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Multicenter External Validation of a Nomogram for Predicting Positive Prostate-specific Membrane Antigen/Positron Emission Tomography Scan in Patients with Prostate Cancer Recurrence

Lorenzo Bianchi[a,b], *Paolo Castellucci*[c], *Andrea Farolfi*[c,*], *Matteo Droghetti*[a], *Carlos Artigas*[d], *Jose Leite*[e], *Paola Corona*[f], *Qaid Ahmed Shagera*[d], *Renata Moreira*[e], *Christian González*[f], *Marcelo Queiroz*[g], *Felipe de Galiza Barbosa*[g], *Riccardo Schiavina*[a,b], *Desiree Deandreis*[h], *Stefano Fanti*[c], *Francesco Ceci*[i]

[a] *Division of Urology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy;* [b] *Università degli studi di Bologna, Bologna, Italy;* [c] *Division of Nuclear Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy;* [d] *Department of Nuclear Medicine, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium;* [e] *PET/CT Center, DASA – Diagnósticos da Américic, Rio de Janeiro, Brazil;* [f] *Fundación Centro Diagnóstico Nuclear (FCDN), Buenos Aires, Argentina;* [g] *Department of Radiology, Hospital Sírio-Libanês, University of Sao Paulo, Sao Paulo, Brazil;* [h] *Nuclear Medicine, Department of Medical Sciences, University of Turin, Turin, Italy;* [i] *Division of Nuclear Medicine and Theranostics, IEO European Institute of Oncology IRCCS, Milan, Italy*

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Abstract

Background: A nomogram has recently been developed to predict ^{68}Ga-labeled prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET)/computed tomography (PSMA-PET) results in recurrent prostate cancer (PCa) patients.
Objective: To perform external validation of the original nomogram in a multicentric setting.
Design, setting, and participants: A total of 1639 patients who underwent PSMA-PET for prostate-specific antigen (PSA) relapse after radical therapy were retrospectively included from six high-volume PET centers. The external cohort was stratified according to clinical setting categories: group 1: first-time biochemical recurrence (n = 774); group 2: PSA relapse after salvage therapy (n = 499); group-3: biochemical persistence after radical prostatectomy (n = 210); and group-4: advanced-stage PCa before second-line systemic therapies (n = 124).
Intervention: PSMA-PET in recurrent PCa.
Outcome measurements and statistical analysis: PSMA-PET detection rate was assessed in the overall population and in each subgroup. A multivariable logistic regression model was produced to evaluate the predictors of a positive scan. The performance characteristics of the model were assessed by quantifying the predictive accuracy (PA) according to model calibration. The Youden's index was used to find the best nomogram's cutoff. Decision curve analysis (DCA) was implemented to quantify the nomogram's clinical net benefit.
Results and limitations: In the external cohort, the overall detection rate was 53.8% versus 51.2% in the original population. At multivariate analysis, International Society of Urological Pathology grade group, PSA, PSA doubling time, and clinical setting were independent predictors of a positive scan (all $p \leq 0.02$). The PA of the nomogram was identical to the original model (82.0%); the model showed an optimal calibration curve. The best nomogram's cutoff was 55%. In the DCA, the nomogram revealed clinical net benefit when

* Corresponding author. Division of Nuclear Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna 40138, Italy. Tel. +39 0512143196; Fax: +39 0516363956.
E-mail addresses: andrea.farolfi6@unibo.it, andrea.farolfi3@gmail.com (A. Farolfi).

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the threshold nomogram probabilities were ≥20%. The retrospective design is a major limitation.

Conclusions: The original nomogram exhibited excellent characteristics on external validation. The incidence of a false negative scan can be reduced if PSMA-PET is performed when the predicted probability is ≥20%.

Patient summary: A nomogram has been developed to predict prostate-specific membrane antigen/positron emission tomography (PSMA-PET) results for recurrent prostate cancer (PCa). The nomogram represents an easy tool in the decision-making process of recurrent PCa.

1. Introduction

The treatment of prostate cancer (PCa) patients with prostate-specific antigen (PSA) failure (namely, biochemical persistence [BCP] and biochemical recurrence [BCR]) after radical treatments is currently changing. Salvage therapies based on the hypothetical risk of local versus systemic recurrence represented the standard practice for many years. However, models based on clinical parameters cannot reliably predict recurrence sites and the extent of metastatic disease [1]. Location (pelvic vs extrapelvic, nodal vs skeletal or visceral) and number of lesions (oligo- vs multimetastatic) are parameters influencing prognosis [2] and represent key information for planning personalized treatment. The application of new-generation imaging in PCa significantly improved the clinical decision-making process, leading to novel "imaging-guided" therapeutic approaches [3]. These strategies have the potential to improve patient's outcome, delaying the administration of systemic therapies [4,5].

Prostate-specific membrane antigen/positron emission tomography (PSMA-PET) emerged as the most accurate novel imaging procedure to restage PCa [6], due to its high accuracy to correctly detect and localize PCa lesions [4]. However, PSMA-PET imaging is not exempt from false negative results, especially in the early stage of recurrence, when the tumor burden and PSA levels are low [7]. Moreover, recurrent/persistent PCa patients represent a highly heterogeneous group of individuals with different sites, burden, aggressiveness, and prognosis. Thus, patient selection criteria for PSMA-PET are essential to optimize nuclear medicine resources that, nowadays, cannot completely satisfy the huge demand of PSMA-PET scans. Therefore, patients at a lower risk should be spared from unnecessary diagnostic examinations [8].

Recently, our research group proposed a nomogram [9] to provide a prediction model able to identify patients at a high risk of positive PSMA-PET during recurrence. While the model showed optimal accuracy, its implementation in clinical practice is still limited by the lack of formal external validation. Accordingly, we aimed to validate the prediction model estimating the likelihood of positive PSMA-PET in recurrent PCa patients after radical treatments through multicenter external validation, collecting collaborative efforts among international high-volume PET centers.

2. Patients and methods

2.1. Study population

The cohort of patients included in this study was enrolled through an open-label, multicenter, retrospective analysis performed in six tertiary high-volume PET centers. In all centers, PET scans were performed in accordance with institutional review board approval, and patients signed an informed consent form prior to the diagnostic procedure as per local requirements. PSMA-PET was performed at each referral center between November 2018 and July 2020 due to BCR (n = 1429) or BCP (n = 210). The definition of PSA recurrence was consistent among all Institutions: BCR was defined as rising PSA levels ≥0.2 ng/ml in patients treated with radical prostatectomy (RP) or PSA ≥2 ng/ml above the nadir in case of primary radiotherapy (RT); in accordance with the Phoenix criteria [10] BCP was defined as a PSA level of ≥0.1 ng/ml at 6 wk after RP [11]. The inclusion/exclusion criteria were consistent with the original publication [9]. Overall, 1833 records were analyzed (Bologna, n = 679; Brussels, n = 255; Buenos Aires, n = 60; Rio De Janeiro, n = 300; San Paolo, n = 176; and Turin, n = 364). Owing to incomplete follow-up, 10.6% of cases (n = 194) were excluded. The analyzed population consisted of 1639 individuals and did not include patients from Bologna used for internal validation cohort of the original model. Patient characteristics of the external and the original cohorts are reported in Table 1.

2.2. Clinical settings

The overall population was grouped into four different categories of PSA recurrence, according to the previously reported classification [9,12]: first-time BCR (group 1), defined as first relapse after primary treatment; PSA recurrence after salvage therapies (group 2); BCP (group 3); and advanced-stage PCa [13] with PSA progression scheduled for second-line systemic therapies, including taxane-based chemotherapy and new androgen-receptor targeted agent (ARTA) therapies (group 4). All patients included in the analysis were chemotherapy and ARTA naïve. No patients received PSMA radioligand therapy.

2.3. Ga-68–labeled PSMA-11 PET/CT and interpretation criteria

At all centers, ^{68}Ga-PSMA-11 was synthesized according to good manufacture practice and in accordance with international procedural guidelines [14,15]. A mean dose of 1.8–2.2 MBq/kg body weight of ^{68}Ga-PSMA-11 was administered intravenously; ^{68}Ga-PSMA-11 PET/computed tomography (CT) was performed with a standard technique [15]. All studies were performed using dedicated PET/CT state-of-the-art scanners. In all cases, low-dose CT was performed for attenuation correction and anatomical location of PET findings. All PSMA-PET images were

Table 1 – Baseline characteristics of the external (n = 1639) and original (n = 703) populations

Patient characteristics	External validation population		Original study population	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Age (yr)	68.8 ± 7.5	69 (63–74)	67.6 ± 6.8	68 (63–73)
PSA at PET/CT (ng/ml)	1.9 ± 3.80	0.8 (0.40–1.72)	1.3 ± 3.0	0.7 (0.4–1.3)
PSA doubling time (mo)	9.5 ± 12.40	6.3 (3.6–10.8)	8.0 ± 7.5	6.0 (3.5–9.6)
PSA velocity (ng/ml/yr)	2.6 ± 6.73	0.8 (0.3–1.9)	1.5 ± 4.4	0.7 (0.3–1.5)
	Frequency	%	Frequency	%
Time to BCR (mo)				
≥12	1186/1639	72.4	492/703	70
<12	453/1639	27.6	211/703	30
T stage				
<T3a	728/1639	44.4	257/703	36.5
≥T3a	911/1639	55.6	446/703	63.5
N status				
N1	203/1639	12.4	127/703	18.0
ISUP grade				
<4	1072/1639	65.4	419/703	59.6
≥4	567/1639	34.6	284/703	40.4
Primary therapy				
RP	1546/1639	94.3	684/703	97.3
Primary radiotherapy	93/1639	5.6	19/703	2.7
PLND at RP				
PLND	1004/1546	64.9	536/703	76.3
Adjuvant treatment				
Adjuvant radiotherapy	346/1639	21.1	182/703	25.9
Adjuvant ADT	254/1639	15.5	126/703	17.9
Therapies during BCR				
Salvage therapy with curative intent	477/1639	29.1	241/703	34.3
ADT at the time of the scan	197/1639	12	116/703	16.5
Clinical setting of PSA relapse				
First-time BCR (group 1)	774/1639	47.2	325/703	46.2
PSA recurrence after salvage therapy (group 2)	499/1639	30.4	241/703	34.3
BCP (group 3)	210/1639	12.8	76/703	10.8
Advanced PCa (group 4)	156/1639	9.5	61/703	8.7

ADT = androgen deprivation therapy; BCP = biochemical persistence; BCR = biochemical recurrence; CT = computed tomography; IQR = interquartile range; ISUP = International Society of Urological Pathology; PCa = prostate cancer; PET = positron emission tomography; PLND = pelvic lymphadenectomy; PSA = prostate-specific antigen; RP = radical prostatectomy; SD = standard deviation.

locally reviewed prior to data sharing, independently by two experienced nuclear medicine physicians and according to reporting international guidelines [14,16].

2.4. Outcomes measurements and statistical analyses

This is external validation of a nomogram designed to predict a positive PSMA-PET scan in recurrent PCa (Fig. 1) [9]. The primary outcome of the study was the identification of independent predictors of a positive PSMA-PET scan. Secondary outcomes were to assess the predictive accuracy (PA), clinical net benefit, and most informative nomogram's derived cutoff to predict the positive results of the PSMA-PET scan, through multicenter external validation. Statistical analyses first consisted of descriptive statistics and PSMA-PET positivity rate in overall and each clinical setting. Chi-square and analysis of variance tests were used to compare, respectively, categorical and continuous variables within different groups. Second, Cox uni- and multivariable logistic regression were performed to identify independent predictors of PSMA-PET positivity in a patient-based analysis. External validation was performed using regression coefficients of the previously published nomogram [9], as follows: pathological International Society of Urological Pathology (ISUP) group (namely, 1 vs 2 vs 3 vs 4 vs 5) in men referred to RP or clinic ISUP group in patients who underwent primary RT, PSA at PSMA-PET (≤0.2 vs 0.21–0.49 vs 0.5–0.99 vs 1–1.99 vs ≥2 ng/ml), PSA doubling time (PSAdt; <3 vs 3–5.99 vs 6–11.9 vs ≥12 mo) [17], ongoing androgen deprivation therapy (ADT; yes vs no), time to recurrence (>12 vs ≤12 mo), and clinical setting of PSA relapse (group 1 vs group 2 vs group 3 vs group 4). Third, the PA of the model in the overall population and in each center was quantified using the Harrell concordance index, according to model calibration, to graphically investigate the extent of over- or underestimation of the observed positive PSMA-PET result in a logistic calibration plot. Moreover, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) for each nomogram's derived probability cutoff were analyzed systematically. Receiver operating characteristic analysis and area under curve (AUC) analyses were used to assess the PA of each nomogram's derived cutoff, and Youden's index was used to find the best nomogram's cutoff in the external cohort. Finally, decision curve analysis (DCA) was implemented, to quantify the net benefit of the proposed nomogram in routine practice. All statistical tests were performed with R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) with a two-sided significance level set at $p < 0.05$.

3. Results

Patients' characteristics in the external cohort were comparable with those of the original ones, as reported in Table 1. The overall positivity rate of PSMA-PET assessed in this multicenter external cohort of 1639 patients was 53.8%, compared with 51.2% in the original population (Table 2). Supplementary Table 1 showed PSA value, PSAdt, and time to BCR according to the different settings of BCR. At multivariable regression analysis, PSA ≥0.5 (all $p \leq 0.001$), PSAdt ≤12 mo (all $p \leq 0.001$), ISUP grade group 5 ($p = 0.02$), and clinical settings ($p \leq 0.02$) were found to be independent

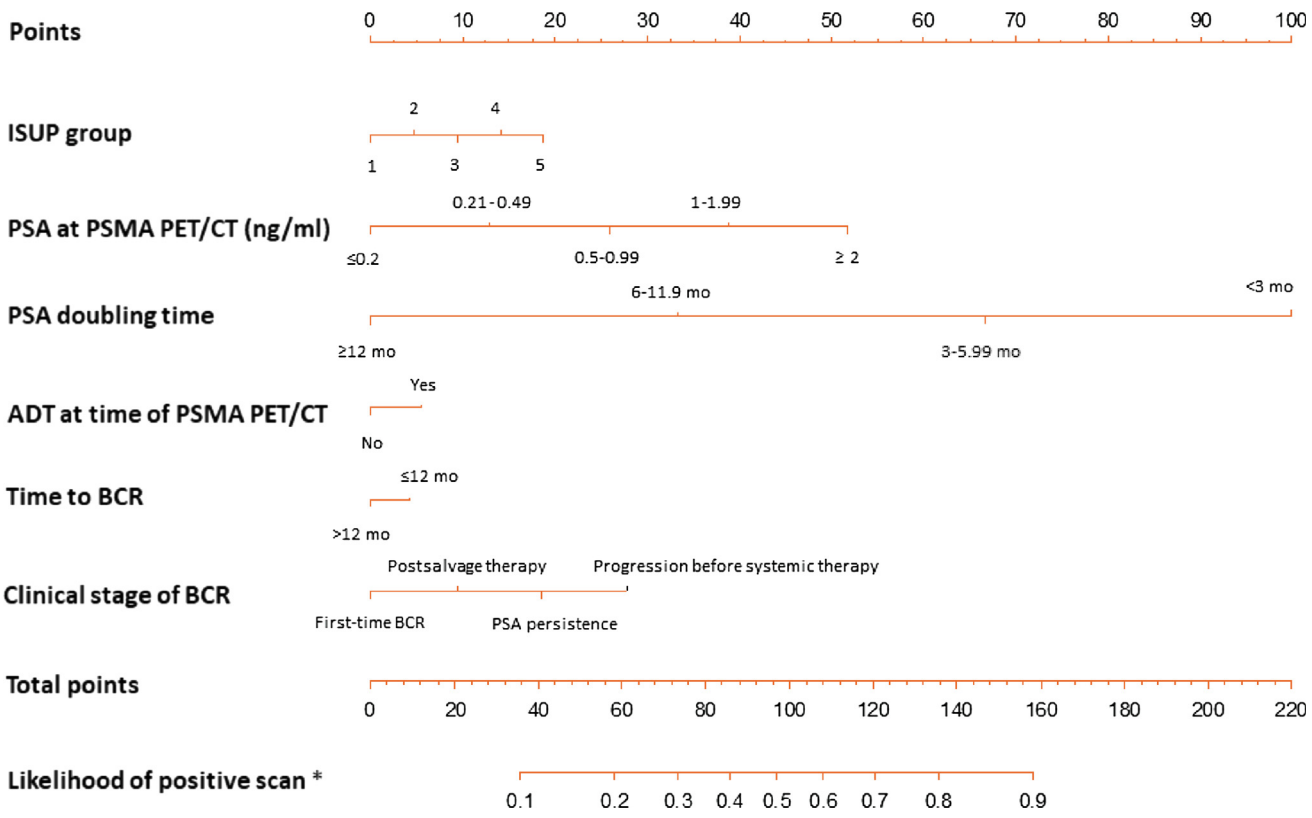

Fig. 1 – Nomogram predicting the likelihood of positive ^{68}Ga-PSMA-11-PET/CT for patients with different clinical settings of PSA failure after radical treatment for prostate cancer in the original population (DOI: 10.1007/s00259-019-04505-2). ADT = androgen deprivation therapy; BCR = biochemical recurrence; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; PSMA PET/CT = prostate-specific membrane antigen positron emission tomography/computed tomography.

Table 2 – Diagnostic performance of PSMA-PET in the external (n = 1639) and original (n = 703) populations

Clinical setting	External validation population		Original study population	
	Number of patients with positive PSMA-PET/ number of patients included	Detection rate (%)	Number of patients with positive PSMA-PET/ number of patients included	Detection rate (%)
Overall	881/1639	53.8	360/703	51.2
First-time BCR (group 1)	337/774	43.5	131/325	40.3
PSA recurrence after salvage therapy (group 2)	286/499	57.3	130/241	54.0
BCP (group 3)	124/210	59.0	46/76	60.5
Advanced PCa (group 4)	134/156	85.9	53/61	86.9

BCP = biochemical persistence; BCR = biochemical recurrence; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

predictors of a positive scan (Table 3). The calibration of the model using the original regression coefficients was applied to perform external validation of the original nomogram. The external validation confirmed optimal accuracy of the model, since the resulting PA was identical to that reported in the original model (82.0%) with an optimal calibration curve (mean absolute error 0.019; Fig. 2). Supplementary Table 2 shows the diagnostic performance and PA of the nomogram in each center. Furthermore, nomogram-derived predicted probabilities of positive PSMA-PET are categorized into each nomogram's derived cutoff. The number of patients having a negative scan and those with a positive one as well as sensitivity, specificity, PPV, NPV, and accuracy are described for each cutoff in Supplementary Table 3. The best nomogram's cutoff to predict positive PSMA PET/CT was 55% (AUC = 0.74, confidence interval [CI]: 0.72–0.77; Supplementary Fig. 1), compared with 40% (AUC = 0.76, CI: 0.72–0.79) in the original published nomogram. Applying this nomogram cutoff of 55%, 571 out of 1639 patients (35%) would be correctly spared from PSMA-PET and a positive scan would be missed in 245 patients (15%). Finally, in the DCA, the nomogram revealed

Table 3 – Univariate and multivariate logistic regression to identify predictors of positive PSMA-PET in the external (n = 1639) and original (n = 703) populations

Variables	Univariate analysis		Multivariate analysis			
	External validation population		External validation population		Original study population	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
ISUP grade						
1	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
2	0.97 (0.69–1.37)	0.9	0.99 (0.65–1.52)	0.9	1.34 (0.64–2.82)	0.4
3	1.15 (0.82–1.61)	0.4	1.17 (0.77–1.76)	0.5	2.02 (1.02–3.99)	0.04
4	1.60 (1–12–2.30)	0.01	1.32 (0.84–2.03)	0.2	1.76 (0.86–3.59)	0.1
5	2.14 (1.45–3.15)	≤0.01	1.76 (1.09–2.84)	0.02	2.35 (1.12–4.94)	0.02
PSA at PET-CT (ng/ml)						
<0.2	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
0.2–0.49	1.78 (0.95–3.30)	0.07	1.45 (0.73–2.88)	0.2	1.83 (0.67–4.97)	0.2
0.5–0.99	4.07 (2.19–7.56)	≤0.01	3.65 (1.84–7.24)	0.001	4.52 (1.66–12.26)	0.003
1–2	6.69 (3.56–12.59)	≤0.01	6.27 (3.11–12.65)	0.001	6.09 (2.20–16.87)	0.001
>2	14.75 (7.75–28.10)	≤0.01	13.5 (6.56–27.75)	0.001	5.39 (1.78–16.35)	0.003
PSA doubling time (mo)						
>12	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
6–<12	2.84 (2.10–3.87)	≤0.01	2.84 (2.01–4.0)	0.001	6.52 (3.24–13.10)	<0.001
3–<6 mo	8.45 (6.13–11.66)	≤0.01	9.90 (6.88–14.26)	0.001	23.68 (11.57–48.47)	<0.001
<3	15.06 (10.27–22.08)	≤0.01	14.19 (9.21–21.85)	0.001	39.99 (17.91–89.29)	<0.001
Ongoing ADT						
No	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	2.68 (1.92–3.73)	≤0.01	0.66 (0.39–1.12)	0.1	1.04 (0.56–1.93)	0.9
Time to BCR (mo)						
>12	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
≤12	1.24 (0.99–1.54)	0.05	1.01 (0.72–1.42)	0.9	1.03 (0.64–1.68)	0.9
Clinical setting						
First-time BCR (group 1)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
PSA recurrence after salvage therapy (group 2)	1.74 (1.39–2.19)	≤0.01	1.37 (1.04–1.80)	0.02	1.30 (0.85–1.98)	0.2
BCP (group 3)	1.87 (1.38–2.55)	≤0.01	1.20 (0.77–1.76)	0.4	1.43 (0.70–2.90)	0.3
PSA progression before second-line systemic therapies (group 4)	7.90 (4.92–12.67)	≤0.01	5.14 (2.59–10.21)	0.001	6.05 (2.14–17.11)	0.001

ADT = androgen deprivation therapy; BCP = biochemical persistence; BCR = biochemical recurrence; CI = confidence interval; CT = computed tomography; ISUP = International Society of Urological Pathology; OR = odds ratio; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; Ref = reference.

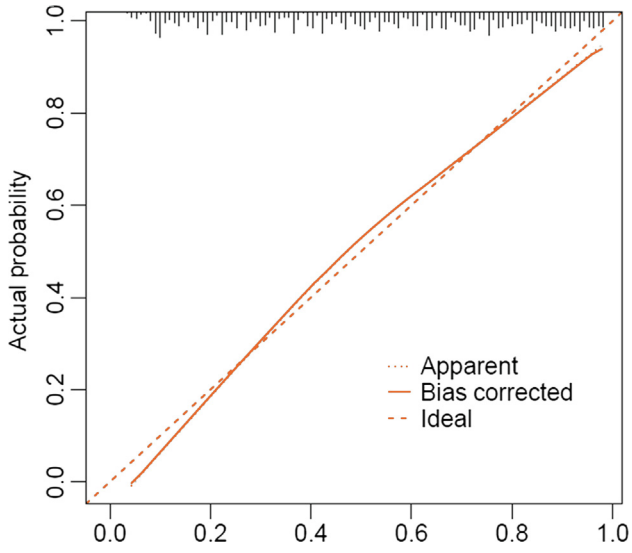

Fig. 2 – Nomogram calibration plot in the external validation cohort. The predicted probability of the multivariable model is shown on the *x* axis, and the observed proportion of men with positive PSMA-PET is shown on the *y* axis. The 45° line indicates location of the ideal nomogram, in which the predicted probability and the observed proportion of men with positive PSMA-PET are identical. The broken line indicates actual nomogram performance. PSMA-PET = prostate-specific membrane antigen/positron emission tomography.

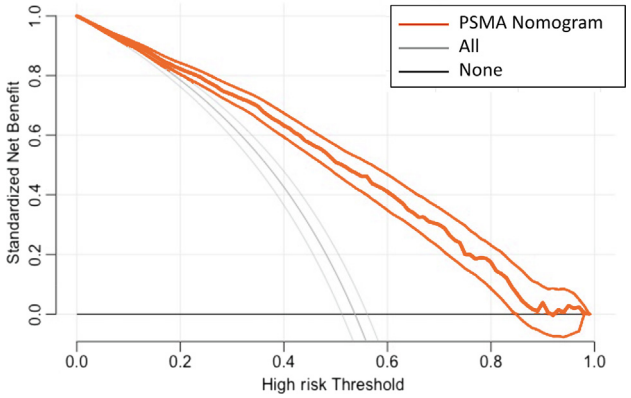

Fig. 3 – Decision curve analysis demonstrating the clinical net benefit associated with the use of a nomogram to predict positive PSMA-PET. The clinical net benefit is evident with a minimum threshold level >20% (where the red line and the gray ones split up). PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

a clinical net benefit when the threshold probability of the positive scan is >20%. With a nomogram-derived probability threshold of ≥55%, the use of the nomogram would result in a net benefit gain of 48% (Fig. 3).

4. Discussion

At present, PSMA-PET is considered the leading imaging procedure in case of recurrent PCa, and treatments such as stereotactic ablative radiotherapy (SABR) [18] and radiogu-

ided surgery [19] after oligometastatic disease detection have demonstrated delaying of the start of ADT and disease progression. Furthermore, the real innovation of inhibitors targeting PSMA is represented by the theranostic approach. Radioligand therapy with [177Lu]-PSMA-617 improves patients' overall survival by decreasing the risk of death in more than one-third of metastatic castration-resistant PCa patients [20–22] who have progressed after conventional treatments. Novel PSMA-targeting immunotherapies, small molecules, and antibody therapies are currently in clinical development, also in earlier stages of PCa, with emerging evidence of antitumor activity [23]. However, patient selection is crucial to avoid a false negative scan, thus optimizing health economic resources [24]. When patient management will not be influenced by the results of the scan and the likelihood of positivity is low, patients might be spared by uninformative diagnostic investigation. For this purpose, we proposed a clinical nomogram [9] to provide an individualized model for the identification of recurrent PCa patients with positive PSMA-PET. The model includes the information generally provided by referring physicians in clinical practice, such as pathological parameters (ISUP grade), biochemical characteristics (PSA, PSAdt, ongoing ADT, and time to relapse), and different clinical scenarios of recurrence (early recurrence vs advanced setting). The external validation in a large multicentric cohort showed high concordance of the predicted probabilities and actual PSMA-PET findings, with optimal calibration characteristics throughout the range of predicted positive PSMA-PET results. The optimal performance of the original model in the external validation confirmed the ability of this nomogram to correctly identify patients with a higher probability of positive PSMA-PET. In the external cohort, the overall detection rate of PSMA-PET was 53.8% versus 51.2% in the original population. As a consequence, roughly half of PCa patients with BCR had negative PSMA-PET with limited impact on clinical management and the impossibility to perform PSMA-guided therapeutic approaches. Moreover, the detection rate of PSMA-PET was slightly different after stratifying to center mainly due to inherent different patient characteristics; however, the PA of the model was consistent within all the centers. We identified the best nomogram cutoff at 55%. Slight cutoff differences among the external cohort (55%) and the original population (40%) might be explained by the inclusion of a larger population with slightly different characteristics, even if the PA of the models was identical. However, the DCA showed that the nomogram also revealed a clinical net benefit when the probabilities of positive PSMA-PET are >20% (Fig. 3). While the optimal clinical benefit is achieved when the nomogram-predicted probability is >55%, for probability rates between 20% and 55%, the nomogram still holds value in clinical practice if PSMA-PET results affect the treatment strategy. Thus, during management of patients with different settings of relapse, when the calculated risk of positive PSMA-PET based on proposed nomogram is $\geq$20%, the DCA analysis strongly support the decision to perform PSMA-PET due to relevant clinical benefit. On the contrary, for nomogram's probability <20%, the DCA does not support the decision to refer patients to PSMA-PET (low clinical benefit), and patients should be spared PSMA-PET, thus sensibly reducing the incidence of uninformative imaging and optimizing health care resources. However, patients with disease recurrence having negative PSMA-PET are generally (1) handled with active surveillance and/or repeated PSMA-PET in

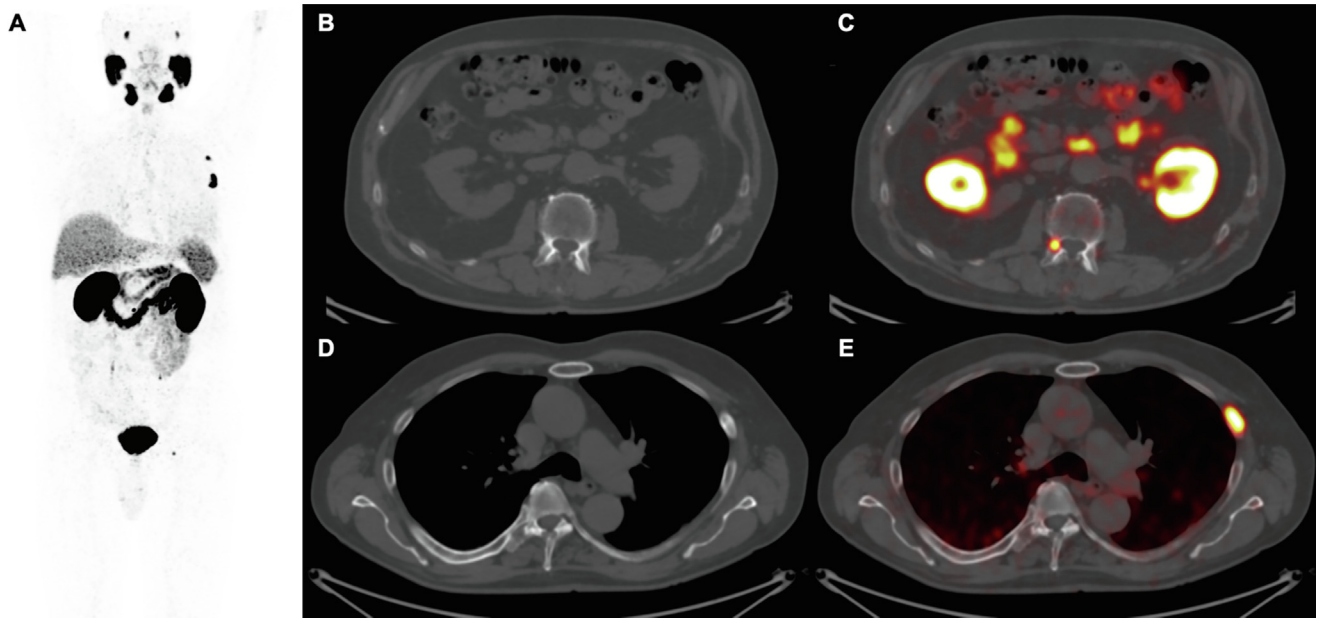

Fig. 4 – A 61-yr-old man underwent radical prostatectomy with pelvic lymph node dissection (iPSA = 7.5 ng/ml, pT3a pN0, ISUP 4, negative surgical margins). PSA at 6 wk after surgery was 0.06 ng/ml. Seven months later, first BCR occurred (PSA = 0.22 ng/ml, PSAdt = 3.4 mo). Salvage radiotherapy was scheduled as the best clinical practice option. The patient was referred to PSMA-PET. The predicted probability of positivity applying our nomogram was 72%. Indeed, PSMA-PET revealed (A) four bone metastases with high PSMA uptake, (B and C) two lesions without significant CT alterations, and (D and E) two other lesions corresponding to two osteosclerotic lesions on CT. The patient was treated with ADT instead of salvage radiotherapy. ADT = androgen deprivation therapy; BCR = biochemical recurrence; CT = computed tomography; iPSA = initial PSA; ISUP = International Society of Urological Pathology; PET = positron emission tomography; PSA = prostate-specific antigen; PSAdt = PSA doubling time; PSMA = prostate-specific membrane antigen.

case of a higher likelihood of positive imaging (eg, changes in biochemical parameters reflecting a more aggressive recurrence, such as faster PSAdt) and (2) treated with salvage therapy without positive imaging considering the risk of local or nodal or systemic recurrence based on clinical and pathological characteristics (Fig. 4). At present, there is a lack of information (mainly derived from ongoing randomized controlled trials) regarding a more favorable oncological outcome in patients treated with PSMA-guided therapy versus the conventional approach. Moreover, further study investigating PSMA staining with immunohistochemistry obtained by surgical specimens might increase the significance of patient selection. Approximately 5% of patients do not overexpress PSMA on PCa cells, even in case of high-risk clinical features. These patients should not be referred to PSMA-PET and investigated with other imaging modalities (eg, choline or fluciclovine PET and whole-body magnetic resonance imaging). Previously, Rauscher et al [25] proposed two different clinical nomograms (compact and comprehensive models) to predict positive PSMA-PET results. This model was proposed for a selected cohort of patients (BCR after RP and PSA $\leq$1 ng/ml). The reported PA of the model was 67%. PSA and concurrent ADT were the only significant predictors. The same group proposed in-house validation of the model in an external cohort [26], showing high concordance of the calculated probabilities and PSMA-PET findings, while further external validation [27] did not confirm these results, showing an overestimation throughout the range of predicted positive PSMA-PET probabilities. However, this model cannot be fully compared with our nomogram, considering the strict patient selection and the lack of clinical data (eg, PSAdt and clinical setting). Finally, patients affected by recurrent PCa represent a broad clinical scenario with a heterogeneous disease burden in terms of the number of lesions, site, and aggressiveness. This heterogeneity affects patients' clinical management and their outcome. This external validation (Table 2) confirmed the different diagnostic performance of PSMA-PET at different stages of disease recurrence [9,12].

4.1. Limitations

This study is not exempt from limitations. Histopathological confirmation of PSMA-PET findings has not been obtained, since few pathological confirmatory data were available, and validation is based on radiological findings. However, some registry trials [28–30] already proved the high PPV specific for PSMA-PET. Despite retrospective design, all PSMA-PET images were evaluated with a local review, by PSMA-PET–experienced nuclear medicine physicians according to international reporting procedural guidelines [16]. Finally, further implementation of the model with an immunohistochemistry analysis to test for PSMA staining might improve the model accuracy, as tumor subtypes with low PSMA expression may cause false negative results [27].

5. Conclusions

The external validation of our nomogram, performed in a large multicentric cohort of recurrent PCa, confirmed the high PA (82.0%) of the model, and the optimal concordance between the calculated probabilities and PSMA-PET results. This nomogram represents an easy tool to help clinicians in the decision-making process of recurrent PCa. In clinical practice, the incidence of a false negative scan will be reduced if PSMA-PET is performed when the nomogram-predicted probability is >20%. This nomogram, integrated in an online risk calculator, can assist in clinical trial design and individual clinical decision-making.

***Author contributions*:** Andrea Farolfi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ceci, Bianchi, Castellucci.
Acquisition of data: Ceci, Farolfi, Castellucci, Droghetti, Artigas, Leite, Corona, Shagera, Moreira, González, Queiroz, de Galiza Barbosa.
Analysis and interpretation of data: Ceci, Bianchi.
Drafting of the manuscript: Ceci, Bianchi, Castellucci, Farolfi, Artigas.
Critical revision of the manuscript for important intellectual content: Bianchi, Castellucci, Farolfi, Droghetti, Artigas, Leite, Corona, Shagera, Moreira, González, Queiroz, de Galiza Barbosa, Schiavina, Deandreis, Fanti, Ceci.
Statistical analysis: Bianchi.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2021.12.002.

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