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

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In early biochemical recurrence, traditional imaging approaches (eg, computed tomography [CT], magnetic resonance imaging [MRI]) and choline-based positron-emission tomography (PET) often fail to localize disease. PET targeting the prostate-specific membrane antigen (PSMA) holds high promise to enhance imaging in prostate cancer (PC) patients. Early biochemical recurrence represents the clinically most relevant subgroup offering the possibility of potential curative salvage therapy concepts that might have major impact on patients' outcome [1,2]. Despite multiple, mainly retrospective, analyses, ^{68}Ga-PSMA-ligand PET/computed tomography (CT) data in the literature (1) suffer from heterogeneous patient collectives, (2) suffer from limited size, (3) include different stages of biochemical recurrence, and (4) include limited numbers of patients with early recurrence after a specific

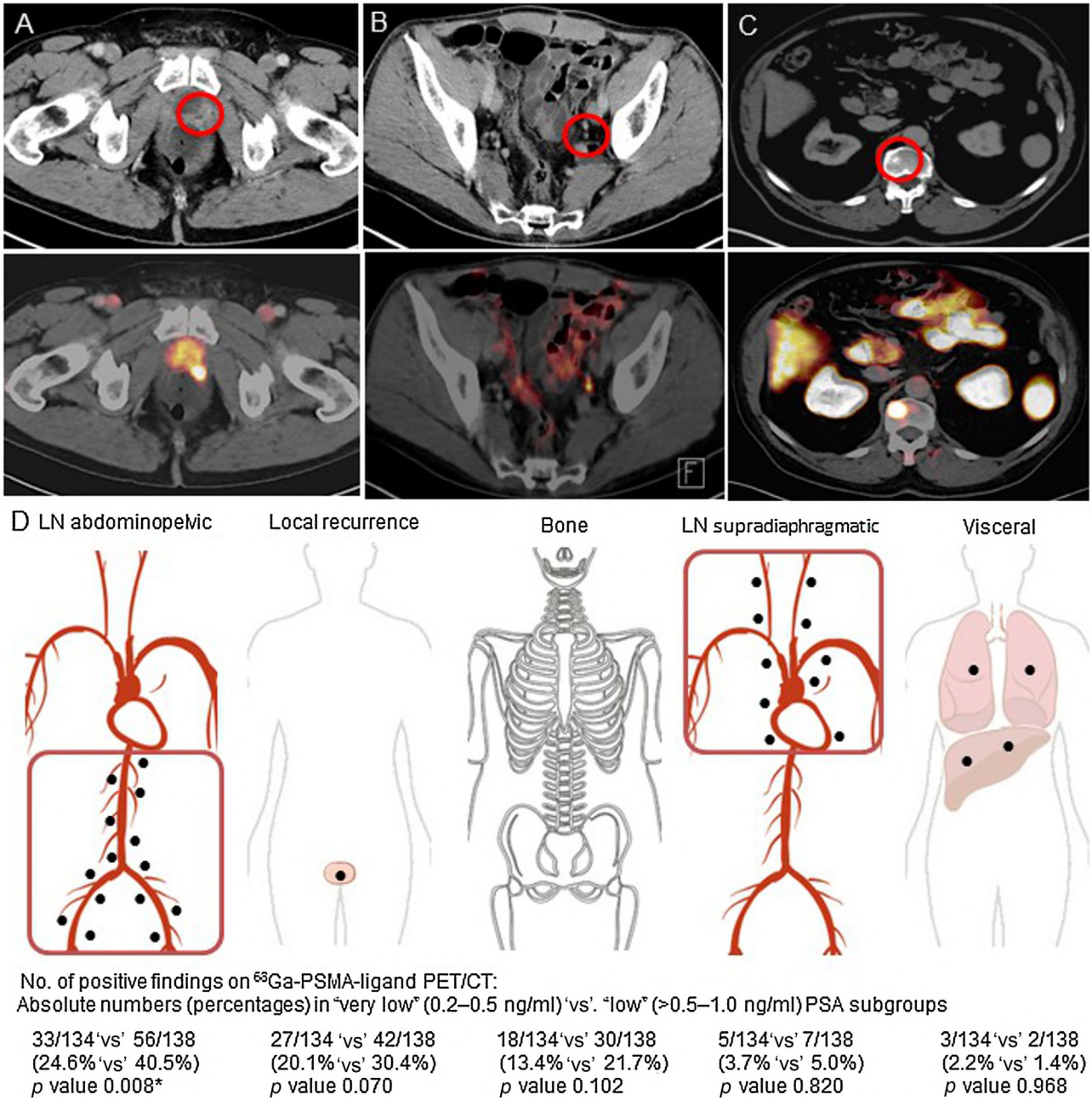

Fig. 1 – Examples of ^{68}Ga-PSMA-ligand PET/CT in early recurrent PC after RPE. Upper row shows CT datasets and lower row fused PSMA-ligand PET/CT studies. (A) A 65-yr-old male with biochemical recurrence (PSA 0.39 ng/ml) 3 yr after RPE (pT3a, pN0, R0, grade group 5) with intense, focal PSMA-ligand uptake in the left dorsal prostate bed highly suggestive of local recurrence. (B) A 67-yr-old male with biochemical recurrence (PSA 0.63 ng/ml) 2 yr after RPE (pT3b, pN1, R0, grade group 5) with intense PSMA-ligand uptake in a morphologically unsuspicious lymph node near the left internal vessels highly suggestive of a single lymph node metastasis. Metastatic involvement of this lymph node was histologically proved (positive in HE staining and PSMA immunohistochemistry staining) after PSMA-radioguided surgery. (C) A 76-yr-old male with biochemical recurrence (PSA 0.33 ng/ml) 6 yr after RPE (pT3b, pN0, R1, grade group 5) and 4 yr after salvage radiation therapy of the prostate bed with intense PSMA-ligand uptake in the T-spine highly suggestive of bone metastasis. (D) Localization of positive findings on ^{68}Ga-PSMA-ligand PET/CT according to PSA subgroups.
CT = computed tomography; HE = hematoxylin and eosin; LN = lymph node; PC = prostate cancer; PET = positron-emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RPE = radical prostatectomy. * A significant difference ($p \leq 0.05$).

treatment [3–5]. This raises concerns about the precision and reliability of its reported statistical values and results in contradictory literature on potential predictive factors. Therefore, the aim of this retrospective study was to: (1) evaluate the diagnostic efficacy of ^{68}Ga-PSMA-ligand PET/CT in a large homogeneous and well-defined patient population after radical prostatectomy (RPE) with prostate-specific antigen (PSA) values between 0.2 and 1.0 ng/ml; (2) identify predictive clinical variables; and (3) propose prediction nomograms for ^{68}Ga-PSMA-ligand PET/CT positivity.

A total of 1697 consecutive patients undergoing PSMA-ligand PET/CT with ^{68}Ga-labelled HBED-CC for biochemically recurrent PC were extracted from the institutions' database (from March 2013 to December 2015). Inclusion criteria for the final cohort of 272 patients were as follows: hormone-sensitive biochemical recurrence, RPE as primary treatment, PSA values between 0.2 and 1.0 ng/ml at the time of imaging (Supplementary Fig. 1 and Supplementary Table 1). All patients signed a written informed consent form for the purpose of anonymized evaluation and publication of their data (Ethics Committee of the Technical University Munich, permit 5665/13). Imaging datasets were evaluated by a double-trained, board-certified nuclear medicine physician and radiologist. Suspicious lesions for recurrent PC were noted and grouped as follows: (1) local recurrence, (2) lymph node metastases (abdominopelvic vs supradiaphragmatic), (3) bone, and (4) visceral metastases (eg, lung, liver).

Subgroups were defined as very low (0.2–0.5 ng/ml) versus low (>0.5–1.0 ng/ml) PSA values, and absolute and relative frequencies of detection including exact 95% confidence intervals (CIs) are reported. Logistic regression models were fitted to the data to estimate odds ratios for relevant variables. A full comprehensive prediction model including all available clinical variables and a compact prediction model based on a backward variable selection procedure are proposed and illustrated by nomograms. Receiver-operating-characteristic (ROC) analysis was conducted to compare associations of binary variables with PSMA-PET positivity and discriminatory ability of the prediction model. All statistical tests performed were two sided, and a significance level of $\alpha = 5\%$ was used. Details on statistical analyses are presented in the Supplementary material.

In total, ^{68}Ga-PSMA-ligand PET/CT was positive in 65% (176/272; 95% CI 59–70%) of patients. Representative examples are shown in Figure 1A–C. Detection rate was lower in patients with very low compared with low PSA values (55%, 74/134, 95% CI 46–64% vs 74%, 102/138, 95% CI 66–81%; Supplementary Table 2). Main sites for lesions were pelvic or retroperitoneal lymph node metastases, followed by local recurrence and bone metastases with higher probability in the low versus very low PSA subgroup (Fig. 1D). Supradiaphragmatic lymph node metastases and visceral metastases were detected in <10% with no association to PSA subgroups. Findings were validated in 52% (92/176) of patients. Details are presented in the Supplementary material.

Univariate analysis revealed PSA value, primary locally advanced tumors (pT ≥ 3a), initial pN+ disease, grade group

Table 1 – Univariate and multivariable analysis of predictive factors for positive ^{68}Ga-PSMA-ligand PET/CT

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Continuous PSA value: 0.2–1.0 ng/ml	6.43 (2.04–20.30)	0.002*	4.20 (1.15–15.37)	0.03*
Initial T stage: ≥pT3a vs ≤pT2c	1.93 (1.14–3.27)	0.01*	1.26 (0.66–2.41)	0.5
Initial N stage: pN1 vs pN0	2.09 (1.07-4.08)	0.031*	1.19 (0.55–2.60)	0.7
Initial grade group: ≥4 vs ≤ 3	2.11 (1.19–3.73)	0.01*	1.83 (0.92–3.62)	0.09
Radiotherapy after RPE: yes vs no	2.03 (1.16–3.55)	0.01*	1.36 (0.69–2.68)	0.4
ADT at time of ^{68}Ga-PSMA-ligand PET: yes vs no	15.73 (2.10–118.0)	0.007*	9.25 (1.17–73.31)	0.035*
Time interval from RPE to ^{68}Ga-PSMA-ligand PET (yr)	1.01 (1.95–1.08)	0.7	1.00 (0.92–1.10)	>0.9

ADT = androgen deprivation therapy; CI = confidence interval; CT = computed tomography; OR = odds ratio; PET = positron-emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RPE = radical prostatectomy.
* A significant difference ($p \leq 0.05$).

Table 2 – Models to predict the probability of a positive ^{68}Ga-PSMA-ligand PET/CT based on clinical characteristics

Compact model	
1.1.1	$P(\text{lesion}) = \frac{\exp(-0.57 + 1.58 \cdot \text{last PSA} + 0.65 \cdot (\text{grade group} \geq 4) + 2.42 \cdot \text{ADT})}{1 + \exp(-0.57 + 1.58 \cdot \text{last PSA} + 0.65 \cdot (\text{grade group} \geq 4) + 2.42 \cdot \text{ADT})}$
Comprehensive model	
1.1.2	$P(\text{lesion}) = \frac{\exp(-0.82 + 1.44 \cdot \text{last PSA} + 0.23 \cdot (\text{pT} \geq 3a) + 0.18 \cdot \text{pN1} + 0.60 \cdot (\text{grade group} \geq 4) + 0.31 \cdot \text{RTX} + 2.23 \cdot \text{ADT} + 0.003 \cdot \text{TI})}{1 + \exp(-0.82 + 1.44 \cdot \text{last PSA} + 0.23 \cdot (\text{pT} \geq 3a) + 0.18 \cdot \text{pN1} + 0.60 \cdot (\text{grade group} \geq 4) + 0.31 \cdot \text{RTX} + 2.23 \cdot \text{ADT} + 0.003 \cdot \text{TI})}$

ADT = androgen deprivation therapy; CT = computed tomography; PET = positron-emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RPE = radical prostatectomy; TI = time from RPE to ^{68}Ga-PSMA-ligand PET in years.
Please note that for PSA value and time interval in years the respective numbers have to be used when applying the formulas. For all other variables, the presence of a given feature (eg, "radiotherapy" or "grade group ≥ 4") is accounted for "1," whereas the absence of this given feature is accounted for "0."

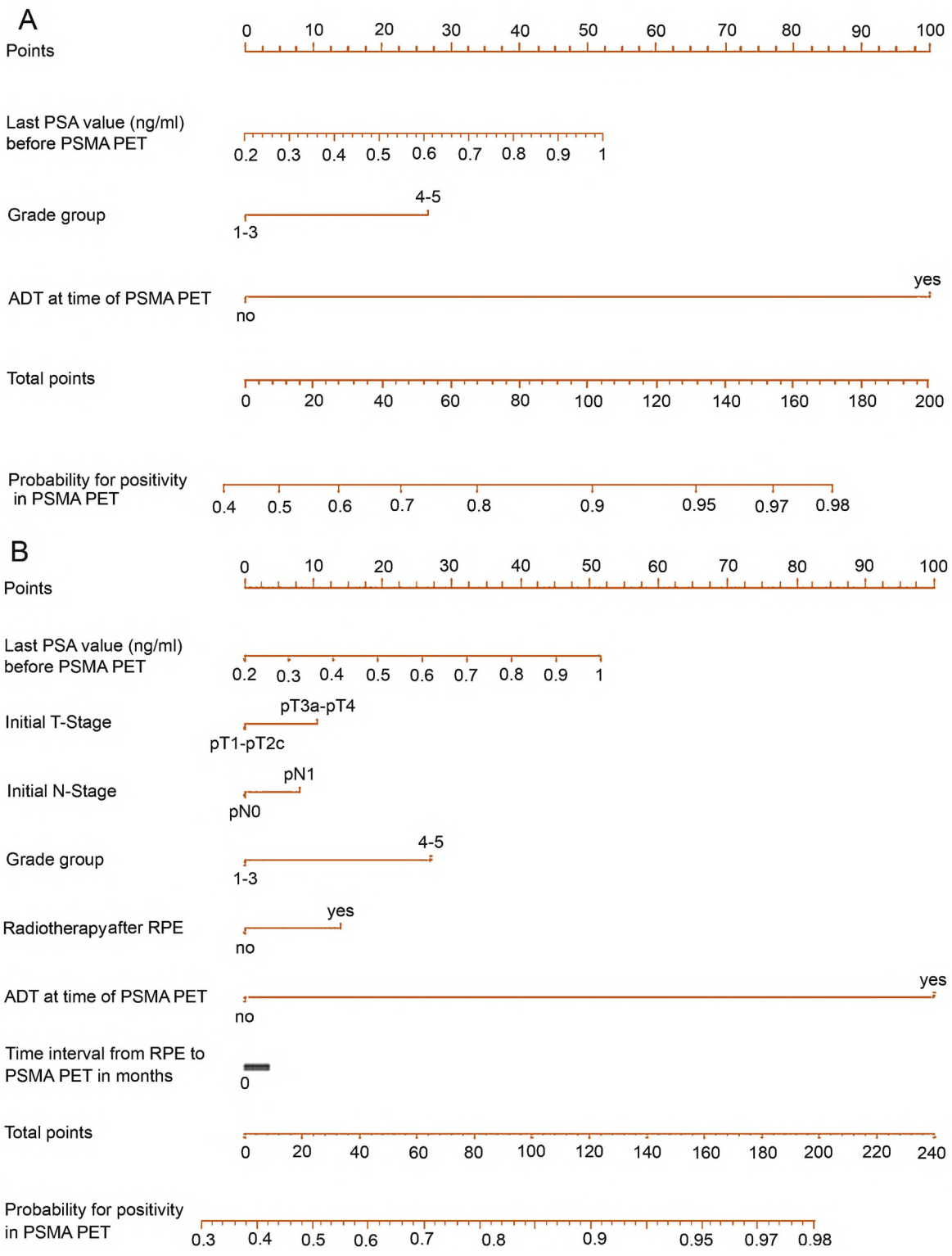

Fig. 2 – Nomograms for predicting positivity in ^{68}Ga-PSMA-ligand PET/CT. (A) The compact model includes the three most relevant predictors (PSA value before PET, concurrent ADT, and grade group) compared with (B) the comprehensive model that uses all clinical variables. For both nomograms, points from selected clinical variables (top scale) are summed up to a total score (lower scale) associated with an estimated probability for ^{68}Ga-PSMA-ligand PET/CT positivity. Draw a line straight upward to the point axis to determine how many points toward the probability of positive ^{68}Ga-PSMA-ligand PET/CT the patient receives for different clinical values. Repeat the process for each additional variable. Sum the points for each of the predictors. Locate the final sum on the total point axis. Draw a line straight down to find the patient's probability of having a positive ^{68}Ga-PSMA-ligand PET/CT. The area under the ROC curve of the compact prediction model was 0.67 (95% confidence interval 0.60–0.74) and that of the comprehensive model was 0.69 (95% confidence interval 0.62–0.76), indicating moderate discriminatory ability. ADT = androgen deprivation therapy; CT = computed tomography; PET = positron-emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; ROC = receiver-operating-characteristics; RPE = radical prostatectomy.

≥4, previous radiation therapy, and concurrent androgen deprivation therapy (ADT) at time of imaging as potential predictive factors for positive ^{68}Ga-PSMA-ligand PET/CT. In multivariable analysis, only PSA value and concurrent ADT were identified as significant independent predictors; initial grade group showed a clear, yet not significant, association (Table 1). These three variables were also identified as most relevant predictors in a backward variable selection procedure using Akaike's information criterion.

Results of the multivariable models are illustrated by nomograms for predicting positivity in ^{68}Ga-PSMA-ligand PET: a nomogram for a compact model was created including only PSA value, concurrent ADT, and grade group as predictors. A nomogram for a comprehensive model includes all available clinical information. The formulas and paper-and-pencil diagrams are shown in Table 2 and Figure 2A and B. The estimated probability for ^{68}Ga-PSMA-ligand PET/CT positivity is determined for both nomograms by summing up points from the selected clinical variables to a total score. Supplementary Figure 2 illustrates the association of different clinical variables with the presence of positive scans and discriminatory ability for a combination of all variables using ROC analyses.

Multiple, mainly retrospective, series have recently investigated the detection efficacy of ^{68}Ga-PSMA-ligand PET/CT. However, the reported number of patients with early biochemical recurrent PC after RPE (0.2–1 ng/ml) is limited, asking for a more comprehensive analysis and description of potential predictive factors in a patient cohort with anticipated high clinical impact [1,2]. We report positive findings using ^{68}Ga-PSMA-ligand PET/CT in 65% of 272 patients (55% for 0.2–0.5 ng/ml and 74% for >0.5–1.0 ng/ml PSA values). To our knowledge, this is not only the largest study of ^{68}Ga-PSMA-ligand PET/CT in this well-defined patient cohort, but also the first presentation of prediction nomograms to assess a priori the probability of ^{68}Ga-PSMA-ligand PET positivity based on clinical variables. These nomograms may assist the urologist in the decision for ordering a ^{68}Ga-PSMA-ligand PET/CT as well as in discussion with patients. Nomograms are commonly used in uro-oncology mainly assessing the likelihood of T or N stage of primary PC using Partin tables or the Kattan nomogram [6,7]. Our approach represents the first attempt to incorporate a variety of different clinical variables to estimate the probability of a positive imaging test. It could be a first step toward better patient selection, and potentially help spare resources for those subgroups in which positive ^{68}Ga-PSMA-ligand PET/CT might tailor salvage procedures and potentially influence outcome. Nevertheless, this hypothesis has to be proved by future prospective studies.

Our results for detection efficacy fit well to a recently published meta-analysis reporting pooled positivity for ^{68}Ga-PSMA-ligand PET/CT in 58% for PSA range 0.2–0.99 ng/ml [5]. Afshar-Oromieh et al [3], analyzing 1007 cases, report similar data for 227 patients with PSA range 0.2–1 ng/ml, but include patients with both RPE and radiation therapy as primary treatment. Meredith et al [8] reported substantially lower detection rates (27% and 53% for PSA 0.2–<0.5 and 0.5–<1 ng/ml, respectively) in 126 patients after RPE. However, only focal ^{68}Ga-PSMA-ligand findings were judged positive if they corresponded to a suspicious lesion on CT, which is a major drawback.

Guidelines recommend salvage radiotherapy to patients with a PSA value of up to 0.5 ng/ml, but acknowledge that 40% of these patients will not achieve an undetectable PSA value. Results of our study might provide potential explanations as even in the PSA range of 0.2–0.5 ng/ml, a substantial number of patients presented with lymph node, bone, or visceral metastases (Fig. 1). The ^{68}Ga-PSMA-ligand PET/CT might modify otherwise unsuccessful local salvage radiotherapy or enable targeted surgical salvage procedures.

In our study, the two most relevant predictors for ^{68}Ga-PSMA-ligand PET/CT positivity in multivariable analysis were PSA value and concurrent ADT. Correlation of higher PSA values with increasing scan positivity is in line with previous reports [5,9]. Data in literature on the higher frequency of positive scans under ADT at the time of ^{68}Ga-PSMA-ligand PET/CT are contradictory, but previous negative correlations might be related to low sample sizes. The known upregulation of PSMA by ADT might explain the higher diagnostic efficacy in our study [10].

Our study has limitations: positive findings were validated only in a limited number of patients (n = 17). Notably, follow-up imaging was available in >50% of cases. However, histopathological correlation in systemic or distant tumor recurrence is often not feasible due to ethical and practical reasons. Nevertheless, evidence on histopathological correlation of positive soft-tissue findings outlining high specificity and positive predictive value for ^{68}Ga-PSMA-ligand PET is increasing [11,12]. Despite growing evidence of non–PC-related PSMA-ligand uptake, most of these potential pitfalls can be solved in the clinical context or in correlation with morphological imaging [13]. False-negative results can only be determined on patient base and are represented by all imaging negative cases in our study. However, negative ^{68}Ga-PSMA-ligand PET should not preclude early salvage radiotherapy, as most recently a negative ^{68}Ga-PSMA-ligand PET was shown to predict a high response to salvage fossa radiotherapy [14].

In conclusion, our study investigates in depth and presents robust data on the high efficacy of ^{68}Ga-PSMA-ligand PET/CT for early biochemical recurrence after RPE. It detects local and nonlocal lesions in more than half of the patients and thus might significantly influence further treatment. Our results on predictive factors and proposal of prediction nomograms might facilitate patient selection for ^{68}Ga-PSMA-ligand PET/CT.

Author contributions: Isabel Rauscher 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: Eiber, Schwaiger, Gschwend, Maurer, Rauscher.

Acquisition of data: Düwel, Heck, Rischpler, Rauscher.
Analysis and interpretation of data: Rauscher, Eiber, Maurer, Düwel, Heck, Rischpler.
Drafting of the manuscript: Rauscher, Eiber, Maurer.
Critical revision of the manuscript for important intellectual content: Eiber, Schwaiger, Gschwend, Maurer, Rauscher, Düwel, Heck, Rischpler, Haller.
Statistical analysis: Haller, Eiber, Maurer, Rauscher.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Schwaiger, Gschwend, Eiber, Maurer.
Other: None.

Financial disclosures: None.

Funding/Support and role of the sponsor: Matthias Eiber certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Markus Schwaiger has received funding from the European Union Seventh Framework Program (FP7) under Grant Agreement No. 294582 ERC Grant MUMI. The development of 68Ga-PSMA synthesis was supported by SFB 824 (DFG Sonderforschungsbereich 824, Project Z1) from the Deutsche Forschungsgemeinschaft, Bonn, Germany. Matthias Eiber received funding from the SFB 824 (DFG Sonderforschungsbereich 824, Project B11) from the Deutsche Forschungsgemeinschaft, Bonn, Germany.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.01.006.

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