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Original Article

Updated Prostate Cancer Risk Groups by Prostate-specific Membrane Antigen Positron Emission Tomography Prostate Cancer Molecular Imaging Standardized Evaluation (PPP2): Results from an International Multicentre Registry Study

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Abstract

Background and objective: We established prognostic nomograms incorporating prostate-specific membrane antigen (PSMA) positron emission tomography (PET) parameters standardised by Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE; PPP1). Here, we develop an updated PPP2 risk score from a large international multicentre registry study.

Methods: We included 6128 prostate cancer patients who underwent PSMA-PET at 20 hospitals in Europe, USA, and Australia between 2013 and 2022. Investigator sites were split 2:1 into the development (4044 patients) and validation (2084 patients) cohorts. We created nomograms of version 2 (PPP2) based on Cox regression models with the least absolute shrinkage and selection operator penalty for overall survival (development cohort). Performance of both nomograms was measured using Harrell's C-index and calibration plots and a head-to-head comparison with the National Comprehensive Cancer Network (NCCN) risk score by receiver operating characteristic curves (validation cohort).

Key findings and limitations: Predictors were distant metastases (extrapelvic nodal metastases [M1a], bone metastases [M1b], and visceral metastases [M1c]), PSMA expression score, and total lesion count (visual PPP2) or total tumour volume (quantitative PPP2). C-indices (95% confidence interval) in the validation cohort were 0.80 (0.78–0.82; visual) and 0.80 (0.79–0.82; quantitative), respectively. Accuracy of both the PPP2 nomograms was superior to the NCCN risk score (n = 1034, area under the curve 0.84 vs 0.76; $p < 0.001$). The retrospective design represents a limitation of the study.

Conclusions and clinical implications: PPP nomograms were improved in an international multicentre study to predict accurately the 3- and 5-yr overall survival probabilities of prostate cancer. PPP2 yielded superior accuracy to the NCCN risk score. A free software tool has been created for PROMISE and PPP2 assessments (promise-pet.org).

ADVANCING PRACTICE

What does this study add?
We, for the first time, established an independent prognostic imaging biomarker through prostate-specific membrane antigen positron emission tomography and Prostate Cancer Molecular Imaging Standardized Evaluation (PPP2) to predict overall survival of prostate cancer patients in all disease stages. The developed prognostic nomograms stratified, for the first time, patients into low-, intermediate-, and high-risk groups.

Clinical Relevance
While PSMA PET has become a cornerstone in the staging and localization of prostate cancer, most published therapeutic trials have largely relied on conventional imaging methods such as bone scan and computed tomography. As a result, the prognostic value of PSMA PET for cancer outcomes remains unestablished. In this study, the authors conducted a multi-institutional analysis of patients with prostate cancer across all stages who underwent PSMA PET imaging. By integrating PET findings with additional clinical variables, they developed a nomogram that significantly outperforms existing prognostic models for survival. This nomogram is now available for clinical use and should be prioritized as a tool in trial design, with the potential for a rapid integration into routine clinical practice. Associate Editor: Gianluca Giannarini, M.D.

Patient Summary
In this study, we provide new risk assessment tools based on prostate-specific membrane antigen positron emission tomography imaging standardised by the Prostate Cancer Molecular Imaging Standardized Evaluation criteria to predict 3- and 5-yr overall survival probability of prostate cancer patients across all disease stages.

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1. Introduction

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) delivers superior accuracy to conventional imaging for the assessment of disease spread when [1,2]. Therefore, indications for and availability of PSMA-PET imaging for prostate cancer staging and restaging increased rapidly over the past decade.

Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) is a novel framework to standardise the reporting of PSMA-PET–based disease stage (molecular imaging tumour-node-metastasis [TNM] stage), tumour burden (total lesion count and total tumour volume), and PSMA expression [3,4].

We have previously shown that PSMA-PET by PROMISE is a spatial prognostic biomarker for overall survival (OS) [5]. Based on PROMISE metrics, novel visual and quantitative PSMA-PET PROMISE (PPP1) nomograms for the prediction of OS were created previously, which showed equal or superior prognostic accuracy to clinical risk scores. However, statistical modelling was conducted on a unicentric database and allowed only binary (low/high) risk stratification, which may have limited the accuracy and generalisability of our previous model.

To overcome this limitation, we initiated an international PROMISE Registry (NCT06320223, promise-pet.org) study and expanded patient recruitment and follow-up. Here, we present updated PSMA-PET PROMISE (PPP2) nomograms based on large multicentric data and longer follow-up for risk stratification.

2. Patients and methods

2.1. Patients

We report interim findings from an on-going retrospective, international, multicentre registry study (ClinicalTrials.gov ID NCT06320223).

We now report PROMISE Registry entries from 20 sites in North America, Europe, and Australia (Supplementary Table 1 and Supplementary Fig. 1) that conducted either ^{68}Ga-based or ^{18}F-based PSMA-PET computed tomography or whole-body PET magnetic resonance imaging in prostate cancer patients between May 29, 2013 and December 15, 2022.

Eligible for this registry study were adult patients at any age with any histologically proven subtype of prostate cancer, except neuroendocrine, at any disease stage, who underwent any type of PSMA-PET for staging or restaging purposes, with at least 36 mo of OS follow-up after PSMA-PET available in survivors. Patients were ineligible in case of a missing pathology report for prostate cancer, missing patient characteristics, primary diagnosis of neuroendocrine prostate cancer, or disseminated malignancies other than prostate cancer.

Based on available patient files before PSMA-PET, patients were classified into clinically relevant subgroups as described previously [5]. Patient files include laboratory, histopathology, and clinical data and conventional imaging reports as per local site practice.

Each investigator site submitted their data centrally using a REDCap (Research Electronic Data Capture) platform hosted on servers from the Nuclear Medicine Department of the University Hospital Essen, Germany. This multicentre registry study was approved by the ethics committee at the Medical Faculty of the University Duisburg-Essen (number 23-11501-BO). The need for study-specific patient consent was waived.

2.2. Procedures

Patients underwent PSMA-PET examination as part of their routine care as per local site practice in line with the international consensus guidelines [6]. Based on PSMA-PET images and clinical PET report, molecular imaging TNM (miTNM) status and PSMA expression score were analysed in concordance with the PROMISE V2 criteria [4]. The PSMA expression score is a simple visual metric to report the spectrum of disease positivity. A PSMA expression score of 1, 2, or 3 indicates visual uptake above the blood pool, liver/spleen, or parotid gland, respectively [4]. Total tumour load (total lesion count and total tumour volume) as well as average PSMA expression (mean standardised uptake value [SUV_{mean}]) was obtained. For the assessment of total tumour volume, we required absolute standardised uptake value thresholds according to Gafita et al [7] regardless of the software used. The National Comprehensive Cancer Network (NCCN) clinical risk score [8], the European Association of Urology (EAU) clinical risk score for biochemical recurrence (BCR) subgroup [9], and patient characteristics were obtained from medical record entries. The variables and definitions used to calculate the NCCN and EAU risk scores are presented in Supplementary Table 2.

Our primary endpoint OS was defined as the time from PSMA-PET to death from any cause. Follow-up was calculated as the time from the date of PSMA-PET to the date of the last time the patient was known to be alive. Vital status of patients was requested as per local site practice based on on-going therapies, electronic medical records, or cancer registry datasets.

2.3. Statistical analysis

We report the descriptive data as frequency and proportion for qualitative metrics, and as median and interquartile range for continuous metrics. Entire investigator sites were separated pair-wise into development and validation cohorts considering 2:1 cohort size and the following site characteristics in decreasing priority: staging group, number of patients, country, follow-up time, age at PET, and prostate-specific antigen level at PET. With respect to different site characteristics, this approach increased generalisability.

A univariate Cox regression analysis in the development cohort was examined to identify the potential predictors of OS in prostate cancer patients. We calculated hazard ratios (HRs) and 95% confidence intervals (95% CIs) for an existing factor for categorical metrics and an increase per unit for continuous metrics. A correlation analysis of the predictors using Pearson's correlation coefficient was conducted before we chose seven predictors based on the findings in

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a univariate regression analysis (local tumour, locoregional lymph nodes, extrapelvic lymph nodes, bone metastases, visceral metastases, total tumour load, and PSMA expression) for penalised Cox proportional hazard models using the least absolute shrinkage and selection operator (LASSO) penalty [10]. In case of a correlation of $r > 0.60$, we chose one of the correlated predictors based on clinical relevance and HR in the univariate analysis.

Based on the hazard models, we built new PPP2 nomograms on the basis of visual and quantitative parameters to predict 3- and 5-year OS probabilities. Harrell's C-indices with 95% CIs and survival curves were measured in the development and validation cohorts for discrimination. Calibration plots were calculated for the prediction accuracy of both nomograms in the validation cohort. For more informative calibration plots and better visualisation, we excluded patients with a 3-yr OS probability of ≥95% or a 5-yr OS probability of ≥90%. These groups of patients were added separately to the calibration curves.

We applied both nomograms to the development cohort and measured the optimal cut-off points to classify patients according to their risk stage by ensuring the largest difference between risk stages when maximising the sum of sensitivity and specificity. The final models and appropriate cut-off points are presented in the Supplementary material. Patients of the overall multicentre cohort were stratified into three-tier risk groups (high, intermediate, and low risks).

Our reassessed PPP2 nomograms using continuous risk scores were compared with the established clinical NCCN risk score (validation cohort and its initial staging subgroup) with very low, low, intermediate, high, very high, and conventional metastatic risk groups [8] and with the EAU risk score (BCR subgroup) with high- and low-risk groups [9] in the validation cohort using the area under the receiver operating characteristics curves (AUC-ROC) at the time point of PSMA-PET. We used data from patients with complete relevant data for this analysis (complete case analysis). Significance was tested using the DeLong test.

In a subanalysis, PROMISE disease categories were systematically translated from V2 to previous V1. Nomograms using PROMISE V1 [3] versus V2 [4] features were created, and continuous risk scores were compared using AUC-ROC at the time points of PSMA-PET and DeLong test.

We compared the discriminative ability of previous PPP1 nomograms [5] with that of our new PPP2 nomograms. C-indices were calculated using the current validation cohort.

A comparison of potential predictors separated for [^{68}Ga]Ga-PSMA-11 and ^{18}F-based PSMA radiopharmaceuticals, that is, [^{18}F]-PSMA-1007 and [^{18}F]-rhPSMA-7.3, was conducted in the overall cohort using a univariate regression analysis. Other radiopharmaceuticals were not taken into account for this analysis (ie, [^{68}Ga]Ga-PSMA-I&T [n = 129, 2.1%], [^{18}F]-DCFPyl [n = 11, 0.2%], and radiopharmaceuticals mentioned as "other" [n = 15, 2.4%]).

All statistical analyses were calculated using R (version 4.2.1). R packages "glmnet", "survival", "rms", "pROC", and "survMisc" were used. A p value of <0.05 was considered to indicate statistical significance.

3. Results

In total, 6310 patients were eligible across 20 international investigator sites, of whom 182 were excluded due to insufficient quality of PET imaging regarding volumetric assessment. Therefore, investigator sites with retrospectively collected data of a total of 6128 patients were allocated into the development (n = 4044) and validation (n = 2084) cohorts using previously described criteria (Supplementary Fig. 2).

Patients' baseline characteristics in this multicentre cohort were balanced between the development and validation cohorts (Table 1). The date of data cut-off was September 30, 2024, when 1915 patients had died. At this time point, 4213 patients were still alive at 36 mo after PET or later.

Findings of the univariate regression analysis for the development cohort showed that all the 16 features, except for local tumour stages T2u (unifocal expression), T2m (multifocal expression), T3a (extracapsular extension), and Tr (presence of local recurrence after radical prostatectomy), were predictors of OS (Fig. 1).

We built new quantitative and visual PPP2 nomograms in our multicentre development cohort to predict the 3- and 5-yr OS probabilities. A correlation analysis between prognostic features revealed high correlation between tumour SUV_{mean} and PSMA expression score (r = 0.68), as well as the lowest and highest PSMA expression scores (r = 0.78). Therefore, we decided to include only the PSMA expression score (highest) as a predictor in both PPP2 nomograms based on clinical relevance and HR in the univariate analysis.

The visual and quantitative PPP2 nomograms, created using the development cohort, are presented in Fig. 2. The predictors selected for the visual nomogram using a Cox regression analysis with LASSO penalty were extrapelvic lymph node metastases, bone metastases, visceral metastases, total lesion count, and PSMA expression score (highest). We reached C-indices of 0.81 (0.80–0.83) in the development cohort and 0.80 (0.78–0.82) in the validation cohort. Calibration plots, generated using the validation cohort, are presented to demonstrate the model's predicted OS probability versus observed OS probability, showing slight deviation from the ideal line for some patients. The majority of patients revealed ideal prediction accuracy. The predictors included in the quantitative nomogram were extrapelvic lymph node metastases, bone metastases, visceral metastases, total tumour volume (per litre), and PSMA expression score (highest). C-indices remained stable in the development (0.82 [95% CI 0.80–0.83]) and validation (0.80 [0.79–0.82]) cohorts. The calibration plot for the quantitative PPP2 nomogram show slight deviation from the optimal prediction for some patients, while the majority of patients revealed ideal prediction accuracy.

We stratified patients in the total cohort into low-, intermediate-, and high-risk groups by optimal cut-off points for both PPP2 nomograms. Survival curves present risk group stratification for the initial staging and BCR subgroups in Fig. 3, and for the nonmetastatic castration-

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Table 1 – Patient characteristics in the development (n = 4044), validation (n = 2084), and combined (n = 6128) cohorts

	Development cohort		Validation cohort		Total cohort	
Number of cases	4044		2084		6128	
Number of cases per staging group						
Initial staging	719	(18)	277	(13)	996	(16)
BCR	2139	(53)	1197	(57)	3336	(54)
nmCRPC	246	(6.1)	85	(4.1)	331	(5.4)
mCRPC	618	(15)	341	(16)	959	(16)
mHSPC	322	(8.0)	184	(8.8)	506	(8.3)
Died as of data cut-off						
Yes	1210		705		1915	
Age at PET (yr)	71	(65–76)	70	(64–75)	71	(65–76)
Management after PET						
Surgery	199	(4.9)	154	(7.4)	353	(5.8)
Radiation therapy	1239	(301)	441	(21)	1680	(27)
ADT	403	(10)	140	(6.7)	543	(8.9)
Androgen-receptor pathway inhibitors	156	(3.9)	35	(1.7)	191	(3.1)
Chemotherapy	133	(3.3)	35	(1.7)	168	(2.7)
Immunotherapy	3	(0.1)	1	(0)	4	(0.1)
Other	295	(7.3)	254	(12)	549	(9.0)
Missing	1616	(40)	1024	(49)	2640	(43)
PSA level at PET	3.1	(0.7–12)	2.4	(0.7–9.4)	2.9	(0.7–11)
miT						
miT0	2217	(55)	1369	(66)	3586	(59)
miT2	770	(19)	340	(16)	1110	(18)
miT3	277	(6.8)	88	(4.2)	365	(6.0)
miT4	129	(3.2)	54	(2.6)	183	(3.0)
miTr	651	(16)	233	(11)	884	(14)
miN						
miN0	2694	(67)	1323	(64)	4017	(66)
miN1	694	(17)	418	(20)	1112	(18)
miN2	656	(16)	343	(16)	999	(16)
miM						
miM0	2248	(56)	1014	(49)	3262	(53)
miM1a	1093	(27)	652	(31)	1745	(29)
miM1b	1197	(30)	733	(35)	1930	(32)
miM1c	218	(5.4)	155	(7.4)	373	(6.1)
Total lesion count						
0–5	3020	(75)	1488	(71)	4508	(74)
6–20	483	(12)	258	(12)	741	(12)
>20	541	(13)	338	(16)	879	(14)
Total tumour volume, ml (IQR)	2.0	(0–18)	2.1	(0–22)	2	(0–19)
Total tumour SUVmean (IQR)	6.4	(0–9.0)	6.3	(2.1–8.8)	6.3	(0–8.9)
PSMA expression score (highest)						
0	1051	(26)	445	(21)	1496	(24)
1	721	(18)	431	(21)	1152	(19)
2	1036	(26)	557	(27)	1593	(26)
3	1236	(31)	651	(31)	1887	(31)

ADT = androgen deprivation therapy; BCR = biochemical recurrence; IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; PET = positron emission-tomography; PSMA = prostate-specific membrane antigen; PSA = prostate-specific antigen; SUVmean = mean standardised uptake value.
Data are n (%) or median (IQR) unless otherwise stated.
[†]Androgen-receptor pathway inhibitors include abiraterone, enzalutamide, darolutamide, and apalutamide.

resistant prostate cancer (nmCRPC), metastatic hormone-sensitive prostate cancer, and metastatic castration-resistant prostate cancer subgroups in Fig. 4. Discrimination ability for stratification into low- versus intermediate- versus high-risk group was accurate (all $p < 0.001$), regardless of disease stage.

We calculated continuous risk scores according to PPP2 for patients with the available NCCN and EAU (BCR subgroup) data in the validation cohort (n = 1034, ie, complete case analysis). The AUC-ROC values of the visual and quantitative PPP2 nomograms for the entire validation cohort, initial staging, or BCR subgroup were significantly higher when compared with the NCCN or EAU risk score (Table 2). Survival plots represent the discrimination ability of NCCN versus visual versus quantitative PPP2 nomograms for the entire validation cohort (Supplementary Fig. 3).

Differences of PROMISE V1 versus V2 in miTNM stages were detected for 784 (13%) patients in the overall cohort. Prognostic accuracy were accurate, regardless of PROMISE version (V1 vs V2; n = 2084; AUC PPP2 visual: 0.79 [0.78–0.79] vs 0.79 [0.79–0.79], p = 0.11; AUC PPP2 quantitative: 0.79 [0.79–0.80] vs 0.79 [0.79–0.80], p = 0.56; data not shown).

External validation of PPP1 versus PPP2 nomograms was conducted using the current international, multicentre validation cohort. C-indices of new PPP2 nomograms were slightly superior to those of PPP1 nomograms (0.79 [0.77–0.80]) in the current validation cohort.

We present a univariate regression analysis for [^{68}Ga]Ga-PSMA-11 (n = 5119, 84%) and ^{18}F-based PSMA (n = 937, 15%) imaging in the overall cohort in Supplementary Fig. 4. HRs of all predictors were similar for

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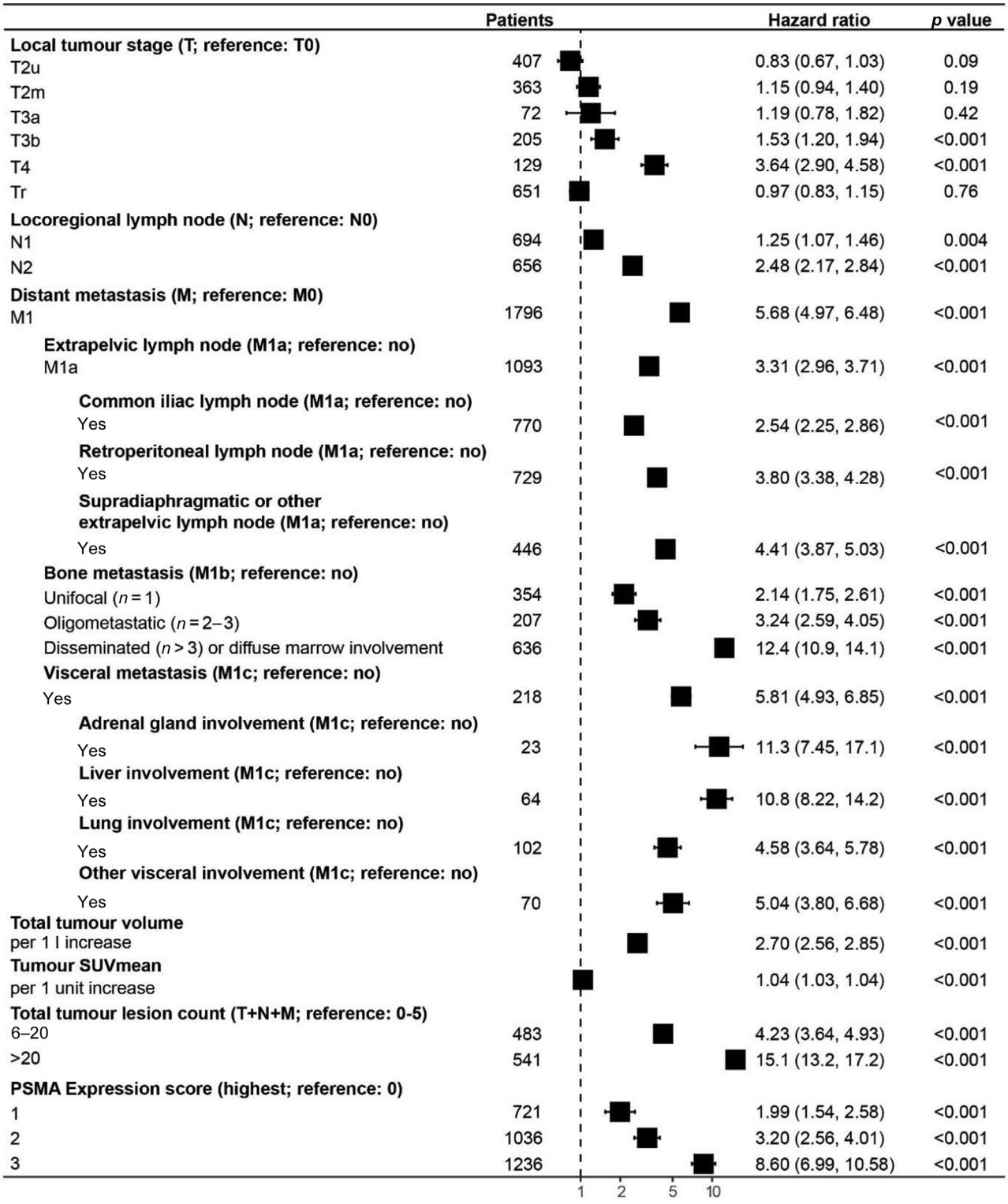

Fig. 1 – Univariate regression findings of PROMISE and PSMA-PET features in the development cohort (*n* = 4044). Forest plot summarises the univariate regression analysis of PROMISE features to identify the potential predictors of overall survival in the development cohort (*n* = 4044). Estimates are hazard ratio with 95% CI. T, N, and M refer to, respectively, tumour, node, and metastasis in the molecular imaging TNM classification. CI = confidence interval; PET = positron emission tomography; PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation; - PSMA = prostate-specific membrane antigen; SUVmean = mean standardised uptake value.

both radiopharmaceuticals, except for distant metastases (M1), bone metastases with disseminated or diffuse marrow involvement (M1b), total lesion count (>20), and PSMA expression score (highest = 3). Overall, the HR pattern for both radiotracers was similar. Stratification into low- versus intermediate- versus high-risk group was accurate, regardless of the radiopharmaceutical used (Supplementary Fig. 5).

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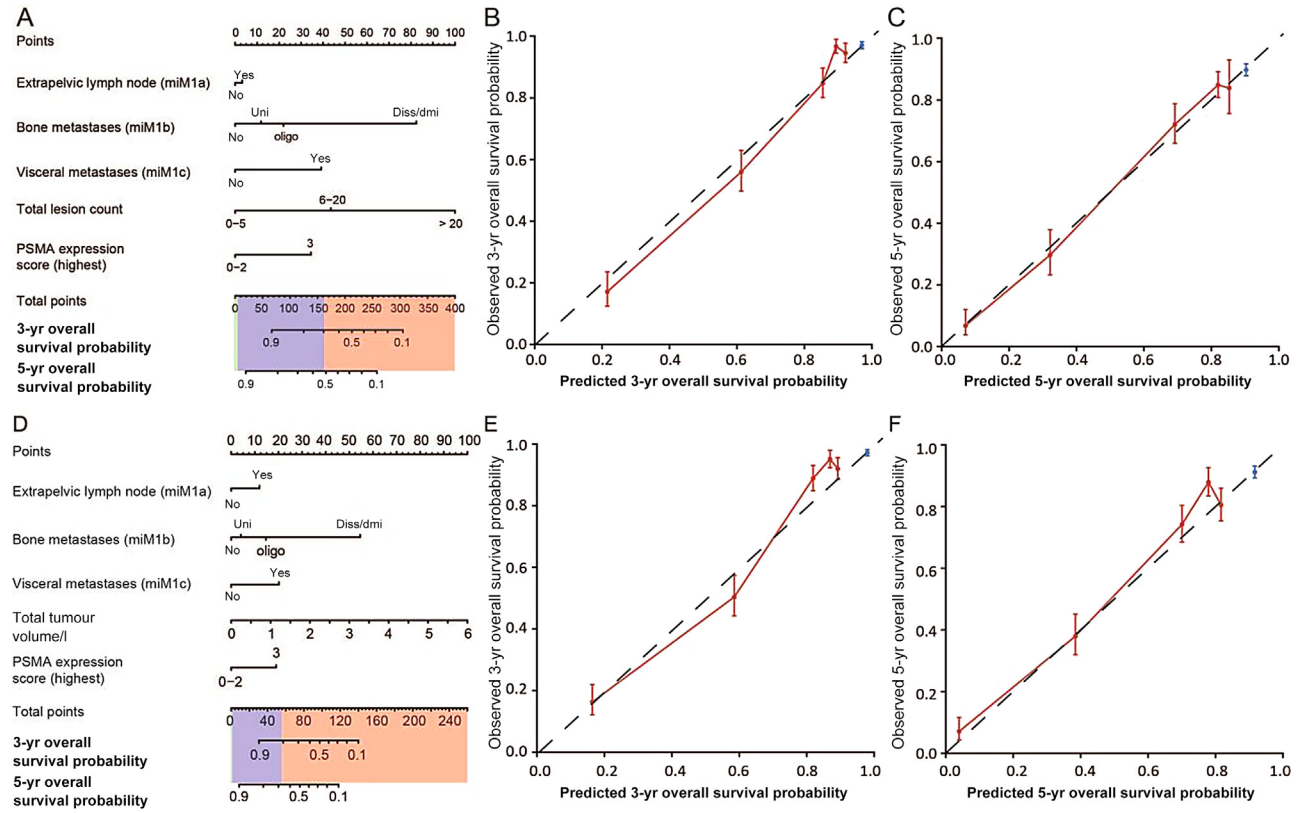

Fig. 2 – Visual and quantitative PPP2 nomogram to predict the overall survival probability in prostate cancer patients at 3 and 5 yr following PSMA-PET. (A and D) The nomogram created based on the development cohort combines PROMISE features indicating a certain number of points in the top row for each feature. The sum of points (total points) determines survival probabilities and respective risk groups (green = low risk, blue = intermediate risk, and red = high risk). Calibration plots generated based on the validation cohort illustrate the nomogram-predicted overall survival probability on the *x* axis and the observed overall survival probability on the *y* axis for (B and E) 3 yr and (C and F) 5 yr. The dashed diagonal line represents identical predicted and observed probabilities and thus ideal calibration. For more informative calibration (red), patients with a 3-yr overall survival probability of ≥95% or a 5-yr overall survival probability of ≥90% were added separately to the calibration curve (blue). Diss/dmi = disseminated (*n* > 3) or diffuse marrow involvement; Oligo = oligometastatic (*n* = 2–3); PET = positron emission tomography; PPP2 = PSMA-PET PROMISE version 2; PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation; PSMA = prostate-specific membrane antigen; Uni = unifocal (*n* = 1).

4. Discussion

PSMA-PET provides quantifiable and reproducible spatial data for disease spread and PSMA expression in patients with prostate cancer, previously summarised as a PSMA spatial biomarker [11]. In a previous unicentric cohort, we created nomograms for the prediction of OS outcomes based on the PROMISE reporting standard. However, reassessment in an international multicentre dataset is needed for improved accuracy and reproducibility of the model.

Updated PPP2 nomograms were created from an international registry study. PPP2 nomograms stratify risks across the entire disease spectrum of prostate cancer. Furthermore, a simple visual score for PSMA expression level was introduced, which facilitates fast and reproducible interpretation. Overall, the performance of visual versus quantitative PPP2 prognostication was similar, which facilitates universal PPP2 risk stratification at imaging or oncology centres worldwide. Implementation of PROMISE and PPP2 is supported by a free software and web application provided by the Essen University Hospital (promise-pet.org).

The C-index of PPP2 nomograms was 0.80 in the validation cohort, which indicates ideal prognostic discrimination. Updated PPP2 nomograms were more accurate than the previous PPP1 or clinical NCCN or EAU criteria in independent validation cohorts. In line, previous external validation of the NCCN criteria for a subgroup of intermediate-risk patients [12,13] and for a subgroup of high-risk and very–high-risk patients revealed no difference in outcome [14]. Previous external validation of the EAU risk score indicates moderate discriminative ability for BCR patients [9].

The risk prediction ability of PPP2 is robust and reproducible across different applications. PPP2 delivered significant stratification in the entire cohort and all subgroups. Stratification was not impacted considerably by the choice of radioligand (^{68}Ga vs ^{18}F) or PROMISE version (V1 vs V2).

The reassessed quantitative PPP2 nomogram reached slightly higher concordance for survival prediction than the visual PPP2 nomogram. Metrics of both nomograms are similar, except for the total tumour load. Total tumour volume is a continuous predictor that depicts a broad range for disease load, whereas total lesion count was limited to categories. Several previous studies confirm a prognostic value of PSMA total tumour volume quantified in accor-

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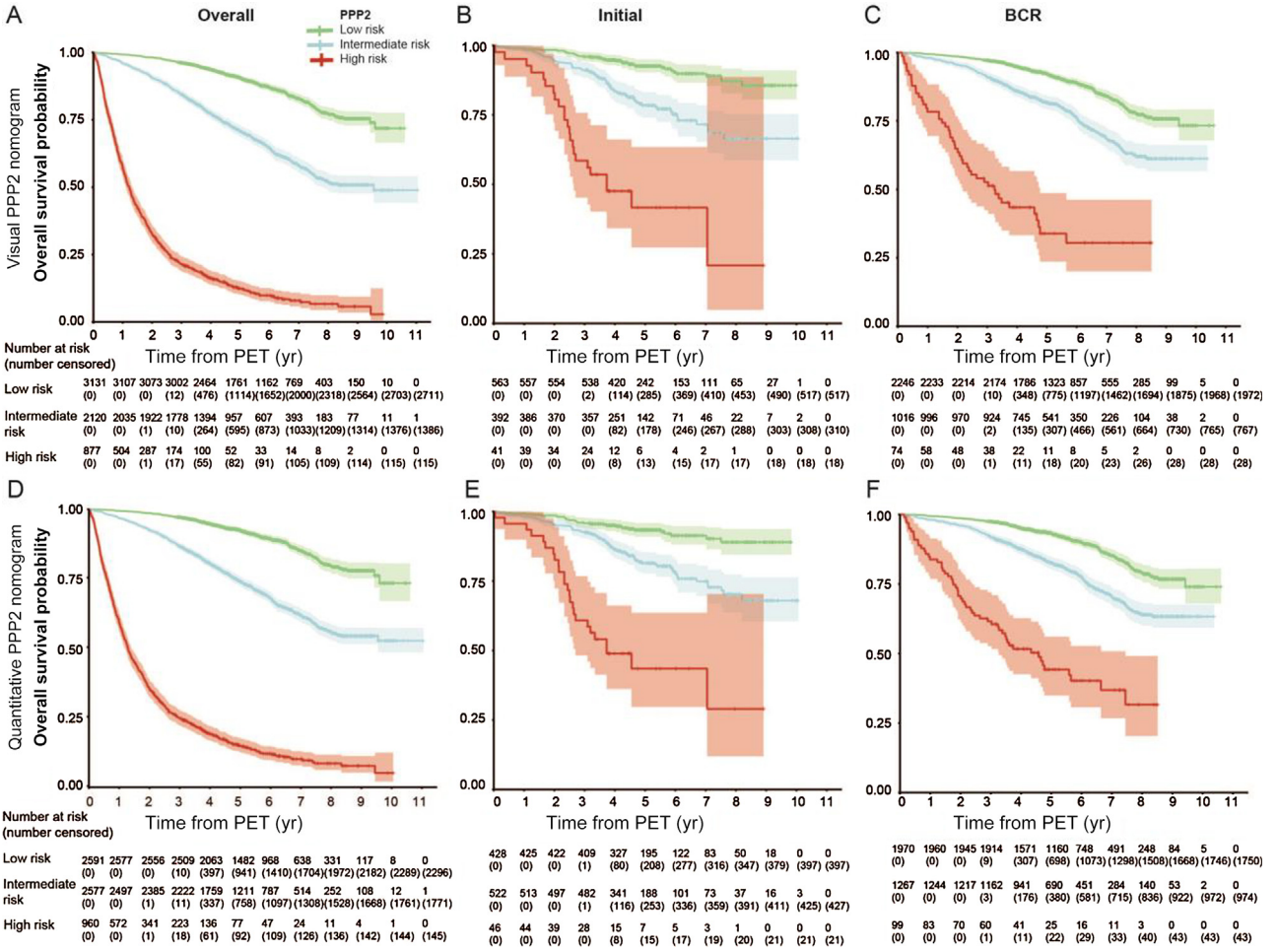

Fig. 3 – Overall survival curves for the total cohort, initial staging, and biochemical recurrence subgroups. All patients were stratified into low-, intermediate-, and high-risk groups by (A) visual and (D) quantitative PPP2 nomograms. In addition, subgroups for (B and E) initial staging and (C and F) BCR are presented. BCR = biochemical recurrence; PET = positron emission tomography; PPP2 = PSMA-PET PROMISE version 2; PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation; PSMA = prostate-specific membrane antigen.

dance with Gafita et al [7,15–17]. These findings underline the need to introduce software solutions for the assessment of whole-body tumour volume on PSMA-PET imaging in routine clinical practice.

Here, we introduce several novel aspects to risk assessment: (1) PET-based prostate cancer pan-stage risk assessment has now been validated in a large multicentric patient cohort; (2) PPP2 offers a three-tier framework that is essential for incorporation into future research protocols and management strategies; specifically, PPP2 could inform decisions ranging from observation to local or low-intensity therapy versus more aggressive systemic treatment, tailored to low-, intermediate-, and high-risk groups; (3) PPP2 accurately risk stratifies patient subgroups with BCR or nmCRPC, for which current risk models were either moderately accurate [9] or nonexistent; and (4) robustness of PPP2 predictions across different disease stages, interpretation criteria, and radiotracer protocols underlines validity and reproducibility of PSMA spatial biomarker data. Reproducible PPP2 assessment is of critical importance given a large number of PET or single photon emission computed tomography radiotracers are expected to enter clinical use in the near future.

Although the 3- and 5-yr OS probabilities can be predicted accurately, categorisation of risk does not lend itself to the practice of individualised medicine. In many cases, the patient's preference and current medical status will guide treatment decisions. Therefore, for decision-making, actual risk prediction should be provided rather than a categorised risk group.

Our study comes with limitations. A lack of prospective study design results in heterogeneous procedures and varying levels of completeness in patient files. Imaging centres are focused on the PSMA-PET procedure, and thus deeper information on Gleason pattern, clinical or pathological T stage, and biopsy cores may not always be available to calculate the NCCN and EAU risk scores in clinical routine. Timing of PET and type of reporting were not standardised before the indication of PSMA-PET. However, PET was reviewed centrally and standardised using the PROMISE V2 criteria for this study. The limited availability of PSMA-PET after its introduction might have led to a selection bias due to the inclusion of patients in early disease stages with a higher risk according to D'Amico et al [18] or the NCCN [8]. Furthermore, the number of patients and disease stage varied between investigator sites and countries, depending

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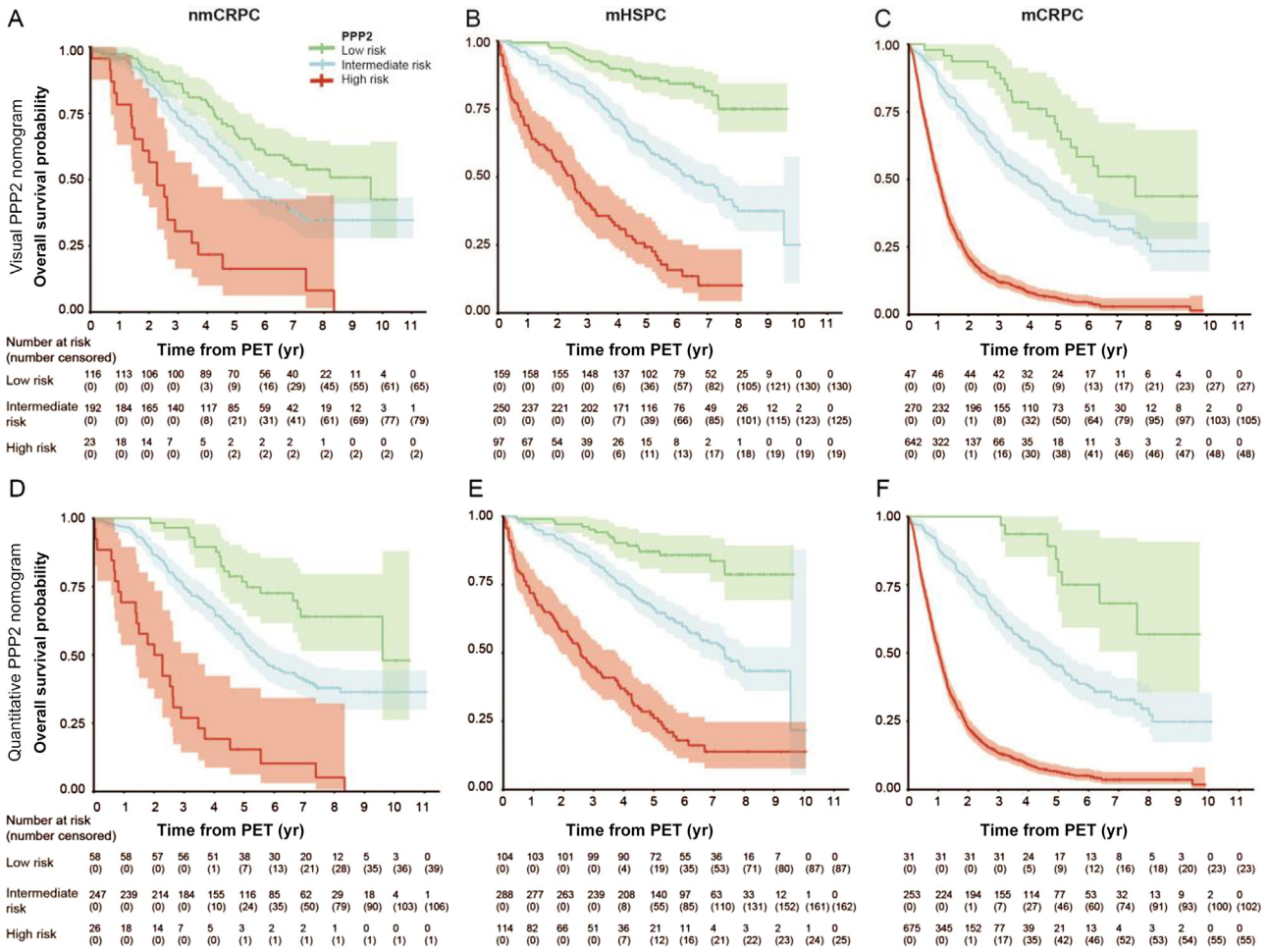

Fig. 4 – Overall survival curves for the nmCRPC, mHSPC, and mCRPC subgroups. Subgroups of patients for nmCRPC, mHSPC, and mCRPC were stratified into low-, intermediate-, and high-risk groups considering optimal cut-off points for (A–C) visual and (D–F) quantitative PPP2 nomograms. mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; PET = positron emission tomography; PPP2 = PSMA-PET PROMISE version 2; PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation; PSMA = prostate-specific membrane antigen.

Table 2 – Prognostic accuracy of continuous PPP2 nomograms compared with the NCCN and EAU clinical risk scores in the validation cohort using a complete case analysis

		AUC PPP2 nomogram		AUC clinical risk score		*p* value [a]
NCCN (validation cohort, *n* = 1034)	Visual PPP2 nomogram	0.84	(0.78–0.90)	0.76	(0.64–0.87)	<0.0001
	Quantitative PPP2 nomogram	0.84	(0.78–0.91)	0.76	(0.64–0.87)	<0.0001
NCCN (initial staging subgroup, *n* = 85)	Visual PPP2 nomogram	0.76	(0.69–0.82)	0.52	(0.11–0.93)	0.0060
	Quantitative PPP2 nomogram	0.74	(0.68–0.80)	0.52	(0.14–0.90)	0.0070
EAU (BCR subgroup, *n* = 344)	Visual PPP2 nomogram	0.59	(0.56–0.61)	0.46	(0.21–0.70)	0.016
	Quantitative PPP2 nomogram	0.61	(0.56–0.66)	0.46	(0.19–0.72)	0.0050

AUC = area under the receiver operating characteristics curve; BCR = biochemical recurrence; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; PPP2 = PSMA-PET PROMISE version 2; PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation; PSMA-PET = prostate-specific membrane antigen positron emission-tomography.

[a] *p* values = comparison between AUC of the PPP nomogram and AUC of the NCCN or EAU clinical risk score using the DeLong test.

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on availability and reimbursement. Our international study design increased the generalisability of nomograms, but also a potential selection bias. To reduce the bias, sites with similar characteristics were paired and split into development and validation cohorts to ensure comparability. Although cancer-specific survival has advantages compared with OS, the absence of a pathology review as the standard procedure for death certificates in the majority of patients limits the use of cause-specific survival as the primary endpoint. Detailed treatment data following PET were missing in a considerable number of patients, but this does not impact the survival analyses. However, treatment decisions cannot be derived from PPP2 alone. Management pathways must first be discussed and defined by interdisciplinary expert groups.

5. Conclusions

In summary, improved PSMA-PET PROMISE nomograms (PPP2) were created from our large international multicentre registry study, which predict 3- and 5-yr OS probabilities for prostate cancer accurately. PPP2 is a new independent risk stratification tool for clinical trials and routine practice, also available as a web application (promise-pet.org).

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Supplementary data

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