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Prediction Nomogram for 68 Ga-PSMA-11 PET/CT in Different Clinical Settings of PSA Failure After Radical Treatment for Prostate Cancer

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# **Prediction nomogram for <sup>68</sup>Ga-PSMA-11 PET/CT in different clinical settings of PSA failure after radical treatment for prostate cancer**

**Running head:** Nomogram to predict positive PSMA PET/CT in recurrent prostate cancer

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## **ABSTRACT**

**Background:** The prompt identification of the site of prostate cancer (PCa) recurrence with  $^{68}\text{Ga}$ -Prostate Specific Membrane Antigen Positron Emission Tomography/Computed Tomography ( $^{68}\text{Ga}$ -PSMA-11-PET/CT) may change the disease management, potentially improving the survival outcomes.

**Objective:** To develop a clinical nomogram to predict  $^{68}\text{Ga}$ -PSMA-11-PET/CT positivity in different clinical settings of PSA failure.

**Design, setting, and participants:** Seven-hundred-three (n=703) PCa patients with confirmed PSA failure after radical therapy were enrolled. Each patient underwent  $^{68}\text{Ga}$ -PSMA-11-PET/CT to identify the site of recurrence. Patients were stratified according to different clinical settings of recurrence (first-time biochemical recurrence [BCR]: group-1; BCR after salvage therapy: group-2; biochemical persistence after radical prostatectomy [BCP]: group-3; advanced stage PCa before second-line systemic therapies: group-4).

**Outcome measurements and statistical analysis:** First, we assessed  $^{68}\text{Ga}$ -PSMA-11-PET/CT positivity rate. Second, multivariable logistic regressions analyses were used to determine which co-variables independently predicted positive scan. Third, regression-based coefficients were used to develop a nomogram predicting positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT result and 200 bootstrap resamples were used for internal validation. Fourth, Receiver operating characteristic (ROC) analysis was used to identify the most informative nomogram's derived cut-off to predict the positive scan. Decision curve analysis (DCA) were implemented to quantify nomogram's clinical benefit in clinical practice.

**Results and limitations:** <sup>68</sup>Ga-PSMA-11-PET/CT positivity rate was 51.2 %, while was 40.3% (group-1), 54% (group-2), 60.5% (group-3), 86.9% (group-4) (p<0.001). At multivariable analyses Gleason Grade, PSA, PSA<sub>dt</sub> and clinical setting were independent predictors of a positive scan (all p≤0.04). A nomogram based on covariates included in the multivariate model demonstrated a bootstrap-corrected accuracy of 82%. At ROC analysis, 40% resulted the best nomogram's cut-off. Finally, in DCA, the nomogram revealed clinical net benefit when the threshold probabilities of positive <sup>68</sup>Ga-PSMA-11-PET/CT is >10%.

**Conclusions:** We developed and internally validated the first nomogram aimed at predicting the likelihood of <sup>68</sup>Ga-PSMA-11-PET/CT positivity in different stages of PSA failure. It showed good performance characteristics and it might guide clinicians to select the best candidates for <sup>68</sup>Ga-PSMA-11-PET/CT.

**Patient summary:** In this study, we evaluated patient with PSA persistence or PSA recurrence after radical treatments for prostate cancer. Our clinical nomogram showed good accuracy to stratify patients with higher likelihood of <sup>68</sup>Ga-PSMA-11-PET/CT positivity. <sup>68</sup>Ga-PSMA-11-PET/CT vary considering clinical setting of PSA failure. In this scenario, ideal candidates to be investigated with PSMA based PET imaging in recurrent setting were those men with more aggressive disease, namely with higher serum PSA and faster PSA doubling time.

**Key words:** prediction nomogram; <sup>68</sup>Ga-PSMA; PET/CT; recurrence; prostate cancer; PSA failure.



## INTRODUCTION

The clinical management of patients experiencing PSA failure (namely biochemical persistence [BCP] and biochemical recurrence [BCR]) after radical treatment for prostate cancer (PCa) includes blinded treatments based on the hypothetical risk of local vs. aggressive systemic recurrence. However, clinical models cannot reliably predict recurrence sites and the extent of metastatic disease<sup>1</sup>. The introduction of novel imaging technologies significantly changed the clinical management of recurrent PCa, leading to novel "imaging-guided" approaches<sup>2</sup>. These techniques have the potential to improve patient outcome and to spare or delay the toxicity associated with the use of systemic therapies<sup>3</sup>. The use of <sup>68</sup>Gallium-Prostate Specific Membrane Antigen Positron Emission Tomography/Computed Tomography (<sup>68</sup>Ga-PSMA-11-PET/CT) revealed favourable sensitivity and specificity profiles compared to Choline or Fluciclovine PET imaging techniques<sup>4,5</sup>. Recently, the use of PSMA PET has also been introduced by the EAU guidelines, which currently suggest to perform this imaging modality in all men with BCR or BCP<sup>6</sup>. However, whether such an approach is really cost-effective remains largely unknown. This is key since men with recurrent/persistent disease represent a highly heterogeneous patient group with different prognosis and profiles of disease aggressiveness. As a consequence, selecting the proper candidates for PSMA PET is key to optimize its use and to spare possible unnecessary expensive staging approaches in those at lower risk. We hypothesized that men with positive <sup>68</sup>Ga-PSMA-11-PET/CT and PSA failure after primary treatment can be accurately identified<sup>7</sup>.

To test our hypothesis, we developed and internally validated a clinical nomogram able to assess the likelihood of each patient, in different setting of PSA failure after primary

treatment, to have a positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT. This tool might be markedly important as a guide to clinicians for the best use of PSMA based PET imaging.



## **MATERIALS AND METHODS**

### *Study population*

The cohort of patients included in this analysis was enrolled through an open-label, single-center, prospective registry study performed at our institution (Prot. PSMA-PROSTATA; Eudract: 2015-004589-27 OsSC), and in accordance with the Declaration of Helsinki ethical principles. All patients provided signed informed consent prior to PET/CT scan. All men received  $^{68}\text{Ga}$ -PSMA-11-PET/CT at single referral center (Nuclear Medicine, University of Bologna, Italy) between March 2016 and September 2018 due to BCR (n=627) or BCP (n=76) during follow-up. All clinical, pathological and follow-up data were available for all patients. BCR was defined as two consecutive PSA assays  $\geq 0.2$  ng/ml in patients treated with radical prostatectomy (RP) as primary treatment with/without post-operative radiotherapy (RT) and as PSA  $\geq 2$  ng/mL above the nadir in patients treated with primary RT, in accordance to the Phoenix criteria<sup>6</sup>. BCP was defined as a PSA  $\geq 0.1$  ng/ml at 6 weeks after RP<sup>8-10</sup>.

### *Clinical settings*

Different clinical settings of PSA relapse were identified by referring physicians (urologist, radiation oncologist and clinical oncologist) in a single-center multidisciplinary tumor board (Prostate Cancer Unit) and the overall population was grouped into 4 different categories of PSA recurrence, namely: first-time BCR (Group-1, n=325) defined as first relapse after primary treatment, PSA recurrence after salvage therapies (Group-2, n=241), BCP (Group-3, n=76) and advanced stage PCa<sup>11</sup> with PSA progression under androgen deprivation therapy (ADT) and candidate to second-line systemic therapies (including taxane-based chemotherapy and new androgen-receptor targeted therapies

[ARTA]; Group-4, n=61). All patients included in the analysis were chemotherapy and ARTA-naïve.

#### *<sup>68</sup>Ga-PSMA11 synthesis and PET/CT acquisition*

<sup>68</sup>Ga-PSMA-11 was synthesized at the radio-pharmacy of Nuclear Medicine, University Hospital of Bologna and prepared in a similar procedure as described by Eder et al<sup>14</sup> and in our previous publication<sup>7,12</sup>. A mean dose of 2 MBq/Kg body weight of <sup>68</sup>Ga-PSMA-11 was administered intravenously. <sup>68</sup>Ga-PSMA-11-PET/CT was performed with a standard technique<sup>13</sup>. All studies were performed using a dedicated PET/CT state-of-the-art system (Discovery 690; Discovery MI. GE Healthcare, Milwaukee, WI, US).

#### *Images Interpretation*

All <sup>68</sup>Ga-PSMA-11-PET/CT images were analysed with dedicated software (eNTEGRA; GE Healthcare) and were independently interpreted by two nuclear medicine physicians with more than 5 years of experience (FC, PC). In cases of disagreements between readers, the final diagnosis was reached by the opinion of a third reader (SF). Images were interpreted according to procedure guidelines<sup>16</sup>, as reported in our previous publication<sup>7,14</sup>. PET-positive lesions were classified as suspected local relapse (prostate/prostate bed recurrence), nodal relapse (including both pelvic and extra-pelvic lymph nodes), skeletal and visceral metastases (including soft tissue metastases and other systemic localization of recurrence). Basing on PET/CT results, oligometastatic state includes patients with 1 to 3 detected lesions, while multi-metastatic stage comprehends men with more than 3 lesions.

#### *Outcomes*

The primary outcome of the study was to investigate the independent predictors of positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT results in men with PSA relapse after primary treatments and to develop a clinical nomogram aimed to assess the likelihood of each patient to have a positive scan. Secondary outcome was to assess the most informative nomogram's derived cut-off to predict the positive results of  $^{68}\text{Ga}$ -PSMA-11-PET/CT.

### *Statistical analyses*

Statistical analyses first consisted of descriptive statistics on the overall positivity rate of  $^{68}\text{Ga}$ -PSMA-11-PET/CT and the positivity rate of pelvic/distant recurrence and oligometastatic/poly-metastatic disease. Population was stratified according to different clinical stages of PSA relapse. Chi-squared test and ANOVA test were used to compare categorical variables and continuous variables, respectively. Second, univariable and multivariable logistic regression analyses were performed to assess independent predictors of positive scan on patient-based analysis. We included the following co-variables: pathologic 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 underwent to primary RT, PSA at  $^{68}\text{Ga}$ -PSMA-11 PET/CT ( $\leq 0.2$  ng/ml vs 0.21-0.49 ng/ml vs 0.5-0.99 ng/ml vs 1-1.99 ng/ml vs  $\geq 2$  ng/ml), PSA doubling time ([PSAdt] <3 months vs 3-5.99 months vs 6-11.9 months vs  $\geq 12$  months), on-going ADT (yes vs no), time to recurrence (>12 months vs  $\leq 12$  months) and clinical setting of PSA relapse (Group-1 vs Group-2 vs Group-3 vs Group-4). Third, regression-based coefficients were used to develop a nomogram predicting positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT result. The predictive accuracy of the nomogram was quantified using the Harrell concordance index (discrimination) and the extent of over- or underestimation of the observed positive PET/CT result was

explored graphically in logistic calibration plots. The nomogram was subjected to 200 bootstrap resamples for reduction of overfit bias and for internal validation. Fourth, we systematically analyzed specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) for each nomogram derived cut-off. Receiver operating characteristic (ROC) analysis and the area under curve (AUC) was used to assess the predictive accuracy of each nomogram's derived cut-off and to identify the most informative cut-off to predict positive scan. Moreover, we implemented with decision curve analysis (DCA), in order to quantify the nomogram's clinical benefit in routine clinical practice<sup>15</sup>. DCA investigates the theoretical relationship between the threshold probability of positive PSMA PET/CT and the relative value of false-positive and false-negative findings to assess the net benefit of the predictive multivariable model<sup>15</sup>. Finally, to investigate which patients with different stage of PSA relapse would benefit from <sup>68</sup>Ga-PSMA-11-PET/CT, dedicated multivariate logistic regression models were performed to predict positive scan in each group of PSA relapse (namely, Group-1, Group-2, Group-3 and Group-4). All statistical tests were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) with a 2-sided significance level set at  $P < 0.05$ .

## RESULTS

### *Overall population*

Table 1 depicts the baseline characteristics of patients included in the study. Median PSA at  $^{68}\text{Ga}$ -PSMA-11-PET/CT and median PSA<sub>dt</sub> were 0.7 ng/ml (Interquartile range [IQR] 0.4- 1.3) and 6 (3.5-9.6), respectively. Out of 703 individuals, 116 (16.5 %) were receiving ADT at the time of PET/CT. Median time to PSA recurrence was 27 months (IQR 11.1-54.3). Overall, 325 (46.2%), 241 (34.3%), 76 (10.8%) and 61 (8.7%) patients were referred to  $^{68}\text{Ga}$ -PSMA-11-PET/CT due to first-time BCR (Group-1), PSA recurrence after salvage therapies (Group-2), BCP (Group-3) and advanced stage PCa with PSA recurrence prior to second-line systemic therapy (Group-4), respectively. The overall positivity rate of  $^{68}\text{Ga}$ -PSMA-11-PET/CT was 51.2 % (95% Confidence Interval [CI] 46.8–71.3%).

### *Clinical Nomogram*

Multivariable regression analysis revealed that ISUP group 3 and 5 (all  $p \leq 0.04$ ),  $\text{PSA} \geq 0.5$  ng/ml (all  $p \leq 0.003$ ),  $\text{PSA}_{dt} \leq 6$  months (all  $p \leq 0.001$ ) and the presence of a PSA progression before second-line treatments (Group 4) were independent predicting factors of positive scan (Table 2; all  $p \leq 0.04$ ). Multivariable derived coefficients were used to develop a novel nomogram to predict positive  $^{68}\text{Ga}$ -PSMA-11 PET/CT result (Figure 1). After bootstrap-correction the discrimination accuracy of the model was 82% (95% CI= 0.79-0.85; **Supplementary figure 1**). The calibration plot of predicted probabilities against observed positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT indicated good concordance (Figure 2).

Moreover, nomogram-derived predicted probabilities of positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT are categorized into each nomogram's derived cut-off. The number of patients having negative  $^{68}\text{Ga}$ -PSMA-11-PET/CT and those with positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT as well as sensitivity, specificity, PPV, NPV and accuracy are depicted for each cut-off in Table 3. At ROC analysis, the best nomogram's cut-off to predict positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT was 40% (AUC=0.76; 95% CI=0.72-0.79; **Supplementary Figure 2**). With this premise, using a nomogram cut-off of 40%, 282 of 703 patients (40.1%) would be spared  $^{68}\text{Ga}$ -PSMA-11-PET/CT and positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT would be missed in 55 patients (15.3%). The sensitivity, specificity and NPV associated with 40% as cut-off were 84.7%, 66.2%, and 80.5%, respectively (Table 3). Finally, in DCA, the nomogram revealed clinical net benefit when the threshold probabilities of positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT is >10% (Figure 3). **For example, applying a nomogram-derived probability threshold of 40% above which a man would be counselled to perform PSMA PET/CT, use of the nomogram would result in a net benefit gain of 13. This net benefit when compared with the scenario of treating none would be 33<sup>15</sup>. The net benefit of 33 at a threshold probability of 40% can be interpreted in terms that use of the model, compared with assuming that all patients do not experience positive PSMA PET/CT, leads to the equivalent of a net 33 true-positive results per 100 patients without an increase in the number of false-positive results (Figure 3).**

### *Sub-groups analyses*

The detection rate of  $^{68}\text{Ga}$ -PSMA-11-PET/CT was significantly different between the four groups: 40.3 %, 54%, 60.5% and 86.9 % in Group-1, 2, 3 and 4, respectively (Table 4;  $p < 0.001$ ). However, we observed no significant difference with respect of oligometastatic ( $\leq 3$  lesions) disease detection rate between men at different setting. In patients with first-time BCR (Group-1), only  $\text{PSA} \geq 0.5$  ng/ml (all  $p \leq 0.01$ ) and  $\text{PSA dt} \leq 6$  months (all  $p < 0.001$ ) were independent predictors of positive  $^{68}\text{Ga}$ -PSMA-11 PET/CT at multivariate analysis (Supplementary Table 1). In patients with PSA recurrence after salvage therapy (Group-2), only  $\text{PSA dt} \leq 6$  months (all  $p \leq 0.001$ ) was independent predictor of positive PET/CT at multivariate analysis (Supplementary Table 2). In BCP (Group-3), only PSA ( $p = 0.04$ ) and ISUP group 5 ( $p = 0.04$ ) were independent predictors of positive scan (Supplementary Table 3). Finally, in patients with advanced PCa with PSA relapse prior to second-line systemic therapy (Group-4), only  $\text{PSA dt}$  ( $p = 0.01$ ) was independent predictor of positive PET/CT (Supplementary Table 4).

## DISCUSSION

Although phase-3 trials are still on-going<sup>16</sup>, preliminary results showed promising results for image-guided radiotherapy<sup>17</sup> and radio-guided surgery<sup>18</sup> to control the disease in the recurrent setting. Since different therapies can be offered to patients at different time-points in the natural history of recurrent PCa (BCP vs. early recurrence vs. advanced stages), the accuracy of <sup>68</sup>Ga-PSMA-11-PET/CT should be investigated in different clinical settings regardless of PSA absolute value only. Accordingly, referent physicians should be aware about which parameters will influence <sup>68</sup>Ga-PSMA-11-PET/CT performance in different clinical stages. Our study confirmed in a wide cohort the overall good performance of <sup>68</sup>Ga-PSMA-11-PET/CT in recurrent PCa (51.2%)<sup>7,19</sup> attesting different rates of positivity among the different settings: 40.3% in Group-1, 54% in Group-2, 60.5% in Group-3 and 86.9% in Group-4 (Table 3,  $p < 0.001$ ), respectively. Accordingly, we support the inclusion of clinical setting of PSA relapse as selection criteria when considering <sup>68</sup>Ga-PSMA-11-PET/CT (Figure 1). Furthermore, our data confirmed PSA and PSA<sub>dt</sub> as independent predictors of positive scan at multivariate analysis.

In this scenario, our nomogram could be considered a comprehensive and useful tool able to guide physicians in the most appropriate use of <sup>68</sup>Ga-PSMA-11-PET/CT. The model includes both pathologic parameters (ISUP grade) and biochemical characteristics (PSA, PSA<sub>dt</sub>, on-going ADT and time to relapse). Moreover, since <sup>68</sup>Ga-PSMA-11 PET/CT had difference performance according to different scenarios of relapse<sup>20</sup>, we included in the model the clinical setting of PSA relapse, in order to predict the likelihood of positive <sup>68</sup>Ga-PSMA-11 PET/CT in each patient's subgroup. The innovative advantage of the proposed nomogram is to select patients with likelihood of positive <sup>68</sup>Ga-PSMA-11-



PET/CT in each patient sub-group. Thus, identifying patients with high probability to have a positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT we can identify suspicious PCa recurrence and properly adjust treatments strategy accordingly. Conversely, in men with low likelihood of positive PET/CT we can spare expansive examinations that would not solve the dilemma of unknown/undetected site of recurrence and the treatments options would not have been changed accordingly.

In our cohort, we investigated two sub-cohorts with similar PSA values and suitable for similar salvage therapy. Patients who had PSA nadir  $<0.1$  ng/mL after RP and subsequently experienced first BCR (Group-1) had lower rates of positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT (40.3%) and different predictors, compared to BCP patients (Group-3) who had persistent high PSA values (PSA nadir  $>0.1$  ng/mL) after RP (60.5%). As a consequence, when referring BCR patients to  $^{68}\text{Ga}$ -PSMA-11-PET/CT, PSA and its kinetics derivate should be evaluated in order to reduce the incidence of false negative scan. On the contrary, BCP patients showed generally higher likelihood of positivity despite having lower PSA values and shorter time from surgery to PSA relapse. The persistence of malignant tissue within or outside the pelvis may explain the higher positivity rate and the lower impact of independent predictors.

Using the best nomogram's cut off to predict positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT (namely, 40%), only 15.3% of patients would be erroneously counselled against  $^{68}\text{Ga}$ -PSMA-11-PET/CT, with a sensitivity, specificity, NPV and accuracy of 84.7%, 66.2%, 80.5% and 76%, respectively. To note, the global discrimination accuracy of our nomogram was good (79–85%) and the model benefited from favourable calibration characteristics (Figure 2) throughout the range of predicted positive PET/CT results. Finally, DCA showed that the

nomogram revealed clinical net benefit across the entire range of threshold probabilities (Figure 3).

Finally, we observed no significant difference with respect of oligometastatic ( $\leq 3$  lesions) disease detection rate between men at different setting. However, despite Group-4 PET/CT revealed higher multi-metastatic ( $>3$  lesion) PCa (50.9%), a not negligible rate of multi-metastatic disease was found even in Group-2 (4.6%), Group-3 (11.2%) and Group-4 (21%). This evidence might support the use of  $^{68}\text{Ga}$ -PSMA-11-PET/CT to detect higher unexpected disease volume and site of recurrence, with consequent change in the treatment plan<sup>21</sup>.

Previously, Rauscher et al<sup>22</sup>, proposed a clinical nomogram to predict positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT results. This model was proposed for a selected cohort of men with BCR after RP and  $\text{PSA} \leq 1$  ng/ml and it was not tested in different stages of PSA relapse. In their analysis, the only features associated with a positive scan were PSA and concurrent ADT. Data in the literature on the higher frequency of positive scans concomitant ADT are contradictory<sup>22,24</sup>. Basing on choline experience, PET/CT detection rate is still optimal in patients with rising PSA values and on-going ADT at the time of imaging (castration-resistant), while conversely decrease in case of hormone-sensitive disease<sup>25</sup>. Thus, rising PSA during ADT is not a condition reflecting an early stage of BCR. In our population, concomitant ADT was not found to be independent predictor of positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT. Accordingly, the introduction of clinical setting as independent predictor of positivity may help physicians to identify more accurately the best candidates for PET/CT scan.

Our study is not devoid of limitations. Retrospective design of our analyses may have affected our results. Then, as many other studies investigating the role of imaging in recurrent PCa, we did not test  $^{68}\text{Ga}$ -PSMA-11-PET/CT sensitivity, specificity and accuracy at lesion-based analyses since few pathologic confirmatory data were available. Of note, the routine practice considers biopsy of suspected metastases in a limited number of cases and generally, it is not feasible due to ethical and practical reasons. Thus, the proposed cut off 40% to suggest  $^{68}\text{Ga}$ -PSMA-11-PET/CT is based on radiologic findings.

## **CONCLUSION**

This novel nomogram proved its good accuracy to predict a positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT results. The 40% cut off was the most informative threshold probability to predict positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT. This tool might be markedly important as a guide to clinicians in the best use of PSMA-based PET imaging, in order to select the best treatment option. Furthermore, this model can be applied to further prospective trials evaluating the efficacy of  $^{68}\text{Ga}$ -PSMA-guided therapies. External validation of the model is needed to test whenever the performance accuracy would be confirmed in the different cohort of patients.

## REFERENCES

1. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 1999;17(5):1499-1507.
2. Ost P, Bossi A, Decaestecker K, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol*. May 2015;67(5):852-863.
3. Schiavina R, Bianchi L, Borghesi M, Sabbatini R, Brunocilla E. Toward the future of the functional imaging of advanced prostate cancer. *European urology focus*. Apr 2017;3(2-3):240-242.
4. Perera M, Papa N, Christidis D, et al. Sensitivity, Specificity, and Predictors of Positive <sup>68</sup>Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*. Jun 27 2016.
5. Calais J, Fendler WP, Herrmann K, Eiber M, Ceci F. Comparison of (68)Ga-PSMA-11 and (18)F-Fluciclovine PET/CT in a Case Series of 10 Patients with Prostate Cancer Recurrence. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. May 2018;59(5):789-794.
6. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. Apr 2017;71(4):618-629.
7. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid (6)(8)Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. May 2015;56(5):668-674.
8. Bianchi L, Nini A, Bianchi M, et al. The Role of Prostate-specific Antigen Persistence After Radical Prostatectomy for the Prediction of Clinical Progression and Cancer-specific Mortality in Node-positive Prostate Cancer Patients. *Eur Urol*. Jun 2016;69(6):1142-1148.
9. Wiegel T, Bartkowiak D, Bottke D, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. *International journal of radiation oncology, biology, physics*. Feb 1 2015;91(2):288-294.
10. Van den Broeck T, van den Bergh RCN, Arfi N, et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. *Eur Urol*. Oct 17 2018.
11. Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. May 2 2016.
12. Farolfi A, Ceci F, Castellucci P, et al. (68)Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA <0.5 ng/ml. Efficacy and impact on treatment strategy. *European journal of nuclear medicine and molecular imaging*. Jun 15 2018.

13. Fendler WP, Eiber M, Beheshti M, et al. (68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *European journal of nuclear medicine and molecular imaging*. Jun 2017;44(6):1014-1024.
14. Fanti S, Minozzi S, Morigi JJ, et al. Development of standardized image interpretation for 68Ga-PSMA PET/CT to detect prostate cancer recurrent lesions. *European journal of nuclear medicine and molecular imaging*. Sep 2017;44(10):1622-1635.
15. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Medical decision making : an international journal of the Society for Medical Decision Making*. Nov-Dec 2006;26(6):565-574.
16. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol*. Feb 14 2019.
17. Schmidt-Hegemann NS, Stief C, Kim TH, et al. Outcome after PSMA PET/CT based salvage radiotherapy in patients with biochemical recurrence after radical prostatectomy: a bi-institutional retrospective analysis. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. Jul 12 2018.
18. Maurer T, Robu S, Schottelius M, et al. (99m)Technetium-based Prostate-specific Membrane Antigen-radioguided Surgery in Recurrent Prostate Cancer. *Eur Urol*. Apr 2019;75(4):659-666.
19. Pereira Mestre R, Treglia G, Ferrari M, et al. Correlation between PSA kinetics and PSMA-PET in prostate cancer restaging: A meta-analysis. *European journal of clinical investigation*. Mar 2019;49(3):e13063.
20. Ceci F, Castellucci P, Graziani T, et al. (68)Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy. *European journal of nuclear medicine and molecular imaging*. Jan 2019;46(1):31-39.
21. Calais J, Czernin J, Cao M, et al. (68)Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. Feb 2018;59(2):230-237.
22. Rauscher I, Duwel C, Haller B, et al. Efficacy, Predictive Factors, and Prediction Nomograms for (68)Ga-labeled Prostate-specific Membrane Antigen-ligand Positron-emission Tomography/Computed Tomography in Early Biochemical Recurrent Prostate Cancer After Radical Prostatectomy. *Eur Urol*. May 2018;73(5):656-661.
23. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *European journal of nuclear medicine and molecular imaging*. Aug 2017;44(8):1258-1268.
24. Afshar-Oromieh A, Debus N, Uhrig M, et al. Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive

- prostate cancer. *European journal of nuclear medicine and molecular imaging*. Nov 2018;45(12):2045-2054.
- 25.** Ceci F, Castellucci P, Mamede M, et al. (11)C-Choline PET/CT in patients with hormone-resistant prostate cancer showing biochemical relapse after radical prostatectomy. *European journal of nuclear medicine and molecular imaging*. Jan 2013;40(2):149-155.

## FIGURE LEGEND:

**Figure 1.** Nomogram predicting the likelihood of positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT for patients with different clinical settings of PSA failure after radical treatment for prostate cancer. ISUP: International Society of Urological Pathology; PSA: prostate Specific Antigen; PSMA PET/CT: Prostate Specific Membrane Antigen Positron Emission Tomography/Computed Tomography; ADT: androgen deprivation therapy; BCR: biochemical Recurrence.

Instructions: Locate the patient's ISUP group (pathologic ISUP for patients treated with RP and clinical ISUP for those treated with RT) on the ISUP group axis. Draw a line straight upward to the point axis to determine how many points toward the probability of positive PSMA PET/CT the patient receives for his ISUP group. Repeat the process for each additional variable. Sum the points for each predictor. Locate the final sum on the total-point axis. Draw a line straight down to find the patient's probability of having positive PSMA PET/CT.

**Figure 2.** Nomogram calibration plot. The predicted probability of the multivariable model is shown on the x-axis, and the observed proportion of men with positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT 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  $^{68}\text{Ga}$ -PSMA-11-PET/CT are identical. Broken line indicates actual nomogram performance.



**Figure 3.** Decision curve analysis demonstrating the net benefit associated with use of the nomogram for the prediction of men with positive  $^{68}\text{Ga}$ -PSMA-11-PET/CT. The net benefit is represented by the gap between the continuous line and the dotted line.

**Supplementary Figure 1.** Receiver-operator characteristic (ROC) and area under curve (AUC) of the nomogram in overall population to predict positive PSMA PET/CT results (AUC=82% (95% CI= 0.79-0.85)).

**Supplementary Figure 2.** Receiver-operator characteristic (ROC) and area under curve (AUC) of each nomogram derived cut off to predict positive PSMA PET/CT results. The best nomogram's cut-off to predict positive PSMA PET/CT was 40% (AUC=0.76; 95% CI=0.72-0.79)