Nomograms to predict outcomes after ^{177}Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study

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Summary

Background Lutetium-177 (^{177}Lu) prostate-specific membrane antigen (^{177}Lu-PSMA) is a novel targeted treatment for patients with metastatic castration-resistant prostate cancer (mCRPC). Predictors of outcomes after ^{177}Lu-PSMA to enhance its clinical implementation are yet to be identified. We aimed to develop nomograms to predict outcomes after ^{177}Lu-PSMA in patients with mCRPC.

Methods In this multicentre, retrospective study, we screened patients with mCRPC who had received ^{177}Lu-PSMA between Dec 10, 2014, and July 19, 2019, as part of the previous phase 2 trials (NCT03042312, ACTRN12615000912583) or compassionate access programmes at six hospitals and academic centres in Germany, the USA, and Australia. Eligible patients had received intravenous 6·0–8·5 GBq ^{177}Lu-PSMA once every 6–8 weeks, for a maximum of four to six cycles, and had available baseline [^{68}Ga]Ga-PSMA-11 PET/CT scan, clinical data, and survival outcomes. Putative predictors included 18 pretherapeutic clinicopathological and [^{68}Ga]Ga-PSMA-11 PET/CT variables. Data were collected locally and centralised. Primary outcomes for the nomograms were overall survival and prostate-specific antigen (PSA)-progression-free survival. Nomograms for each outcome were computed from Cox regression models with LASSO penalty for variable selection. Model performance was measured by examining discrimination (Harrell's C-index), calibration (calibration plots), and utility (patient stratification into low-risk *vs* high-risk groups). Models were validated internally using bootstrapping and externally by calculating their performance on a validation cohort.

Findings Between April 23, 2019, and Jan 13, 2020, 414 patients were screened; 270 (65%) of whom were eligible and were divided into development (n=196) and validation (n=74) cohorts. The median duration of follow-up was 21·5 months (IQR 13·3–30·7). Predictors included in the nomograms were time since initial diagnosis of prostate cancer, chemotherapy status, baseline haemoglobin concentration, and [^{68}Ga]Ga-PSMA-11 PET/CT parameters (molecular imaging TNM classification and tumour burden). The C-index of the overall survival model was 0·71 (95% CI 0·69–0·73). Similar C-indices were achieved at internal validation (0·71 [0·69–0·73]) and external validation (0·72 [0·68–0·76]). The C-index of the PSA-progression-free survival model was 0·70 (95% CI 0·68–0·72). Similar C-indices were achieved at internal validation (0·70 [0·68–0·72]) and external validation (0·71 [0·68–0·74]). Both models were adequately calibrated and their predictions correlated with the observed outcome. Compared with high-risk patients, low-risk patients had significantly longer overall survival in the validation cohort (24·9 months [95% CI 16·8–27·3] *vs* 7·4 months [4·0–10·8]; p<0·0001) and PSA-progression-free survival (6·6 months [6·0–7·1] *vs* 2·5 months [1·2–3·8]; p=0·022).

Interpretation These externally validated nomograms that are predictive of outcomes after ^{177}Lu-PSMA in patients with mCRPC might help in clinical trial design and individual clinical decision making, particularly at institutions where ^{177}Lu-PSMA is introduced as a novel therapeutic option.

Funding Prostate Cancer Foundation.

Introduction

Lutetium-177 (^{177}Lu) prostate-specific membrane antigen (^{177}Lu-PSMA) is a radiolabelled small-molecule inhibitor that binds with high affinity to prostate-specific membrane antigen (PSMA) and delivers β particle radiation. Several phase 2 studies and larger multicentre retrospective analyses have established the antitumour activity and favourable safety profile of ^{177}Lu-PSMA in men with metastatic castration-resistant prostate cancer (mCRPC).[1,2] The TheraP trial[3] showed superior prostate-specific antigen (PSA) responses and progression-free survival in patients who received [^{177}Lu]Lu-PSMA-617 compared with

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For the **online risk calculator** see https://www.uclahealth.org/nuc/nomograms

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published in English from database inception to April 23,2019, with the terms "LuPSMA", "prognosis", "nomogram", "PSMA", and "mCRPC". Our search yielded identification of five prognostic models that were developed using data from patients who were in an early stage of metastatic castration-resistant prostate cancer (mCRPC) and had received first-line or second-line treatments. We found no prognostic models described for late-stage mCRPC for patients treated with lutetium-177 (^{177}Lu) prostate-specific membrane antigen (^{177}Lu-PSMA).

Added value of this study

An international database containing data from men with late-stage mCRPC treated with ^{177}Lu-PSMA at six institutions in Germany, the USA, and Australia was established. Using both clinical trial and real-world data, a collaborative group of clinical experts and biostatisticians developed prognostic models for outcomes after ^{177}Lu-PSMA, which, to our knowledge, are the first such models. Previously identified variables in early-stage mCRPC were reinforced, and additional variables derived from [^{68}Ga]Ga-PSMA-11 PET/CT were identified with novel interactions between covariates. To enable immediate clinical implementation on a large scale, an online risk calculator was developed and is available online.

Implications of all the available evidence

Our nomograms for outcomes after ^{177}Lu-PSMA in late-stage mCRPC could help in trial design and provide guidance for clinicians. Robust and accurate risk assessment might aid physician decision making regarding treatment plans and clinical trial patient stratification. These models can be updated as new clinical trial data become available.

patients who received cabazitaxel. In the phase 3 VISION trial,[4] [^{177}Lu]Lu-PSMA-617 improved overall survival and imaging-based progression-free survival when added to standard of care in patients with mCRPC. Since the first prospective signals of its efficacy,[1] the number of clinical trials of ^{177}Lu-PSMA and compassionate use of the treatment are expanding rapidly. Hence, there is growing need for predictors of outcomes after ^{177}Lu-PSMA to support clinical implementation of this novel therapy and rationale design for the next generation of ^{177}Lu-PSMA trials. The armamentarium for mCRPC has greatly expanded in the past decade with novel agents, and more than seven drugs are currently available for mCRPC.[5] Identification of patient candidates most likely to benefit from a certain therapy represents an unmet need in the therapeutic landscape of advanced prostate cancer.

See Online for appendix

PSMA ligands are also used for diagnostic purposes using whole-body PET imaging (PSMA-PET).[6] Candidates for ^{177}Lu-PSMA are typically screened with a PSMA-PET scan to verify sufficient PSMA expression of tumour lesions. Guiding treatment decisions with PSMA-specific vectors such as findings from the entry PSMA-PET might lead to better treatment outcomes. Considerable efforts have been dedicated to understanding tumour heterogeneity and developing prognostic nomograms in men with mCRPC who receive first-line or second-line treatments.[7,8] However, there are still no models that adequately assess the prognosis for patients who are later in the mCRPC course and are candidates for ^{177}Lu-PSMA therapy.

We aimed to develop nomograms to predict outcomes in patients with mCRPC who are candidates for ^{177}Lu-PSMA. We hypothesised that a combination of baseline PSMA-PET-derived and clinical parameters can improve evidence-based selection of candidates for this therapy and aid clinical decision making and subsequent implementation in clinical trials.

Methods

Study design and participants

We did a multicentre, retrospective study. Nomograms for predicting outcomes after ^{177}Lu-PSMA treatment were developed and validated using data from six hospitals and academic institutions in Germany, the USA, and Australia (appendix p 5).

We screened patients who had received [^{177}Lu]Lu-PSMA-617 or [^{177}Lu]Lu-PSMA-I&T between Dec 10, 2014, and July 19, 2019, as part of the previous phase 2 clinical trials (NCT03042312, ACTRN12615000912583) or compassionate use access programmes at the participating sites. Eligible patients had been treated with ^{177}Lu-PSMA administered by intravenous injection of 6·0–8·5 GBq once every 6–8 weeks, for a maximum of four to six cycles in absence of progression or severe toxicity according to the treating physician. Eligible patients had available baseline [^{68}Ga]Ga-PSMA-11 PET/CT scan, clinical data, and survival outcomes (appendix p 5). We excluded patients who received ^{18}F-labelled PSMA-PET at baseline.

We followed a prospectively defined protocol (appendix), which was approved by the institutional review board of the University of California Los Angeles (number 19-000896). The requirement to obtain informed consent for inclusion in this analysis was waived by the institutional review board.

Procedures

We divided the study dataset into development and validation cohorts (approximately 2:1) and followed predefined criteria to ensure comparability between the cohorts. Each cohort had an equal number of institutions,

included patients enrolled in both clinical trials and compassionate access programmes, and included patients treated in different countries. 26 pretherapeutic parameters were collected (appendix p 6); these included information about demographics, initial diagnosis of prostate cancer, treatment history, baseline clinical status, baseline laboratory tests, and baseline [^{68}Ga]Ga-PSMA-11 PET/CT tumour characteristics. 18 (69%) of 26 collected parameters were tested in the models as putative predictors for outcome after ^{177}Lu-PSMA. A number of 18 putative predictors allowed for nine to ten events per predictor for the primary outcomes in the training cohort, which satisfied the recommended minimal number of events per predictor.[9] The putative predictors were chosen based on previous work that showed their potential prognostic value in mCRPC, and based on the investigators clinical experience with ^{177}Lu-PSMA.[2,10–13]

Clinical laboratory assessments were done within 24 h before each cycle. Screening [^{68}Ga]Ga-PSMA-11 PET/CT was done within 10 weeks of treatment initiation. Treatment and imaging protocols are detailed in the appendix (pp 1, 8). [^{68}Ga]Ga-PSMA-11 PET/CT scans were analysed centrally by a nuclear medicine physician (AG). [^{68}Ga]Ga-PSMA-11 PET/CT tumour characteristics included the pattern of spread by molecular imaging TNM classification system,[14] calculated using a semi-automatic tool (ePROMISE version 1.0), and quantitative whole-body tumour burden assessment using a semi-automatic software (qPSMA version 1.0).[15] Output parameters from qPSMA tested in the models were number of metastatic lesions and tumour average standardised uptake value (SUV_{mean}) as a surrogate measure of tumour PSMA target expression (PSMA-PET SUV correlates significantly with tumour PSMA expression measured by immunohistochemistry).[16]

Outcomes

The primary outcomes for the nomograms were overall survival and PSA-progression-free survival. The secondary outcome was PSA decline of 50% or more (PSA50) from baseline at any time during treatment. Overall survival was defined as the time from treatment initiation to death from any cause; PSA-progression-free survival was defined as the time from treatment initiation to PSA progression or death from any cause.[17] PSA progression, according to Prostate Cancer Clinical Trials Working Group 3 criteria, was defined as a 25% or greater increase in PSA and at least 2 ng/mL above the nadir.[17] The first reported PSA progression was confirmed by repeated PSA measurements at least 3 weeks later whenever possible, or by unequivocal tumour progression as measured by imaging, clinical assessment, or both. PSA-progression-free survival was chosen as an endpoint instead of radiographical progression-free survival because inconsistent timepoints and different imaging modalities were used for radiological assessment across the cohorts. By contrast, PSA concentrations were measured uniformly across the study centres in each treatment cycle.

Statistical analysis

The sample size was derived on the basis of the available data and no power calculation for sample size was done upfront. Descriptive statistics were reported as frequencies and proportions for categorical variables, and median (IQR) or mean (SD) for continuous variables. The median (95% CI) overall survival and PSA-progression-free survival were estimated using the Kaplan-Meier method. Patients who did not have survival data available were not included in the final analysis. The proportion of patients who had a PSA50 was recorded. Differences in overall survival and PSA-progression-free survival between the development and validation cohorts were determined using the log-rank test. The distribution of putative variables between the development and validation cohorts was compared using the Wilcoxon Mann-Whitney test (for continuous variables) or exact Fisher test (for categorical variables).

Model building followed a prospectively defined plan. A penalised Cox's proportional hazards model using the adaptive least absolute shrinkage and selection operator (LASSO) was used.[18] Cox regression analyses were applied to estimate the hazard ratios (HRs) or odds ratios and their 95% CIs or p values. Prediction accuracy of overall survival and PSA-progression-free survival models was evaluated using two methods. First, the discrimination was measured by the Harrell's concordance index

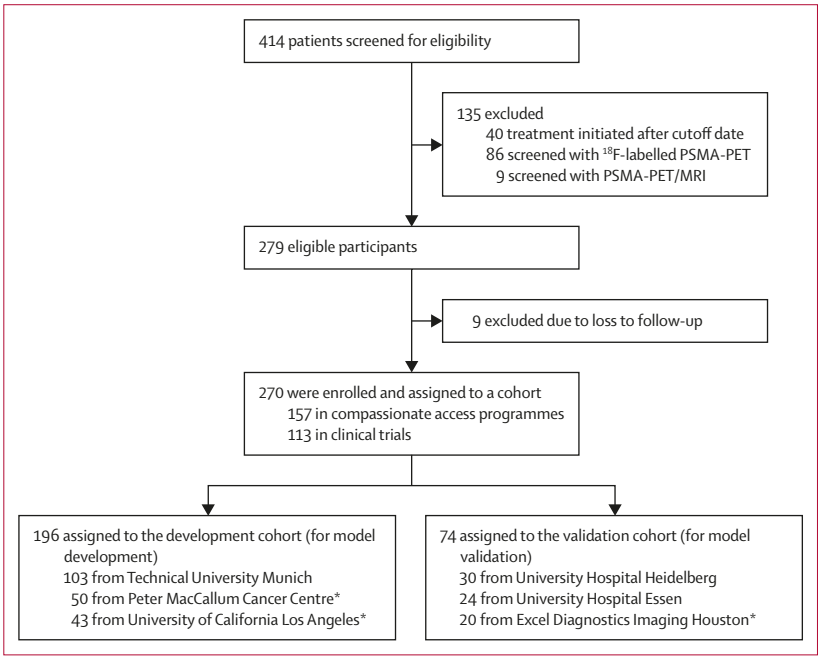

Figure 1: **Study profile**
https://publikacije.stat.gov.rs/G2021/Pdf/G20211180.pdf. *Patients enrolled in phase 2 clinical trials (NCT03042312, ACTRN12615000912583).

	Development cohort (n=196)	Validation cohort (n=74)	p value*
Median age, years	72 (67–76)	70 (65–76)	0·17
Median time since initial diagnosis, years	7 (4–12)	6 (4–12)	0·21
Initial NCCN risk group			0·41
Low risk	7 (4%)	4 (5%)	..
Intermediate risk	39 (20%)	9 (12%)	..
High risk	76 (39%)	29 (39%)	..
Metastatic	74 (38%)	32 (43%)	..
Treatment history			
Previous docetaxel	160 (82%)	59 (80%)	0·72
Second-line chemotherapy	66 (34%)	26 (35%)	0·88
Androgen receptor signalling inhibitor	189 (96%)	68 (92%)	0·19
Baseline clinical status			
ECOG performance status ≥2	23 (12%)	17 (23%)	0·033
ECOG performance status <2	173 (88%)	57 (77%)	..
Symptomatic disease	140 (71%)	38 (51%)	0·0024
Asymptomatic disease	56 (29%)	36 (49%)	..
Baseline laboratory tests			
Alkaline phosphatase ≥ULN	76 (39%)	37 (50%)	0·099
Alkaline phosphatase <ULN	120 (61%)	37 (50%)	..
Median PSA, ng/mL	117 (30–391)	135 (62–387)	0·61
Median haemoglobin, g/dL	11·3 (10·2–12·6)	10·8 (9·3–12·9)	0·14
PSMA-PET tumour characteristics			
Number of metastases (≥20)	147 (75%)	55 (74%)	1·00
Number of metastases (<20)	49 (25%)	19 (26%)	..
SUV_{mean}	8·6 (6·7–10·8)	7·9 (6·5–10·7)	0·22
Pelvic nodal involvement (N1)	96 (49%)	36 (49%)	1·00
Distant nodal involvement (M1a)	129 (66%)	50 (68%)	0·88
Bone involvement (M1b)	179 (91%)	68 (92%)	1·00
Liver involvement	30 (15%)	11 (15%)	1·00
Superscan appearance	29 (15%)	5 (7%)	0·099
Primary endpoint: overall survival, months			
Median (95% CI)	13·0 (11·4–14·6)	12·9 (9·2–16·5)	0·32†
Events	170 (87%)	55 (74%)	0·0077
Primary endpoint: PSA-progression-free survival, months			
Median (95% CI)	4·4 (3·4–5·4)	3·9 (2·3–5·5)	0·15†
Events	180 (92%)	65 (88%)	0·34
Secondary endpoint: PSA decline ≥50%	89 (45%)	32 (43%)	0·81

Data are median (IQR) or n (%) unless otherwise stated. N, M1a, and M1b refer to molecular imaging TNM classifications. NCCN=National Comprehensive Cancer Network. ECOG=Eastern Cooperative Oncology Group. ULN=upper limit of normal. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. SUV_{mean}=mean standardised uptake value. *p values compare the patient characteristics and outcome events in the development and validation cohorts using Wilcoxon Mann-Whitney test or exact Fisher test depending on whether the variable is continuous or categorical. †Log-rank test.

Table 1: **Participant characteristics and treatment outcomes**

(C-index) and its 95% CI. Second, models' calibration was evaluated by calibration plots predicting the probability of death at 12 and 18 months and PSA progression at 3 and 6 months versus observed probability. These timepoints were chosen on the basis of the observed median overall survival and PSA-progression-free survival. One nomogram was computed from each model and individual risk scores were obtained by applying the nomograms on the development cohort. An optimal cutoff point for the risk score for each model was computed to stratify patients into low-risk or high-risk groups. The optimal cutoff was determined using log-rank statistics to provide the largest discrepancy in overall survival and PSA-progression-free survival between the risk groups (*cutp* function; SurvMisc package in R).

Model validation was done in two steps. First, we did an internal validation using a bootstrap resampling process to provide an unbiased estimate of model performance (validate.cph package in R), as the C-index. The original development cohort was resampled to obtain a dataset of the same size. Second, to assess external validity, prediction accuracy of overall survival and PSA-progression-free-survival models was determined on the validation cohort by computing the C-indices and calibration plots. The nomograms were applied to the validation cohort to obtain the individual risk scores. The optimal cutoff obtained in the development cohort was used to stratify patients in the validation cohort into low-risk or high-risk groups. Clinical utility of the nomograms was evaluated by using the log-rank test to determine if the survival distributions differed between the low-risk and high-risk groups. Two-sided p values of less than 0·05 were considered significant. For the PSA50 model, a penalised logistic regression model using the adaptive least absolute shrinkage and selection operator (LASSO) penalty was considered. Model discrimination was determined using the area under the curve and its 95% CI, and calibration was evaluated by predicting the probability of achieving PSA50. To evaluate the model's accuracy, the cutoff point of a sensitivity of 90% or greater (independent of the specificity) in the development cohort was determined. A specificity of 90% or greater was rationalised as offering sufficient confidence in using the nomogram in a clinical environment to identify non-responders. The utility of the model was assessed by computing the sensitivity, specificity, positive predictive value, and negative predictive value based on the cutoff in the development and validation cohorts (appendix pp 2–3). Study data were curated using REDCap data capture tools.[19] All statistical analyses were done using R version 3.6.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 23, 2019, and Jan 13, 2020, 414 patients were retrospectively screened; 270 (65%) of whom met the eligibility criteria and were divided into development (n=196; datasets from Technical University Munich, Peter MacCallum Cancer Center, and University of California Los Angeles) and independent validation (n=74; datasets from Heidelberg University Hospital, University Hospital Essen, and Excel Diagnostics Imaging Houston) cohorts

(figure 1). 144 (35%) of 414 patients were excluded: 40 (10%) started treatment after the cutoff date (Dec 1, 2018), 86 (21%) were imaged with ^{18}F-labelled PSMA-PET, nine (2%) were imaged with PSMA-PET/MRI, and nine (2%) were lost to follow-up. 113 (42%) of 270 patients were enrolled in clinical trials, whereas 157 (58%) received ^{177}Lu-PSMA as part of compassionate access programmes. ^{177}Lu-PSMA was administered for a median of 3 cycles (IQR 2–4) per patient. The median number of previous mCRPC systemic treatments was 3 (IQR 2–4). 257 (95%) of 270 patients had received second-generation anti-androgens, and 219 (81%) had previously been treated with chemotherapy. Baseline characteristics and outcome data were well balanced between the two cohorts except for Eastern Cooperative Oncology Group (ECOG) performance status and symptomatic status (table 1). The median duration of follow-up was 21·5 months (IQR 13·3–30·7). 225 (83%) of 270 patients had died by the last follow-up and 245 (91%) experienced PSA progression. The median overall survival and PSA-progression-free survival were similar between the development and validation cohorts (table 1).

The estimated 12-month overall survival was 54% (95% CI 48–60) and the estimated 18-month overall survival was 34% (29–40). Predictors selected in the overall survival model were time since diagnosis of prostate cancer, chemotherapy status, baseline haemoglobin concentration, bone involvement status, liver involvement status, number of metastatic lesions, and tumour SUV_{mean} (table 2, appendix p 7). On the calibration plots, the model's predicted probabilities were close to the observed probabilities, but deviated slightly at 12 months when higher probabilities were predicted (figure 2). The C-index of the overall survival model was 0·71 (95% CI 0·69–0·73). Similar C-indices were achieved at internal validation (0·71 [0·69–0·73]) and external validation (0·72 [0·68–0·76]). The nomogram built based on the overall survival model is shown in figure 2C.

The estimated 3-month PSA-progression-free survival was 64% (95% CI 58–70) and the estimated 6-month PSA-progression-free survival was 38% (32–43). Predictors selected in the PSA-progression-free survival model were time since diagnosis of prostate cancer, chemotherapy status, pelvic nodal status, bone involvement status, liver involvement status, and tumour SUV_{mean} (table 2, appendix p 7). On the calibration plots, the model's predicted probabilities were close to the observed probabilities, but deviated slightly (figure 3). The C-index of the PSA-progression-free survival model was 0·70 (95% CI 0·68–0·72). Similar C-indices were achieved at internal validation (0·70 [0·68–0·72]) and external validation (0·71 [0·68–0·74]). The nomogram built based on the PSA-progression-free survival model is shown in figure 3C.

Patients in the development cohort, validation cohort, and complete set were stratified into two risk groups (high risk *vs* low risk) using the calculated optimal cutoff for the risk scores (197 points for overall survival nomogram and 178 points for PSA-progression-free survival nomogram). Median overall survival for low-risk patients versus high-risk patients was 19·1 months (95% CI 17·1–21·1) versus 8·4 months (7·4–9·4; p<0·0001; figure 4A) in the development cohort, 24·9 months (16·8–27·3) versus 7·4 months (4·0–10·8; p<0·0001; figure 4B) in the validation cohort, and 19·9 months (17·5–22·3) versus 8·2 months (7·2–9·1; p<0·0001; figure 4C) in the complete set. Median PSA-progression-free survival during ^{177}Lu-PSMA for low-risk patients versus high-risk patients was 9·4 months (95% CI 6·6–12·1) versus 3·3 months (2·9–3·7; p<0·0001; figure 4D) in the development cohort, 6·6 months (6·0–7·1) versus 2·5 months (1·2–3·8; p=0·022; figure 4E) in the validation cohort, and 8·8 months (7·3–10·3) versus 3·3 months (2·8–3·7; p<0·0001; figure 4F) in the complete set.

Results of the PSA50 model are shown in table 2 and the appendix (pp 3, 9). The area under the curve of the PSA50 model in the validation cohort was 0·78 (95% CI 0·68–0·88). Using a cutoff of 41 points, the sensitivity for patient stratification into responders or non-responders in the validation cohort was 94%, the specificity was 38%, the positive predictive value was 54%, and the negative predictive value was 89%.

	Definition	Estimate HR or OR (95% CI)	p value
Overall survival			
Time since diagnosis	Continuous, years	0·92 (0·89–0·95)	<0·0001
Chemotherapy status	Previous chemotherapy *vs* no chemotherapy	1·53 (1·01–2·37)	0·044
Baseline haemoglobin	Continuous, g/dL	0·85 (0·77–0·95)	0·0035
Number of metastases	≥20 *vs* <20	1·66 (1·12–2·44)	0·0031
Tumour SUV_{mean}	Continuous, no unit	0·94 (0·90–0·98)	0·0078
Bone involvement	M1b *vs* no M1b	1·10 (0·57–2·13)	0·77
Liver involvement	Liver metastases *vs* no liver metastases	2·11 (1·38–3·23)	<0·0001
PSA-progression-free survival			
Time since diagnosis	Continuous, years	0·94 (0·92–0·97)	0·00012
Chemotherapy status	Previous chemotherapy *vs* no chemotherapy	1·55 (1·03–2·34)	0·028
Tumour SUV_{mean}	Continuous, no unit	0·92 (0·88–0·96)	0·00052
Pelvic nodal involvement	N1 *vs* N0	0·70 (0·51–0·97)	0·035
Bone involvement	M1b *vs* no M1b	1·93 (1·07–3·52)	0·032
Liver involvement	Liver metastases *vs* no liver metastases	2·59 (1·69–3·95)	<0·0001
PSA decline ≥50%			
Chemotherapy status	Previous chemotherapy *vs* no chemotherapy	0·32 (0·13–0·77)	0·012
Tumour SUV_{mean}	Continuous, no unit	2·88 (1·80–4·62)	<0·0001
Pelvic nodal involvement	N1 *vs* N0	1·87 (0·96–3·62)	0·062
Liver involvement	Liver metastases *vs* no liver metastases	0·29 (0·11–0·81)	0·018

Estimates are hazard ratios for the overall survival and PSA-progression-free survival analyses, and odds ratios for the PSA decline of 50% or greater analysis. HR=hazard ratio. OR=odds ratio. SUV=standardised uptake value. PSA=prostate-specific antigen.

Table 2: **Multivariate analysis of predictors selected by LASSO regression procedure in the development cohort**

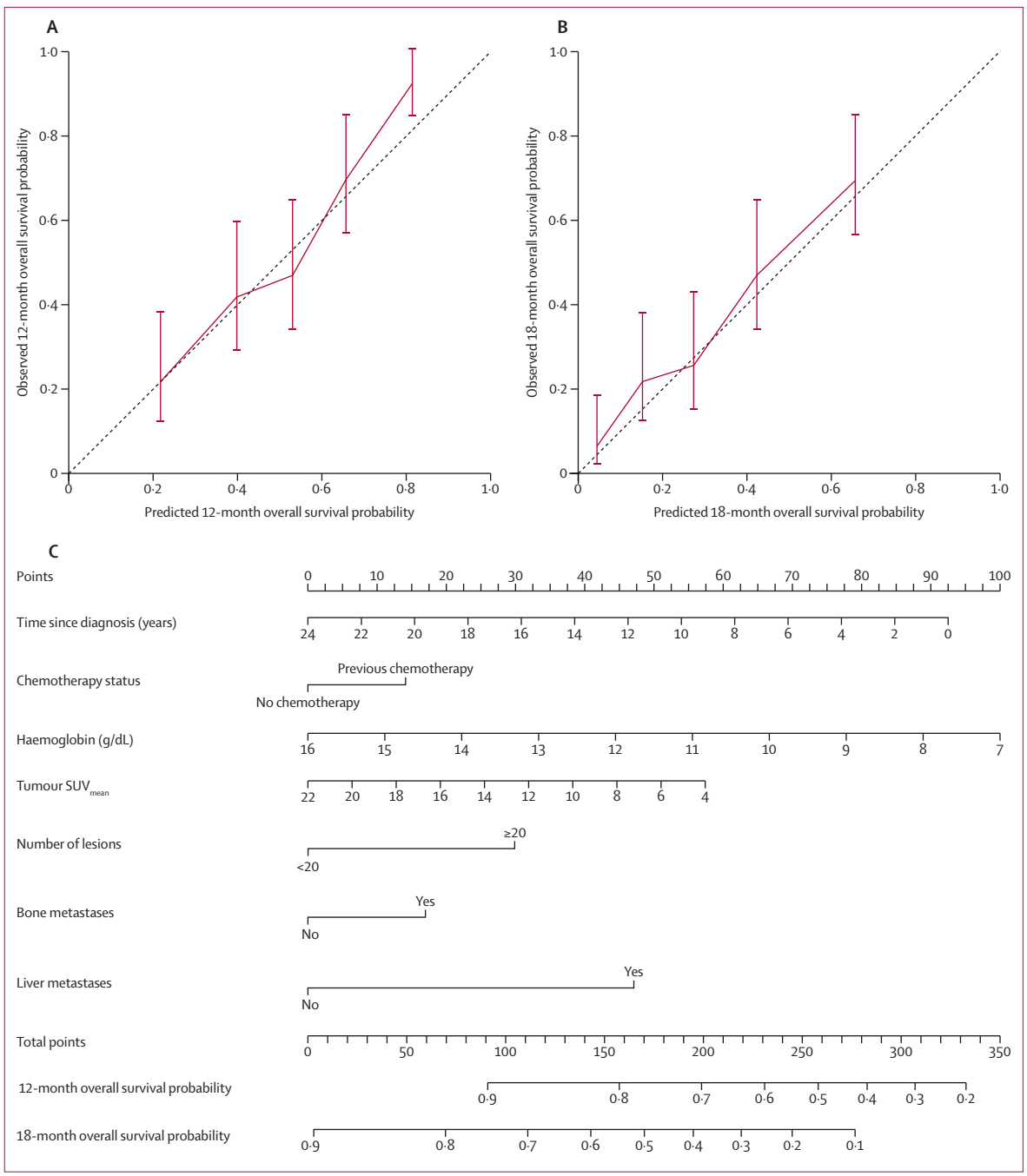

Figure 2: **Overall survival probabilities**
Calibration plots of overall survival probabilities at 12 months (A) and 18 months (B). Nomogram-predicted overall survival is plotted on the x-axis, with observed overall survival on the y-axis. Dashed lines along the diagonal line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (C) Nomogram for predicting probability of overall survival at 12 months and 18 months. The presence or absence of each clinical characteristic indicates a certain number of points. Number of points for each clinical characteristic is on the top row. For each characteristic, absence is assigned 0 points. The presence of characteristics is associated with a number of points generated using the nomogram function, SvyNom package in R based on the results of LASSO analysis. The points for each characteristic are summed together to generate a total-points score. The total points correspond to respective 12-month and 18-month overall survival probabilities. SUV=standardised uptake value.

Discussion

Our nomograms for overall survival, PSA-progression-free survival, and PSA50 combine traditional clinical prognostic variables (ie, time since diagnosis, history of chemotherapy, and haemoglobin levels) and incorporate several novel prognostic variables that are relevant in this

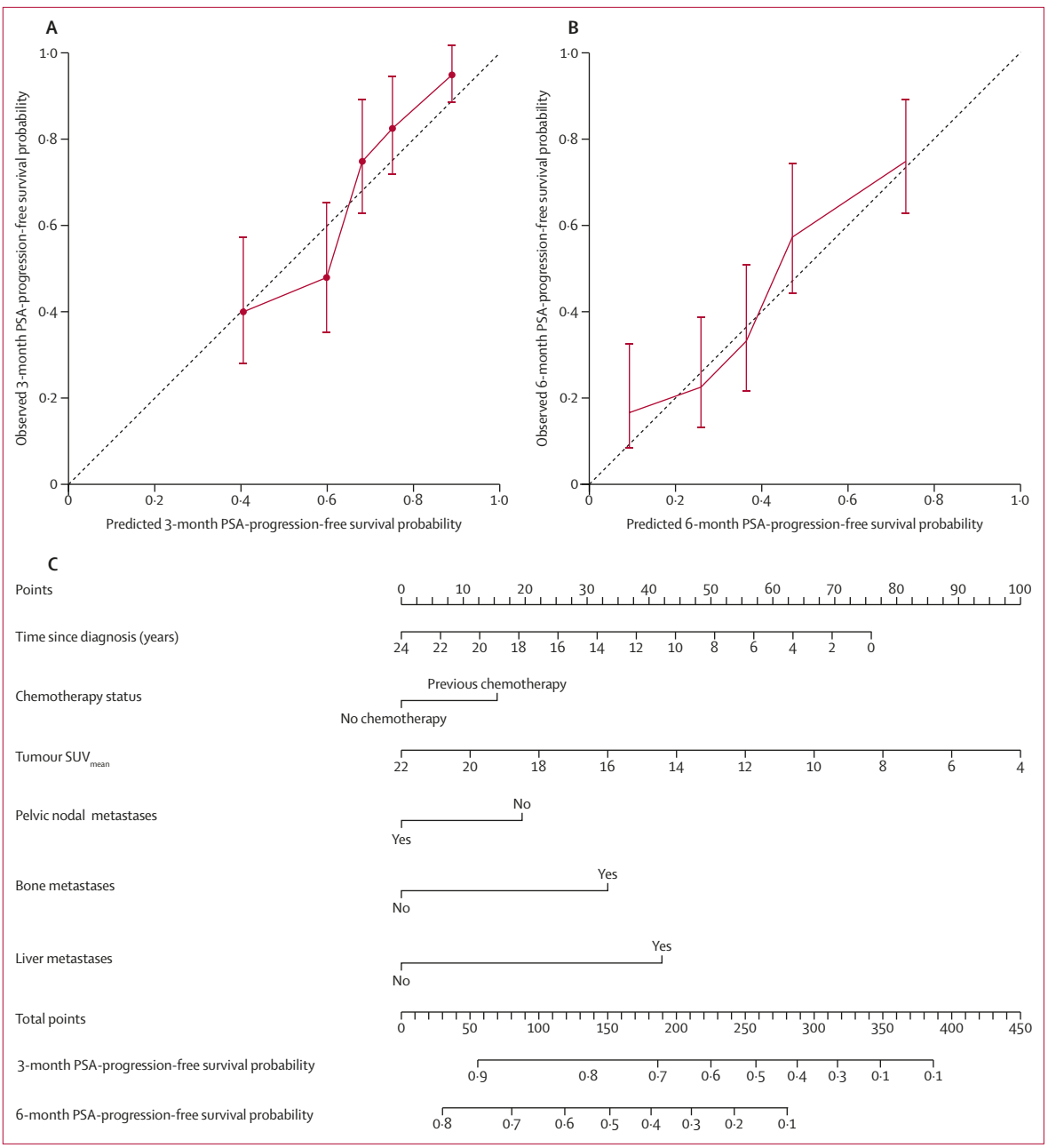

Figure 3: **PSA-progression-free survival probabilities**
Calibration plots of PSA-progression-free survival probabilities at 3 months (A) and 6 months (B). Nomogram-predicted PSA-progression-free survival is plotted on the x-axis, with observed PSA-progression-free survival on the y-axis. Dashed lines along the diagonal line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (C) Nomogram for predicting probability of PSA-progression-free survival at 3 months and 6 months. The presence or absence of each clinical characteristic indicates a certain number of points. Number of points for each clinical characteristic is on the top row. For each characteristic, absence is assigned 0 points. The presence of characteristics is associated with a number of points generated using the nomogram function, SvyNom package in R based on the results of LASSO analysis. The points for each characteristic are summed together to generate a total-points score. The total points correspond to respective 3-month and 6-month PSA-progression-free survival probabilities. PSA=prostate-specific antigen. SUV=standardised uptake value.

patient population: tumour PSMA expression, number of PSMA-positive metastatic lesions, and disease site based on molecular imaging TNM classification system.[14] Tumour PSMA expression correlates with prostate cancer aggressiveness and poor outcomes,[20] but higher PSMA expression leads to improved delivery of ^{177}Lu-PSMA to the tumour targets. Current and colleagues[21] showed that higher PSMA expression results in higher deposition

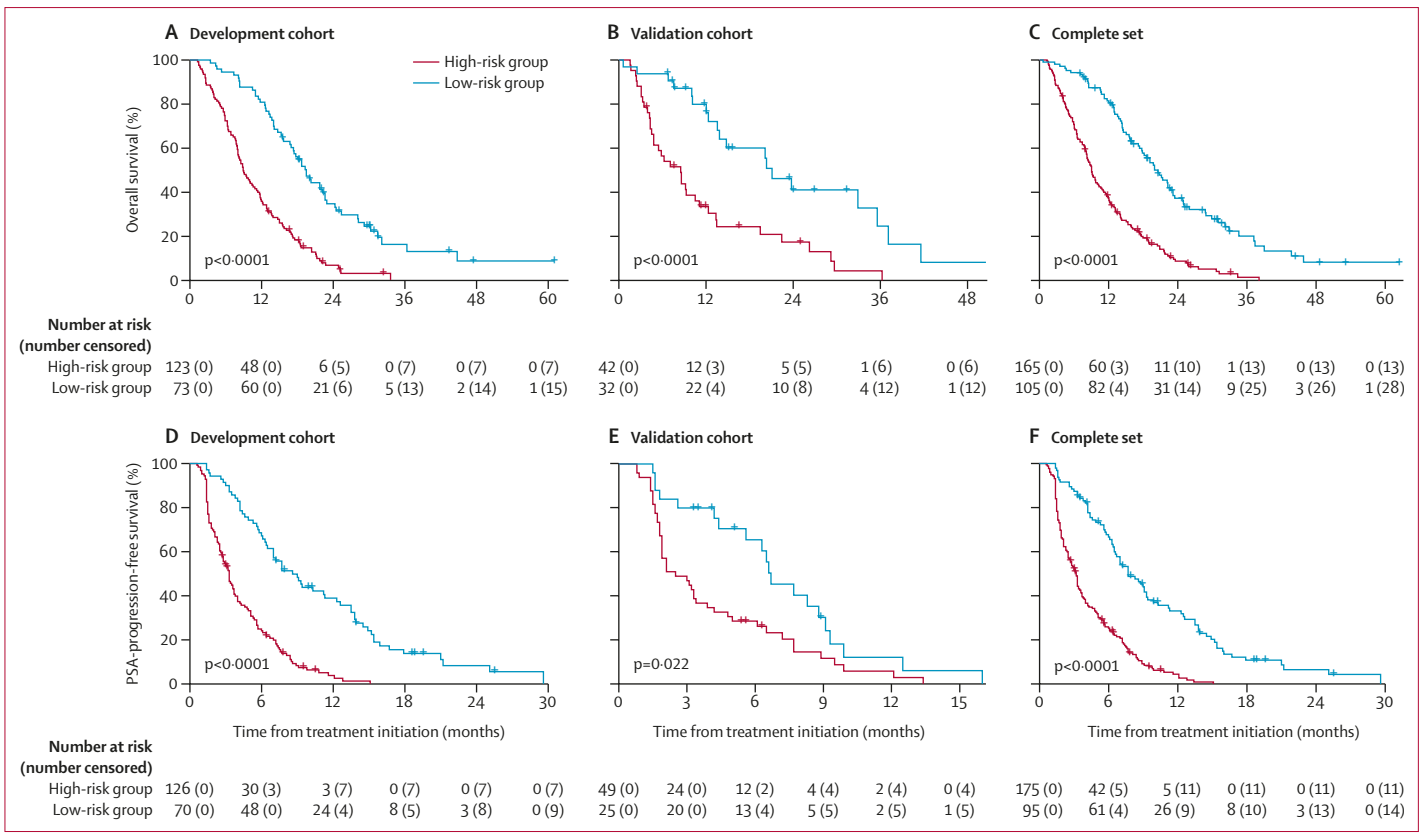

Figure 4: **Survival curves by risk groups**

Overall survival curves for the development cohort (A), validation cohort (B), and complete set (C), stratified into low-risk and high-risk groups by optimal cutoff point. PSA-progression-free survival curves for for the development cohort (D), validation cohort (E), and complete set (F), stratified into low-risk and high-risk groups by optimal cutoff point. PSA=prostate-specific antigen.

dose of ^{177}Lu-PSMA and consequent higher levels of DNA damage in mouse models. Our nomograms support preclinical findings and suggest that high levels of tumour PSMA expression is a requisite for favourable outcome following ^{177}Lu-PSMA (higher PSMA expression is associated with longer overall survival and PSA-progression-free survival, and greater likelihood of PSA 50% decline). As observed clinically and previously reported,[22] our nomograms show that bone disease is less likely to be adequately controlled with ^{177}Lu-PSMA (patients with bone metastases have shorter overall survival and PSA-progression-free survival, and are less likely to have PSA 50% decline than patients without bone metastases). Several factors might be responsible for the resistance mechanism of bone metastases from prostate cancer: tumour microenvironment (bone lesions have a higher net growth rate compared with soft-tissue lesions[23] and can contain prosurvival factors absent in other organs[24]) and lower target expression (lower tumour uptake in bone *vs* lymph nodes[25]). By contrast with chemotherapy status, previous use of androgen receptor signalling inhibitors was not associated with outcome of our models. This finding might be related to low statistical power, as 95% of the patients in this study had received abiraterone or enzalutamide before ^{177}Lu-PSMA.

This study has several advantages compared with studies that previously identified prognostic markers for ^{177}Lu-PSMA.[2,12,26] Our analysis included a larger multicentric population, and modelled 18 clinicopathological and imaging variables simultaneously using regression models with LASSO penalty for variable selection. Unlike other statistical modelling methods, the LASSO procedure uses shrinkage property, which results in more stable variable selection. Additionally, the identification of predictive factors does not rely on statistical significance. Other strengths of this study include external validation of the findings and the use of both clinical trial and real-world data. Previous studies showed that baseline characteristics of mCRPC trial populations differ from real-world populations, leading to differential treatment and survival.[27] Although building nomograms on the basis of data from phase 3 trials is meritorious, the validity of these trial-tailored models in clinical practice requires further validation in a real-world population. As such, we specifically sought to build and validate the nomograms by use of both non-trial and prospective trial data. By contrast with previous prognostic models for mCRPC that were built using data from first-line or second-line mCRPC treatments,[7,8] we included patients who were later in their disease

course, often having exhausted most standard treatment regimens. Clinical prognostic markers previously identified in early stages of mCRPC were also selected in our final models, which validates their importance even in late-stage disease.[8] Nomograms using PSMA-PET imaging were developed previously to predict the probability of a positive scan or upstaging in patients with early disease stage, but not for outcome of patients with mCRPC.[28,29] Lastly, our models meet the acceptance criteria of the American Joint Committee on Cancer for inclusion of risk models for individualised prognosis in the practice of precision medicine.[30]

This study has important clinical implications. Following the positive results of the phase 3 VISION trial,[4,31] approval of [^{177}Lu]Lu-PSMA-617 is imminent. There is currently little evidence on patient selection for ^{177}Lu-PSMA therapy and no standardised criteria have been developed to date. Our predictive models for outcomes following ^{177}Lu-PSMA could therefore play an important role in further optimisation of trial design and individual care. These prognostic tools could aid clinical decision making, particularly at institutions where this therapy is introduced as a novel therapeutic option. To enable implementation of the nomograms in the clinical environment, we integrated our findings into an interactive risk calculator, which provides automatic prediction of patient outcomes. Nevertheless, the nomograms should not displace the well informed clinical judgment of physicians, but should instead be utilised as a complementary tool for treatment plan decision making or during discussions with patients. The nomograms can be used for patient selection in clinical trials on the basis of their predicted outcome, and randomisation can be stratified using the high-risk and low-risk grouping. The required sample size of therapy trials is calculated on the basis of the estimated percentage of treatment responders, and a higher number of non-responders requires a larger sample size. Being able to enrich trial participation with patients who are most likely to respond will result in smaller sample size, and thus reduce costs and time, and reduce the risk of exposing patients to an ineffective drug. Notably, 89% of the patients classified by our PSA50 model as non-responders did not have a PSA response, which shows the model's usefulness in identifying patients who are likely to be PSA non-responders with ^{177}Lu-PSMA.

Applicability of the current models includes patients with mCRPC who progressed on (or are unfit to receive) chemotherapy and androgen receptor signalling inhibitor agents, and have received a screening [^{68}Ga]Ga-PSMA-11 PET. This patient population is representative of the VISION patient cohort. Ongoing trials investigating ^{177}Lu-PSMA in the chemotherapy-naive mCRPC setting (NCT04663997, NCT04419402) or the metastatic hormone-sensitive setting (NCT04343885,[32] NCT04443062) might lead to expansion of ^{177}Lu-PSMA use with respective nomogram updates in the future. Patients enrolled in this study were treated with ^{177}Lu-labelled PSMA-617 or PSMA-I&T. These different compounds share similar biodistribution and tumour uptake,[33] which supports the use of our models in candidates for radionuclide therapy scheduled to receive either [^{177}Lu]-PSMA-617 or [^{177}Lu]Lu-PSMA-I&T. [^{68}Ga]Ga-PSMA-11 PET is currently established for screening candidates for ^{177}Lu-PSMA, but ^{18}F-labelled PSMA ligands are expected to be increasingly used. Despite no reported differences in detection rates, ^{18}F-labelled PSMA ligands have higher tumour uptake than [^{68}Ga]Ga-PSMA-11.[34] The application of our nomograms in patients who received ^{18}F-labelled PSMA-PET could lead to an overestimation of prognosis in our models, therefore, increasing use of ^{18}F-labelled PSMA ligands for screening candidates for ^{177}Lu-PSMA might necessitate adaptations of the nomograms in the future.

The major limitations of this study are the absence of a prospective validation of the models and the small size of the validation cohort. Although the recommended number of at least ten events per predictor variable was followed,[9] validation of the models in larger patient populations is warranted. The C-indices of the models when applied to the development and validation cohorts were similar, which provides evidence against overfitting the data. The prognostic discrimination (C-index: 0·72 for the overall survival model and 0·71 for the PSA-progression-free survival model) of the models were in the range of previously developed nomograms for mCRPC;[7,8] however, the performance was not ideal. Addition of further parameters on a larger patient population might increase the prognostic discrimination. Using multicentric data collected across several countries increased the generalisability of the model, but it also increased the risk of selection bias. Also, previously identified risk factors in mCRPC, such as lactate dehydrogenase or albumin, were not available or were not collected systematically and consequently not tested in the models. Similarly, 2-[^{18}F]FDG-PET was available only in a minority of patients in this study and thus could not be tested in the models. Dual-tracer PET imaging with [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG-PET can improve patient selection for ^{177}Lu-PSMA therapy;[26] however, several steps are required to establish 2-[^{18}F]FDG-PET as a screening tool for ^{177}Lu-PSMA in practice (ie, confirmation of its prognostic value in a multicentre setting, standardisation of image interpretation, inclusion in drug label and guidelines, and insurance coverage). Lastly, we could not include genomic data, which was shown in a case series to be responsible for non-response to PSMA-targeted treatment despite high PSMA expression,[35] although this has not yet been validated in a large patient population. Cancer-specific survival has well known advantages as an endpoint over overall survival, but is often difficult to evaluate in this population with old age and multiple comorbidities. Future models should consider cancer-specific survival as an endpoint whenever reliable data is available. Re-staging PSMA-PET was not homogenously implemented among centres for treatment response evaluation and was not

For the **interactive risk calculator** see https://www.uclahealth.org/nuc/nomograms

included in the progression-free survival analysis. The role of PSMA-PET for response evaluation is being investigated in a separate study.

In conclusion, three nomograms to predict overall survival, PSA-progression-free survival, and PSA50 in men with mCRPC receiving ^{177}Lu-PSMA radionuclide treatment were developed and externally validated. Our findings validate PSMA-PET companion imaging as a gatekeeper for patient selection and as a quantitative prognostic biomarker. Our nomograms, integrated in an online risk calculator, can assist in clinical trial design and individual clinical decision making. These models can be further tested and updated as new clinical trial data become available.

Contributors

AG, ME, WPF, JCa, JCz, MSH, and CK were involved in the conception, design, or planning of the study. JCz, ME, WPF, KH, JCa, CK, UH, ESD, CD'A, and DE provided resources and administrative support. AG, HW, MW, HR, RE, WRA, AR, PT, WPF, JCa, and RT collected the data. AG, TRG, and WRA analysed the data. AG, TRG, and WRA accessed and verified the underlying data. TRG and AG did the statistical analyses. AZ developed the software application. AG, ME, and WPF wrote the first draft of the manuscript with contribution from all authors. AG, ME, WPF, JCa, MSH, BH, SS, MBR, and RT critically reviewed or revised the manuscript for important intellectual content. All authors reviewed the interim drafts and the final version of the manuscript, and agree with its content and submission. AG had final responsibility for the decision to submit this manuscript for publication.

Declaration of interests

JCa reports previous consulting activities for Curium Pharma, GE Healthcare, Janssen Pharmaceuticals, and Point Biopharma, outside of the submitted work. BH reports personal fees from ABX, Bayer, Lightpoint Medical, Janssen, Bristol-Myers Squibb, and Astellas and travel fees from AstraZeneca, Janssen, and Astellas, outside of the submitted work. KH reports personal fees from Bayer, SIRTEX, Adacap, Curium, Endocyte, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Novartis, Y-mAbs, Bain Capital, and MBM Capital; personal fees and non-financial support from Sofie Biosciences; non-financial support from ABX; and grants and personal fees from BTG, outside the submitted work. JCz is a founder, board member, and holds equity in Sofie Biosciences and Trethera Therapeutics (intellectual property is patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics); and was a consultant for Endocyte (VISION trial steering committee), Actinium Pharmaceuticals, and Point Biopharma, outside of the submitted work. MSH reports personal fees from Janssen (lecture honorarium), Mundipharma (lecture honorarium), Astellas (lecture honorarium), AstraZeneca (lecture honorarium), and MSD (advisory forum); and research support from Endocyte, AAA, and Novartis, outside of the submitted work. WPF has been a consultant for Endocyte and BTG, and has received fees from RadioMedix and Bayer, outside of the submitted work. ME reports previous consulting activities for Blue Earth Diagnostics, Progenics Pharmaceuticals, and Point Biopharma, and a patent application for rhPSMA, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Deidentified participant data will be made available to researchers conditionally upon receipt of an approved study proposal along with evidence of approval of the proposal by an accredited ethics committee. Methodologically sound proposals for any purpose will be considered by the study committee. Proposals should be made by email to the corresponding author. To gain access, data requesters will need to sign a data access agreement.

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