AIC, 2140; Brier score, 0.117) in the training cohort was obtained for seed = 7332 (eTable 7 in Supplement 1). On multivariable Cox proportional hazards regression analysis, pre-sRT PSA level (hazard ratio [HR], 1.80

Table. Patients' and Treatment Characteristics

Characteristic	Patients, No. (%)			
	Total cohort (N = 1029)	Training set (n = 708)	Internal validation set (n = 271)	External outlier validation set (n = 50)
Age at sRT, median (IQR), y	70 (64-74)	70 (64-74)	69 (63-74)	72.5 (68-76)
pT stage				
2	460 (44.7)	310 (43.8)	122 (45.0)	28 (56.0)
3a	327 (31.8)	230 (32.5)	86 (31.7)	11 (22.0)
3b	235 (22.8)	163 (23.0)	61 (22.5)	11 (22.0)
4	7 (0.7)	5 (0.7)	2 (0.7)	0
Resection status in surgery				
R0	673 (65.4)	448 (63.3)	181 (66.8)	44 (88.0)
R1	327 (31.8)	244 (34.5)	77 (28.4)	6 (12.0)
R2	3 (0.3)	1 (0.1)	2 (0.7)	0
Rx	26 (2.5)	15 (2.1)	11 (4.1)	0
ISUP grade in surgery				
1 + 2	371 (36.1)	254 (35.9)	101 (37.3)	16 (32.0)
3	324 (31.5)	226 (31.9)	84 (31.0)	14 (28.0)
4	156 (15.2)	102 (14.4)	44 (16.2)	10 (20.0)
5	178 (17.3)	126 (17.8)	42 (15.5)	10 (20.0)
PSA persistence after surgery				
No	750 (72.9)	511 (72.2)	197 (72.7)	42 (84.0)
Yes	279 (27.1)	197 (27.8)	74 (27.3)	8 (16.0)
PSA before sRT, ng/mL				
0.01-0.2	246 (23.9)	178 (25.1)	63 (23.3)	5 (10.0)
>0.2-0.5	385 (37.4)	258 (36.4)	111 (41.0)	16 (32.0)
>0.5-1	172 (16.7)	122 (17.2)	41 (15.1)	9 (18.0)
>1	226 (22.0)	150 (21.2)	56 (20.7)	20 (40.0)
Local recurrence after PSMA-PET				
No	592 (57.5)	396 (55.9)	153 (56.5)	43 (86.0)
Yes	437 (42.5)	312 (44.1)	118 (43.5)	7 (14.0)
Pelvic lymph nodes after PSMA-PET				
No	716 (69.6)	507 (71.6)	206 (76.0)	3 (6.0)
Yes	313 (30.4)	201 (28.4)	65 (24.0)	47 (94.0)
Dose to the prostatic fossa, Gy[a]				
<66	103 (10.0)	47 (6.6)	10 (3.7)	46 (92.0)
66-70	551 (53.6)	390 (55.1)	157 (57.9)	4 (8.0)
>70	375 (36.4)	271 (38.3)	104 (38.4)	0
sRT to elective pelvic lymphatics				
No	633 (61.6)	455 (64.4)	174 (64.2)	4 (8.0)
Yes	395 (38.4)	252 (35.6)	97 (35.8)	46 (92.0)
Dose to elective pelvic lymphatics, Gy[a]				
≤50	312 (30.3)	197 (27.8)	71 (26.2)	44 (100)
>50	47 (4.6)	34 (4.80)	13 (4.79)	0
Unknown	36 (3.5)	21 (3.0)	13 (4.8)	2 (4.0)
Irradiation to positive pelvic LNs[b]				
No	712 (69.2)	505 (71.3)	204 (75.3)	3 (6.0)
Yes	317 (30.8)	203 (28.7)	67 (24.7)	47 (94.0)
Dose to positive pelvic LNs, Gy[a,b]				
≤50	15 (1.5)	11 (1.6)	4 (1.5)	0
50-60	149 (13.5)	113 (16.0)	36 (13.3)	0
>60	128 (12.4)	63 (8.9)	20 (7.4)	45 (90.0)
Unknown	25 (2.4)	16 (2.3)	7 (2.6)	2 (4.0)

(continued)

Table. Patients' and Treatment Characteristics (continued)

Characteristic	Patients, No. (%)			
	Total cohort (N = 1029)	Training set (n = 708)	Internal validation set (n = 271)	External outlier validation set (n = 50)
ADT				
No	704 (68.4)	475 (67.1)	189 (69.7)	40 (80.0)
Yes	325 (31.6)	233 (32.9)	82 (30.3)	10 (20.0)
Duration of ADT admission, mo				
<6	65 (23.1)	50 (24.4)	15 (22.7)	0
6-12	110 (39.2)	79 (38.5)	24 (36.4)	7 (70.0)
>12-24	57 (20.3)	39 (19.0)	18 (27.3)	0
>24	49 (17.4)	37 (18.1)	9 (13.6)	3 (30.0)
Unknown	44 (4.3)	28 (4.0)	16 (5.9)	0

Abbreviations: ADT, androgen deprivation therapy; ISUP, International Society of Urological Pathology; LN, lymph node; PSA, prostate-specific antigen; PSMA-PET, prostate-specific membrane antigen positron-emission tomography; sRT, salvage radiotherapy.

SI conversion factor: To convert PSA to to micrograms per liter, multiply by 1.0.

[a] Dose is given in equivalent dose 2 Gy (EQD2, α/β = 1.6 Gy).

[b] Positive lymph node defined by PSMA-PET imaging or based on localization of pN+ status in surgery.

[95% CI, 1.41-2.31]), International Society of Urological Pathology grade in surgery specimen (grade 5 vs 1+2: HR, 2.39 [95% CI, 1.63-3.50], pT stage (pT3b+pT4 vs pT2: HR, 1.91 [95% CI, 1.39-2.67]), surgical margins (R0 vs R1+R2+Rx: HR, 0.60 [95% CI, 0.48-0.78]), ADT use (HR, 0.49 [95% CI, 0.37-0.65]), sRT dose (>70 vs ≤66 Gy: HR, 0.44 [95% CI, 0.29-0.67]), and nodal recurrence detected on PSMA-PET scans (HR, 1.42 [95% CI, 1.09-1.85]) were associated with FFBF.

Internal and External Validation of the Nomogram

Figure 1 depicts the predictive nomogram, and **Figure 2** depicts the calibration plots for the outcomes of FFBF. The GND test showed a good fit of the calibration curves for the internal (χ^2 test = 6.76; P = .15) and the external outlier cohort (χ^2 test = 3.36; P = .16), respectively. The mean (SD) C index value was 0.72 (0.06) for the internal validation cohort and 0.67 (0.11) for the external outlier validation cohort. In 10-fold cross-validation the C index was 0.69 (range, 0.56-0.73) for the entire cohort. Inclusion of center as a mixed variable was associated with a significant likelihood ratio test in comparison to our final nomogram.

FFBF for High-risk vs Low-risk Groups According to the Nomogram

Patients in the training cohort had a median value of 229 points in the nomogram. This value was used as a cutoff to define high-risk and low-risk subgroups of patients in both validation cohorts. **Figure 3** represents the Kaplan-Meier curves of the respective risk groups showing a significant difference in FFBF for the internal validation and trend for significant differences in FFBF in the external outlier cohort.

FFDM Analysis

From 923 patients with known metastatic status after sRT, 167 patients (18.1%) had distant metastases; the median time from the end of sRT to distant metastases was 20 months (IQR, 13-32 months). For 146 of 167 patients (87.4%) the distant metastases were detected on PSMA-PET scans or CT scans. The mean (SD) C index values for the internal validation cohort was 0.70 (0.11) and for the external outlier validation cohort was 0.61 (0.13) for all patients with known metastatic status. For the patients with PSMA-PET scan or CT scan for restaging after sRT, the mean (SD) C index values for the internal validation cohort was 0.75 (0.10) and for the external outlier validation cohort was 0.61 (0.13). In **Figure 4**, the Kaplan-Meier curves of the respective risk groups show a significant difference in FFDM for the internal validation cohort and no significant differences in FFBF in the external outlier cohort.

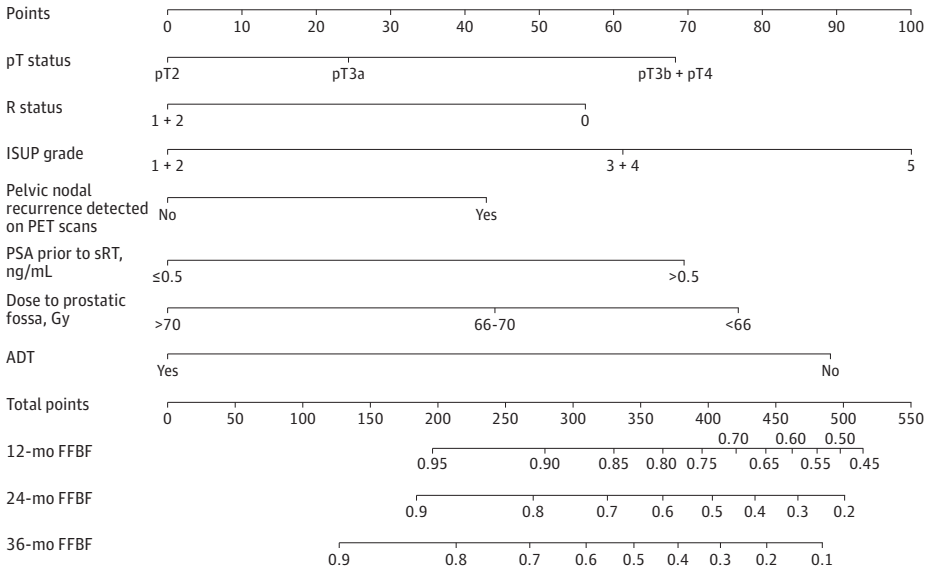
Discussion

Predictive nomograms could help physicians and patients to make decisions about sRT. Although PSMA-PET is increasingly used in this disease stage, all the currently available nomograms were

created before the implementation of PSMA-PET for sRT guidance. To our knowledge, this multicenter study developed the first nomogram to predict FFBF for PSMA-PET–based sRT in recurrent prostate cancer. Besides clinical and therapeutic characteristics including pre-sRT PSA, ISUP grade, pT stage, surgical margins, ADT use, and sRT dose to the fossa, nodal recurrence on PSMA-PET was significantly associated with FFBF in multivariate analysis. The final nomogram achieved a C index of 0.72, which can be translated into a significant patient risk stratification and good calibration in the internal validation cohort. The model was additionally tested on a significantly different external test cohort and retained a C index of 0.67 and a good calibration.

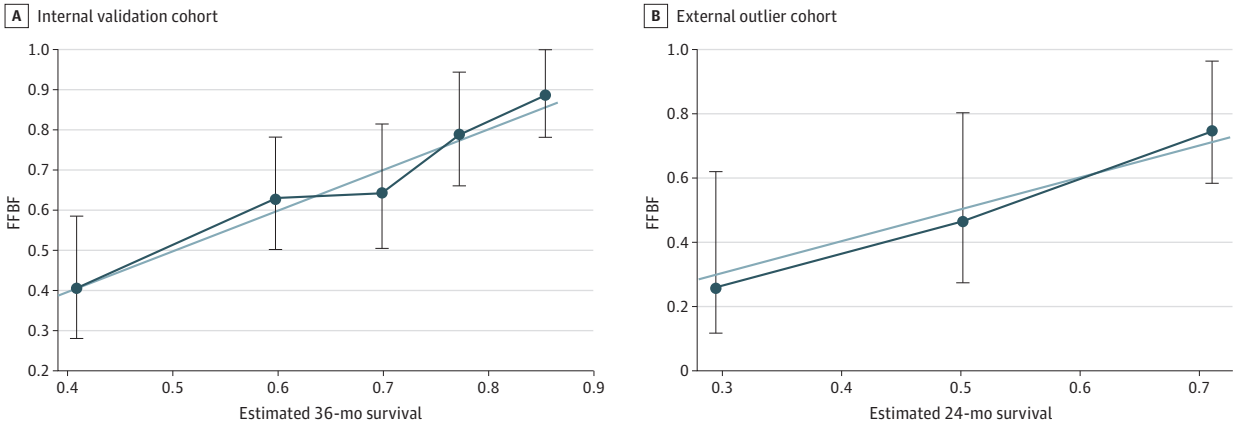
Tendulkar et al[4] developed a nomogram for patients receiving sRT in the pre–PSMA-PET era. As in our study, patients with nodal recurrences or macroscopic local recurrence were not formally excluded. However, the authors did not report on their frequency, as the staging results were not analyzed. In parallel to our study, pre-sRT PSA, ISUP grade, surgical margins, ADT use, and sRT dose, as well as extraprostatic extension and seminal vesicle invasion were significant in multivariate Cox

Figure 1. Nomogram for Freedom From Biochemical Failure (FFBF) After Prostate-Specific Membrane Antigen Positron-Emission Tomography–Guided Salvage Radiotherapy (sRT)



ADT indicates androgen deprivation therapy; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; and R status, resection status. Dose to the fossa is given in equivalent dose 2 Gy (EQD2, α/β = 1.6 Gy). SI conversion factor: To convert PSA to to micrograms per liter, multiply by 1.0.

Figure 2. Calibration Plots for Internal and External Outlier Validation Sets

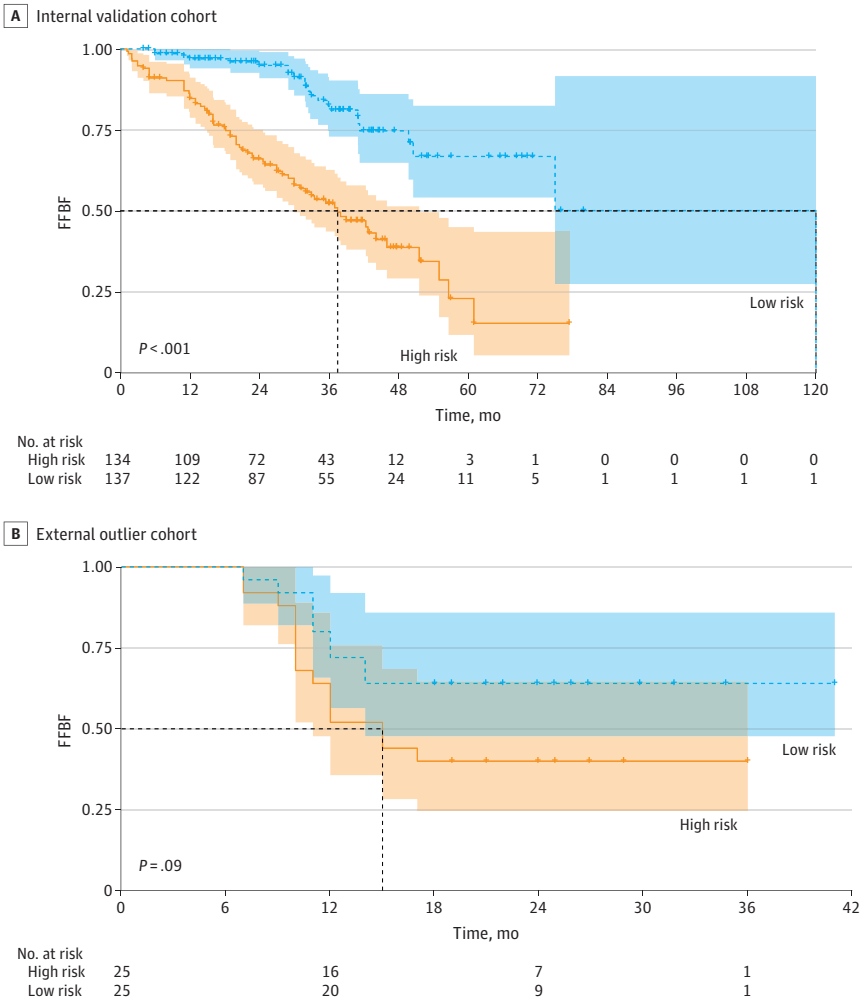


A, Internal validation cohort. B, External outlier validation cohort. FFBF indicates freedom from biochemical failure. The error bars indicate 95% CIs.

proportional hazards regression. Our study further demonstrates that the knowledge of PSMA-positive lymph node status adds an additional factor relevant for outcome prediction. With a C index of 0.72, our nomogram ultimately performed better than the nomogram by Tendulkar and colleagues[4] (C index, 0.68 for FFBF in internal validation).

In contrast to Tendulkar et al,[4] we tested our nomogram within an external outlier validation cohort. As this cohort was separated from the initial total cohort, this validation reflects a Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) type III validation.[12] We chose a patient cohort that became apparent as outliers in homogeneity analyses. The cohort differed significantly in terms of the percentage of patients with positive lymph nodes detected on PET scans, resection status, dose to the prostatic fossa, and use of ADT for patients with positive lymph nodes detected on PET scans. Despite these differences, the nomogram retained predictive performance with a C index of 0.67 and achieved significant patient stratification for FFBF. The loss in performance is to be expected when patients have different properties or were treated differently compared with the training cohort. Thus, our nomogram performs acceptably for heterogeneous cohorts with large differences in patient and treatment characteristics, such as no administration of ADT for patients with PET-positive lymph nodes within the pelvis. However, our nomogram works best for patients who are treated using similar treatment algorithms as in our training cohort.

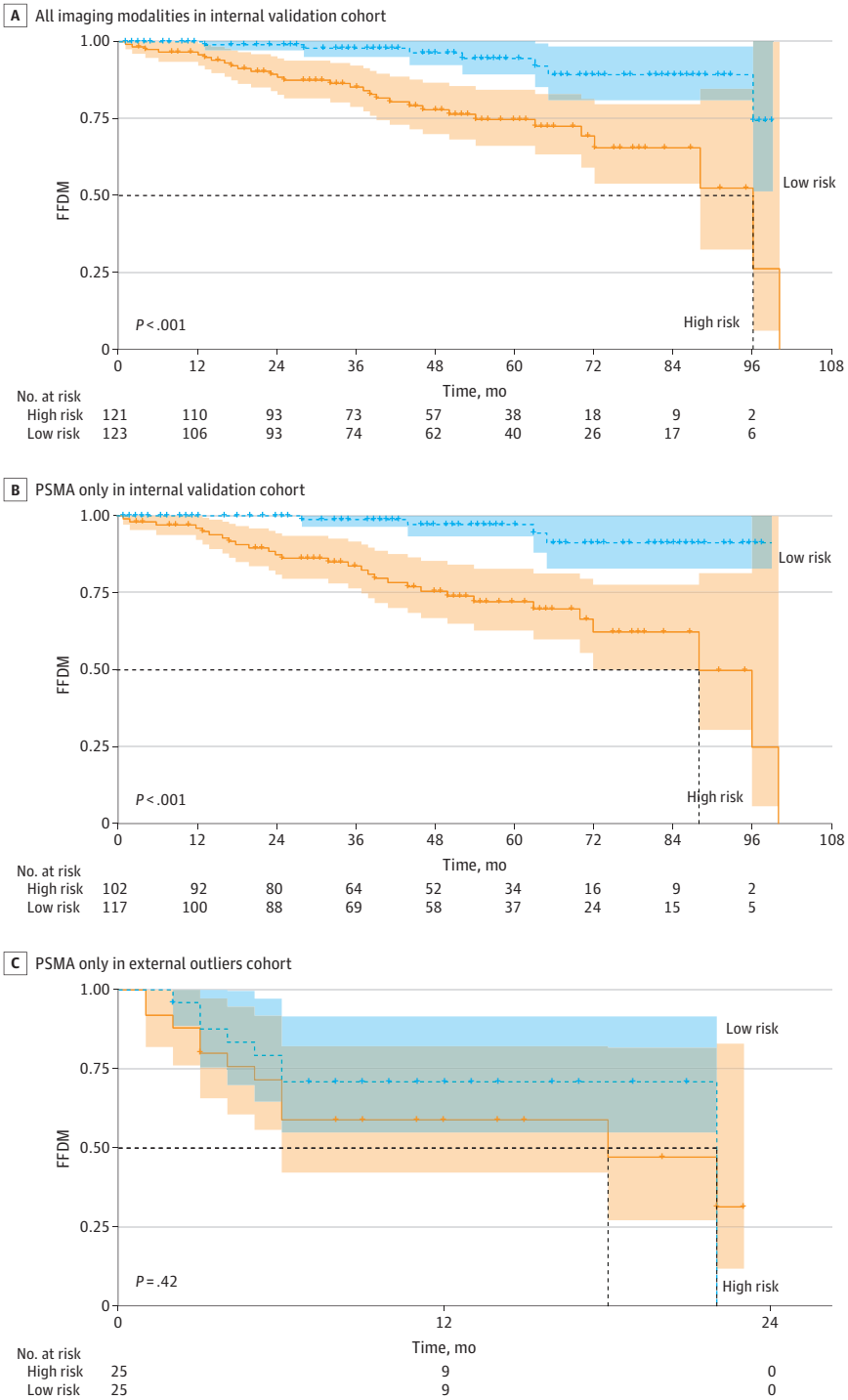
Figure 3. Kaplan-Meier Plot for Freedom From Biochemical Failure (FFBF)



A, Internal validation cohort. B, External outlier validation cohort. The Kaplan-Meier curves show patients stratified by their risk group according to their points on the nomogram. The cutoff value of 229 was defined as the median nomogram value in the training cohort. The groups showed a significant difference in FFBF for the internal validation cohort and a trend toward a significant difference in FFBF in the external outlier cohort using the log-rank test. The dotted lines represent the time points for 50% FFBF.

The maximum prescribed dose to the fossa or, if present, to the local recurrence was significantly associated with FFBF in our study. This finding appears to contradict the recently published Swiss Group for Clinical Cancer Research (SAKK) 09/10 trial.[13] The SAKK 09/10 trial was a multicenter, phase 3 trial that randomly assigned a radiotherapy dose to the entire prostatic fossa of 64 Gy or 70 Gy. There was no significant difference in FFBP rates but there was an increased risk of late gastrointestinal adverse effects with the higher dose group. There are 3 major differences

Figure 4. Kaplan-Meier Plot for Freedom From Distant Metastases (FFDM)



A, All imaging modalities in internal validation cohort. B, Prostate-specific membrane antigen positron-emission tomography (PSMA-PET) only in internal validation cohort. C, PSMA-PET only in external outliers cohort. The Kaplan-Meier curves show patients stratified by their risk group according to their points on the nomogram for freedom from biochemical failure prediction. The cutoff value of 229 was defined as the median nomogram value in the training cohort. The groups showed a significant difference in FFDM for the internal validation cohort but not for the external outlier cohort using the log-rank test. The dotted lines represent the time points for 50% FFDM.

between this prospective trial and our retrospective multicentric cohort. First, in the SAKK 09/10 trial pre-sRT staging consisted of either CT scan (61% of patients) or magnetic resonance imaging of the abdomen and pelvis. In contrast, all our patients received PSMA-PET for staging purposes, which has been shown to have significantly higher accuracy than conventional imaging.[14] In the salvage situation, PSMA-PET achieved a sensitivity of 0.90 in cases with histologic validation in a prospective trial.[15] The SAKK 09/10 trial most likely included a proportion of patients with nodal or metastatic disease nondetectable on conventional imaging. In contrast to our study, no treatment of the pelvic lymphatics was performed and no ADT was given. Therefore, untreated metastatic or nodal disease may have had a negative association with biochemical progression despite local control. Second, in the SAKK 09/10 trial patients with evidence of macroscopic recurrences or nodal disease (defined by short diameter >1 cm) were excluded. We deliberately included patients with evidence of local and/or nodal recurrence. Patients with a higher tumor volume may require higher radiotherapy doses for adequate tumor control. Third, dose escalation in the SAKK 09/10 trial was performed to the entire prostatic fossa. In our cohort, all but one center performed sRT to the prostatic fossa, including a dose escalation on the PET scan–positive local recurrences with biological equivalent doses (EQD2 $\alpha/\beta = 1.6$ Gy) of up to 83.9 Gy. In primary prostate cancer, a meta-analysis by Vogelius and Bentzen[16] demonstrated a dose-response association with improved "biochemical no evidence of disease" with radiotherapy doses up to 80 Gy. Recent trials performing focal dose escalation of the dominant intraprostatic lesion achieved benefits in biochemical disease-free survival with doses up to 113.8 Gy.[17,18] Focal sRT dose escalation to PET-defined local recurrences with higher total doses may thus provide more benefit than dose escalation in the complete prostatic fossa. This theory, however, needs to be tested in a prospective trial.

The nomogram in our study was created to predict biochemical relapse, which was not a surrogate end point for overall survival in recurrent prostate cancer in the NRG/RTOG 9601 study collective.[19] However, 16% to 22% of patients with prostate cancer worry about PSA recurrence, which is associated with poorer quality of life.[20] Thus, an international working group recommended implementing PSA-related outcome measurements in a standard set of patient-centered outcomes.[21] In contrast, metastasis-free survival was a strong surrogate parameter for overall survival in the RTOG 9601 study,[19] in which no PSMA-PET imaging was used for restaging in case of biochemical relapse after sRT. In our study, PSMA-PET or CT was performed for 87% of patients with distant metastases after sRT and it remains unknown whether metastasis-free survival is still a surrogate end point for overall survival for patients staged with PSMA-PET.[10] Nevertheless, the nomogram performed well for FFDM prediction in the internal validation cohort, especially when considering only patients with PSMA-PET scans or CT scans for restaging (C index, 0.75). The moderate results (C index, 0.61) for the external outlier validation cohort might be explained by the low number of patients with distant metastases (n = 20), the short follow-up time, and the different treatment characteristics.

Limitations

Although our study includes a relatively large patient cohort, there are several limitations. First, due to the multicentric nature, treatment regimens differed between institutions. Likewise, the significant likelihood ratio test between a model incorporating center as a mixed effect signals the relevance of institutional practice. However, to allow our model to be transferable to centers outside of our consortium, center was not included as variable in the final model. This fact also demonstrates that there is a need for prospective trials to better define new treatment standards. Second, to guarantee anonymization and standardization of features, continuous clinical variables including the PSA measurement or radiotherapy doses were recoded into ordinal scale. This loss of information may have hindered even better prognostic assessment. Third, the number of patients in the external outlier validation cohort is relatively small, at 50 patients. This could affect the generalizability of the nomogram to patients with the respective characteristics. Fourth, due to the design our study experiences risk of bias, inherent to all retrospective studies. Optimally, our nomogram should be validated in a future prospective trial.

Conclusion

We developed, to our knowledge, the first nomogram to predict FFBF in a contemporary multicenter patient cohort receiving PSMA-PET–based sRT after radical prostatectomy that achieved competitive prognostic value. The presence of pelvic nodal recurrences detected on PSMA-PET scans was introduced as a new significant variable. The nomogram achieved stable prediction even within an external validation set that had significantly different patient and treatment characteristics.

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SUPPLEMENT 1.

eTable 1. PSMA PET Imaging Protocols Center
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SUPPLEMENT 2.

Data Sharing Statement